1973

Progress Report No. 9

Biomedical Computer Laboratory

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PROGRESS REPORT

No. 9

1 July 1972 - 30 June 1973

Biomedical Computer Laboratory
Washington University School of Medicine
St. Louis, Missouri
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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1972 through June 30, 1973. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine in the application of advanced computer techniques to problems in biology and medicine. This often requires work in areas stretching from basic physiology through mathematical models to equipment design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect.

One class of computer applications requires strong coupling of the computer to its environment. These applications often involve the use of a small computer such as a Laboratory Instrument Computer (LINC) or a Programmmed Console (PC). We have pursued these applications by bringing signals from investigator's laboratories to BCL by means of either analog tape recordings or telephone lines and, more frequently, by taking the computers to the investigator's laboratory.

A second class of applications requires a computer strongly coupled to its environment and also the advanced information processing capabilities available from large central machines. To meet the demands of this particularly difficult class of applications we have connected most of our laboratory-style computers via telephone lines to the IBM 360 Model 65 at the Washington University Computing Facilities.

A final class of applications requires extensive use of large scale computational services. Many investigators are assisted in their research through the use of generalized numerical, non-numerical, and statistical routines. This work is carried out in part by staff members of BCL, but primarily by members of the Division of Biostatistics under the direction of Dr. Reimut Wette, and the University Computing Facilities whose director during the past year has been Dr. Jon Strauss.

The Washington University Computer Laboratories (WUCL) is a federation of computer research activities which includes the Biomedical Computer Laboratory and the Computer Systems Laboratory. This federation of laboratories functions through a coordinating committee composed of the laboratory directors and in addition, the Vice Chancellor for Medical Affairs, the Vice Chancellor for Research (vacant since March), the Director of the University Computing Facilities and the Associate Director of BCL.

The Computer Systems Laboratory, which is under the direction of Dr. Charles E. Molnar, is active in the design, development and evaluation of a compatible set of "macromodules" useful in the experimental design of arbitrarily large, complex, or specialized computer systems and in the continuing adaption of such systems to problems in information processing and in biological research.
A National Advisory Panel assists in planning health-related activities of the Biomedical Computer Laboratory and Computer Systems Laboratory under the NIH Biotechnology Research Resources grant. Currently the Committee has the following membership:

W. A. Clark  Consultant and Past Director of Computer Systems Laboratory  Cambridge, Massachusetts

D. M. Kipnis  Busch Professor and Head of the Department of Medicine  Washington University School of Medicine

F. M. Richards  Professor in Molecular Biophysics and Chemistry  Yale University

R. S. Snider  Professor of Anatomy and Director of Center for Brain Research  University of Rochester

The Advisory Committee meets periodically with the WUCL Coordinating Committee to review developing techniques and to advise upon desirable areas of applications.
II. SOURCES OF SUPPORT

During the period covered by this report the primary source of support for the Biomedical Computer Laboratory was a grant from the National Institutes of Health:

RR 00396 A Resource for Biomedical Computing

Partial support was received by the laboratory for a training grant program in Health Care Technology:

HS 00074 Technology and Health Care

A contract to study the relationship of arrhythmias and sudden death sponsored by the National Heart and Lung Institute has continued in collaboration with the Department of Medicine and the Jewish Hospital:

NIH-71-2481 Relationship of Ventricular Arrhythmias to Sudden Death in Survivors of Myocardial Infarction

Collaboration with other investigators often involved work already supported by other grants. Most of this support was from the Public Health Service:

AM 01921 Transport Processes in Mammalian Cells
AM 13332 Metabolic Regulation and Interacting Enzyme Systems
AM 15531 Membrane Transport of Amino Acids
AM 51159 Special Research Fellowship
CA 03980 Mechanisms of Biological Hydrogen Transfer Reactions
CA 04483 Effects of X-Rays on Normal and Malignant Cells
CA 10702 Mathematical Biology of Neoplastic Growth
CA 13053 Clinical Cancer Radiation Therapy Research Center Grant
GM 01311 Training Program in Biochemistry
GM 01747 Training Program in Radiology (Nuclear Medicine)
GM 01827 Training Program for Engineering Biophysics
GM 21514 Magnetic Investigation of Acyl CoA Dehydrogenases
GM 21863 Career Development Award
HL 12820 Lipid Protein Interaction in Blood Clotting
HL 13851 Cyclotron Produced Isotopes in Biology and Medicine
HL 14147 Specialized Center of Research in Thrombosis
HL 52357 Proteolysis by Factor X in Prothrombin Activation
LM 00106 Biomedical Librarianship
NS 03856 Auditory Communication and its Disorders
NS 05159 The Metabolism of Inositols and Inositides
RR 06115 Health Science Advancement Award

Advanced Research Projects Agency:
SD-302 Macromodular Computer Design

Air Force Office of Scientific Reserve:
F 44620 Control Guidance and Information Fundamentals of Aerospace

Atomic Energy Commission:
AT(11-1)1653 Biologic Considerations in Anatomic Imaging with Radionuclides

HEW Subcontract from Harvard:
HSM-110-72-267 Development of Data Demonstrations in Training Centers

Health Services and Mental Health Administration:
MH 07081 Research Training - Biological Sciences
MH 20717 Morphine Tolerance and High Sensitivity Measurement

National Science Foundation:
GB 26483X Enzyme Structure and Function
GK 32239 Information Processing for Doubly-Stochastic Poisson Processes
III. PERSONNEL

EMPLOYEES

Personnel employed by the Biomedical Computer Laboratory during the period covered by this report were:

Director
Jerome R. Cox, Jr., Sc.D.

Associate Director
Lewis J. Thomas, Jr., M.D.

Assistant Director for Engineering
V. W. Gerth, Jr., M.S.

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Associate Professor
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Assistant Professors
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William F. Holmes, Ph.D., Biochemistry
Thomas F. Martin, M.D., Cardiology

Research Instructor
Kenneth B. Larson, Ph.D.

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A. Maynard Engebretson, D.Sc.
Floyd M. Nolle, D.Sc.

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James M. Baker, B.S.
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Rexford L. Hill, III, M.S.
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Margaret C. Jost, B.A.
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Michael D. McDonald, B.S.
Joanne Markham, B.A.
J. Philip Miller, B.A.
Nizar A. Mullan, B.S.
James M. Pexa, M.S.
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Kenneth L. Ripley, B.A.
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Robert N. Tatum, B.S.
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Thomas F. Schuessler, B.S.
Clinton L. Watson

Technical Assistants
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Stanley A. Garfield
Betty J. Greenwood
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James B. Minard
Emil D. Scheifler
John J. Sueme

Machinist
Kenneth J. Spraul
Librarian
Loretta C. Benso, M.A.

Business Manager
Virginia M. Bixon, B.S.

Secretaries
Sandra Cole
Shirley Gonzales-Rubio
Sandra E. Katzen, B.S.
Linda C. Stites
Frances M. Wroton

Summer Personnel

In addition, the following people worked at the laboratory for brief periods:

David P. Bax
William H. Cloud, Jr., B.S.
Terrence J. Coleman
Ola-Olu Daini, B.A.
Donald E. Gayou
Ronald Inselberg
Mitzi C. Kenner
Gregory W. MacCordy
Larry N. McCord
James W. Oetting
John A. Ritter
Richard V. Sanders
Robert W. Scheifler
James B. Sellinger
Michael D. Sutter, B.S.
Mark D. Sutton
Alan J. Tiefenbrunn, B.A.
Hildegard C. Wette

RESEARCH COLLABORATORS

During the period covered by this report the following investigators from other laboratories, departments, or institutions, collaborated with BCL staff members on problems of joint interest:

Washington University
U. T. Aker, M.D., Medicine
P. O. Alderson, M.D., Radiology
K. A. Arnold, M.D., Surgery
W. E. Ball, D.Sc., Applied Mathematics and Computer Science
L. J. Banaszak, Ph.D., Physiology and Biophysics
D. J. Bates, A.B., Biochemistry
D. M. Bier, M.D., Medicine
H. A. Bomze, Ph.D., Preventive Medicine
R. L. Boshans, A.B., Psychiatry
W. S. C. Chang, Ph.D., Electrical Engineering
R. E. Clark, M.D., Surgery
W. A. Clark, B.A., Computer Systems Laboratory
R. E. Coleman, M.D., Radiology
F. M. Domke, Radiology
G. R. Drysdale, Ph.D., Biochemistry
J. O. Eichling, Ph.D., Radiology
C. T. Esmon, B.A., Biochemistry
R. G. Evens, M.D., Radiology
N. J. Falvey, B.S., Computing Facilities
T. P. Fang, B.S., Computer Systems Laboratory
A. Feldman, Ph.D., Radiology
P. M. Fishman, M.S., Applied Mathematics and Computer Science
R. H. Forrester, Jr., M.S., Electrical Engineering
H. Fotenos, Radiology
C. Frieden, Ph.D., Biochemistry
S. Goldring, M.D., Neurosurgery
R. O. Gregory, D.Sc., Electrical Engineering
R. L. Grubb, Jr., M.D., Radiology
J. Hecht, A.B., Radiology
B. R. Heib, M.D., Medicine
G. Hill, B.S., Radiology
L. S. Hillman, M.D., Pediatrics
R. E. Hillman, M.D., Pediatrics
R. M. Hochmuth, Ph.D., Chemical Engineering
E. J. Hoffman, Ph.D., Radiology
W. H. Holland, A.B., Psychiatry
C. M. Jackson, Ph.D., Biochemistry
L. Jarett, M.D., Pathology
S. A. Jones, B.A., Radiology
I. N. Katz, Ph.D., Applied Mathematics and Computer Science
J. Kenner, B.S., Preventive Medicine
D. M. Kipnis, M.D., Medicine
R. E. Kleiger, M.D., Medicine
K. A. Krohn, Ph.D., Radiology
S. Lang, Ph.D., Physiology and Biophysics
M. M. McCrate, B.S., Biostatistics
T. F. Martin, M.D., Medicine
F. S. Mathews, Ph.D., Physiology and Biophysics
J. W. Mathews, M.S., Computer Systems Laboratory
J. M. Metzger, Ph.D., Radiology
C. E. Molnar, Sc.D., Computer Systems Laboratory
G. C. Oliver, Jr., M.D., Medicine
G. O. Oliver, Ph.D., Radiology
W. G. Owen, Ph.D., Biochemistry
P. M. Packman, M.D., Psychiatry
G. T. Perkoff, M.D., Preventive Medicine
Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year projects of joint interest have been continued with:

Artronix Instrumentation, Inc., Brentwood, Missouri - A radiation treatment planning system and a cardiac catheterization laboratory system.

Mennen-Greatbatch Electronics, Inc., Clarence, New York - An ECG rhythm monitoring system.
IV. PHYSICAL RESOURCES

On April 15, 1964, the Biomedical Computer Laboratory was formed and the original staff moved into 5,515 square feet (gross) of laboratory space at 700 South Euclid Avenue, just across the street from the main building of the Washington University School of Medicine. Equipment then available for Laboratory applications of digital computers was a single LINC (Laboratory INstrument Computer). This small stored-program computer had been designed specifically for use in biology and medical laboratories where there is a requirement for strong coupling between the computer, the investigator, and other experimental equipment. Since that time some twelve LINC's and five PDP-12's, a newer implementation of the LINC, have been added to the resources of the Washington University medical community.

In 1966 the Programmed Console was designed at BCL to function as a combined stored-program digital computer and remote display console for the IBM 360 Model 50 installed during May, 1966, at the Washington University Information Processing Center. (The Model 50 was converted to a Model 65 in April, 1973). BCL's computational facilities now include three specialized Programmed Consoles built at the laboratory. In addition, thirteen Programmed Consoles have been built by SPEAR, Inc., from plans and specifications developed at BCL. Of these, six were evaluated under an NIH sponsored program as an aid to radiation treatment planning at radiology centers in Stanford, California; Bethesda, Maryland; Houston, Texas; Boston, Massachusetts; Philadelphia, Pennsylvania, St. Louis, Missouri; and Toronto, Canada. Two Programmed Consoles manufactured by SPEAR, Inc. are in use in other projects at BCL. In 1972, five new PC-1200 Programmed Consoles manufactured by Artronix, Inc. were installed at BCL in support of a variety of new and existing projects. All of the evaluation centers except that at Toronto, Canada have now replaced their SPEAR PCs with new Artronix PC-1200 systems.

An IBM System 7 was installed at the laboratory in April, 1972 to become a major component of a system for the high speed analysis of electrocardiograms. 1972-73 also marked the beginning of routine use of the inventory of Macromodules for significant work supporting research in hearing and speech, high speed ECG processing, and higher-level language performance improvements. Other laboratory facilities include a data transmission distribution system, a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules, and both analog and digital tape recorders.

During the past seven years the laboratory space has been increased by 1526 square feet in the basement, 2762 square feet on the ground floor and 3171 square feet on the second floor of 700 South Euclid, and by 3463 square feet on the second floor and 1257 square feet of the basement of the building just south of the original space. Facilities for computational applications, laboratories, staff offices and a WUCL research library are provided in these
acquired spaces. Direct communications with the IBM 360 Model 65 at the Washington University Information Processing Center is provided via phone lines, Programmed Consoles and LINC's.

On October 1, 1969, an on-line computer monitoring system was installed by BCL in the Cardiac Care Unit of the Barnes Hospital complex. The computer equipment is housed in 360 square feet of specially designed space within the unit. Key BCL staff members occupy 260 square feet of office space nearby.

A computer-based Surgical Intensive Care Monitoring System designed and built by BCL was installed in Barnes Hospital in March, 1973. The computer and related hardware are located in a room within the intensive care facilities.
V. RESEARCH PROJECTS

Summary

The major goal of the Laboratory is the application of computer techniques to problems in medicine and biology. This often requires work in areas stretching from basic physiology through mathematical models, to equipment design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect. The Laboratory's research program has been organized into several major project areas with many of the Laboratory staff grouped into teams whose interests focus in one of these project areas.

A. Radiation Therapy. The programmed console (PC) developed at BCL for radiation treatment planning is now in widespread use. About 75 systems for quantitative treatment planning are now installed or on order either through Artronix and their PC-1200 or through the Digital Equipment Corporation and a similar system called the RAD-8. New PC-1200 computers have now been installed in four of the five institutions participating in the original PC evaluation program. The prototype information system for patient data handling and retrospective therapy evaluation is taking shape. The project is developing at two levels, a national data base and a local patient information entry and filing system. The teleprocessing capabilities of the PC have been used to communicate with a computer utility for experiments relating to the national data base and for use of specialized treatment planning programs.

Although much of the original work on the PC Radiation Treatment Planning System was carried out at the Biomedical Computer Laboratory recent years have seen a transition of effort to the Department of Radiology. Now the major portion of support for this program comes from grants directly to Radiology and most of the work is carried out by staff from that department. This change in the center of gravity of effort from BCL to Radiology seems to us to be appropriate as the project matures and becomes a viably independent effort.

B. Electrocardiographic Rhythm Monitoring. For the past three and a half years the Argus Computer System for continuous ECG rhythm monitoring has been in operation at the Barnes Hospital Coronary Care Unit. The first copy of a commercial version of this system developed by Mennen Greatbatch was installed in a community hospital about a year ago. The second copy has been installed in our Coronary Care Unit and is currently undergoing an evaluation of its technical performance. A medical evaluation of the clinical import of the system was begun last year, but was deferred in the absence of financial support.

Our study to investigate the causes of sudden cardiac death through a better understanding of the role played by arrhythmias continues. The computer system for this study Argus/H, is now operational and provides high speed analysis of tape recorded data from ambulatory subjects in whom the presence
of coronary artery disease has been documented by recent myocardial infarction. This system uses a scheme for compact digital coding of ECG data so that up to one day of recorded data can be stored on a single digital tape. These tapes are produced at sixty times real time by use of a special macro-modular preprocessor. An IBM System/7 computer decodes the tapes and processes them using the Argus algorithms. The results are then examined by viewing reconstructed ECG segments of approximately 16 seconds duration surrounding each detected premature ventricular contraction (PVC). Editing facilities allow the user to make corrections in the computer's identifications. The eventual goal of our Argus/H system is to produce a data stream which describes the ECG rhythm in accurate beat-by-beat detail. Measurements of PVC frequency, coupling intervals, and other rhythm details can then be compiled automatically.

A program to gather data from subjects with coronary artery disease has to date enrolled 156 patients and recorded 975 Holter tapes. These tapes have been qualitatively scanned and demographic data has been obtained for comparison with both the manual qualitative scan and the automated quantitative scan. These studies have already shown a rather surprising stability of the Lown classifications of the subjects at different recording dates post-infarction. Initial results with the Argus/H system show it to be superior to manual scanning in almost all cases.

We have begun to develop techniques for the preparation of an annotated test tape for automatic arrhythmia detectors. Test data will be recorded digitally, annotated by a panel of cardiologists, and the results made available to those collaborating in a group interested in the evaluation of arrhythmia detectors.

C. Regional Tracer Kinetics. For the past two years our work in regional tracer kinetics has moved toward attempts to attain fundamental understanding through the study of mathematical models. We hope these models will form the basis of future clinical applications of computers to regional tracer kinetics. The first such study relates blood-tissue exchange rates of substances that can be radioactively labeled to measurements obtained by external monitoring. A second study involves the estimation of parameters of physiological interest from dynamic radiotracer data and assumes the arrival of photons can be modeled by an inhomogeneous Poisson process. The maximum-likelihood estimate of these parameters has been derived and practical means for making the computations are being studied. A third study concerns a theory for the distribution of transit times for nondiffusible tracers. Because of the stochastic features of the structure of vasculatures, a model utilizing probability theory has been developed and it appears to be successful in explaining the important attributes of transit-time curves. Finally, a dual-injection method for the measurement of mean transit time provides a valid theoretical basis for taking the effects of tracer recirculation into account. This method has been previously reported but is now in use in experimental and clinical studies.

In collaboration with the Radiation Sciences Division of the Department of Radiology, a new computer system for data gathering and analysis is being interfaced to a number of experiments. Of particular note is an array of 26 probes for the measurement of human cerebral hemodynamics and metabolism.
We hope that in the future these mathematical and instrumental developments will find applications in useful clinical measurements. Meanwhile, however, clinical studies have continued on cerebral glucose utilization, cerebral blood flow and volume, cardiac ejection fraction, ventilation and perfusion in the lung and gastric emptying.

D. Monitoring the Critically Ill. The digital computer portion of the monitoring system for the new surgical intensive care unit has been installed and in operation since early spring. The reliability of this system has been quite satisfactory. Only two hardware failures have occurred since installation and only minor software modifications have been necessary to meet re-defined clinical requirements. The general functions performed by these programs, however, remain unchanged and the acceptance by surgeons and nurses is excellent. A reliability study of the local bus communication system within the SICU showed no errors in more than 10^10 transactions.

E. Communications for Information Processing. Conversion of the network connecting small computers at the School of Medicine to the University's IBM System/360 was carried out uneventfully when the Model 65 replaced the Model 50 this spring. The use of the network has become more intermittent with fewer steady users primarily as a result of an increased capability at each of the satellite computers. Our work on wide-band communication over multi-pair cables and optical paths continues and a model for cross-talk in multi-pair cables carrying digital information has been verified experimentally. A prototype optical communication system has successfully sent data at about a megabaud rate using near infra-red light. Several theoretical studies have been completed in support of this optical communications work.

F. Cardiac Catheterization Laboratory. Last summer the cardiac catheterization laboratory system was revised completely to incorporate improvements that had been identified during use of the prototype system the previous year. At the same time the system was made available for commercial development by Artronix Incorporated. A PC-1200 had been installed in the Jewish Hospital Catheterization Laboratory and during the year the finishing touches have been made to the system by Artronix. A study of the variability in the subjective analysis of left ventricular function from cineangiograms has shown the need for more quantitative measurements and, consequently, a staged program has been begun to automate this analysis. In the first phase of this program the ventricular contours are traced by hand from processed film into the computer. The requirement for high-speed automatic pattern recognition is, thereby, eliminated, but considerable technician time is still required. In the second phase of the program we plan to develop semi-automatic digitization of the video information obtained directly from the image intensifier tube. Our work in this and other projects in the cardiac function will be enhanced by the installation this fall of a PC-1200 in the Barnes Catheterization Laboratory to replace the outdated developmental system that has been used for the past four years.

G. Mass Spectrometry and Biochemical Kinetics. The past year has seen a substantial growth in interest by clinicians in the mass spectrometry computer system. The system, operating on a PDP-12 and revised and expanded, is now in use in a number of mass spectrometer centers around the world. Of particular
clinical interest has been the addition to the system of a means for multiple ion detection by computer control of the spectrometer accelerating voltage allowing selection of a few masses for concentrated attention. With this system quantitative measurements have been made on samples as small as 40 picograms. Thus, it appears that serious biochemical mapping of the nervous system at the level of detail of several cell nuclei is a distinct possibility. Already several very interesting clinical applications of the technique have been carried out, including stable isotope tracer measurements of the turnover of glucose and alanine in hypoglycemic children.

Work on the searching of mass spectrometric files is proceeding. Two such programs have been developed; one automatically compares each spectrum file against the unknown spectrum and displays the ten chemical compounds with the best matches while the other utilizes an interactive technique wherein the user can adjust his search criteria to obtain a reasonably small number of spectra from the file. Thus the user can employ his chemical knowledge and laboratory experience to select just those masses that he believes represent ions that are significant and relatively unique to the compound.

H. Speech and Hearing. The past year has seen the development of a set of tools for research in speech and hearing. A speech processing system has been developed that includes a computer, a floating point processor, a graphic input tablet, a large high-speed oscilloscope display, macromodular interfaces using program control and direct memory access, multiple channel analog-to-digital conversion, and a system for amplification and reproduction of sounds in real time. This speech processing system has been used to develop experimental versions of a speech synthesizer, for experiments on a real-time speech analysis system, and for the display of the results of a recently completed mathematical model of the mechanics of the cochlea. Thus the tools are now in place for a quantitative study of important parameters and cues in the generation and recognition of speech.

As an adjunct to the speech processing system, work has continued on a random access programmer for complex audio signals. This system makes possible the random high-speed selection of high-fidelity segments of speech and other sounds for use in the psychoacoustics laboratory. A set of peripherals has been developed that make it possible for an experimental subject to select quickly and easily one of the many sounds stored on the device.

I. Health Care Technology. During the past year the training grant activities in the Health Care Technology area have concluded the phase of rapid growth and the program has reached a steady level of activity. Unfortunately, we were informed in February that the training grant (along with many others in the nation) would be terminated soon. The program has been quite successful with our first group of trainees graduating this past May.

MUMPS-PC developed last year is now working well and routine acquisition of data on patients in the Washington University Medical Care Group is a reality. On a monthly basis the system produces the population and utilization figures

- 21-
known as the Densen Tables. The development of programs to do this job has brought to our attention some shortcomings of our MUMPS implementation and of the language itself. These shortcomings are presently being studied to see if system changes may be helpful. One such effort focuses on more efficient techniques for handling the storage of global data.

J. Other Applications of Computers. Most of this year's reports falling under this heading represent mathematical, equipment or program developments that are useful to two or more of the other project areas. One new development of particular interest is a theory for mass distribution measurement by circular x-ray scanning.

Each year the number of projects described in our annual progress report has increased. This year is no exception. In an effort to control this growth, a new practice has been initiated with this issue. A number of projects of less general interest have been assembled into a supplement to the progress report. These projects were selected because they received only marginal BCL support, because the topic was of primarily local interest, or because the work was incomplete and will be reported in full later. This supplement including 27 items is available by writing to the laboratory.
Individual Projects

A. Radiation Therapy

A-1. Programmed Console - Radiotherapy Package

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D. P. Ragan, Ph.D., Radiology

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The Programmed Console has established its place in modern radiology departments for external beam treatment planning. The Biomedical Computer Laboratory and Artronix, Inc. have worked toward a total radiation therapy dosimetry system consisting of treatment planning, water phantom dosimetry, and film dosimetry.

The water phantom (PR 8, A-3) development has been turned over to Artronix, Inc. who are incorporating it into a Computer Assisted Dosimetry (CAD) package. In addition to the water phantom, a film densitometer has been included in this package. Existing software was adequate for some routine therapy machine checking, but had insufficient resolution to do accurate calibrations or therapy machine acceptance testing. It produced isoanalog values rather than isodose or isodensity contours.

In conjunction with the physics staff at Mallinckrodt Institute of Radiology the specifications of a software system were established so that the calibration procedure can be executed by a technician. Initially, a test strip (with known densities for each step) is read and a 512 word density table is set up such that each entry corresponds to the nine high order bits of the converted analog level. A dosimetry film may then be read, sampling as many as 192 points across the film, in the x direction. Program options set the x and y distances to be scanned, and the x increment. The y increment is set to 1.1 times the x increment. The table of test strip densities and the analog levels (actually, the average of sixteen samples at each point) at all points of the array are stored on tape. The print-out is an array with the same proportions as the original film. Each point is a two-digit ratio of its density to the maximum density found while scanning the film. The print-out may be deferred since the table and all pertinent information are stored on the tape with the data.

A plot of a single scan (in either the x or y direction) will be added to the program. Minor hardware problems with the isodensitometer remain and are being worked out with the manufacturer. This system is presently being used and evaluated by the Mallinckrodt Institute of Radiology (MIR) for acceptance testing of their 35 MEV Clinac.
A-2. PC Telecommunications

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The PC currently has three modes of telecommunications available: asynchronous at 300 baud used for remote terminals to the PC, asynchronous at 1200 baud used primarily for PC RAPID (see E and PR 8, E), and 2000 baud synchronous communications for fast and versatile batch telecommunications.

The 300 baud asynchronous link permits the PC to become - under MUMPS - the central computer in a multi-user system with telecommunication entry. At the present time this facility is used primarily for remote data entry within MIR and for programming by various individuals at BCL; however, since standard phone lines are used, terminals can be used anywhere. In this way a PC with only four partitions can be used by a large number of users for data entry and retrieval.

The synchronous communication link allows the PC to be connected to any IBM System/360 that supports remote batch terminals. As such, programs and data can be submitted to the System/360 eliminating punched cards, useless print-outs and delays. At the present time, a program can be entered either as a LAP6 manuscript or as a MUMPS file. A utility program has been written that converts a MUMPS file to a form compatible with the communications utility (A-4).

Since the synchronous format is widely accepted in the computer industry it is hoped that a larger number of radiotherapy departments will be able to profit from software developments done at Washington University. This system also allows convenient PC to PC communications.

The PC version of the RAPID program (PR 6, A-1) continues in normal use on the 1200 baud network at MIR. Flexibility has been added with a program, RSETUP, which uses the data setup portion of PC-RAPID, complete with rho-theta input, and the option of editing existing data. The Job Control Language (JCL) required for batch execution at either the University's Computing Facilities or the McDonnell Automation Center is added to the acquired data.

The entire program is stored in the manuscript working area of a LAP6-PC tape ready to be saved in a LAP6 file or to be transmitted (using the synchronous communications program) over data lines as batch input to either of the large computers. Changing or adding to the JCL options is trivial, making the program readily adaptable for other installations.

This program provides the facility to save data for subsequent RAPID runs during System/360 down time. It also makes RAPID exportable to other...
radiotherapy departments using a PC-IBM computer link with standard IBM 2780 software support. This has been successfully done using the McDonnell Automation Center's IBM System/370 Model 195. A version of RADCAM (an implant dosimetry program from M. D. Anderson Hospital in Houston) has also been tried in cooperation with Dr. Art Boyer at Massachusetts General Hospital.

A-3. Small Radiotherapy Information System

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The existence of PC computers in small to medium sized radiotherapy departments provides the opportunity for the establishment of complex tumor registries at little or no additional cost. There is an increasing desire by government agencies and clinical medical researchers to have these data available. The feasibility of this in a single-user MUMPS system (PR 8, I) was demonstrated this year. Both tumor registry and department scheduling functions were handled with this system.

To facilitate this development four members of the PC evaluation group (New England Medical Center, M. D. Anderson Hospital, Mallinckrodt Institute of Radiology, and Temple University Medical Center) received PC computers this year. K. C. Tsien's group at Temple University is working toward interfacing their PC to a CDC 3300 system and their own Cancer Information System. Mallinckrodt Institute of Radiology has used their PC directly for a departmental information system and have integrated it into their IBM System/360 based tumor registry.

Since MUMPS was not yet ready for export it was decided to carry out development and feasibility studies at MIR for a PC-based radiotherapy information system. Delivery of the hardware to MIR was made in late December. This consisted of a modified mainframe with a 700 ns cycle time, 16K of core memory, a 6-megabit LINC disk and a Centronics matrix printer. An experimental departmental scheduling system was developed, tested and implemented by late February on an early single-user version of MUMPS (this is a dramatic example of the ease and speed with which a system can be developed in MUMPS). This system provides therapy machine schedules, various sorted lists of current patients and tabularized billing data. It will run on any PC with 12K of core, but has now been replaced by a multiuser system (A-4).

In addition to this radiotherapy scheduling system, a Hodgkin's disease registry was written. Over 20 years of data collected for a protocol study at MIR are being entered. This system will be used as a test system for MUMPS and PC-oriented tumor registries.
A MUMPS-PC system with LINC tape but without disc is extremely slow. For users without a disc, Artronix, Inc., has made available a Fortran-based tumor registry. Although not as flexible as a MUMPS system with a disc, it will run much faster on those systems limited to tape.

Both the MUMPS and the FORTRAN systems have IBM 2780 style telecommunications available (A-2). Thus tumor-registry data generated at a satellite hospital can be fed to a centralized data base and information from a central system can be retrieved by the PC.

A-4. Multi-User Radiotherapy Department System

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From the experience gained in the single-user MUMPS radiotherapy system (A-3) a comprehensive Radiation Therapy Information System on the PC-1200 was developed and is now useful in most parts of the therapy department. Persons relying on the MUMPS system include the billing department, physicians, radiation therapy technicians, students, physicians' assistants, front-office clerks, dispatch, and nursing units. The BCL-developed MUMPS has been expanded by Artronix, Inc. to support four users and we are using this expanded version. The initial hardware (A-3) has now been augmented to include four-user terminals with 300-baud acoustic coupled telecommunications (A-2). The system is expected to expand to eight users, 24K of memory, and 500 megabits of disk storage within the next six months.

The software has already been fully implemented in the radiotherapy department and has become an indispensable part of the department operation. It has both eliminated time consuming manual tasks and provided many services which were unavailable with a manual system. Figure 1 shows the basic information flow. The system is completely interactive and designed for use by untrained clerical and paramedical personnel. There is both prospective and retrospective data.

The basic software system can be examined in three parts:

1) System - subroutines (e.g., date to Julian date conversion) and support systems (e.g., tape library and tape back-up programs) form a basic set of utility programs.

2) File Maintenance - Data entry and editing form the basic program set. We have associated data collection with the people most closely associated with its source and/or use. Table I gives the breakdown of data collection
from different groups within the radiotherapy department. Table II explains how the information is organized. A great deal of effort must be expended in MUMPS to optimize these file structures.

3) Summaries & Schedules - Data once entered into the system is immediately available on any terminal. There is also a steady flow of hard copy output. Table III summarizes this output. Computer times and personnel times in both this and Table I must be viewed as rough estimates.

The development of this system has been accomplished in less than five months with approximately seven man months of programming effort. The input and output content and format are constantly changed to respond to the needs of the users (this easy modification of content and format is one of MUMPS most valuable attributes).

Full utilization of the unique MUMPS-PC features for data communications has been attempted. Among its other functions the system automatically does the daily billing and sends the information via the synchronous communications link (A-2) to the existing IBM 360 accounting system. The user must specify the name of a MUMPS file and whether the standard JCL is to be appended to it. The MUMPS index is searched for the file name and all information stored at the first subscript level is retrieved. This program is general and has been used for information retrieval requests and data transfer functions for other BCL projects. This information is stored (with or without JCL) in the manuscript working area of a LAP6-PC tape. Non-standard JCL may be added by the user either in MUMPS or by adding it to the LAP6 file before transmission.
Figure 1. Time Ordered Information System Flow
Table I - Data Entry. Breakdown of data by the group responsible for collecting it with estimated cost in terms of terminal time and personnel time.

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of Data Items Per Patient</th>
<th>Number of Patients Per Day</th>
<th>Computer Time/Day (In Min.)</th>
<th>Personnel Time/Day (In Min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billing-Initial Data</td>
<td>15</td>
<td>7</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Phys. Asst.'s</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Technicians</td>
<td>2</td>
<td>35</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>Billing-RX Data</td>
<td>2</td>
<td>35</td>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>

Table II - File Structures. These tabularized files must be kept current for cross reference purposes and for efficiency in retrievals.

<table>
<thead>
<tr>
<th>File</th>
<th>Description of File</th>
<th>Number of Data Items Per Record</th>
<th>Number of Characters Per Record</th>
<th>Number of Records</th>
<th>Kept Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPA</td>
<td>Current Patients</td>
<td>21</td>
<td>275</td>
<td>120</td>
<td>Kept Current Basic File</td>
</tr>
<tr>
<td>SPO</td>
<td>Finished Patients</td>
<td>21</td>
<td>275</td>
<td>400</td>
<td>Kept Current Basic File</td>
</tr>
<tr>
<td>SLT</td>
<td>Patients Sorted by Last Initial</td>
<td>1</td>
<td>7</td>
<td>520</td>
<td>Kept Current Can be Regenerated From SPA &amp; SPO</td>
</tr>
<tr>
<td>SMC</td>
<td>Patients Sorted by Therapy Machine File</td>
<td>6</td>
<td>60</td>
<td>100</td>
<td>Kept Current Can be Regenerated From SPA</td>
</tr>
<tr>
<td>SBF</td>
<td>Billing File</td>
<td>14</td>
<td>51</td>
<td>90</td>
<td>Created Daily</td>
</tr>
<tr>
<td>SMW</td>
<td>Administrative Summary Information</td>
<td>32</td>
<td>64</td>
<td>6</td>
<td>Created Daily</td>
</tr>
<tr>
<td>SD</td>
<td>Doctor's Schedule Of Patients</td>
<td>5</td>
<td>60</td>
<td>120</td>
<td>Created Daily</td>
</tr>
</tbody>
</table>
Table III - Information Utilization. Data gathered at one point to be disseminated throughout the department in the form of schedules, logs and summaries.

<table>
<thead>
<tr>
<th>Output</th>
<th>Number of Data Items Per Patient</th>
<th>Number of Patients Per Day</th>
<th>Computer Time/Day (In Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machine Schedules</td>
<td>8</td>
<td>120</td>
<td>10</td>
</tr>
<tr>
<td>Office Schedule</td>
<td>7</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td>Doctor's Schedules</td>
<td>5</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Service Summary</td>
<td>19</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Patient Summaries</td>
<td>21</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Billing Output</td>
<td>14</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>Patients Finished</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Periodic Summaries</td>
<td>Totals of All Patients</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Dispatch Schedule</td>
<td>3</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Therapy No. Log</td>
<td>9</td>
<td>25</td>
<td>5</td>
</tr>
</tbody>
</table>
A-5. National Data Effort

Personnel: M. C. Rigden, B.A., Radiology
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W. E. Powers, M.D., Radiology
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The members of the Radiation Therapy PC Evaluation Group have discussed in considerable detail the feasibility of creating a central data base using standardized data. Each member currently maintains his own data base and agreement on a standard format for a shared system has not been attained. The potential for more efficient data entry procedures using systems like MUMPS-PC has made it difficult to determine at this time an appropriate cost/benefit definition of how much data should be included in a permanent, nationally shared data base. Furthermore, standardization now would make it more difficult to enlist other therapy centers in the effort at some later time. This is particularly true for radiation therapy information systems because of the five to ten year time lag between initial information entry and its maximum usefulness for treatment evaluation purposes.

In order to gain experience on the problems peculiar to radiotherapy data systems we are working very closely with the Mallinckrodt Institute of Radiology (MIR). Before the introduction of the MUMPS-PC systems for departmental administration tasks (A-3 and A-4), MIR relied on its own information system for long term record keeping on treated patients. This system designed and implemented on the University's IBM System/360 Model 50 now runs on the Model 65.

This system, begun in 1968, required the coding of forms by the physicians and their assistants and the subsequent keypunching of the forms for batch entry. Because of the amount of time required of the physician for coding, the information entered was intentionally kept to a minimum. Our experience with this system over the past four years has convinced us that more complete information on each patient is necessary. We need less a computerized "tumor registry," than an information system to aid us in our clinical, teaching, and research efforts in both diagnosis and therapy evaluation. Since the specifications of this information system are continuously modified as we gain experience, our approach must be flexible. Consequently, our new system is designed to permit unanticipated changes in data format, coding, entry, and retrieval.

The current system is still in active use on the System/360 although its operation is costly. Although data retrievals can now be done from the PC, maximum benefit will be achieved only after the PC and System/360 can be more closely integrated. From a technical standpoint, use of the System/360
permitted an empirical evaluation of file design alternatives in terms of the data management requirements peculiar to radiation therapy, particularly those associated with the extended follow-up period.

We have developed specifications and begun work on a centralized information system in which:

1. Each radiation therapy center will have its own patients' data file.

2. These data files will reside at a computer center with national access by telecommunications.

3. All data files will be accessed by a retrieval program using a thesaurus-like directory for determining common data elements among the files and for code translation.

This approach has a number of advantages beyond its general flexibility.

1. The current and potential regional centers will not be required to reduce their data bases which might involve curtailing local projects.

2. No center will be required to gather more data than it is capable of doing under existing constraints.

3. All users will be able to fully utilize the data collected over the past decade without having to recode (usually both practically and theoretically impossible).

4. Each regional center will be free to experiment with changes in its own data base without interfering with the operations of the other centers while at the same time potentially contributing to the national effort.

5. Each center can develop its own file structure, access methods, and communications routines to optimize its own goals and capabilities or they can adopt the system being developed here on a turnkey basis, with minor program changes to account for differing data formats.
The Program Console User's Meeting was held in July, 1972, in Philadelphia, in conjunction with the American Association of Physicists in Medicine meeting. The chairmanship of this meeting and organization of future meetings was turned over to Artronix, Inc.

Artronix outlined their activities for the past year and explained new hardware and software developments. There was discussion among the participants of problems falling into three areas, 1) system reliability, 2) documentation, and 3) programming difficulties. We have monitored the progress of Artronix since the meeting last year and progress is being made in each of the three areas.
B. Electrocardiographic Rhythm Monitoring

B-1. Installation and Evaluation of a Commercial Version of Argus

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The ARGUS/SENTINEL Computer System developed by Mennen-Greatbatch Electronics, Inc., (see PR 8, B-7) has been installed in the Barnes Hospital Coronary Care Unit and is currently undergoing an evaluation of its technical performance. The Aztec, Primitive, and Cycle processing algorithms of the original Argus system form the basis for the six-patient ARGUS/SENTINEL system. However, several factors such as differing hardware configurations and minor evolutionary algorithm changes make difficult the task of performance comparison.

To facilitate performance evaluation, a digital communications path has been installed between the LINC-8 computer used for testing the original Argus system and the PDP-11 computer in the ARGUS/SENTINEL system. At present, the best available set of test data annotated by a cardiologist appears to be that which was used in a published evaluation of the performance of the original Argus system (see PR 7, B-1). Unfortunately, the source data for that evaluation is available only in Aztec form. Consequently, LINC-8 programs are being developed to reconstruct sampled ECG data from Aztec data such that the reconstructed data will uniquely transform into the same Aztec data. The digital communications path will then be used to evaluate beat-by-beat performance of the ARGUS/SENTINEL system on this reconstructed data.

It is expected that this method will prove adequate for the current evaluation requirements of the ARGUS/SENTINEL system. However, it has become clear that a much better method needs to be developed for the overall task of evaluating and comparing arrhythmia monitoring systems. Activities described in another section (B-12) are directed toward that task.
A modified Huffman coding technique has been applied to ECG data to realize a reduction in data storage area on mass storage devices with no reduction in accuracy (see B-11, B-13). Filtered and digitized ECG data sets (250 samples/s at 10 bits per sample) were collected from 45 randomly selected patients in the Barnes Hospital Coronary Care Unit. Computing the second difference on each data set proved useful in reducing source word correlation (zero correlation produces maximum compression). Second difference probability distributions were then computed for each patient. After merging the 45 distributions, a Huffman code was generated, i.e. the most frequent second difference values were assigned short codes (e.g. 2 bits) and infrequent values were assigned long codes (e.g. 10 bits). Since there are 4096 possible second difference values for a 10-bit sample set, the list of codes was empirically truncated by considering code list length vs. average code word length. The final list contained the 50 most probable values, all other values being encoded with a 5-bit prefix code to designate a succeeding 10-bit sampled value.

Computations on source word entropy indicated that we could expect an optimal compression factor of 2.9:1 on the ECG data from which the code was obtained. When each patient's data was tested with the derived code, the average compression factor was 2.8:1, very close to the theoretical limit.

This same procedure was carried out for 500 samples/s data. The compression factor was found to be approximately 4.1:1. Hence, 500 samples/s data, when encoded by the Huffman technique will occupy considerably more storage area than 250 samples/s encoded data. Accordingly, a preliminary investigation has been begun for reconstructing higher sampling rate data from 250 samples/s data. In particular, a simple approximation to the sin x/x reconstruction formula seems to allow good reconstruction of 500 samples/s data.

B-3. Relationship of Ventricular Arrhythmias to Sudden Death - Clinical Data Gathering Activities

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During the past year, data gathering has continued toward an investigation of sudden death in an outpatient population presumed to have died as a result of a cardiac arrhythmia (see PR 8, B-4). We wish to test the hypothesis that patients who die suddenly will manifest at some prior time a disturbance of rhythm which can be detected by appropriate analysis of Holter Monitor tapes. The major population group which has been studied are patients who have been admitted either to the Jewish Hospital or Barnes Hospital Coronary Care Units and who have suffered from an acute myocardial infarction. Those patients who meet certain criteria are entered into our study following discharge from the hospital and receive sequential monitorings throughout the year. For the first six months of the year monthly recordings are made followed by less frequent monitorings. To date 156 patients have been enrolled and 975 Holter tapes have been recorded with most qualitatively scanned by manual means (see B-5). An integral part of the project is the concurrent development of a computer system (Argus/H) for high speed, quantitative scanning of these tapes (see B-6). Demographic data has been obtained on all patients entering the coronary care units. To date, 450 demographic forms have been filled out and have been entered into a SSPS (Statistical Package for the Social Sciences) data file. This data file can be easily manipulated, retrieved, and subjected to statistical analysis allowing correlations to be made between the presenting features and their ultimate course (see B-4).

Although a detailed demographic form is filled out on each patient, we have discovered that additional information which was not on the original coded form is often needed later. To make this kind of data retrieval possible we are microfilming the complete chart of every patient who has entered our study.
Work has progressed towards the accumulation of information on a control population. Out of a large number of subjects who work for a large St. Louis corporation and who had been screened by the St. Louis Heart Association, 51 have been selected who, on careful rescreening have no coronary artery disease risk factors. A 24-hour Holter tape has been obtained on each of these subjects. These tapes have already been analyzed by manual scanning and will be subjected to further analysis by the high speed Argus/H system.

Two additional population groups will be entered into our study and plans have already been outlined for this. A detailed protocol has been written for testing the efficacy of various antiarrhythmic agents on the prevention of arrhythmias in ambulatory patients. Drugs tested will be quinidine, pronestyl, dilantin and placebo. In this protocol, each patient will receive on a random basis one of the four drugs and a Holter recording will be taken while he is on this drug. Both the physician and the patient will be blinded as to which drug he is on at that particular time. An additional study is aimed at the question of whether coronary vein bypass surgery is an effective procedure for eliminating premature ventricular contractions in patients who have severe coronary artery disease. A protocol has been set up to obtain Holter Monitor information before and after coronary vein bypass operations on such patients.

B-4. Relationship of Ventricular Arrhythmias to Sudden Death -- Demographic Data Analysis

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In order to study the phenomenon of sudden death, post myocardial infarction (MI), it is necessary first to study the phenomenon during the acute phase, i.e. during the hospital confinement. While sudden death per se has been virtually eliminated during the CCU and associated hospitalization, in a number of studies the severity and size of the infarct has been shown to be associated with mortality post-hospitalization. It is necessary to have a full understanding of these phenomena in order to establish base lines against which the data of arrhythmias in ambulatory post-hospitalization patients can be evaluated. This latter topic is more thoroughly covered in Section B-5.
The analysis of the data base created on all MI patients admitted to the Coronary Care Units of Barnes and Jewish Hospitals (see B-3) has been initiated. The role of intraventricular conduction defects (IVCDs) in the face of an acute MI has been one topic which has been pursued. The IVCD is an electrocardiographic manifestation of disturbance in the conduction pathway from the atrio-ventricular node through the ventricles. Normally an excess of hospital mortality has been reported in patients exhibiting IVCDs. Our analysis of this data shows that one must be particularly careful in analyzing such data, as the excess mortality seems to be most clearly indicative of extensive myocardial damage. Thus the excess mortality is not due to the IVCD per se, but is rather due to extensive myocardial damage and pump failure, which are frequently associated with IVCDs(1).

Initial analysis of the hospital mortality has identified certain additional features to be indicative of excess mortality. The overall mortality of 16% was increased by demographic characteristics such as old age, female sex, and a history of atherosclerotic heart disease such as a previous MI or a history of congestive heart failure. Patients with anterior infarctions also had an excess mortality. The existence of complications such as cardiomegaly, congestive heart failure, pulmonary infarction, pulmonary edema, and cardiogenic shock during the initial five days of the hospitalization was particularly ominous and mortality increased with increasing numbers of these complications. Early recognition of these clinical features, particularly in young individuals, would appear to offer a rationale for the utilization of more aggressive but less conventional modes of therapy in the CCUs such as counter-pulsation, emergency cardiac revascularization or a combination of both(2).

A follow-up of the patients surviving the hospitalization for their MI is anticipated to relate the characteristics of their hospitalization to subsequent outpatient mortality.


B-5. Relationship of Ventricular Arrhythmias to Sudden Death - Manual Tape Scanning of Study Patients and Controls

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Manual scanning of all Holter tapes has been performed from the ambulatory monitoring of out-patient survivors of myocardial infarction. The results of manual scanning provide preliminary data analysis and immediate information to referring physicians. In addition, the results are available for comparison with the Argus/H system (see B-9). Each tape was graded according to the Lown schemata for representing the severity of ventricular arrhythmias, according to a classification (K classification) of atrial arrhythmias, and according to the incidence of early PVCs (within or abutting the T wave).

The tapes obtained so far have been summarized in various fashions to describe the incidence of ventricular arrhythmias(1). The distribution of the Lown classification for 845 tapes analyzed was: 0, 37%; 1, 19%; 2, 9%; 3, 26%; 4, 8%; 5, 2%. The lack of any systematic alterations in the Lown classification over time was a somewhat surprising result of the analysis. With the limited number (141) of patients currently being surveyed, the six sudden deaths which have occurred have not allowed us to detect any clear relationships between the results of the Lown classification and sudden death or mortality in general.

Early PVCs were found in 7% of the tapes and in 27% of the patients being sequentially monitored(2). Again the incidence of early PVCs does not seem to change as a function of the time post MI and seems, in general, to be unrelated to the classic Lown classification. It has long been assumed that early PVCs are likely to initiate ventricular tachycardia leading to ventricular fibrillation which is assumed to be the mechanism of many sudden deaths. However, in our analysis of 19 episodes of ventricular tachycardia or accelerated idioventricular rhythm (three or more consecutive PVCs) only one of the nineteen episodes observed was initiated by an early PVC. Three of the six sudden deaths and one of the five non sudden deaths exhibited early PVCs. Clarification of the significance of the PVC coupling intervals to sudden death will await quantification of the arrhythmias by Argus/H (see B-6)
In order to be able to compare this group of patients with proven atherosclerotic heart disease, a small select group of individuals identified on careful screening to be relatively free of risk factors for heart disease has been amassed. These 51 subjects had Holter recordings obtained and certain demographic information recorded. Forty-five per cent of these subjects at low risk exhibited PVCs with 22% in Lown classification 1; 10% in 2; 10% in 3; 2% in 4, and 2% in 5. Of those subjects with PVCs, 17% had early PVCs. Atrial arrhythmias were also present with an unexpected frequency with 8 out of the 51 demonstrating ectopic atrial activity. The presence of ventricular arrhythmias was significantly related to age, particularly for those over sixty years (3).


B–6. The Argus/H High Speed ECG Analysis System

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Argus/H is a system of digital computer programs and equipment being developed for quantitative, high speed analysis of ECG rhythms played back from tape at up to 60 times real time (see PR 8, B–5). The basis for
development of Argus/H has been the clinical Argus system algorithms coupled with an interactive method for higher level analysis, editing, and review of the resultant data.

The Argus/H processing system is being constructed from a mixture of general purpose hardware (macromodules), special purpose hardware, and a high-speed digital computer (IBM System/7). The macromodules allow rapid implementation of experimental sub-systems requiring high processing rates, especially in situations requiring on-line processing.* Special purpose hardware development is necessary both for interfacing the various system components including System/7 peripheral devices and for replacing macromodular sub-systems when their development has stabilized (see B-10).

The System/7 computer was acquired slightly more than one year ago. A variety of peripheral devices have been obtained, hardware interfaces have been constructed (see B-8), and program support routines have been developed. Other programming support has also been necessary to provide an adequate base for development.

The development of Argus/H processing algorithms on the System/7 has also proceeded rapidly (see B-7). During the latter half of 1972, the major effort was involved with encoding and testing the Primitive and Cycle processor algorithms. The source data for this effort were Aztec data streams stored on industry compatible tape. The initial Aztec records were relatively short segments of 15 to 20 minutes duration which were rich in PVCs and other arrhythmias and had been used to evaluate the clinical Argus system. A macromodular implementation of the Aztec processor (see PR 7, B-9) was then used to produce at 60 times real time a digital tape library of Aztec data from a variety of 10-hour Holter tapes (see B-9). For purposes of evaluation and debugging, optional outputs were made available for displaying or printing the results of the operation of the various processing stages. In addition, summary data plots and printouts derived from the Cycle data stream were also developed. By using both the summary and evaluation outputs, an investigation into the potential operation of a subsequent data editing scheme was also begun.

As algorithm development proceeded, it became apparent that a library of source tapes containing the original sampled ECG data would be necessary for several reasons. Reconstruction of the ECG waveform from Aztec data was not always adequate for manual diagnosis. Moreover, subsequent modifications and expansion of the Argus/H processing algorithms would require substantial testing, preferably in a manner which would allow exact digital comparison of results. Finally, the increasingly heavy demands on the usage of the System/7 made attractive a separate sub-system for initial data acquisition from the Holter tapes.

*On-time processing is used here to describe tasks which must be performed within definite time periods, even under worst case conditions.
Mass storage of the raw digitized Holter ECGs was impractical because of the high data rate (300,000 bits/s at 60 times real time) and the total data volume (432 megabits for a 24-hour tape). A method for encoding 30,000 samples/s with 10 bits resolution (see B-2) was tested using macromodules. The peak data rates and data storage requirements were also found to be inadequate for routine storage of 24 hours of ECG data on industry compatible tape. The macromodular sub-system was then altered for high speed acquisition of encoded digital ECG data at a real-time sampling rate of 250 samples/s with 10 bits resolution (see B-11).

Program additions were then made to the high speed scanning phase of the System/7. The standard input data stream is now encoded ECG data at 250 samples/s from industry compatible tape. The present software includes very fast programs for decoding the input data, reconstructing 500 samples/s, and performing the Aztec transformation prior to the operation of the Primitive and Cycle processors. In addition, a high speed oscilloscope display shows the reconstructed ECG waveform during the high speed scanning process.

The major thrust of recent developments on the Argus/H system concerns the subsequent data editing phase. At the end of the high speed scanning phase, the System/7 disc storage module contains a Cycle data stream describing the entire ECG on a beat-by-beat basis. An initial segment of encoded ECG data (typically 6-7 hours in duration) is then stored on disc. The current editing program then allows the user to review the results of the high speed computer scan by viewing reconstructed ECG segments of approximately 16 seconds duration with Cycle data annotations. One review option allows rapid random access to segments beginning at any specified time of occurrence. Other options allow sequential access either forward or backward to the next identified PVC, the next identified beat, or the next segment of beats. ECG paper records of the displayed segments may also be obtained. When a request is encountered for access to an ECG segment which is not contained in the disc storage buffer, the user is presented with an option for transferring additional sections of encoded ECG data from tape to disc. In this manner, a disc buffer of many hours of contiguous ECG waveforms is maintained for rapid access and only infrequent tape operations are required as the entire ECG record is being reviewed. Additional data review options are currently being developed as well as methods for editing the data. A mechanism for saving the resultant Cycle data stream on the digital ECG source tape allows subsequent re-editing of the data after review of the results by a cardiologist.

The eventual goal of the Argus/H system is to produce a data stream which describes the ECG rhythm in accurate, beat-by-beat detail. Serious practical problems must be overcome to attain this goal. The most basic problem is that there is no notational scheme available for consistent and systematic labelling of individual beats in the ECG. We are currently attempting to develop such a scheme using clinically meaningful mnemonics whenever possible. In the interim, a smaller subset of labels is being selected for initial production scanning of the Holter tapes.
The Argus/H software package for rapid analysis of long ECG records may be divided into 3 sections: (1) high speed, automatic scanning, (2) interactive data review and editing, and (3) generation of summary results. The programs occupy a data set under the System/7 Disc Support System and a display terminal oriented executive routine is used for passing program control.

High Speed, Automatic Scanning. At present, source data for the high speed scan is a continuous ECG data stream on industry compatible tape. Initially, the source had been preprocessed Aztec data but more recently the source data are encoded second differences from 250 samples/s (see B-6). The source is read from tape and decoded bit by bit using a table lookup procedure with one table reference per bit. The resulting second difference source word is then integrated twice to form a sampled data value for a software Aztec processor. At present, a simple linear interpolation is used to provide alternate samples to obtain 500 samples/s data but a slightly more complex reconstruction algorithm will soon be incorporated (see B-2). The decoded sampled data values are also displayed on the high speed oscilloscope for visual monitoring of the data. This entire process (acquisition of encoded data, decoding, integration, interpolation, display, and Aztec) requires an average of approximately 39 seconds of CPU time per hour of ECG data (an average of approximately 3.2 megabits of source data). The procedures operate on interrupt level 1, the second highest priority level in the System/7.

The Aztec output stream feeds the Primitive processor which operates on interrupt level 2. The Primitive data output stream in turn feeds into the Cycle processor which operates on interrupt level 3, the lowest priority level. Some modifications which have been made to the Argus Cycle processor include the classification of PVCs by type (infrequent, frequent, alternating, pair, run, early) and expansion of the QRS family catalog to 64 members. Each new family of QRS complexes is assigned a sequential serial number and the Cycle data output stream includes the four QRS feature measurements and their ranges for each family. The Cycle data stream is written into a large disc buffer area with the disc routines operating on interrupt level 0, the highest priority level. The operation of the Primitive and Cycle processors requires an average of approximately 30 seconds of CPU time per hour of ECG data, or 120 times real time.
For purposes of evaluation and debugging, optional outputs are available. A display terminal output shows the time of occurrence and the ECG reconstructed from Aztec data, vertical markers for the beginning and end of each QRS as determined by the Primitive processor, and the Cycle family serial number, morphology and PVC classification for each beat. In addition, line printer outputs for combinations of the Aztec, Primitive, and Cycle processors may be obtained. The Argus/H System may be run at maximal speed up to selected portions of the record and then its operation may be examined at leisure using the output options.

Interactive Data Review and Editing and Generation of Summary Results. The operations of these programs are described in some detail in other sections of this report (see B-6, B-9). These programs are currently the focus of developmental effort and consequently are changing quite rapidly. The primary goal is to produce an interactive Sequence processor to arrive at an accurately annotated ECG data tape. In conjunction with this effort, work is currently in progress on developing a version of MUMPS (See I-5) for the System/7. The powerful string processing capability of MUMPS should be useful in later work on analyzing the summary results.

B-8. Argus/H Hardware Development

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A variety of peripheral devices have been interfaced to the System/7 computer in addition to the industry compatible tape drive and classic LINC interfaces previously described (see PR 8, B-5). All interfaces are currently operated through the general purpose 5012 Multifunction Module.

A Tektronix Model 4010 storage oscilloscope display terminal and Model 4610 hard copy unit now provide the primary method for manual interaction with the System/7. The terminal has both alphanumeric and graphic capability and is operated serially at 9600 baud.

A Data Products Model 2310 line printer is operated by parallel byte transfers of ASCII codes. This 80-column printer allows rapid listings of System/7 programs and of voluminous ECG data streams of various types. The printer is shared with two nearby PC-1200 computers via a centrally located manual switch box.
High speed display and hard copy writeout of ECG waveforms are provided by a Hewlett-Packard Model 1310A large screen, electrostatic deflection oscilloscope and a single channel Mennen-Greatbatch ECG paper recorder. The X and Y axes of the high speed oscilloscope are driven by high speed 10-bit digital to analog converters with glitch suppression. Typical ECG waveform displays operate at more than one hundred thousand points per second. The ECG paper recorder pen shares one of the digital to analog converters of the oscilloscope display.

Current hardware design for the System/7 is concerned with developing higher performance peripheral interfaces to the Direct Control Channel. A new Cycle Steal Feature has recently been added for the disc module and will also be used for very high speed devices.

Several hardware developments relate to the macromodular sub-system of Argus/H. A macromodular compatible tape controller has been interfaced to a Pertec buffer formatter and tape drive. This allows continuous, asynchronous storage of data on industry compatible tape at a maximum average data rate of approximately 17 Kbytes/s. Manual front panel controls allow tape file mark writing and file or record spacing operations.

To reduce problems due to 60 Hz interference in the recorded ECG signals, a 3600 Hz notch filter has been constructed for playback at 60 times real time. The filter response is down 28 dB at 3600 Hz and 3 dB at 3350 and 3840 Hz. Finally, a second version of a macromodular compatible analog to digital converter, multiplexer, and controllable sample rate clock (see PR 8, H-3) has been constructed in a more compact package.

B-9. Initial Results with Argus/H

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In December of 1972 a preliminary investigation was made of the current ability of the Argus/H system for qualitative processing of 10-hour Holter tapes. The results are presented here as an early indication of the capability of Argus/H(1).

Using a macromodular Aztec system, 24 ECG tapes, each from a different patient, were processed at 60 times real time to produce a digital tape library of Aztec data. The 24 tapes were selected randomly to yield 4 tapes
from each of the 6 Lown classifications as determined by manual scanning (see B-5). However, because of an error, the actual distribution was slightly different and only 2 Lown 5 tapes were processed. In addition, it was later found that the Aztec data collection for 1 of the Lown 2 tapes had been inadvertently terminated after only a short segment of data had been collected.

The remaining 23 Aztec data tapes were then scanned at high speed by the Primitive and Cycle processors of the Argus/H system. The factors by which real time exceeded analysis time ranged from 67 to 180 with an average of 121 times real time. The Cycle data on disc was then rapidly scanned to produce summary data plots on the display/hard copy terminal of heart rate and PVC rate averaged over 15 minutes. Accompanying percent data loss graphs indicated the percentage of beats which were not cataloged because of artifact or a prolonged absence of signal preceding the beat. In addition, a summary listing of the totals of different types of beats in quarter-hour intervals was also produced. Finally, a listing of the exact time of occurrence and type of each PVC was used to select ECG episodes to be examined in detail for ventricular arrhythmias.

Argus/H was then operated in an evaluation or debug mode to examine the appropriate reconstructed Aztec segments. The Lown classification numbers resulting from this procedure are compared to those obtained by manual scanning in Table I*. In addition, the highest Lown classification (HLC) from manual scanning for each patient is shown in a third column. For 2 patients (49-08 and 18-03 at bottom), the Argus/H scan produced excessive numbers of false positive PVCs so that a comparison of Lown classification numbers could not be made. One of these records (49-08) exhibited continual baseline artifact which was not recognized as such by Argus/H. In the second record (18-03), continual, very realistic artifact was present. A subsequent review of the ECG strips produced by manual scanning for this record showed that a segment of realistic artifact had been mistaken by a cardiologist for couplet PVCs and that the original Lown 4 classification was erroneous.

For the remaining 21 records, several observations may be made, although the data is obviously of a preliminary nature. In 12 records, the Lown classification number was increased by the Argus/H scan. Of these, 8 were increased to class 3 (multiform) and 1 was changed from unifocal and less than 10 per hour (Lown 1) to unifocal and approximately 80 per hour (Lown 2). In 2 records of Lown 3 tapes, couplet PVCs were found and 1 Lown 4 record contained a run of 3 consecutive PVCs. Of the 2 Lown 5 records, one (13-03) had a long run of ventricular tachycardia which was easily detected by Argus/H, but the other record contained a slow run of 3 PVCs including a fusion beat and was missed by Argus, presumably because the requirement for a slight degree of prematurity was not satisfied. For this record, numerous couplets were detected.

*It should be noted that the reconstructed Aztec ECG data does not always allow one to differentiate PVCs from PACs with aberrant conduction. More exact differentiation is now possible with the capability for reconstructing the original sampled ECG.
Another observation is that no Lown 1's and only 1 Lown 2 appear in the Argus/H scan column, suggesting that frequency should be eliminated from a Lown style classification scheme and tabulated as a separate parameter. In addition, excluding the Lown 5 records, although the manual scan Lown classification for only 5 of 19 records was the same as the HLC for all tapes of that patient, the Argus/H Lown classification was the same as the HLC in 15 of 19 records. Finally, in ten hours of one Lown 0 record (62-04) no false positive PVCs were detected and in another (76-03) only one beat was falsely called a PVC.

**TABLE I.** Initial Results Using the Argus/H System

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<th>Patient No.</th>
<th>Manual Scan for this Tape</th>
<th>Argus/H Scan for this Tape</th>
<th>HLC*, Manual Scan for all Tapes</th>
<th>No. Tapes Scanned for HLC</th>
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<tr>
<td>18-03</td>
<td>4/0</td>
<td>see text</td>
<td>2</td>
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*Highest Lown Classification*
In order to free the Aztec macromodules (see B-6) for other, more developmental portions of the Argus/H system, a hardwired, high speed Aztec preprocessor has been designed and is currently being constructed. DEC Register Transfer Modules (RTM) were selected for constructing the hardwired Aztec because of their similarities to macromodules. The control sequence design was quite straightforward from a flowchart of the macromodular Aztec system and the main concern was whether the speed of the RTM system would be adequate.

Calculations of processing times indicated that the longest pathway from input of a single ECG sample to output of an Aztec datum will be approximately 40 μs, and the shortest pathway for a single sample will be approximately 10 μs. Since the inter-sample arrival time is 33.3 μs at 60 times real time, a sampled data buffer is necessary so that the worst case processing times may be accommodated. Accordingly, an integrated circuit FIFO memory is currently being evaluated for suitability as an asynchronous buffer memory for sampled data. In addition, the macromodular Aztec system was augmented to obtain histograms of the frequency of traversal of Aztec processing pathways on a sample-by-sample basis. These histograms indicated that a small sample buffer memory would suffice to allow adequate smoothing of sample-to-sample fluctuations in the RTM Aztec processing times for 60 times real time operation.
A Huffman code developed for ECG data (see B-2) was implemented with macromodules for use in conjunction with the Argus/H system (see B-6). This hardware system has allowed continuous encoding of long segments of ECG data at very high speeds. Ten hour and 24-hour analog ECG data tapes are played back at 60 times real time. After being filtered (3600 Hz notch, 4200 Hz low pass) the signal is sampled at 15,000 samples/s (60 times 250 samples/s), encoded via the macromodules and stored on industry-compatible tape. A 4096 byte FIFO buffer memory was incorporated into the encoder output since the maximum data output burst rate from the encoder occasionally exceeds the maximum data rate for the tape. The predicted average data compression of almost 3:1 (see B-2) has been verified and the system is now being used routinely for initial acquisition of ECG data in the Argus/H system.

A group headed by Professor Charles Feldman of Worcester, Polytechnic Institute has been established to set up methods and procedures for the evaluation of automated arrhythmia detectors. This group has met in conjunction with the Heart Association meetings in Dallas, November 1972, and in conjunction with the Cardiology meetings in San Francisco in February, 1973. Two subcommittees have been formed, one to develop methodology, and
a second to recommend equipment. Jerome R. Cox is the chairman of the equipment committee and G. Charles Oliver is a member of the methodology subcommittee. Experience in previous evaluations at Washington University and in the development of an on-line retrieval system (see B-13) have lead us to the conclusion that test sets stored for evaluation purposes should be in digital form. Analog tapes can be derived from digital source tapes with each derivative tape being as faithful a reproduction as any other. For those who wish digital source tapes, annotation information can be included easily. It has been recommended that a digital data gathering facility be developed that can be shipped from institution to institution so that a wide variety of test data can be assembled. These test data can then be scored by a panel of cardiologists, annotated, and the results made available to anyone within the group who wishes to carry out an evaluation of an automated arrhythmia detector.

The next step in the activities of the group is the development of a source of funds to allow the committee to proceed with the development of the data gathering facility and the establishment of a data repository.

B-13. A System for On-Line Retrieval of Episodic ECG Data from Multiple Patients

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Support: RR 00396

Development has begun on a system for capturing and reproducing long segments of digital ECG data on eight patients simultaneously. This data will enable the study of ECG events up to two hours prior to a cardiac episode. Such a system has two immediate purposes for development. (1) More and more effort is being invested in the arrhythmia monitoring field and a multitude of monitors are currently available. To assist in evaluating such monitors, the system can run in parallel with the monitor under evaluation. For a given patient episode, a permanent file can be made "retrospectively", giving the evaluator a high quality data set with which to check monitor alarms, medical records and observations, etc. to determine monitor accuracy and clinical effectiveness (see PR 8, B-7). (2) Permanent files obtained locally can be decoded and recorded in suitable form to be circulated for cardiologists' annotations (see B-12). Such annotated "standard evaluation tapes" would then provide simulated data streams for evaluation and comparison of other monitors.
The system will have two independent modes of operation: acquisition and reproduction. In the acquisition mode (see Figure 1), digitized ECG data from eight patients will be encoded via software using a Huffman coding scheme (see B-2). This compressed data is then saved in eight circular buffers, each of which is approximately two hours long. If a patient suffers a cardiac episode (e.g., ventricular fibrillation), the computer will be signalled and the patient's circular buffer frozen and transferred to a permanent file (a removable disc platter). As soon as the transfer is complete, acquisition of new ECG data for this patient can continue. The transfer will not disturb the operation of the system for the other seven patients. Other patient data, date and time can later be entered on the permanent files.

In the reproduction mode, the system will retrieve specified data from permanent files, decode and reproduce this data in digital and analog form for output to various devices. For example, a continuous display may be desired on an oscilloscope in addition to occasional written records from a strip chart recorder. The system will be able to provide both.

The present system is in the form of a prototype. The master controller is to be a PC-1200 computer interfaced with two 50 mega bit discs (Pertec Model 3000). The disc interface is under construction. The sampling clock, analog-to-digital converters, and control logic are constructed and await debugging. Software routines for encoding and decoding sampled ECG data have been written and tested.
PATIENT 1-2, PATIENTS 4-5, PATIENT 7-8

--- INTERMITTENT DATA PATH

--- CONTINUOUS DATA PATH

Figure 1

ELECTROCARDIOGRAPHIC DATA ACQUISITION SYSTEM
C. Regional Tracer Kinetics

C-1. A Mathematical Model for Design and Analysis of Experiments to Measure Cerebral Glucose Utilization Rate by External Monitoring of Radioglucone

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Support: RR 00396
HL 13851

The modeling efforts initiated last year and described in the previous Progress Report (PR 8, C-4) have led this year to a successful method for measuring global cerebral glucose utilization rate in the rhesus monkey (see C-3). The data-processing algorithms based on the equations of the model permit glucose utilization to be measured in units of glucose mass per unit of time per unit of brain mass. Data sufficient to provide suitably efficient estimates of glucose utilization and other parameters of metabolic significance can be collected in as little as two minutes after intravenous injection of radioglucone. Thus, instead of providing some mere time-average index of cerebral metabolism, our model leads to a practically instantaneous measure of absolute utilization per hundred grams (say) of brain tissue. This has obvious advantages for measurements intended to assess differences in glucose metabolism between different subjects, or to follow time-varying changes in a given subject.

Ongoing experiments in patients have as their objectives the validation of our method for global measurements in humans. Despite the fact that there is no apparent means of validating our model for regional measurements, we intend to apply it to analyze radioglucone data obtained with the 26-probe system (C-2). For this purpose, we intend to implement our algorithms on a small laboratory digital computer (C-15).

C-2. Twenty-Six Probe System for Human Cerebral Hemodynamics and Metabolism Studies

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Support: RR 00396
HL 13851

The 26-probe system (PR 8, C-9) has been constructed. In addition, a multichannel pulse-height analyzer (MCA) and probe selective switching system
have been incorporated into the system. The MCA is used to set up the 26 single-channel analyzers, check out all the probes, and in a time mode, to monitor the time course of count-rate data during each experiment. The system has been tested for count-rate capabilities (maximum of approximately 1.3 million c/sec), time stability of the high-voltage supplies, phototubes, amplifier and single-channel analyzer, and spatial resolution. The interface to the Interdata Model 70 has been completed and the data-display system is presently being developed (C-15).

The 26-probe system has been used for regional measurements of cerebral glucose metabolism in humans and static imaging with technetium-99m pertechnetate. The major work at this time is in metabolism studies using glucose and ammonia and static or dynamic imaging for cerebral pathology identification. In the near future we hope to extend this work to human studies with a variety of other biological compounds.

In conjunction with the above is a major effort in software development to allow more sophisticated computer data processing and display of the 26-probe data.

C-3. Regional Cerebral Glucose Metabolism Studies

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Support:
RR 00396
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Presently no method exists for the in-vivo measurement of regional cerebral glucose metabolism (rCMRGl) in man. We have developed a method that establishes the foundation for such a tool through use of the positron-emitting isotope carbon-11. The method has been validated in the rhesus monkey, and a current series of measurements in patients has as an objective the investigation of its suitability in humans.

The isotope is injected intravenously. One detector is placed under the head and a second over an external extension of an indwelling peripheral arterial catheter. Blood is withdrawn with this catheter to describe the arterial blood curve. The count-rate information is collected for 2 to 3 minutes and is then pre-processed using a classic LINC computer.
The head reading is corrected for blood radioglucose using a second intravenous injection of the non-diffusible tracer, carbon monoxide, labeled with oxygen-15. The correction is accomplished through application of procedures set forth in a mathematical model (C-1). For the experiments conducted to date, the necessary calculations were done using an IBM System/360 Model 50.

CMRGlut was determined in nine monkeys concurrently by the present carbon-11 method and by the Fick principle employing oxygen-15 labeled water for the measurement of cerebral blood flow. A significant correlation found, viz., CMRGlut (carbon-11) = (1.02 ± 0.15) CMRGlut (Fick) + 0.05 ± 0.63, r = 0.93, p < 0.001. The method thus offers the potential for low-risk means of measuring regional CMRGlut in man when employed with a properly designed multiprobe system.

C-4. Cerebral Ammonia Metabolism

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Support: RR 00396
HL 13851

The malfunction of the nervous system may occur in association with liver disease. This is believed to result from elevated blood ammonia concentration that frequently is seen in conjunction with liver disease. The effects on the brain of this exposure to ammonia are suspected to be related to the observed neurological symptoms. The direct in vivo measurement of ammonia metabolism or ammonia toxicity at high ammonia concentrations in the brain have been impossible to date. Thus, a study was initiated using the cyclotron-produced positron-emitting isotope nitrogen-13 to develop an in vivo model whereby the above studies could be carried out.

These studies have been done on rhesus monkeys by employing our computer-based system (C-1, C-3) for radioglucose studies. As a result of the ammonia metabolism studies, we have also found that nitrogen-13 labeled ammonia, which is a freely diffusible gas, can be used with either an intracarotid or intravenous injection to measure an index of regional cerebral blood flow. This results from the fact that the nitrogen-13 labeled ammonia freely passes into the brain through the blood-brain barrier and is quantitatively retained in the brain. We have experimentally shown that the fraction (extraction fraction) retained is determined by the flow rate and the turnover rate (approximately 75% per second) of the ammonia pool in the
cerebral tissue. We have shown that the extraction fraction is reduced as the flow is increased. Between flows of 25 to 90 (ml/100g)/min there is significant (p<0.001) inverse linear correlation between extraction fraction and cerebral blood flow for either a carotid or intravenous injection. The intravenous procedure offers a non-invasive method for a relative index of regional cerebral blood flow.

C-5. Measurement of Hemodynamic Parameters by Residue Detection in the Presence of Radiotracer Recirculation

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HL 13851

A quantity of interest in many physiological studies of the brain is the cerebral blood volume (CBV). However, its assessment is a difficult task. One approach is to determine the mean transit time of both a "freely-diffusible" tracer and a vascular tracer. This then permits estimation of a relative blood volume (ml blood/100g tissue) from the following equation:

$$\text{CBV(ml/100g)} = \frac{\lambda T_{vas}}{f T_{diff}} \times 100,$$

where $\lambda$ is the tissue-blood partition coefficient of the diffusible tracer (ml/g), $T_{vas}$ is the vascular tracer mean transit time, $T_{diff}$ is the diffusible tracer mean transit time, and $f$ is a factor which corrects for the fact that the vascular tracer is not a whole-blood label, but generally, either a red-cell or a plasma label.

The technique utilized in the Radiology Department to determine the appropriate organ transit times is external residue detection subsequent to serial intracarotid injections of labeled water (diffusible tracer) and labeled red cells (vascular tracer). In both instances, the label is cyclotron-produced oxygen-15, a positron emitter with about a two-minute half-life. The method employed for the evaluation of the water mean transit time is a variation of the Zierler concept(1). Because water recirculates, a first-order correction for this perturbation is achieved by fitting the terminal end of the washout recording (8-17 min.) to the sum of an exponential function and a constant.
This method for assessing the mean transit time yields a cerebral blood flow that agrees well with more conventional techniques, e.g., those using xenon-133, and has been described in detail previously.(2)

The evaluation of the red-cell transit time is also complicated by significant recirculation of labeled red cells. Two methods of analysis have been applied:

1) The mean transit time is computed by the area-over-height method of Zierler,(1) and correction for recirculation is achieved by the so-called Hamilton extrapolation technique,(3) in which the portion of the washout recording prior to recirculation is approximated by a monoexponential function. The terminal portion of the washout, otherwise obscured by recirculation of tracer, is then assumed to be adequately described by the derived function.

2) The mean transit time is also determined by the method of Larson and Snyder.(4) This technique, formulated specifically to include the situation of tracer recirculation, was previously described (PR 8, C-2). Briefly, the method requires normalized arterial and venous injections of the tracer; the mean transit time (T) is computed from the equation

\[
T = \frac{\int_{0}^{\infty} [\tilde{q}_a(t) - \tilde{q}_v(t)]dt}{1 - \tilde{q}_{oo}},
\]

where \( \tilde{q}_a(t) \), \( \tilde{q}_v(t) \), and \( \tilde{q}_{oo} \) are the normalized arterial, venous, and steady-state response curves, respectively, and \( t \) is time after the beginning of each injection.

Results:

1) The mean transit time involving the Hamilton extrapolation(3) appears to systematically underestimate that predicted by the Larson-Snyder method(4) by a small amount (5-10%). This indicates that the simple exponential extrapolation is not strictly valid, i.e., the washout is not completely described by a single half-time. On the other hand, a very small amount (1%) of diffusible contaminant can lead to a serious overestimation of vascular transit time when employing the Larson-Snyder approach. (This should not be construed as a shortcoming of the Larson-Snyder model per se, but rather a consequence of the practical difficulties in meeting the conditions for valid applications of the model.)

2) The calculated cerebral blood-volume by the Larson-Snyder technique yields a volume that agrees remarkably well with that assessed in the same subjects by a radically different approach, namely stimulated fluorescence (PR 8, C-5).
3) In a clinical study involving approximately twenty patients, a surprisingly good correlation was exhibited between the reciprocal of the red-cell transit time and the corresponding cerebral blood flow assessed with oxygen-15 labeled water. 

\[
(CBF = \frac{188}{\bar{\tau}} + 6.3, \text{ where } \bar{\tau} \text{ is in seconds, } CBF \text{ in (ml/100g)/min}, \quad r = .935, \quad \sigma_{188} = 11.7, \quad \sigma_{6.3} = 2.0). 
\]

Thus, at least in this group of patients, the assessment of red-cell transit time appears to be a good index of cerebral blood flow.


C-6. A Mathematical Model for In-Vivo Measurement of Exchange Rates of Substances Between Blood and Tissue by External Monitoring of Radiotracers

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Support: RR 00396
HL 13851

Cyclotrons and other particle accelerators used in medical research have made it feasible, through employment of external detection, to study metabolic processes in vivo. By means of these machines, various short-lived isotopes have been prepared from which it has been possible to synthesize a number of suitable radiopharmaceutical compounds. Because of the advantages offered by external detection using such radiopharmaceuticals, it
seems worth exploring its potential for quantitative measurement of utilization rates of various metabolically important substances. To render such measurements quantitative, mathematical models are generally required. We have therefore sought to generalize the model used successfully in the in-vivo study of glucose metabolism (C-1 and C-3) to the in-vivo measurement of exchange rates between blood and tissue of additional substances. This generalization consists essentially in careful identification and assessment of the relative importance of the various conditions which must be met for valid application of the glucose model (C-1) to the study of the uptake and metabolism of other compounds. The metabolic systems to which our model applies are characterized by the transport across the capillary endothelium of any substance (a) that can be labeled with radioisotope suitable for external detection; (b) for which the relative extraction across the organ of interest is not large (<15%); and (c) whose metabolic products do not turn over appreciably during the time of measurement. Before our model can be successfully employed in the metabolic study of a particular substance, the validity of the above conditions for that substance must be established.

Some of the compounds to which our model may apply for cerebral metabolism studies include ammonia (C-4), amino acids, monocarboxylic acids, ethanol, nicotine, caffeine, and heroin.

C-7. Parameter Estimation for Radioisotope Tracer Data

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Support: RR 00396
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HL 13851

Our efforts in this continuing study (PR 8, C-6) are directed at the development of statistical models for dynamic radiotracer data and in applying statistical estimation theory in conjunction with these models to estimate physiological parameters of interest. Our model for the events detected in a single spatial resolution cell is a conditional, inhomogeneous Poisson process given the parameters \( \lambda(x_1, x_2, \ldots, x_m) \) to be estimated. (1, 2) The maximum likelihood estimates of the parameters \( x \) in terms of the number of events \( n_1, n_2, \ldots, n_k \) observed in \( k \) time intervals \( [0, t_1), [t_1, t_2), \ldots, [t_{k-1}, t_k=T] \) is the value of \( \hat{x} \) that maximizes

\[
\mathcal{L}(\hat{x}) = -\int_0^T \lambda(t, \hat{x}) dt + \sum_{i=1}^{k} n_i \ln\left(\int_{t_{i-1}}^{t_i} \lambda(t, \hat{x}) dt\right)
\]
where $\lambda(t,X)$ is the instantaneous occurrence rate as a function of the unknown parameters. The numerical problem is to find the value of $X$ that maximizes $\ell(X)$ given $n_1, n_2, \ldots, n_k$. A number of algorithms are described in the literature for implementing this search, and we are comparing several of these for $\lambda(t,X)$ in the form of several decaying exponentials. The algorithms in the comparison are: (1), steepest descent; (2), conjugate gradient; (3), variable metric or modified Davidon's method; (4), Newton-Raphson; (5), gradient with respect to a non-Euclidean norm; (6), Sandor's maximum likelihood algorithm; (7), weighted least-squares curve fitting (see (2) for references on these methods.) The comparison between these algorithms is based on the following data sets: (1), simulated data in which $\lambda(t,X)$ is the sum of 1, 2, 3, and 4 decaying exponential time functions for which the corresponding 2, 4, 6, and 8 parameters of $X$ are selected as representative of those found in physiological data; (2), data obtained by monitoring the natural radioactivity decay of mixtures of oxygen-15, and nitrogen-13; and (3), physiological data obtained by monitoring radioactivity over the head due to oxygen-15 tagged carbon-monoxide labeling red cells. The conclusion of this study is only tentative at this time, but it appears now that a combination of algorithms (1) and (5) offers preferred performance for the data sets examined. The combination consists of using the method of steepest descent for a few preliminary iterations in the search for the maximum and then using the modified gradient method. This combination seems to be accurate, to be uncomplicated, to converge in few iterations, and to converge for a wide spread in initial parameter estimates.

We have developed some procedures for estimating the parameters from measurements of the times between detected events. The Poisson process used is a reasonable first approximation model for data obtained in a single spatial-resolution cell, but there are deficiencies. Among these is the neglect of the "dead-time" effect in which the absorption of a photon renders the detector temporarily inoperative so that subsequent photons are lost and not counted for some brief period, typically a few microseconds. While this effect is in our opinion unlikely to be significant at the low count rates where we expect occurrence-time measurements to be most useful, it is of interest to note that the effect can be accommodated by a straightforward conceptual extension of the Poisson model. This extension is described in a monograph (2) and is based on our studies of self-exciting point processes. (3)

Data obtained using a single, large scintillation detector, as in an Anger camera, contains spatial information as well as temporal information. A more general model which accommodates the additional spatial information is presently being developed. A monograph describing this effort is available. (4)

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C-8. Gastric Emptying

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Support: RR 00396
          GM 01747

Patient studies to test a variety of physiologic, pathophysiologic, and pharmacologic factors influencing gastric emptying have continued during the past year (see PR 8, C-15). The previous studies of gastric emptying in hypoglycemia have been reported.(1)


C-9. The Biological Behavior of Fibrinogen Labeled by Four Different Methods of Iodination

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          R. L. Hill, BCL

Support: RR 00396
          GM 01747
          HL 14147

A program has been written to collect data by means of the six probes interfaced to the PDP-12 (PR 8, C-16). The collected data is written on LINC tape in the format required by the existing LINC-PROBE processing programs.(1) In addition, a program to correct for cross-over between channels when viewing multiple isotopes was supplied for the following fibrinogen studies.
Radioiodinated fibrinogen has been used extensively in Britain and Canada for the detection of deep venous thrombosis. Our studies evaluate the biological behavior of products of four different methods of iodination of fibrinogen. Some preparations form large molecular weight aggregates which are rapidly cleared from circulation by the liver and spleen. One aspect of these studies was the evaluation of clearance of radioiodinated fibrinogen injected intravenously into dogs. Such evaluation involves the fitting of plasma activity clearance curves, either by hand or computer, to the sum of three exponential processes. The slowest of these exponential components corresponds to published values for the true catabolic rate of fibrinogen. One method of evaluation of the biological suitability of radioiodinated product is to maximize the total injected dose which has a clearance rate corresponding to the catabolic rate of fibrinogen. This is obtained from the "zero time" intercept of the slowest component. The more rapid components are believed to be related to the intravascular-to-extravascular spread of fibrinogen and the hydrolysis of iodine from the fibrinogen molecule.

Another aspect of these studies was the simultaneous evaluation of two radioiodinated fibrinogen preparations, one with iodine-131 and one with iodine-125, with respect to a reference labeled-plasma protein, technetium-99m albumin. Spaces occupied by these tracers could also be compared by the dilution principle utilizing standards of injection and blood sampling. The activities of these three tracers were observed simultaneously by scintillation monitoring of an external blood loop passed through a perfusion pump. Iodine-125 fibrinogen was injected a short time prior to the mixed injection solution of iodine-131 fibrinogen and technetium-99m albumin. The data were collected in a PDP-12 computer at selected integration times and stored on magnetic tape. Subsequent to collection, the data were computer-corrected for background, isotope decay, and cross-over between respective pulse-height channels. The corrected data were plotted graphically by computer and analyzed manually or by computer. All studies have been completed and part of the results have been reported.


C-10. Molecular Diffusion Effects of Albumin Tracers on Transit Time Distributions Through Small Blood Vessels

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In this study, molecular diffusion effects of albumin tracers on transit-time distributions through a single-flow path of small blood vessels are first investigated. The effects on transit-time distributions through a vascular bed are then deduced.

The criterion for Taylor's diffusion effect in a cylindrical tubing is reinterpreted so it can be applied to flow systems with other configurations. The reinterpreted criterion is found to be satisfied for albumin tracers passing through a single-flow path of small blood vessels in vascular beds. Therefore, it is expected that as far as the transport of albumin tracer is concerned, the velocity profile in small blood vessels can be regarded as uniform, except that the tracer's effective diffusivity is enhanced.

The effects are further studied by a glass model experiment. A large-scale model (~240 times larger) of a typical flow path of small blood vessels in vascular beds is used. The flowing fluid inside the model is water. The flow rates and the tracer used in the model are chosen by similitude studies to simulate the molecular diffusion of albumin tracers flowing inside small blood vessels. The transit-time distributions obtained in the experiment are found to be rather symmetrical (resembling Taylor's diffusion effect in cylindrical tubings), and can be described by the equation,

\[ p_t(s|T) = \frac{1}{\alpha \sqrt{2\pi TS}} \exp \left( -\frac{(T-S)^2}{2\alpha^2 TS} \right) \]

where \( t \) is the real transit time along the flow path, \( s \) is the transit time along the flow path if the flow were a true plug flow, and \( \alpha \) is found to be about 0.2. In other words, the result of the glass model experiment supports the assertion that the criterion for Taylor's diffusion effect is satisfied for albumin tracers flowing through small blood vessels.

For transit-time distributions through a vascular bed, it is found that the molecular diffusion effects can be taken into account by the following equation:

\[ p_T(T) = \int_0^\infty p_t(s|T) p_s(s) ds \]
A mathematically rigorous basis for using probability theory in treating transit-time distributions of nondiffusible tracers is developed.\(^{1}\) For a time invariant flow system, a probability space \((\Omega, \mathcal{F}, \mathbb{P})\) can be specified as follows:

\(\Omega\) (sample space) is the set of all streamlines in the system.

\(\mathcal{F}\) (\(\sigma\)-algebra) consists of all streamtubes in the system and all possible complements, countable unions and intersections of them.

\(\mathbb{P}\) (probability measure) is defined such that for any streamtube \(B\),

\[ P(B) = \frac{\text{flow in } B}{\text{total flow in the system}}. \]

It is assumed that any streamline can be partitioned into many small segments (called levels) so velocity is approximately constant within each level. Then the following random variables can be defined on the probability space \((\Omega, \mathcal{F}, \mathbb{P})\),

\[ t : \text{transit time through the system}, \]

\[ l_i : \text{path length of the } i^{th} \text{ level}, \]

\[ v_i : \text{velocity in the } i^{th} \text{ level}, \]

\[ t_i : \text{transit time through the } i^{th} \text{ level}, \]

\[ N : \text{total number of partitioned levels}. \]

Thus, the formulation for transit time is

\[ t = \sum_{i=1}^{N} \frac{l_i}{v_i}. \quad (1) \]
The density function $p_t(T)$ of the random variable $t$ is shown to correspond to the ordinary transit-time curve, $h(T)$, obtained experimentally, i.e., $p_t(T) = h(T)$. The probability distribution functions of $L_i$'s, $v_i$'s, and $N$ are obtained from the structural and flow properties of the system. The above formulation thus enables us to relate the transit time curve to the structural characteristics of a flow system.

Equation (1) is applied to two simple flow systems and is found to be useful. (1) A proof of the central volume principle by probability theory is also obtained.

With the present formulation, the use of probability theory in constructing the model for transit time curves through vascular beds (PR 8, C-7) is thus legitimized. Equation (1) is expected to be useful also for studying flow system in chemical and environmental engineering.


C-12. Reducing the Motion Artifact in Clinical Studies of the Liver

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Support: RR 00396
GM 01747

The motion correction program described previously (PR 8, C-14) has been used in three ways:

1) To correct for respiratory motion during routine liver scanning. A visual comparison of the computer-generated "corrected" and "uncorrected" images revealed no apparent difference between them, apart from the slightly smaller size of the corrected images. We were unable to appreciate any improvement in the "corrected" images. The failure to appreciate any obvious improvement in the corrected images stems from the coarse array used for collection of the images (32x32) and the small amount of movement of the liver in the upright position.

2) To measure the extent of hepatic excursion in the upright and supine positions and also during normal and deep breathing. These measurements were made from the computer determined displacement of the row with the median count and were compared to
measurements of diaphragmatic excursion made during fluoroscopy. In the upright position the average displacement of the liver during natural respiration was 0.8±0.2 cm, and in the supine position it was 1.1±0.3 cm. Similar figures were found by fluoroscopy (0.8±0.4 cm upright, 1.3±0.5 cm supine). During deep breathing the excursion increased to 1.2-7.5 cm.

3) To measure the improvement in resolution that results from motion correction. For these experiments the pin-hole collimator was used with a Picker thyroid phantom. The phantom was moved artificially beneath the pinhole and the magnified image of one upper pole used for these experiments. A program from Mt. Sinai Hospital, Cleveland, was used to examine the count profile across the defect so that the effective Full Width at Half Maximum of the detection system could be determined in both the corrected and uncorrected images.

Our efforts in this study have been reported. (1)


C-13. Cardiac Ejection Fraction

Personnel: R. H. Secker-Walker, M.D., Radiology
R. L. Hill, BCL

Support: RR 00396
AT(11-1)-1653
GM 01747
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The method and results of studies in 16 subjects and 9 dogs have been described previously (PR 8, C-12). The reproducibility of the calculation of left ventricular ejection fraction has been examined by comparing the results from two different observers and also the results of one observer's efforts six months apart. The correlation between the observers was 0.72 and the mean absolute difference in their results was 0.042 (±0.013 standard error of the mean). The correlation between one observer's efforts six months apart was 0.87 with a mean absolute difference of 0.052 (±0.01 standard error of the mean).

A modified algorithm for the tissue-background calculation was implemented, enabling any fraction of the maximum counts in the end-diastolic-end-systolic image to be used to select the background region. As the fraction increased from 0.1 to 0.9 the calculated ejection fraction fell to

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a plateau for a count fraction of 0.6, so for subsequent calculations we may safely use this latter count fraction.

The calculated tissue-background activity accounted for an average of 77% of the end-diastolic counts in dogs and 72% in the human subjects. The experiments in the dogs lasted four to six hours and show that this method provides a way of monitoring changes in ejection fraction over several hours. Thus, we are hopeful that the effects of therapy can be studied in humans. Our efforts in this study have been reported. (1-3)


C-14. Ventilation-Perfusion Studies Using the Gamma Camera

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The new ventilation-perfusion calculation program (V/Q program) was completed and a large proportion of the studies have been analyzed. More than 400 examinations have been performed since the project began in 1971.

Ventilation-perfusion ratios have been determined in two ways: 1) by using the regional fractional exchange of air per second as a measure of ventilation, and dividing this by the regional perfusion per unit lung volume; 2) by using the regional tidal volume per unit lung volume as an indication of ventilation and dividing this by the regional perfusion per unit lung volume.

Preliminary experiments with intravenous xenon-133 showed a good correlation (r=0.89) between the regional distribution of xenon-133 and technetium-99m macroaggregates, so that regular perfusion scans have been used to measure the distribution of pulmonary arterial blood flow.
Normal values for both methods of determining V/Q ratios have been established and compared to the values in patients with pulmonary embolism and chronic obstructive lung disease. Functional images show striking changes in some patients with pulmonary embolism, but so far have not proved clinically superior to a visual assessment of the images taken from the gamma-camera oscilloscope. The figures for the V/Q ratios, derived from the fractional exchange of air, provide a better separation between the patients with chronic obstructive lung disease and both normal subjects and patients with pulmonary embolism, than do the V/Q ratios derived from the figures for relative ventilation.

In patients with bronchial carcinoma, regional V/Q ratios tended to be outside the normal range when the tumor was unresectable, and this observation could prove useful in deciding whether or not to subject a patient to an exploratory thoracotomy.

An extensive study has been undertaken comparing the radiographic findings of emphysema with evidence of delayed clearance of xenon-133. This has shown that approximately one third of the patients with normal chest radiographs and abnormal perfusion scans had regional abnormalities of ventilation to account for the defects in blood flow. Only severely involved regions were consistently recognized radiographically. Our efforts in this study have been reported (1-5).

Transmission scanning during natural and deep breathing using a planar source of technetium-99m pertechnetate was performed in twenty-three subjects and compared to xenon-133 ventilation studies. Data for the transmission study was collected in sixteen, 16x16 arrays - two images around the peak of inspiration, two around the trough of expiration and six equi-volume images during inspiration and another six during expiration. The events of two minutes of natural breathing and one minute of deep breathing were integrated separately. The logarithm of the difference between inspiration and expiration was determined from the peak and trough images; the rate of change of flux from the six inspiratory and the six expiratory images was determined separately.

In nine subjects with normal ventilation (from their xenon-133 study) there were modest but significant correlations between: tidal volume and the difference in whole-lung transmission; the increase in tidal volume with deep breathing and the increase in transmission; the regional fractional exchange of air per second and the relative regional ventilation. In thirteen patients with evidence of airways obstruction, the correlations were much weaker and rarely significant.

The rate of change of gamma-ray flux during expiration was correlated with the fractional exchange of air, and decreased during deep breathing in the patients with obstructive lung disease - an observation that may be related to the loss of elastic recoil in this group of patients.

Although simple to perform, these results have not encouraged us to pursue this approach any further. The results have been reported (6,7).


C-15. Implementation of a New Computer System for Radiation Physics

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Previously (PR 8, C-3) we described the specification and purchase of new computers and peripherals for the Radiation Physics Division of the Department of Radiology. The past year has been spent in implementing this dual-processor scheme. Figure 1 is a block diagram of the system.

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Fig. 1. Block Diagram of the Radiation Physics Computer System
Versatec Line Printer Interface and Software: An interface was designed and built for the Versatec graphical line printer. The interface is designed to allow for the operation of the line printer in the print, plot, or simultaneous print and plot modes. In the print mode, it is software compatible with the existing Interdata line-printer drivers. A new line-printer driver has been written for the Disc Operating System provided by Interdata. The new driver allows for print, plot, and simultaneous print and plot modes.

Diablo Disc Controller and Interface: The versatile Disc Controller designed and built by BCL (PR 8, J-15) has been interfaced to the Interdata computers. The interface has been designed so that under the normal mode of operation the disc commands and functions are compatible with the Interdata disc controller and thus software-compatible with the disc driver in the Disc Operating System. In the extended mode of operation, the interface can perform most of the flexible functions built into the controller, including reading and writing in 8-or 12-bit word-length formats. This feature enables the data base on this system to be compatible with the data base of most other computers at the School of Medicine.

Direct Memory Access Interface and I/O Structure: Discs and magnetic tape units operate over the Direct Memory Access, Bus since they require fast autonomous access to the memory. The standard DMA interface provided by Interdata has been built for the each processor and duplicates the I/O lines for DMA. These I/O lines are called the Selector Channel Bus. The Selector Channel and the I/O busses have been physically extended from each processor and standard bus buffer boards built.

Bucode Tape Interface: An interface has been built to a Datum NRZI formatter and Bucode Model 4025, 9-track, 800-bits-per-inch, 125-inches-per-second tape drive. The tape system is compatible with all Interdata operating systems and provides an additional set of 16 tape instructions for future expansion. The magnetic-tape driver contained in the Disc Operating System will be modified to take advantage of the read after write and continuous read and write capabilities of the tape drive.

Multi-probe Interface: The multi-probe interface is a general-purpose interface for monitoring the activity of radioactivity detectors. It is used predominantly with sodium iodide detectors to count the number of scintillations that occurred in a particular detector over a specified length of time. Thus, it contains individual scalers for each detector. Features of the multi-probe interface include expandibility from 8 to 64 channels in groups of 8, differential data and control lines from the detectors to the interface, a test mode for checking operation of counters and multiplexers, and provisions for starting data collection from the console or from a remote location. Individual scalers are buffered and fully synchronous, allowing less than one microsecond deadtime between integrations. A crystal-controlled real-time clock, contained in the interface, provides integration times of 10 milliseconds, 100 milliseconds, or 1 second, each selectable under program control.
Interdata-LINC Communications: Interfaces for the LINC and Interdata have been built to provide a data path between these two computer systems. The Interdata interface has been designed to duplicate a high-speed paper tape reader and punch, thus eliminating the need for special communications software on the Interdata system. A special communications package has been written for the LINC to make it behave like a paper-tape unit and to process the data from the 26-probe system. This data is presently collected on the Interdata and then transmitted to the LINC.

C-16. Design of a New PDP-12 Gamma Camera Interface

Personnel: M. C. Jost, BCL
            R. L. Hill, BCL

Support:    RR 00396

The design of the PDP-12 gamma-camera interface implemented previously\(^1\) has been reevaluated. A new interface design has been completed. In addition to providing for all data collection possible with the previous interface, the new interface incorporates several new features which increase the flexibility and usefulness of the camera-computer system in studies similar to those now underway (C-8, C-12, C-13, and C-14).

These new features include:

1. Use of faster analog-to-digital converters, which also provide the possibility of resolution greater than that available in the present interface.

2. Collection of energy data and position data.

3. Collection of data simultaneously from both channels of the dual isotope gamma camera.

4. Collection of data in either histogram or "list" format.

5. Addressing of 16K of core, thus permitting use in data collection of the additional 8K of core recently installed in the PDP-12.

Construction and testing of this new interface, as well as preparation of computer programs to permit its full use, are now in progress.

D. Monitoring the Critically Ill

D-1. A New Surgical Intensive Care Unit

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R. J. Arnzen, BCL
G. J. Blaine, BCL
A. L. Bodicky, BCL
R. E. Clark, M.D., Surgery
M. Evans, Barnes Hospital
V. W. Gerth, Jr., BCL
R. W. Hagen, BCL
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During the past year a computer-based monitoring system for the renovated cardiothoracic surgical intensive care unit (SICU) was completed and installed. This system utilizes much of the conventional analog equipment in former use and retains those components rendered obsolete for back-up purposes. Most of the effort this year has been devoted to finalizing designs, replicating and testing multiple hardware components, developing additional software, installation in the SICU area, and critical evaluation of the system in the first three months of clinical use.

Although the full capabilities of the system have not been made available at this writing, its value to and acceptance by clinical personnel has been most gratifying. Extensive testing of all components in a prototype system at the Biomedical Computer Laboratory greatly facilitated the relatively trouble-free conversion to the computer system in the SICU. As noted in some of the following reports, the implementation of this system in the clinical environment has revealed some unanticipated problems but none has required major design modifications.
D-2. SICU Communications System

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T. F. Schuessler, BCL

Support: RR 00396
Washington University

Communications system activities were principally concerned with assembly, test, and installation of the local bus and local bus terminals (LBT's) for the SICU (PR 8, D-3).

Access to the 48-pair multiconductor bus cable is provided by edge-board connectors soldered to a "thru-bus" printed circuit board. The large size and small tolerances required for the controlled impedance bus board necessitated state-of-the-art circuit board fabrication technology. Sample boards from three vendors were evaluated, and close liaison was maintained with the selected vendor to ensure board quality.

Installation of the bus boards for the local bus was preceded by their evaluation in the prototype system (PR 8, D-3). As each board was installed in the SICU, pulse waveform comparisons for both drive pulse and adjacent pair crosstalk were made to verify proper bus operation.

A closed loop error test was performed using computer generated digital patterns to examine the error performance of the local bus system. LBT write-only modules were used to supply the digital patterns to LBT read-only modules at each of the bus access points. No errors were observed in a study containing more than \(10^{10}\) transactions.\(^{(1)}\)

The design of the Message Shuttle will proceed following the study and performance evaluation of several candidate network configurations.


D-3. SICU - Transducers and Signal Conditioners

Personnel: R. W. Hagen, BCL
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T. F. Schuessler, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

Routine setup and calibration of the SICU transducers and signal conditioners is being performed by BCL personnel. When component failures
occur, BCL technicians isolate the fault to a module and turn the module over to the hospital maintenance department for repair. To ensure accurate data it has been necessary to initiate periodic temperature stability testing of the pressure transducers. Tests have been conducted on a commercial gas flow instrument for use in measuring respiratory flow. Modifications are under consideration to improve the stability and accuracy of this instrument and thereby make it more useful for patient monitoring within the SICU. The fabrication of an improved transducer mounting manifold is being completed and should be installed soon.

D-4. SICU - Computer System Installation and Personnel Training

Personnel:  R. W. Hagen, BCL
        V. W. Gerth, BCL
        K. L. Kunkelmann, BCL
        J. M. Pexa, BCL
        T. F. Schuessler, BCL
        L. J. Thomas, Jr., BCL

Support:  RR 00396

The installation of the SICU computer monitoring system was completed on March 23, 1973. All system components were thoroughly tested before system installation began. The installation and checkout was completed in 5 days with no interruption in patient scheduling.

The initial personnel training was accomplished through a number of lectures and demonstrations. Because of the rotation of staff it is necessary to provide continuous training to personnel. A reference manual has been written for this purpose and informal training is provided by BCL technicians on an individual basis. Acceptance by medical personnel has been enthusiastic with only modest training required for effective use.

D-5. SICU - Programs and Algorithms

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        R. E. Clark, M.D., Surgery
        R. W. Hagen, BCL
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Support:  RR 00396
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The programs written for the basic patient-monitoring functions have been refined and in some cases modified slightly to meet redefined clinical
needs. Their general functions, however, remain unchanged from those reported previously (PR 8, D-5).

Most of the SICD software efforts this past year have been devoted to completing the documentation of the monitoring programs as well as writing a number of utility programs, most of which are called by keyboard sequences and are run at the background (lowest priority) level. Brief descriptions of the added programs are listed below.

1. TRENDS: This program saves the values of the derived variables (up to sixteen for four beds) on LINC tape for subsequent generation of trend displays. The data are stored in three circular buffers on tape for 30 minute, two hour and eight hour trend displays. PC keyboard sequences allow display by bed number, time scale and parameter on the storage scope from which hard copy is available. These displays include alphanumeric labeling of coordinates, date and time and stored patient identification information.

2. ECG GAIN: This program allows individual bed-by-bed manipulation of amplitude and slope criteria for the QRS detection program. Through keyboard input, the algorithm can be altered to function more reliably when confronted with noisy or otherwise challenging waveforms.

3. STUDY: This program allows initiation of long term data collection (using the trend data) on tape for off-line analysis. Options allow selection of tape length (single or double) and data sampling intervals so that up to 144 hours of data can be collected for all sixteen parameters for all four beds on a double length tape.

4. MOVE PT: When patients are transferred from one bed location to another within the care unit, this program rearranges accordingly all bed-specific information (patient identification, ECG gain, trend data and parameter limits) in core and on tape.

5. ALTERREC: This program allows reassignment of either or both channels of the discussion station recorder to any analog input from any bed and provides options for selecting preset gain factors and zero suppressions appropriate to the selected waveforms. The sampling rate is 240/sec in all cases.

6. TESTS: This program provides access to a library of programs written to test and calibrate various system components without interrupting the patient monitoring and data collection functions. Currently included are:

   A. REC CAL: Puts calibration signals on both recorders for setting baseline and gain as well as for checking linearity.

   B. ADCAL: For use with a plug-in module to calibrate the analog-to-digital converter at any bedside. Gain and baseline deviations are displayed in alphanumeric form on the corresponding video bed channel.

   C. TIME: A program has been written to generate a real time clock and calendar (100 year) derived from the sampling pulses.
which are based on the crystal-controlled oscillator in the television sync generator. This information is used to label trend displays with date and time as well as to indicate time of day in digital form on the video monitors. This program provides the capability for resetting the calendar and clock if necessary (e.g., after the program has been interrupted).

D. SELFSCAN: Tests the function of the digital display "selfscan" at any of the nine display modules. The "selfscan" is driven at a rapid rate and sequenced through all the characters in its repertoire.

E. READONLY: The digital value presented to the communication system from any channel of any read-only module in the unit can be displayed on selected "selfscans".

F. CONV ERR: This program checks for deviations between the digital output of the analog-to-digital converters and known input values. It keeps a cumulative record of all bits found to be in error as well as a count of all errors encountered (up to 2047). Once initiated, the program continues to run even though other background programs are called. Results are displayed on the storage scope at any time via a PC keyboard request.

In addition to the above programs, several others were written to facilitate documentation and analysis of system failures (crashes) with a minimum of interruption in system operation. A resident program senses and saves all current program and data origins and calls a core dump sequence from tape. Successive core dumps are saved sequentially on a special tape for later analysis. In conjunction with a formalized crash procedure and report form, this allows prompt collection of all pertinent information and early restart of the system (in one or two minutes) by technical personnel. Three other programs were written to aid in crash analysis. "DUMPTAPE" prints the octal contents of any specified number of blocks starting from any specified block number. "SEARCH" prints all locations within up to 200 blocks on tape where the content is found to match any specified value. "COMPARE" prints all locations where a mismatch is found between corresponding contents for two specified segments (up to 200 blocks each) of tape. In all cases the output may be directed to either a storage oscilloscope or a line printer.

Of the system failures encountered to date (see D-6) none has been attributable to software.
D-6.  The SICU Computer System

Personnel:  V. W. Gerth, BCL
   L. J. Thomas, Jr., BCL

Support:  RR 00396
         Washington University

The SICU computer system has been installed after extensive testing at BCL. The computer, an Artronix PC-1200 with 8K of core memory, has two levels of priority interrupt and three Twin-0 registers for extended addressing. Two of the Twin-0 registers are used for addressing in the interrupt levels while the third is used for DMA addressing in conjunction with LINC tape.

The lowest priority interrupt level is used for background tasks such as trend displays and patient information entered by the medical staff, while the highest level is used for monitoring functions and operates on a 240 sample-per-second time base derived from the video sync generator. The computer system is connected to the digital communication system and video display system by BCL-designed interface cards which plug directly into the PC-1200 input-output bus. Otherwise, the computer is standard in all respects.

Reliability of the computer to date has been good with problems limited to a single power supply failure, an intermittent short on a printed circuit card, and a severe thunderstorm which managed to halt two other computers in the medical center at the same time. In the last case, all monitoring functions were still being performed by the computer but the background program had been disabled.

D-7.  SICU - Mechanical Systems

Personnel:  R. J. Arnzen, BCL

Support:  RR 00396

Within the past year the final phase of mechanical equipment procurement and installation has been completed for the Surgical Intensive Care Unit (SICU) at Barnes Hospital. This final phase has included the manufacture of patient monitors and other components relating to the computer monitoring system and its associated communication system. In addition, construction has included the central nurses'console with its chart recorder, electronic bays, and desk top monitors. Fabrication of these items has been carried out solely in the shop facilities of BCL and CSL.

Installation and functioning of mechanical systems has proceeded smoothly. It appears that all factors related to human interaction with these systems have been successfully executed. At the present time the ongoing work on these systems is strictly in routine maintenance.
The SICU video display system is now in operational use as an integral part of the SICU monitoring system. Two graphic channels and an alphanumeric channel are used for each of the four existing beds to display the ECG and arterial pressure waveforms in addition to dual rate flashing alarm messages and patient information. Although not now used by the SICU software, enough additional graphic and alphanumeric channels have been installed and tested to allow full display for an additional bed plus a remote trend display.

Prior to final installation, the system was run continuously for a number of weeks which allowed a few early semiconductor failures to be identified and corrected. As a result, the reliability after final installation in the SICU has been excellent.

A second video display system is nearing completion which will facilitate software checkout of changes destined for the operational SICU system. In addition, the second video display system will serve as a testbed for further experiments in display technology.

The development of a thermodilution technique for measuring the cardiac output of patients in the SICU has continued. A literature survey has been completed with particular attention directed toward the thermodynamic principles and errors involved in the thermodilution method.

This study defined a set of amplifier specifications. An instrumentation amplifier meeting these specifications has been designed and is being built. Initially tests will be performed in the dog lab. The temperature curves generated will be recorded on analog tape and cardiac outputs will be calculated off-line on a LINC computer at BCL. When an accurate and reliable system is established, it will be interfaced to the SICU monitoring system.
Most membrane oxygenators require two occlusive-pump systems to maintain a minimal positive pressure on the outflow side and prevent high blood pressures within the oxygenator. In the past, for safety, a recirculation line has been used, but this has required the venous pump to have a higher speed than the arterial pump. Shunting occurs through this recirculation line when venous return decreases. To obviate the need for open reservoirs and recirculation lines, control loops have been closed around the venous and arterial pumps. The arterial pump is controlled as described in (PR 8, D-12). This control circuit was redesigned for more reliable operation. Another control system was designed to control the venous pressure by controlling the venous pumping rate.

An intensive and exhaustive electrical survey was conducted on the power and grounding networks of the SICU in order to evaluate system integrity after sixteen months of operation. These networks were specifically designed to provide a low-noise and equipotential electrical environment maximally isolated from electrical activity elsewhere in the hospital. The tree-like grounding structure and associated insulated environment have been described previously (PR 8, D-9).

Ground loop impedances, potential measurements, leakage current measurements and isolation resistance measurement were obtained in each of the four patient rooms. The equipotential environment was observed to be within the 3 millivolt standard, prescribed by the NFPA standard. The ground loop impedances from any receptacle to any other ranged up to 0.28 ohms. Consideration of the ratio of resistances of the ground wire (#4
copper) to the neutral conductor (#12 copper) indicates a maximum resistance of approximately 0.04 ohms from patient available ground to the room reference ground which is within the 0.05 ohm constraint implied by the standard.\(^{(1)}\)

Isolation measurements of other available metal in the patient vicinity indicated maintenance of the insulated environment. Monitoring of the ground current in the trunk of the ground tree network revealed the only violation of the system to be through the protruding head of a finishing nail. This was summarily corrected.

E. Communications for Information Processing

E-1. Transmission Line Studies

Personnel: G. J. Blaine, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

Digital transmission requirements for the hospital environment encompass rates ranging from several transmissions per hour for trend data to mega-transmissions per second for computer transactions. Distances range from a few feet to several thousand feet.

Although line-of-sight optical transmission (E-2, E-3) is being developed, cable is currently the most readily obtainable communications medium for digital data transmission within the hospital complex. Multi-conductor cables permit high transmission rates and eliminate the necessity for parallel to serial conversion. Successful performance of a multi-conductor transmission scheme requires a systematic approach to the analysis of crosstalk.

As previously reported, (PR 8, E-5), a simple model has been developed to characterize both near-end and far-end crosstalk for multipair cable used in a single-ended configuration. Studies have been conducted to verify the model both theoretically and experimentally. A preliminary description of the model is reported in BCL Monograph No. 198.(1)


E-2. Digital Communication Systems

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W. R. Lang, M.S., Electrical Engineering

Support: RR 00396
GK 32239

A 0.96 million bits per second simplex communication system using near-infrared light as the carrier and Fresnel lenses as the antennas has been constructed. The system uses a bi-phase intensity-modulated light-emitting diode as the transmitter and a correlation detection receiver structure. The system is described in a monograph.(1)

At this time, the system has been partially tested over a 250 foot path between BCL and CSL. The encoding and decoding logic at the transmitting and
receiving ends of the system are presently being constructed. We expect soon to install the system between the Jewish and Barnes Hospitals, as previously described (PR 8, E-4).


E-3. Optical Communication System Theory

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Support:
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Communication systems employing modulated light appear to offer advantages in certain situations encountered in hospital complexes, particularly in those situations where there exists a line of sight between high data-rate terminals. As indicated above (E-2), we are gaining experience in building inexpensive optical communication systems. We are also engaged in theoretical studies of these systems to better understand their operation and limitations. Some papers and reports have been written which describe these efforts in detail. (1-3)


E-4. Teleprocessing for the PDP-12
Personnel: E. Van Patten, BCL
W. F. Holmes, BCL
Support: RR 00396

A utility program for maintenance of IBM System/360 Model 65 disc files has been written for the PDP-12 under its operating system, DIAL. To the user it is the same as the LINC Utility program (see E-5 for a more detailed description). An overlay structure is not required because of the PDP-12's larger core size.

The utility program includes a communications routine which is completely modular and may be incorporated into other programs. The calling sequence is the same as for the corresponding LINC communications subroutine. (1)


E-5. Teleprocessing for the Classic LINC
Personnel: E. Van Patten, BCL
Support: RR 00396

The LINC Utility program for maintenance of IBM System/360 Model 65 disk files has been completed (PR 8, E-2). By means of an option display and auxiliary displays the storing of data on disk files, retrieving from them, deleting members, changing member names, copying members, viewing a file directory, and feeding data into the input stream of HASP for batch execution, all are made fairly simple to do. Editing (GTPT) was not included because this is so easily done under LAP6; otherwise, these are the same functions that the PC-UTILITY program performs. Experience, however, led to adding some refinements. One time-saving feature (for the user) is the capability of specifying a file name and subsequently performing any number of operations on it without having to type it in again. There is, of course, the option of changing it at will. There is also the ability to print out a file directory on a teletype.

Error handling procedures have also been introduced, such that any request is retried three times (in the event of failure) before informing the user. Attempts are made to analyze the cause of the failure: e.g., repeated reception of EOT's following the sending of requests is clear indication of hardware failure; during a PUT (Replace or Copy) a Cancel
followed by the "file-is-busy" response to the resend of the request probably means that the file has been overfilled; etc. Explanatory scope displays indicate the logical place to begin looking for the trouble.

The program requires one overlay for GET and PUT operations. Retrieving from and storing into LAP6 files was considered, but discarded because of the added complexities and the feeling that the program would largely be used with data tapes. Therefore, data are retrieved from and stored into absolute block numbers, on either unit.

The revision of the meta command "FD" under LAP6 has also been completed, allowing the sending of either the binary or the manuscript working area. This program has also been adapted for LAP6 under the PC1200 and the Retrofit PC.
F. Cardiac Catheterization System

F-1. Clinical Experience with the Cardiac Catheterization System

Personnel:  B. R. Hieb, M.D., Medicine
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            J. M. Baker, BCL
            W. V. Glenn, M.D., Public Health Service
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            R. S. Rosenfeld, M.D., U.S. Air Force

Support:  Jewish Hospital
          Washington University
          RR 00396

The Cardiac Catheterization Laboratory (Cath Lab) System has been in use at Jewish Hospital since June, 1972. Over 130 cases have been analyzed since that time using a number of different versions of the system (see F-2). The response time of the system has been considerably improved in its most recent versions. It is now unusual for the computer to cause any delay during the catheterization procedure and in any case delays never exceed 5 seconds. Data collection and analysis is currently being performed by a cardiology fellow. Results are usually placed in the patient's chart before he leaves the catheterization laboratory.

Pressure analysis, based on human pattern recognition, has agreed well with results obtained by hand, as would be expected. Fick cardiac output determinations by the computers have agreed closely with those calculated by hand. It is anticipated that in the near future the computer system will become the primary system for cardiac catheterization analysis and the paper chart recorder will be used only as a backup system.

F-2. Modification of Cardiac Catheterization System

Personnel:  J. M. Baker, BCL
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Support:  RR 00396
          Jewish Hospital
          Washington University

The Cath Lab System has been revised to permit analysis of simultaneously collected left ventricular (LV) volumes and pressures. LV contours are recorded using a cine camera and the contours are then entered into the computer using a rho-theta position transducer. LV volumes are determined and pressure volume hysteresis loops and stroke-work displayed (F-3).
Long-term storage of data has been facilitated through the addition of a filing system. Entire catheterization records or catheterization summaries can be stored on a file tape for future reference.

An algorithm has been implemented to detect premature ventricular contractions (PVCs). Spurious duration values caused by PVCs are detected and ignored. The system also detects and ignores off-scale pressures.

F-3. Ventricular Cineangiogram Analysis

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Support: Jewish Hospital
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A computer program for the extended analysis of left ventricular angiograms has been under development for the past year. Goals of the system include: 1) Digital Storage of left ventricular contours, 2) Segmental analysis of the left ventricle, 3) Ability to analyze the temporal sequence of events, and 4) Convenient and clinically useful outputs. Cineangiograms are projected frame-by-frame on a frosted glass surface and traced with a rho-theta position transducer. The contour data is then compressed using "Freeman coding"\(^{(1)}\) to achieve an eight to one reduction in the amount of core space required to store the contour.

Contour analysis is performed using a grid with major axis from apex to mid-aortic valve and from one to fifteen hemiaxes perpendicular to the major axis. Ventricular wall motion is analyzed by observing the time course of the length of each hemiaxis. Ventricular volume is determined for each frame using the major axis length and the area of the contour.

Work is presently being done on programs to display the ventricular contours and results of other analyses in a clinically useful manner. Outputs will include: ventricular contours with grid and hemiaxis lengths, superimposed sequential contours, volume-time and pressure-volume displays, ejection fractions, cardiac outputs, and wall segment motion. Work has also begun on a system to permit on-line acquisition of raw cineangiogram data for automated pattern recognition by the system (F-5).

Clinical Evaluation of Ventricular Contours

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An assessment of left ventricular (LV) function is important in evaluating patients with cardiovascular disease. A computer program to evaluate LV function is being developed (see F-3). This study was undertaken to determine the amount of interobserver variation present in the commonly used subjective method for evaluation of LV function from cineangiograms. In this method the cineangiogram is projected like a motion picture. An experienced observer watches the sequence of contractions and from this forms an opinion as to the contractile properties of the left ventricle.

Twenty-six randomly selected LV angiograms (19 abnormal and 5 normal) were independently graded by three experienced cardiologists accustomed to reading angiograms together. The left ventricle was divided into seven segments (three anterior, three posterior, and one apical) and the motion of each segment was graded on a 1 (normal) to 3 (markedly diminished) scale. The overall ventricular function was graded on a 1 to 4 scale. At the end of the grading period, the results of each of the three independent observers were tabulated and subjected to statistical analysis.

For overall ventricular function, there was complete agreement between the observers in 12 out of 26 (46%) cases. In 23/26 (88%) of the angiograms, the overall ventricular functions correlated moderately well (Kendall's tau-B=0.64). There was, however, much more marked variation between observers in the assessment of the motion of individual segments. Observer variance was least in the evaluation of the mid-anterior and mid-posterior wall motion and greatest in the evaluation of the basal portions of the left ventricle. For example, in segment R-1 (anterior segment of the left ventricle nearest the aortic valve) the average tau-B was only 0.27. In contrast, for segment R-3 (midportion of anterior segment), tau-B was 0.63. Based on the findings of the study, it is concluded that there are significant differences between observers in evaluating ventricular function. This variance is particularly striking when attempts are made to estimate segmental function. This study clearly points out the need for more quantitative measurements of left ventricular contractility.
G. Mass Spectrometry and Biochemical Kinetics

G-1. Mass Spectrometer Analysis System

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A revised and expanded version of the original mass spectrometry computer system(1) (PR 8, G-1) has been under development, with many of the new facilities in use (G-2, G-3, and G-4). A new display program was written that provides for assigning and subtracting background spectra and normalizing spectra to a selected peak or the highest one. The processed spectra are displayed immediately, and are also available for plotting or file searches (G-5). A program was written to use the Versatec 1100A electrostatic printer/plotter for rapid plots of mass spectra. Complete spectra can generally be plotted in four to eight seconds, which is comparable to the speed at which data is acquired. The user can plot the last spectrum displayed or an entire set at once. The background spectrum assigned to the display can automatically be subtracted from each new spectrum before plotting. The spectra can also be normalized. The size of the mass scale is variable, with the plot automatically sectioned into several pieces if it is too large to fit on one section of plotter paper.

The mass spectrometry computer system is now used in five laboratories outside Washington University.


G-2. Multiple Ion Detection for Mass Spectrometry

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The computer controlled variable high voltage source developed last year (PR 8, G-2) has been improved in design and installed as a variable accelerating
voltage source for use as a multiple ion detector\(^{(1,2)}\). A new high voltage amplifier, the KEPCO NTC-2000, has replaced the BE-134. The new amplifier has a 2000 volt range and is wired in series with a fixed high voltage supply, the Fluke 415B, which is floating with respect to ground. The combination has a variable range of 2000 volts and a maximum of 4100 volts. Since the standard accelerating voltage of the LKB-9000 is 3500 volts, this range is more than sufficient, being limited at the high end by the danger of arcing, and at the low end by a severe loss of sensitivity due to lower ion energies. The circuit is not limited to the LKB-9000; it can be used with any magnetically scanned mass spectrometer with an accelerating voltage of 4100 or less, which is true for most instruments. The low voltage portion of the circuit can also be used to drive the other common class of low resolution mass spectrometers, quadrupoles. These instruments are controlled by a low voltage input which is linearly proportional to mass. The 15 bit D/A converter in our circuit has sufficient resolution and voltage range for such an application.

Multiple ion detection is a name applied to mass spectrometer control circuits that focus the mass spectrometer on a few selected masses, ignoring everything in between. This procedure is a much more sensitive method of measuring fragment ions at the selected masses than the standard method of generating a continuous scan over the mass range containing the ions. Since more time is spent monitoring each ion, the net signal is increased with improved sensitivity and precision. It is very difficult to change a magnetic field in sudden steps, thus multiple ion detection with magnetic instruments is accomplished by switching the accelerating voltage while keeping the magnet at a fixed setting. Since the mass in focus is inversely proportional to the accelerating voltage, only a limited mass range can be used at one setting of the magnet. We are currently operating with a 30\% mass range, but a 60\% range is possible with the LKB-9000 before a prohibitive loss of sensitivity is reached. Quadrupole instruments do not have this limitation; full mass range multiple ion detection is quite practical. An eight mass channel multiple ion detection program was written for the PDP-12. Exact masses are typed in and converted to D-A converter values that will produce the correct accelerating voltages.

Each second all eight of the mass channels are sampled, allotting 100 ms to each channel. After the accelerating voltage and ion signal are allowed to settle for 16 ms, the fragment ion intensity is sampled over 320 times, averaged, and stored. During the remaining 200 ms period in each second, any one of the eight mass channels is scanned by generating a small ramp voltage centered around the mass specified. The fragment ion intensity signal is sampled as the scan proceeds and saved temporarily for a display of the shape and position of the fragment ion (if any) at that mass.

The sampling mode operates simultaneously with two alternative displays, using the interrupt and the programmable clock to create 1 ms time slices. About 50\% of the time is devoted to either of the two displays. The first display shows the fragment ion signal obtained by the computer generated scan over one of the mass channels, a curve of intensity versus mass. This display is used to adjust the mass spectrometer slits so as to produce wide flat-topped fragment peaks to minimize the effects of drift,
which can be corrected simultaneously for all eight mass channels by adjusting the magnet focus knob. In practice, the instrument is used routinely for measurements above mass 500 with only occasional adjustments, generally between gas chromatograph injections. Drift has been a considerable problem at these high masses with commercial special purpose circuits for multiple ion detection. Thus the stability obtained in use by the computer circuits must be considered a substantial benefit in itself.

The other display shows time curves of the intensity signal for each mass channel. Three channels can be displayed simultaneously for comparisons. Two movable pointers on the display are used to select a peak for a printout of peak height, time and area. Background subtraction is also provided using a movable horizontal line on the display. A more elaborate data processing program has been developed for mass chromatograms with tape storage and output on an incremental or electrostatic plotter (G-3). A revision of the current program is nearly complete which will use both multiple ion detector data and mass chromatograms as an input to this processing program.

The multiple ion detector program has been used in two types of experimental situations. First it is used to measure ratios of fragment ion peaks much more precisely than is possible by magnetic scanning. These ratios are necessary for stable isotope tracer measurements, where the two peaks represent the same fragment ion differing only in the isotopic composition of one or more atoms within the fragment. Using the multiple ion detector, a tracer level of 1% deuterium has been detected with 2% standard error in a study of the rates of turnover of alanine and glucose in hypoglycemic children (G-6). The other basic use is for experimental situations requiring increased sensitivity. Quantitative measurements have been made of 40 picograms of myo-inositol, a substance found in nerve cells (G-9). A plasticizer has been found in heart tissue obtained post mortem from newborn infants that received intravenous feeding with an umbilical catheter (G-8). It is expected that this type of assay will become increasingly common, especially for studies of drug levels and drug metabolism, where the sensitivity and specificity are greatly needed.

The total cost of the circuit is $2,500. This compares with special purpose commercial circuits costing from $8,000–$25,000. Although a computer is required, this is already a necessity for full use of a mass spectrometer. Using the computer as a controller and waveform generator eliminates the need for expensive accessory circuits for the mass spectrometer. The same circuit could be used as a peak matcher for calculating fractional masses. Another application is producing continuous scans with increased speed and sensitivity by jumping electrically in one mass unit steps over the allowable mass range, thus monitoring every fragment ion.

A set of programs has been written to generate, display, and plot mass chromatograms. In this mode of analysis, a set of repetitively scanned mass spectra are sorted so that the intensity peaks at each mass are separately stored as a function of time or scan number. Thus the mass spectrometer acts like a gas chromatograph (GC) with hundreds of detectors, one at each mass. Mass chromatograms are a very useful method of screening data, by examining masses which are common to a subclass of all those compounds that might be found in the mixture under analysis. A typical mass chromatogram will have many fewer peaks than a GC curve of total mass or total ions. Another use is determining whether a particular GC peak contains more than one compound. If there is only one compound present, each mass chromatogram peak should have the same shape and position. The first program in the set generates mass chromatograms from a file of mass spectra, storing them in another file if desired. The second program displays freshly generated or filed chromatograms as a function of time. Up to four chromatograms can be simultaneously displayed for comparison purposes, with a different gain factor allowed for each mass channel because of the wide dynamic range involved. A computer knob permits rapid selection by mass of the entire set of stored chromatograms. When examining a single GC peak for purity, a normalizing mode will set the highest intensity of each chromatogram to 100%. If the GC peak is pure, all the mass chromatogram peaks should superimpose.

A printed output is available for quantitative analysis. Two pointers are used to select a mass chromatogram peak. The peak height, peak time, and the area between the pointers can be listed along with the mass. The pointers can also specify a sloping line for background (baseline) subtraction. Two alternative forms of area calculation are provided, the area between the peak half-height values, and the sum of a selected number of intensity values centered around the peak. These three methods of area calculation were devised in an effort to meet the problem observed by ourselves and others in multiple ion detector applications (G-2). Although the peak area should have increased precision relative to the peak height,
in fact it does not. This is probably due to problems with reproducibly setting limits on the area combined with the substantial relative contribution near the edges of a peak from a large and noisy background. This display and output program along with the plot programs described below are intended for use with multiple ion detector data, which is identical in format.

Any mass chromatogram display can be plotted exactly as it looks on either an incremental or Versatec 1100A electrostatic plotter. The current display can be plotted immediately or stored in a file as a special data structure for plotting later. In this way the user can set up a whole series of displays using the programmable knobs, storing each one without interrupting his preliminary evaluation of the data. The entire set of displays can then be plotted at a convenient time with no further attention. The data is stored in a format which is almost but not quite independent of its origin as a mass chromatogram. It is planned to use a graphic format completely independent of origin in the future, so that a single output program can be used for each display and plotting device now in use or that might be added in the future. The mass chromatogram programs could clearly be directly used for standard gas chromatography or liquid chromatography analysis. The new operating system (G-4) would support a variety of input programs such as on-line data acquisition, analog recorders, or LINC tape.

G-4. An Operating System for Acquiring and Processing Mass Spectrometry Data

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It has become apparent that further extension of mass spectrometry computer applications requires a filing system suitable for on-line data acquisition as well as off-line processing. Not only does the user need a method for keeping track of a large and varied set of data, but a number of fundamentally different data structures are necessary. These include mass spectra, mass chromatograms, various forms of condensed spectra for file searches, and graphic formatted output for display and plotting. The file and operating systems available for the PDP-12 or PDP-8, DIAL, AIPOS and OS, are not suitable to these applications, so an entirely new file oriented operating system was written. The system consists of a permanently resident file subroutine plus a set of file programs. The filing system is organized into a three level hierarchy, units, files, and file members. The lower unit numbers, 0-7 correspond to the eight possible tape units of the PDP-12. Higher unit numbers are assigned to sections of a disk system recently designed for the PDP-12 (J-3). A single subroutine is used for all tape and disk input-output, with the unit number specified in the subroutine call.
The unit number is examined by the subroutine, and the appropriate instructions issued for the tape or disk. Thus it is quite simple to adapt the system to various types of storage devices that may be used in the future. The only requirement is that the storage device be block oriented and have a block size of 256 or a submultiple.

Each unit contains a unit identification block, a file index, and a complete set of file programs. The unit identification provides a means for the user to keep track of his data tapes or disk cartridges. He can type in whatever information he wishes. Each file on the unit also contains an identification block for detailed comments on the contents of that file. The files are subdivided into members, one or more blocks long, identified only by the sequence number in the file. Each file has a name, a file code, and a write status. The file code is used to identify the data structure of the file members, such as mass spectra or mass chromatograms. Since a single program may use several types of data files it is very important that the user be prevented from making a mistake, especially if writing in files is involved. Mistakes are prevented by including a file code in each call to the file subroutine. This code is compared with the code of the file that the user selected, and if they do not match an error message is displayed and the program is terminated. Similar protection is provided by the write status. Reference files can be protected so that an attempt to write in one will fail.

In practice the user opens one or more files by name, assigning a letter to each for program use. The file letter, name, code, and write status of all opened files is displayed. When a file is opened, the file member index is read into memory so that all references to members of the file can be made without reading in the index each time. This is essential for high speed sequential access of file members on magnetic tape, where the tape must stay in motion during simultaneous tape access and processing. The system has been designed to work well with two tape units. In principle even a single tape unit could be used, since the programs are themselves organized into a file. This would not work in a practical sense because of storage and speed limitations, but does illustrate that the system is designed so that none of the operations are dependent on the number of units. All references are to files, which may be on one or several units. Disk units will speed up many operations; however, considerable effort has been expended on the programs thus far developed so that they are not dependent on a disk for efficient use. This effort is both time consuming and restrictive to program development, so full exploitation is planned for the disk hardware when it is completed. Once the appropriate files are opened, the user selects the processing program he wishes to use. The program then calls the files as needed by letter. If there is any mismatch of the letter, file code or write status, the program terminates and displays an error message. This is followed by reentry into the initial file opening program so that the user can try again.

The programs are in a separate and protected file, which can reside on tape or disk. Each major program is a file member. Within each file member, overlay sections are accessed by a block address relative to the first block in the file member. Thus the entire set of programs can be
relocated anywhere on tape or disk and new programs added, merely by moving the programs and creating a new file index. This method is not quite as convenient as filing each program by name, but in practice it takes very little time to add a new program to the system compared with the time spent in writing it. The system currently reserves 500 octal blocks for the programs in use and potential extensions. At present 172 blocks are used, and about 100 blocks are under active development.

A complete set of file programs is present on each unit to facilitate working with the files. There are displays of the file index and each file member index, access to the identification blocks, and provisions for making, changing, deleting, and copying files and file members. A data conversion program is available to convert data obtained from our original mass spectrometry programs into the revised format. Space is reserved for programs to convert other data forms which may be available on LINC or DEC tapes.

G-5. Mass Spectrometric File Searches

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Two mass spectrum file search programs have been developed for the PDP-12. The first program compares each spectrum in the file against the unknown spectrum using a difference taking algorithm that produces a match factor between zero and one (PR 8, G-3). The ten highest match factors and the names of the corresponding chemical compounds from the file are displayed when the search is completed, with an optional printout. The unknown mass spectrum is selected for searching using a display program (G-1). The user may first assign a background spectrum and subtract it from the unknown. He then normalizes the spectrum and proceeds to the search program. The search is not completely automatic. Some interaction is provided through the use of a mass filter. A selected set of masses as well as all those below a lower bound can be excluded from the search. This is important because many of the spectra in the file will represent compounds that were chemically derivatized to make them volatile using the same reagent employed on the unknown compound. These spectra will very likely all contain a few high intensity peaks that represent fragments from the derivatizing reagent rather than from the compound derivatized. Such fragments are well known, and their corresponding masses can be routinely eliminated from the search.

The current search file contains 187 mass spectra obtained from Dr. Sanford Markey of the University of Colorado Department of Pediatrics, who
is participating in a large scale screening program involving the chemical identification of compounds found in urine. Dr. Markey is assembling a larger file from various laboratories which will contain an estimated 1500-200 mass spectra of derivatized compounds found in urine. These include naturally occurring compounds, drugs and drug metabolites, and some compounds picked up from the environment. This file will make it possible for the first time to use file searches in a general way for biomedical applications. A large number of biochemical compounds are water soluble and need to be chemically derivatized before they are volatile enough for mass spectrometric analysis. The derivatization methods have only been applied extensively in the last few years, so that commercially obtainable files of mass spectra are nearly useless for biomedical applications.

The search file will be used to help diagnose metabolic lesions leading to neurological defects. A number of patients with such problems show abnormal peaks when extracts of their urine are subjected to gas chromatography. The mass spectrometer has been used during the past year to help identify some of these peaks (G-7). The extended file should be very helpful, since many common compounds are missing from the current one. However, preliminary work with the search program indicates that the correct compound will be at or near the top of the list of best matches if it is in the file.

Another type of search program has been written using the basic procedure of a method developed at the Division of Computer Research and Technology of the National Institutes of Health. (1) This procedure requires an active interaction with the user, who specifies the search parameters. A set of masses are selected for the search along with an intensity range for each mass. A molecular weight range may also be specified. The program then searches the file for all those spectra that satisfy the search criteria, and displays the total number found. If the number is large the user can tighten his criteria till only a reasonably small number of spectra are found that meet all the criteria. The names of these spectra can be displayed and printed. This search procedure is complementary to automatic file search techniques. The user employs all his chemical knowledge and laboratory experience to select just those masses that he believes represent ions that are significant and relatively unique to the compound. The NIH system has been set up on a time-sharing PDP-10 with remote input over dial-up telephone lines using typewriter terminals. A commercial system is being established for a General Electric time sharing computer at a cost of a few dollars per search. However, practical files for biomedical applications like the extended Markey file will fit nicely on the dual cartridge disc unit designed for the PDP-12 (J-3). Search times should be comparable to those on the large computers, since it is primarily limited by disc access times.

In Vivo Measurement of Rates of Gluconeogenesis and Glucose Utilization with Stable Isotopically Labelled Alanine and Glucose

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Failure to maintain normoglycemia is a common pediatric problem. Because of the reluctance to use radioactive isotopes in children, little quantitative data are available concerning the pathogenesis of hypoglycemia in these children. Therefore, we have developed microtechniques using intravenous infusions of stable isotopically labelled glucose and alanine (the principal gluconeogenic amino acid in the fasting state) to study glucose metabolism in children.

Measurements of stable isotopic enrichment in 50-500 $\mu$l of blood plasma were performed both by standard full-sweep magnetic scanning using the display oriented mass spectrometer/PDP-12 computer system with a tabular listing, and by the PDP-12 computer controlled variable accelerating voltage multiple ion detection system (G-2).

Because of the speed and precision (1.5 - 2.0% coefficients of variation between replicate measurements) of the multiple ion detection system, many samples can be analyzed in a single day's work. This represents a significant improvement over the rate-limiting nature of the long measurement times needed previously for stable isotope ratio measurements using magnetic scanning, and allows for processing the large number of samples that will be generated by routine clinical studies. Preliminary studies were carried out in a large number of dogs in order to verify the accuracy of stable isotope techniques compared to radioactive substrate turnover rates obtained simultaneously in the same animals. These investigations also demonstrated the ability of stable isotope tracers to monitor perturbations of the steady state induced by hormonal administration.

The above results, obtained with infusions of deuterium or carbon-13 labeled alanine or with heptadeutero- or 6,6-dideuteroglucose, were then applied to the study of glucose metabolism in man. Measurement of alanine and glucose turnover rates in 5 adults with stable isotopically labelled substrates gave values within the normal range obtained previously by other investigators using

-98-
radioactive tracer or hepatic vein catheterization techniques. Furthermore, two children have now been studied with infusions of alanine-d₄ and the results of these studies represent the first alanine turnover rates obtained in children. These latter investigations are the initial ones in an on-going project to delineate the pathogenesis of hypoglycemic conditions in childhood.

G-7. Identification of Abnormal Metabolites in Urine Derived from Patients With Inborn Errors of Metabolism

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The use of a gas chromatograph linked mass spectrometer has become an essential technique in the investigation of patients with inborn errors of metabolism. No other type of instrumentation allows such rapid evaluation of substances in biological fluids. Identification and quantitation of products of intermediate metabolism have allowed the verification of several suspected new diseases and have provided a means for the objective evaluation of therapy.

The configuration of the on-line computer equipment in this institution has unique advantages for this type of work. The programs for rapid visual scanning and plotting have allowed the evaluation of complex mixtures of compounds from both blood and urine. The evolving search program has provided immediate identification of commonly seen serum and urinary organic acids.

Present investigations by the medical genetics group using this equipment have included the following studies: 1) identification of two new errors of isoleucine catabolism; 2) Evaluation of tyrosine metabolism in liver disease and in strokes in children; 3) investigation of phosphoribosyllethanolamine excretion in bone disease; 4) development of a safe rapid screening test for ketotic hypoglycemia in children; 5) evaluation of fatty acid metabolism in patients fed medium chain triglycerides. Projects in the development stage include: 1) measurements of folic acid derivatives in biological fluids; 2) studies of placental transfer of drugs and neonatal metabolism.

(1) R. E. Hillman and J. P. Keating, "β-ketothiolase Deficiency as a Cause of the Ketotic Hyperglycinemia Syndrome," Pediatrics, in press.
We have used the multiple ion detection system (G-2) to measure the plasticizer 2-(diethylhexyl)-phthalate in heart tissue of newborn infants that have been supported by intravenous feeding using an umbilical catheter and have subsequently died. This plasticizer is very widely used in the United States. It has been observed as a component of serum from adults, is present in blood collected and stored in blood bags, and has been found in mitochondria of bovine heart. It is a neutral lipid and not readily catalyzed by esterases. Apparently it is taken up by membranes and held for a considerable time. Some toxicity is known; for example, beating heart cells in tissue culture stop beating in the presence of small amounts of the compound. We have observed the substance in dairy milk stored in plastic containers and detected it in the neonatal tissues at a low level. The work has not progressed far enough to be certain that contamination post mortem or in the work-up for analysis is not contributing; however, control samples do not contain the plasticizer. Considerably more work must be done to be sure, but it is possible that the newborns are getting the plasticizer from the catheters. We are not yet in a position to make a confident statement, however.

Toxicity aside, and toxicity of this plasticizer is subtle, not gross, the presence in newborn tissues is still another example of the pervasiveness of our technological environment.


Myo-Inositol is ubiquitous in living tissues of all kinds. It has one known function, as the precursor of a family of lipids known as the phosphoinositides which are also widespread as cell membrane components. Tissue levels of myo-inositol are quite high, attaining levels of up to 0.1 moles/kg in some
reproductive tissues and one tenth that in the nervous system. These levels seem high for a precursor-only function and many feel that myo-inositol has other functions, though these are not known. A sense of the importance of this substance is conveyed by the fact that no human cells have been found which can survive in tissue culture in the absence of added myo-inositol, in spite of the fact that many of these tissues are capable of producing the compound from glucose. One approach to learning more about the functions of this inositol is to study its distribution and concentrations at the cellular level in order to find the types of cells it is associated with. This requires great sensitivity in the analytical method used. Fortunately, myo-inositol is easily gas chromatographed as its trimethylsilyl (TMS) ether. Further, the TMS ether gives a good ion yield in the mass spectrometer, and some of the high abundance ions are quite unique to TMS inositols. This ion uniqueness plus the added parameter of chromatographic retention time, which itself has a degree of uniqueness, allows us to use the multiple ion detection (MID) system (G-2) with great effectiveness to measure myo-inositol in tissues.

Dried tissue samples are dissected from frozen brain sections and cut to sizes that are small enough to comprise a few neurons of a single type. The weights of these samples are about 10 nanograms. The dry sample is reacted with 10 microliters of TMS reagent containing about 200 picograms of deuterated myo-inositol. After 24 hours as much of the sample is injected into the gas chromatograph of the mass spectrometer-MID system as can be taken up into a microsyringe. Conditions are set so the TMS myo-inositol elutes from the gas chromatograph in 4 minutes without interference by other substances, and the ion channels which represent the deuterated and undeuterated (tissue) inositol are monitored. The data collected represents the relative amounts of tissue inositol compared with deuterated internal standard. Since the original amount of deuterated inositol is known, the amount of tissue inositol can be calculated. In this way we have begun to measure myo-inositol in tissue samples as small as seven nanograms and, by extrapolation, can see that one nanogram is within the scope of the method. A one nanogram sample could be a single large neuron, one or several cell nuclei (from large cells) or the cytoplasm surrounding these nuclei. A ten-fold increase in sensitivity seems within reach and thus serious mapping of the nervous system with respect to myo-inositol is an eventuality.

The precision of the method in its present state is notable: eleven samples of cerebellum ranging from 8-15 nanograms in weight were measured at 30.0 ± 1.0 millimoles/kg dry weight. This is a low level region; other areas containing three times this level of myo-inositol would be correspondingly easier to measure.

In principle, any substance that can be gas chromatographed can be measured by this technique including steroids, amino acids, sugars, fatty acids, and brain transmitter amines.
G-10. Chemical Derivatives of Carbohydrates Designed for Use in Mass Spectrometry

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The formation of derivatives of carbohydrates and other substances to increase their volatility so that they can be gas chromatographed affords an opportunity to control other parameters of the molecular structures. Two features that are desirable are, the formation of structures that fragment in simple, predictable ways in the mass spectrometer, and creating structures which give high ion yields to increase the sensitivity of the mass spectrometric method, especially for use with multiple ion detection (G-2). We have been preparing some boron derivatives over the last year, the basic structure of which is:

alkyl-B-O-R

O-R

These derivatives form selectively with polyhydroxy compounds such as sugars as well as other chemical types. A useful feature is that the derivatizing reagent has marked steric requirements and thus does not react with every compound containing active hydrogen. Thus only certain substances in a mixture are derivatized so that they can be gas chromatographed. This effects a cleanup of tissues at the derivatization stage, simplifying the analysis. Further, these derivatives readily lose the alkyl group in the mass spectrometer to give a high abundance ion which retains all the carbon and hydrogen of the parent compound, e.g., a sugar. The latter property is extremely important if stable isotope labels such as deuterium or carbon-13 are being employed in labeled compounds for metabolic studies. In fact, it seems that these are derivatives of choice for isotope tracer work such as the study of the rate of glucose turnover in hypoglycemic children (G-6).
G-11. Oxaloacetate and L-Malate Induced Exchange of Acyl CoA Esters on Citrate Synthase

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CA 03980
RR 00396

The citrate synthase-catalyzed exchange of the alpha protons of acyl-CoA esters with those of the medium, induced by oxaloacetate or L-malate, has been studied under conditions where there is no net chemical change. When D2O is used in place of H2O in the solution, it is observed that deuterium atoms are substituted for hydrogen atoms at the alpha position. After the exchange reaction is complete, the CoA esters are hydrolyzed, acidified and the acids extracted into ether. The acids are then converted to the methyl esters with diazo-methane and analyzed for deuterium content on the LKB-9000/PDP-12 mass spectrometer computer system. The multiple ion detection system (G-2) has also been used several times in these studies.

G-12. Biochemical Kinetic Simulation and Data Analysis

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Support:  RR 00396
AM 13332
GB 26483X
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A new method of data entry was incorporated into the kinetic simulation system (PR 8, G-4). The output from the Durrum-Gibson stopped flow apparatus for rapid kinetic analysis is always displayed as a time curve on the storage oscilloscope monitor. Before the FM recorder data acquisition system was installed (PR 8, G-5), these curves were routinely transferred to tracing paper as a permanent record. A considerable number of these curves contain data that was not satisfactorily fitted using paper and pencil methods. These curves can be traced into the PC with the rho-theta transducer and transmitted by telephone line to the IBM System/360 Model 65 for storage on disk (PR 6, E-4). A new program was written to transmit data between the PDP-12 and the Model 65 (see E-4 and PR 7, E-2). This program has been modified so that data transfers go directly between the Model 65
files and the files of the AIPOS operating system(1) under which the kinetics programs run. In this manner the older kinetic data curves can be easily entered for data fitting.

The AIPOS files are available to the FOCAL-12 interpretive program language that operates on the PDP-12. Thus the curve entry system is applicable to many kinds of data analysis involving continuous curves, so long as the data processing program is not too large or time consuming. Two utility programs have been written for the Versatec electrostatic printer/plotter. The first program allows AIPOS/FOCAL-12 files to be combined and plotted on graphs containing as many as eight curves. Thus a complete graphic input/output system is available for small scale data processing, using a display oriented interpretive language. FOCAL-12 itself is being modified to produce direct plots of FOCAL point displays on the Versatec. Another utility program samples four channels from an FM tape recorder, storing one thousand points from each channel. The sampling rate is under user control. The points can be displayed on the computer oscilloscope and plotted on the Versatec.

Since the completion of the current version of the kinetic simulation system(2), work centered around its use has involved 1) the continuation of kinetic studies of glutamate dehydrogenase in the presence and absence of purine nucleotide effectors(3); 2) a kinetic study of the cytoplasmic malic dehydrogenase; and 3) molecular weight changes of phosphofructokinase. The simulation system has been used to obtain kinetic parameters for these systems, particularly with respect to time dependent changes which are induced in the presence of ligands, and general cases for the use of the program have been discussed(4). It seems likely that such effects are important in the control of metabolic regulation by these and other enzyme systems.


(3) D. J. Bates and C. Frieden, "Full Time Course Studies on the Oxidation of Reduced Coenzyme by Glutamate Dehydrogenase", submitted for publication.

(4) D. J. Bates and C. Frieden, "Treatment of Kinetic Data III. The Use of the Full Time Course of a Reaction, as Examined by Computer Simulation, in Defining Enzyme Mechanisms", submitted for publication.
The sedimentation equilibrium analysis program (PR 8 G-6) was used to process data acquired from the analytical ultracentrifuge. Molecular weights were measured for prothrombin, a zymogen involved in blood coagulation, and four derivatives of prothrombin formed when prothrombin is activated to thrombin, the enzyme which catalyzes the formation of a visible clot.

A goal of the investigation was to determine the changes which occurred in prothrombin during activation. Relatively small changes in the molecular weight occur necessitating a large number of runs for good averages. Since five proteins were involved, the speed of the sedimentation equilibrium system was particularly useful.


H. Speech and Hearing

H-1. Random Access Programmer for Complex Audio Signals (RAP-I)

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            A. M. Engebretson, BCL and Central Institute for the Deaf
            J. R. Cox, Jr., BCL
            A. F. Niemoeller, D.Sc., Central Institute for the Deaf
            D. A. Ronken, Ph.D., Central Institute for the Deaf
            J. D. Miller, Ph.D., Central Institute for the Deaf

Support:    RR 00396
            NS 03856

The RAP-I system as described in PR 8, H-3 has been completed. The
system has been used in the research department of Central Institute for the
Deaf for several months to evaluate performance in an experimental setting.
It was found that the RAP system is extremely useful in an unexpected appli­
cation of measuring the spectra of short segments of complex waveforms such
as bird calls, group conversation or cocktail party noise. We are adding
the interface logic that will permit the use of RAP with a variety of per­i­
pheral devices (H-7) and laboratory computers in the research department.


Personnel:  M. D. Lien, BCL
            J. R. Cox, Jr., BCL

Support:    RR 00396

Development of a mathematical model of the mechanics of the cochlea has been completed.(1) As described previously (PR 7, F-18 and PR 8, H-1)
the model includes the solid mechanics of the basilar membrane, the effects
of viscosity, compressibility, and the three dimensional motion of the
cochlear fluid. The three dimensional problem is solved by using Green's
function techniques, thereby allowing for fluid motion of all wavelengths.

Results computed from the model are in rather good agreement with
measurements of Bekesy, Johnstone et al., and Rhode. Variation of the Q
of the basilar membrane displacement curve is in the right direction. Phase
characteristics are similar to those obtained from Mossbauer measurements,
cochlear microphonics, and auditory nerve fiber responses.

All previous mathematical models assumed either a long-wave or a short­
wave fluid motion in the cochlea, and none showed phase characteristics and
a variation of Q similar to those from experimental measurements. The present
model is quite suitable for use in our speech and hearing research.
Impulse responses for 100 points on the basilar membrane have been computed by using the IBM System/360 Model 65. They are first converted to a floating point format (H-8) and then stored in the PC partition. Finally, they are transmitted via the 360/LINC communications system(2) to a LINC tape for use in the PC-1200 in the study of speech perception (H-6).


(2) E. Van Patten, "360 LINC, LINC/360 Communications Subroutine" BCL Monograph No. 112.

H-3. A Speech Processing System

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
J. R. Cox, Jr., BCL
J. D. Miller, Ph.D., Central Institute for the Deaf
W. Fisher, BCL and Central Institute for the Deaf

Support: RR 00396
NS 03856

The equipment for a relatively sophisticated speech processing computer system has been assembled. The system makes use of a PC-1200 computer, various macromodular systems, and special hardware that has been built at BCL. The rationale for the system and some of the preliminary work has been described (PR 8, H-2).

The system now includes: an 8-channel analog to digital converter, a programmable crystal clock, a graphic input tablet (H-9), a high-speed oscilloscope display unit (H-4), a 2-channel digital to analog converter, and a macromodule-computer interface (J-4 and PR 8, J-13).

To increase the arithmetic capacity of the system, a floating point processor (H-8) was added to the computer. The floating point processor can perform approximately 100,000 operations per second with an accuracy of 1 part in 32,000. The range of the floating point number system is approximately $10^{-36}$ to $10^{+36}$.

The addition of the graphic input tablet and output display makes it more convenient to manipulate graphical data and to interact with the system. The tablet is interfaced directly with the computer. The oscilloscope display is driven by a self contained macromodular controller. The computer is therefore freed from the display task and need only modify the contents of the controller memory. This makes it possible to generate elaborate displays without excessive flicker and perform complex arithmetic operations simultaneously. The graphic display and input tablet are compatible in the sense
that the coordinate systems and working areas are the same. The working area is about 10 inches by 10 inches. The resolution of the tablet and display are .01 inches and .0025 inches respectively.

In the near future a 50 million bit disc unit (J-2) that is compatible with the RAP-l system (H-1) and a digital plotter will be added to the system. This should complete the first stage of equipment design and installation.

H-4. A Macromodular Graphic Display Controller

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf

Support: RR 00396
NS 03856

An experimental display controller has been built to test some ideas about an appropriate display for the speech system (H-3). The experimental version is also serving as an interim controller so that software development can proceed. Two programs have been written to date that would not have been possible without a free-standing, buffered, display controller. One is a real-time speech analysis program (H-6) that displays an acoustic tube model of the vocal tract and speech spectrum. The real-time analysis left little time for display purposes. The second program is an interactive speech synthesis program (H-5) that uses an elaborate display of speech parameters that can be modified via the graphic input tablet. The storage scope of the computer could not be used since single points of the display are continually modified.

At this time the display controller has three display modes: a line display, a function display, and a character display. Control codes at the beginning of each display sequence specify the display mode. A fourth code is used to terminate the display scan. Two additional bits are assigned to each control code to cause portions of the display to blink or to be turned off.

Display sequences are loaded from the PC into the controller memory (4K by 12 bits). Each of the control codes is executed in sequence starting at location zero. When a terminate code is encountered, the display scan returns to zero. Once the controller memory is loaded, the PC is free for other tasks. An interlock macromodule permits the controller memory to be updated asynchronously by the computer. In addition, data that is stored in the memory as part of the function display sequence can be accessed by the computer. This eliminates the need to store the same data both in the computer for computational purposes and in the controller for display purposes.
H-5. A Speech Synthesizer

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J. D. Miller, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

The first version of a system to generate speech-like sounds has been completed and is now under test. The program Speaker, the heart of the system, runs in the speech processing system (H-3), digitally simulating the vocal tract under control of parameters entered by the user as arbitrary curves via the graphic tablet.

A three-format speech model is used enabling us to generate speech-like stimuli with systematic variation of certain important parameters. For example, a set of stimuli can be generated in which only the initial transition of the first formant is changed. The program displays the center frequency and bandwidth of each of the three formant filters, the pitch period, and voiced and unvoiced excitation as a function of time on the oscilloscope display. These parameter traces can be sketched in by using the graphic tablet (H-9) and the resulting sounds can be synthesized and listened to within seconds. Speaker has been designed with a high degree of parameterization and modular organization in order to facilitate further development.

H-6. A Real-Time Speech Analysis System

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Support: RR 00396
NS 03856
ARPA SD-302

A sixth-order linear predictor system has been implemented that displays the speech spectrum and vocal tract area function derived from the linear predictor parameters. To achieve real-time operation it was necessary to use macromodules to store the incoming speech samples and to calculate for each pitch period of the speech wave its covariance matrix (equivalent to the autocorrelation matrix since speech has zero mean). The speech processing system (H-3) was used to invert the covariance matrix to obtain the linear predictor parameters and to compute the speech spectrum and an equivalent vocal tract area function. These functions are displayed in real-time on a high-speed oscilloscope display that is driven by a macro-modular display controller. Additional features were implemented from time
to time with macromodules to display the linear predictor error function, to display the reconstructed speech wave, and to compute the amplitude histograms of the linear predictor error and the original speech wave.

As has been reported in the literature, the linear predictor method becomes unstable under certain conditions. One such condition occurs when the covariance matrix becomes singular and the inverse matrix is undefined. A second condition of instability can occur when the computed poles of the transfer function fall on or outside the unit circle in the z-plane. In the most recent version of the program special procedures were implemented to correct for these two conditions. The procedures chosen were relatively simple so that the additional computational time would not be excessive. In the first case, the elements of a diagonal matrix were tested and if the value of a diagonal element was "vanishingly" small, the order of the model was reduced until the diagonal matrix did not include that element. This prevents singularity since the diagonal elements are the only divisors in the computation of the matrix inverse. In the second case, a bound was placed on the ratio between two adjacent sections of an equivalent acoustic tube model of the vocal tract forcing all poles to fall within the unit circle. Although these corrective procedures improve the stability of the system, the additional computation tends to detract from the inherent simplicity of the basic linear predictor method.

As a measure of system performance, amplitude histograms were computed for the original sampled speech wave and for the linear predictor error function. The entropy (data rate) was computed from the histograms. Values obtained for the ratio of error entropy to speech entropy varied from .88 for the vowel /e/ to .72 for the vowel /o/ for two male talkers. For fricatives such as /s/ and /sh/ the ratios were .99 and .98 respectively.

The above described work is part of an ongoing program to investigate various methods for analyzing speech. Our primary goal is to develop methods that have application in the general area of speech research and in more specific areas of clinical methods and training aids for the deaf. A typical example of a system for use in the classroom is one that can extract various parameters such as pitch period, frication, or nasality from the speech wave to provide feedback to the deaf child learning to talk.

The linear predictor method and similar statistical methods are attractive because the speech wave can be efficiently reduced to a set of parameters that are uniquely related to the vocal tract. We have begun to study the correspondence between the acoustic tube model derived from the linear predictor parameters and the cross sectional area of the vocal tract. Acoustic horns have been constructed with inside shapes that approximate the vocal tract configuration for several vowels. Sounds generated with these horns will be analyzed and a comparison made between the computed area function and the actual area function of the horn. In addition, the excitation waveform can be varied to study the effects of excitation on the area function calculation.
H-7. **RAP-1 Peripherals**

**Personnel:**  
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**Support:**  
RR 00396  
NS 03856

Several peripheral devices have been built for use with RAP-1 (H-1). These are an operator keyboard, a paper tape reader, and a subject keyboard. The peripheral devices operate through an interface that contains a small memory that can store up to 16 items. Each item consists of a starting track number and the number of tracks occupied by a particular sound stored on the disc.

The operator keyboard contains a numeric key array for numbers 0 through 9 and six function keys. The function keys correspond to interface control functions such as load "track number" register, load "number of tracks" register, store item (the contents of these registers) in item memory, and play item. The operator keyboard is intended to provide a means for loading the item memory and in some psychological experiments to enable the experimenter to control the stimulus presentation.

The paper tape reader is interchangeable with the operator keyboard (numeric and function codes are identical) and is intended for use in experiments that require a larger variety of different sounds. The paper tape reader can be used to load the item memory. In addition, for experiments involving more than 16 sounds, tapes can be prepared to control the stimulus presentation directly. Programs are being written for a PDP-8S computer that will generate tapes for the random presentation of standard word lists for speech discrimination testing.

The subject keyboard consists of a 3 by 4 array of keys that are assigned to each of the 12 locations in the item memory. One of 12 items (sounds) can be played by pressing the appropriate key. The subject keyboard is intended for use in psychophysical experiments where sounds are to be compared in various ways. For example, the task might be to rank 12 different sounds in order from most pleasant to least pleasant. The subject can repeatedly listen to and compare all of the 12 sounds until he is satisfied with the ranking.

A fourth peripheral device, a modified Bell and Howell Language Master, is under construction. The modified Language Master will be interchangeable with the paper tape reader and operator keyboard and will be used to load the item memory and to select items to present to the subjects. The item information and control codes will be recorded on the Language Master cards in digital form.
H-8. A Floating Point Processor

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
D. J. Bax, BCL

Support: RR 00396
NS 03856

The floating point processor is a self-contained unit that communicates with the PC-1200 via the I/O bus. The basic parts of the unit are the control register, address register, origin registers (for extended addressing), the arithmetic unit, the floating point accumulator, and the PC interface. The arithmetic unit, which has the capability of the four basic operations of add, subtract, multiply, and divide, was designed as a class project by students in J. R. Cox's course, Digital Computer Design offered in the Spring of 1971. Additional control and interface logic was added to adapt the arithmetic unit to work with the PC and the operations load, store, float, and fix were added to the four basic arithmetic operations. Floating point numbers are contained in two contiguous locations in the PC memory and are represented as an 8 bit exponent and a 16 bit fraction. Typical execution times for floating point operations are about 10μs per operation with the time divided about equally between PC memory cycles and the arithmetic operations.

Both deferred and indexed or nonindexed indirect modes can be used for addressing the operand. A deferred origin register and four indirect origin registers provide extended addressing for up to 32K of memory. The indexing operation is performed on the effective address (includes the indirect origin registers) so that data arrays occupying more than 4K locations can be accessed conveniently.

Each of the eight possible floating point operations are represented by a 3 bit control code with a fourth bit to designate indexed or nonindexed addressing.

To minimize IOT instruction overhead, any number of floating point operations can be executed by one IOT instruction. The operation codes and index bits are packed three to a 12 bit word in memory and followed by three arguments (an address for each operation). This sequence can be repeated until a given calculation is completed. A deferred address fix operation terminates the floating point IOT instruction.
H-9. A Graphic Tablet

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
D. J. Bax, BCL

Support: RR 00396
NS 03856

A graphic tablet has been interfaced to the speech processing system (H-3) to facilitate the use of graphical input. When used in conjunction with the display scope, a stylus can be used to move a cursor around, to select program options from a menu displayed on the scope and to enter data into the computer by free hand sketching or tracing. The graphic tablet chosen is similar in operation to the Rand tablet. An array of flat coils embedded near the surface of the tablet is sensed by a pickup coil in the tip of the hand held stylus. The position coordinates of the tip of the stylus are encoded as 10 bit values that are available from the tablet on parallel data lines. Additional bit lines are provided to indicate pen proximity to the tablet surface, pressure applied to the stylus tip, and the state of various function switches.

The coordinates of the stylus and the additional control bits are stored in a 24-bit interface buffer at the end of each encoding period (450 μs). By executing an appropriate IOT instruction, the contents of the buffer register are transferred to two locations in the PC memory following the IOT instruction. The 10-bit coordinates are left-justified to be compatible with the display scope and the PC storage scope coordinate systems. The least significant two bits in each location are assigned to pen pressure, pen proximity, and two function switches.
I. **Health Care Technology**

I-1. **Patient Data Base and Encounter Summaries for the Medical Care Group**

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J. Zimmerman, BCL

Support: HS 00074  
HSM-110-72-267

We are using **MUMPS-PC** (I-3) to capture a data base on all patients who obtain ambulatory medical care with the Washington University Medical Care Group (MCG). These patients comprise the enrolled population of about 1,800 prepaid patients (PPP) eligible for care at any time since June 1, 1972, and the registrant population of about 1,300 fee-for-service patients (FFS) receiving care since January 1, 1973. We have continued to capture a summary of each patient's encounter (PR 8, I-3), but have developed more efficient programs and data-handling techniques than those in operation last year; these innovations are based on a philosophy of ease and speed in data entry.

Each patient is assigned a unique 6-digit ID number; the first digit codes the method of payment; the second digit codes the patient's sex, and the last 4 digits are sequentially-issued numbers. A base-10 check digit is entered at the end of the 6-digit number during computer entry of data. This allows computer checking of possible invalidity of the ID number. The ID data on each patient are stored at a unique node in a data file, the node being determined by the ID number. The data for one patient are stored in a 21-character string, and the data comprise the birth date, age group at current time, group policy, sex, date of last visit, relationship to subscriber, primary physician, total number of visits to date, family size, employer, entry date (subscribers only) and ID number of associated subscriber (non-subscribers only). Such ID data must be entered for any patient before their encounter-form data will be accepted by the system. We are in the process of collecting for each patient their name, race, marital status (subscriber only) and entry and exit dates.

The encounter data are essentially those collected in last year's experimental setup. The structure of the data file is radically different, however: these data are stored in a separate file, each node of which depends uniquely upon the date of the encounter and the patient's ID number.

A very flexible **MUMPS** program has been written for entry of the encounter-form data. This program utilizes some of the special features of our Beehive terminal (such as an addressable cursor) to provide the terminal operator with the capability for complete or partial duplication of encounter-form data for the same or another patient on the same or another day. This avoidance of repetitious data input is very important in speeding data entry. Associated programs allows for easy changing of any stored ID or encounter-form data.
Concurrent with the entry or change of any data, a hardcopy record is printed out on our Centronix printer. This is done for ID and for encounter data, and is very useful in error-checking the freshly-stored information.

Many different print-outs are produced at need. Useful listings of selected ID data have been produced, ordered either numerically (by ID number), or by employer and alphabetically (by patient or subscriber name). Specific print-outs for daily health-care management include monthly lists of patients due for annual check-ups, and lists of patients eligible for Medicare.

Any encounter of any individual on any day may be inspected; data may be printed for all encounters on any one day or set of days. Monthly summaries are produced of the total number of patient appointments each day of any month; these totals are broken down by health-care-provider type (e.g. internist) for kept appointments, and by appointment status (e.g. patient did not keep appointment; doctor did not keep appointment) for unkept appointments. We produce a modified subset of the monthly Population and Utilization Densen Tables(1).

All of these data are very useful to the administration of MCG, in helping them to understand the characteristics of their population (particularly age, sex and family-size distributions) and the utilization characteristics of this population (number of visits made to each health-care provider, age and sex dependence of visit rates, etc). During the next three years, the number of patients served by MCG will increase by about an order of magnitude; the data summaries we are providing to MCG contain much pertinent information on which to base their expansion plans.

In the immediate future of this MUMPS application, our primary intention is to improve the validity of the PPP ID data base, with particular regard to the dates of entry to and exit from MCG. We must establish an efficient mechanism for information exchange with the PPP third-party carriers (at present, there is frequently a lag of months or years before we receive information about an addition to or loss from the enrolled population), and we must prevent all avoidable deficiencies in the data base. Also, we will reconsider the data stored in the data base, in terms of their usefulness and their validity. Then we will complete the utilization-rate Densen Tables and finally the Financial Densen Tables.

I-2. Internship Program

Personnel: J. Zimmerman, BCL
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Support: HS 00074

Following the success of the 1972 Health Care Technology Internship Program (PR 8, I-1), a similar program was organized this year for our second group of Health Care Technology students. The primary goal of the twelve-week internship program is to allow the students to gain a familiarity with many different aspects of medical care by seeing health-care delivery systems in daily operation, and by discussing these systems with the appropriate medical, technical, administrative and other personnel.

A highly-organized visit schedule was devised for the first six weeks of this twelve-week program. Nine students (one doctoral candidate and eight master's-degree candidates) were grouped into pairs and trios, and made visits which lasted between one and three days. The many institutions visited include Barnes Hospital, Blue Cross, City Hospital (Starkloff), Children's Hospital, Christian Hospital Northwest, Deaconess, DePaul, Firmin Desloge, Jewish, Mallinckrodt Institute of Radiology, McDonnell Douglas Automation, Meditech, St. John's, St. Joseph's, St. Louis County, St. Luke's, St. Mary's, the V. A. Hospitals (Cochran and Jefferson Barracks), and the Yeatman Clinic.

The visits were scheduled for Monday to Thursday of each week. Each Friday, the students and staff held a group meeting at which the students described and discussed their activities for the week, and handed in written reports on their experiences. For each of the six weeks, a set of main topics was chosen to serve as a common basis for discussion: In the first week, the topics were ECG and EEG analysis, and the operation of cath labs, stress testing and heart stations; in the second week, admitting and emergency-room operations were studied; in the third week, surgery, ICU and radiation therapy were investigated; the fourth week was spent primarily in clinical laboratories and pharmacies; in the fifth week, medical records and clinics were studied; finally, in the sixth week, data processing and information systems were investigated.

These first six weeks were very successful in exposing the students to a wide range of health-care delivery locations. Each student is spending the second half of the Internship Program on an in-depth study of a particular location which especially interested him during the first half of the program.
I-3. MUMPS Development

Personnel: W. E. Long, BCL
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B. F. Spenner, BCL

Support: HS 00074
RR 00396
Jewish Hospital

During this year, several new versions of single-user MUMPS-PC (PR 8, I-2) were released. The extended capabilities of these new versions included interfacing with fixed-head and moving-head disk systems, use of twin-O's (different extended-addressing hardware), and an experimental Macromodular MUMPS assembly (the latter is described in I-6). New input-output devices interfaced with MUMPS-PC include a Centronix Printer and a G.E. TermiNet 300 printing terminal. A course of MUMPS instruction classes was taught in the Fall, and another such course is planned for this year.

Our versions of MUMPS have evolved to be heavily dependent on our primary terminal, the Beehive III A. With the acquisition of, and search for, other terminals (both printing and CRT) we have become aware of the gross divergence of the Beehive (and hence our MUMPS) and of other terminals from the American National Standard for Information Interchange. We are currently attempting to conform our equipment and our MUMPS more closely to the national standards.

A moving-head-disc version of MUMPS is in active operation and used routinely for the applications in the Medical Care Group (I-1). The twin-O system has been installed at Jewish Hospital, where it will be used to establish an information system for the Department of Cardiology; the information stored will include patient demographic data, procedures performed, and test results.

We collaborated with Artronix in the development of their multi-user MUMPS system. This system is currently used in the Division of Radiation Oncology (A-4). Within the coming year, a similar system will probably be maintained and modified within BCL for use of the Biomedical students and the MUMPS-class attendees.

I-4. MUMPS-Data Organization

Personnel: J. Zimmerman, BCL
S. R. Holmes, BCL

Support: HS 00074

In the course of using MUMPS (especially in our major application described in I-1) it became clear that considerable care was required to
optimize data organization, in order to minimize the space taken up by the
data and minimize program execution time. This is true both of local data
(stored in core, in the symbol table) and of global data (stored on mass-
storage in a tree-like file).

Local-Data Storage. During execution of a MUMPS-PC program, signifi-
cant time is spent on symbol-table searches for local data—so much time is
spent that some hardware improvements are being developed to improve the per-
f ormance of this and associated activities. Meanwhile, a useful re-
duction in program-execution time (in an extreme case the execution time
is halved) may be achieved by suitable symbol-table organization and handling.
We deduced various rules of thumb, based primarily on some execution timings
of different commands and functions, and partly upon discussions with MUMPS
programmers who use other systems. The most important rules are:

1. At the very start of the symbol table, put all FOR-loop index
variables;

2. Next put the most frequently accessed variables;

3. However, if there are any variables which are frequently reset
to expressions of different lengths, place these at the end of the symbol table.

Global-Data Storage. In order to minimize the amount of storage space
required for global data, we have studied the design of global files. The
number of disc accesses required to reach a datum should also be minimized to
reduce total program execution time. By a common-sense approach to global-data
data organization we derived various rules, the most useful of which are:

1. Try to fill blocks as completely as possible, especially those at
the first levels of a global tree;

2. The first levels should usually contain subscripts and pointers,
but negligible data;

3. Design each global tree to have as few levels as possible, and
so minimize the number of vertical searches made in the tree while concurrently
making a reasonably small number of horizontal searches (This is achieved quite
effectively by organizing a global into well-filled blocks, by appropriate
subscript assignment, and also by splitting a global array into several dif-
ferently-named global arrays.);

4. Use various data-compression techniques (e.g., coding limited sets
of items with single characters) and thus reduce the number of characters
stored.

We are developing a more sophisticated approach to this "space and
time" optimization, by setting up a group of equations which describe the
storage space and access time. We hope these equations will allow a more ele-
gant approach to the design of global files.
I-5. MUMPS Design Manual

Personnel: W. E. Long, BCL  
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Support: HS 00074  
RR 00396  

The "MUMPS-PC Design Manual", Monograph 172, was released during the year. This manual is meant to serve as a maintenance manual for MUMPS-PC. It is also intended as a guide for implementation of MUMPS at other installations on machines other than the PC.

I-6. Macromodular MUMPS Character Processor

Personnel: W. E. Long, BCL  
P. S. Berger, BCL  

Support: HS 00074  
RR 00396  

During the year an experimental Macromodular MUMPS was set up. Character-processing routines were removed from the interpreter and implemented in macromodules. The interpreter uses four character pointers; each pointer stores the effective address of a part of the user's partition. The pointers store the address of a location containing respectively the user's source code, the string accumulator, the execution stacks and the symbol table; the implemented routines use these pointers to load or store indirectly (indexed or non-indexed) a 6-bit character. Other routines implemented in the character-processor experiment were branches conditional on the type of character (e.g., alphabetic, numeric, a comma, etc.) loaded. The remainder of the interpreter continued to operate in the PC-1200.

The resulting changes in the execution times were as follows:

<table>
<thead>
<tr>
<th>Software</th>
<th>Macromodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Load character</td>
<td>92 µs</td>
</tr>
<tr>
<td>Store character</td>
<td>101 µs</td>
</tr>
<tr>
<td>Branch on alphabetic</td>
<td>75 µs</td>
</tr>
<tr>
<td>Benchmark program</td>
<td>3.35 sec</td>
</tr>
</tbody>
</table>

The Benchmark program was one move in the game of NIM.

Thus, the experiment showed that specialized hardware to perform character processing would be an excellent starting point for increasing
MUMPS-PC execution speed. The time taken by transfers between the macro-modules and the PC-1200, however, was substantial and future specialized hardware will use a more efficient method for such transfers.

I-7. Patient Waiting Times and Doctor Utilization in a Medical Center—A SIMSCRIPT Simulation

Personnel: E. L. Morofsky, BCL
Support: HS 00074

A model incorporating the arrival and servicing of various patient types in a medical-center setting has been implemented in the SIMSCRIPT simulation language. The model generates a pattern of patient and doctor arrivals, processes patients at a reception desk before routing them to their physician and handles walk-in patients, cancellations, no-shows, and emergencies. The behavior of the system is studied as it operated over time. Arrival times of patients and doctors are given by random samples of pre-selected distributions. Arriving patients may have appointments, or be walk-ins with their own previously assigned physician, or be new patients requiring assignment of a physician. Appointments may be cancelled or patients may simply fail to arrive (no-shows). Open (including cancelled) appointment slots may be filled by new patients as they arrive. Emergency patients are given priority at the reception desk and receive the immediate attention of a doctor. Waiting queues are associated with the reception desk and each doctor. The reception-desk queue is a FIFO, while the doctor queues are ranked according to appointment and arrival time. Telephone calls may interrupt personnel at the reception desk. The input data are primarily: the number of doctors with associated schedules and appointments; the number of old and new walk-ins; emergencies; cancellations; no-shows; phone calls; and the distributions from which the occurrence times are chosen. The output data, calculated as the simulation progresses are:

1. the mean, variance and maximum patient waiting times at the reception desk and in doctor queues.

2. the mean, variance and maximum of queue lengths.

3. doctor percentage of busy time and total time to service patients.

The general objectives of the simulation are to determine the relative effects of the input variables on the output data, and to indicate which combinations of inputs and resources can keep doctors busy and handle expected
patient loads within acceptable waiting times. The model is useful in predicting the maximum capacities of various types of patient loads for a given facility, staff requirements for expansion, the impact of doctor lateness, the effects of adjusting appointment intervals or encouraging more walk-ins or emergencies and the consequences of penalizing late arrivals by decreasing their priority in the doctor queue. The design of automated protocols could also benefit from a knowledge of the associated queueing times. Some preliminary results for a hypothetical center are given in BCL Monograph No. 215, together with program listings and documentation.

I-8. Establishment of Computer Assisted Instruction Programs at the Medical Center

Personnel: R. H. Greenfield, BCL
          L. Smith, M.S., Medical Library
          J. Zimmerman

Support:   HS 00074
           LM 00106
           RR 00396

In July, 1972, BCL acquired access to the Massachusetts General Hospital's (MGH) Computer Assisted Instruction (CAI) programs via the Lister Hill National Center for Biomedical Communication's network. This was done primarily because of our interest in MUMPS, the programming system used to support MGH's CAI programs. BCL demonstrated the system to various departments in the Medical Center. This generated little response except for the Department of Neurology and the Medical Library. Neurology found one of the programs COMA, to be quite a good teaching tool. The Health Care Technology students taking BMED 549 (Engineering Aspects of Health Care Delivery) used the programs and commented on their experience. Many of the students' comments were relayed to MGH which has used them to correct and to improve their programs.

In December, the Medical Library made the CAI programs available to its patrons on a terminal in the Library's Main Reading Room. The Library organized extensive publicity to medical students and staff, and this greatly increased the interest in and usage of the programs.

In February we became "trial users" of the Lister Hill CAI programs, and therefore obligated to provide bimonthly reports to Lister Hill (three such reports have now been sent to Lister Hill). Also in February, we requested access to the programs provided by the University of Illinois at the Medical Center and by Ohio State University in order to provide other material to our medical students and personnel, and to allow us to compare the MGH programs with some others. We immediately found that all three

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systems were so different that changes had to be made to our terminals (G. E. TermiNet 300's) before they could be used on all three systems. A report, "Comments Regarding Access to the NLM Computer Assisted Instruction Network" was prepared discussing differences between the three systems and sent to Lister Hill and to the three institutions supplying the CAI programs.

As well as finding differences in system hardware and response characteristics we found many differences in educational philosophy, technique, and emphasis. The Library has been monitoring student response via questionnaires and informal discussions. Response has been for the most part enthusiastic, since many programs complement material covered in class and the mode of instruction is different and interesting. This is especially true for second and third year students. The students enjoy working in groups of two to four, and energetically discuss the computer programs.

Our monitoring of the offerings of the three institutions and of student usage shows continual expansion of educational areas as well as improvements in older programs, systems performance, hours of availability and human back-up. This plus the variety of interesting material presented shows that such programs have a useful place at a medical center.
J. Other Applications of Computers

J-1. Shift Register Memory for HERO

Personnel: R. N. Tatum, BCL
          L. J. Tolmach, Ph.D., Radiology
          B. F. Spenner, BCL

Support: RR 00396
        CA 04483

The broadcast system(1) initially designed for the automatic drug injection system (PR 8, J-12) used a loop of paper tape as the source of broadcast information. This tape loop proved to be an unacceptable source of information since the paper tape would mechanically fail after approximately eight hours of operation. For this reason, the paper tape system has been replaced by a system which uses an MOS shift register as the source of broadcast information. The initialization of the MOS memory is provided by the paper tape reader, but once initialized, the MOS memory operates independently of the tape reader. The MOS memory is capable of storing 4096 nine-bit characters which exceeds the maximum required broadcast information capacity.


J-2. Design and Implementation of a Disc Controller

Personnel: B. F. Spenner, BCL
          N. A. Mullani, BCL
          R. L. Hill, BCL
          J. G. Green, BCL

Support: RR 00396

Early in 1972 a need was realized for a fast access mass storage device which could be connected to the laboratory's small computers. The mass storage device chosen for this application was an IBM compatible 2315 disc drive. The 2315 compatible disc file was chosen because it provides an average track access time of less than 40 ms and a storage capacity of approximately 25 megabits.

Fulfilling the need for mass storage provided an opportunity to establish a compatible data medium for all of the laboratory's various computers. Commercially available disc controllers could not meet this requirement for compatibility and therefore a controller was designed at BCL.
The design was completed last year (PR 8, J-15) and five disc controllers have been constructed, tested, and put into service this year. Three controllers have been connected to PC-1200's, one has been connected to an Interdata Model 80 (C-15), and one has been connected to a PDP-12 (J-3). Pertec Model 30 disc files are used with all but the Interdata system which uses a Diablo Model 33 disc file.

The disc controllers have proved themselves to be extremely reliable. Only two part failures and one read checksum error have occurred over a six month period.

J-3. PDP-12/PERTEC Disc Controller Interface

Personnel: P. S. Berger, BCL
W. F. Holmes, BCL

Support: RR 00396

An interface has been designed to allow recently constructed disc controllers (J-2) to operate with the PDP-12 computer. The interface design was guided by the intention of using as much of the DEC RK8-E disc software as practicable to maintain the greatest functional similarity between the two systems. Insofar as possible, the RK8-E instruction set was used, and some of these instructions were augmented to provide greater flexibility and to take advantage of certain disc controller features not available in the RK8-E system. The features include addressing a second platter in each disc unit, expanded controller status reporting and the ability to transfer 8-bit or 12-bit words under program control.

Another important feature of the interface is the ability to retrieve the contents of various interface and controller registers for diagnostic examination by the programmer. In this way, maintenance and troubleshooting should be eased considerably.

The hardware has yet to be implemented; the software maintenance package has been written in its initial form and is being updated for use with disc installation and debugging.
Use of the PC/Macromodule Interface (PR 8, J-13) made it clear that a better, faster means of transferring data between the PC memory and macromodules was needed. Therefore, a direct memory access (DMA) unit was designed and constructed to speed up and simplify data transfers. The device has been operating successfully for about ten months.

The MM/PC DMA UNIT provides cycle-stealing operation in the Programmed Console computer by making the PC appear to be a macromodule. Appropriate READ and WRITE control ports are provided along with data ports for address and input-output information. The unit also provides control ports which enable the user to cause the PC to pause until another signal arrives at the CONTINUE port. All ports are compatible with macromodules. A single circuit board which plugs into the PC input-output bus provides signal conditioning and bidirectional transmission between the DMA unit and the PC over an eight foot cable bundle. The DMA unit uses the +5VDC power provided by the PC, but supplies its own -5.2VDC from an internal power supply. There are two control port pairs for every control command except PRESET.

Operation of the DMA unit is straightforward with the same rules as macromodules. The DATA OUT ports provide buffered storage which will retain the last value read from PC memory. The signals at the control return ports indicate that the particular operation last initiated is complete with stable data at the data ports. Therefore, if a DMA operation is requested during program execution, the control return signal will be delayed until the PC is actually committed to performing the requested operation. The single exception to this rule is the CONTINUE control return which occurs immediately.

The DMA unit will not process control commands while the PRESET signal is applied. Once the computer pauses, a CONTINUE control signal or a STOP command from the console will cause the computer to terminate the pause. The DMA unit participates in both the interrupt and cycle-stealing priority chains and can, therefore, be inserted anywhere on the PC input-output bus. DMA operation may take place during any time that the PC is not in the STOP mode.
As a result of the announcement of the EMI X-Ray Scanner\(^{(1)}\) during the Fall of 1972, we have studied the problem of calculating an underlying two-dimensional x-ray absorption density from measured x-ray attenuation data. Our understanding of this problem as of December 21, 1972 is summarized in a BCL monograph.\(^{(2)}\) Equations are given in the monograph for determining the distribution of mass in an inhomogeneous, two-dimensional section of some object such as the head. X-ray attenuation measurements taken in the plane of the section and at all aspect angles are assumed to be available for determining mass distribution. Several analytical examples are given. After completing the monograph, we discovered that several authors, the earliest dating from 1956,\(^{(3)}\) had previously obtained identical results. Since completing the monograph, we have observed that a substantial simplification in the computational implementation of the equations to recover the absorption density is possible. Also, we have identified what we feel is an improved method for collecting the x-ray scan data; this procedure relies on compound angular scanning.

\(^{(1)}\)"EMI-Scanner" (a manufacturer's prospectus), EMI Limited, Control Research Laboratories, Shoenberg House, Trevor Road, Hayes, Middlesex, England.


Previously described efforts (PR 8, J-11) on the mathematical study of stochastic point and jump processes have continued. A set of notes for a graduate course on this topic is currently being written, and chapters four and five are now available. (1), (2) Several papers and reports dealing with point and jump processes have appeared. (3)-(7)


J-7 . Arithmetic Routines

Personnel: M. D. McDonald, BCL

Support: RR 00396

A system of programs called INTERP has been written for the LINC. These programs manipulate data points which are in the floating point format of DBLFLT(1) and stored on tape in the block format of the LINDSY(2) plotting system.

Provision is made for inputting x,y data points either by the keyboard in FORTRAN (in integer, fixed or scientific format) or as stored on tape in the format of the PC-1200 floating point hardware (H-8). This data is then entered in a LAP6W(3) file under a user specified name. The user may then specify that he wishes a new file of data generated by interpolation on an already existing file by designating minimum and maximum x values, number of points to be generated and the degree of interpolation. The degree of interpolation is limited only by the number of points of data on which interpolation is being performed and storage limitations; available core also limits the degree to no more than 63.


VI. TRAINING ACTIVITIES

During the year the Biomedical Computer Laboratory engaged in the following training activities:

Programming for Medical Information Systems, Fall, 1972

This course was taught by Walter E. Long and was on how to program in MUMPS. Programming examples from hospital and ambulatory care settings were included. Attending the course were:

Joseph o. Flynn  
Teresa P. Germanson, B.A.  
Joseph G. Green  
Robert H. Greenfield, M.S.  
Betty J. Greenwood  
Phillip J. Haas, M.B.A.  
Susan R. Holmes, B.A.  
Mary J. Kenner, B.S.  
J. Philip Miller, A.B.  
Edward L. Morofsky, Ph.D.  
William F. Pickard, Ph.D.  
Terry F. Plasse, B.A.  
Donald P. Ragan, Ph.D.  
Michael C. Rigdon, A.B.  
Kenneth L. Ripley, B.A.  
Linda C. Smith, M.S.  
Joan Zimmerman, Ph.D.

- Artronix  
- Biostatistics  
- BCL  
- Health Care Research  
- BCL  
- BCL  
- Electrical Engineering  
- Medicine  
- Radiology  
- Psychology and Radiology  
- BCL  
- Medical Library  

Introduction to Programming the Laboratory Computer, Spring 1973

This course was taught by Michael D. McDonald and included generalized description of logical design of digital computers; decimal, octal, and binary number systems; machine language programming for the LINC. Attending the course were:

Don P. Altholz, B.S.  
Michael R. Bedford, B.S.  
James C. Boyd, B.S.  
Jon D. Cooksey, M.D.  
Stanley A. Garfield  
Mohammad F. Ghanie, M.D.  
Margaret C. Jest, B.A.  
Alan N. Kohn, M.S.  
Theresa E. McKenzie  
Phyllis J. Oster, B.A.  
Renato B. Reyes  
Carole L. Ripley, B.A.  
Linda C. Smith, M.S.  
Beatrice Y. J. Tan, M.S.  
Vincent T. Yue, M.S.  
Joan Zimmerman, Ph.D.

- Electrical Engineering  
- Biomedical Engineering  
- Medical Student  
- Preventive Medicine  
- Applied Mathematics and Computer Science  
- Cardiology  
- Electrical Engineering  
- Medical Student  
- Physiology and Biophysics  
- Psychology  
- Psychology  
- Psychology  
- Medical Library  
- Biochemistry  
- Chemistry  
- BCL
Selected Topics in Programming, Spring 1973

This course was taught by Michael D. McDonald and included description and comparison of several laboratory computers, including the LINC, LINC-8, PDP-12, and PC along with their usage and the design of algorithms for programming. Attending the course were:

Michael R. Bedford, B.S.
James C. Boyd, B.S.
Stanley A. Garfield
Ram K. Gupta, M.S.
Alan N. Kohn, M.S.
Michael C. Rigden, A.B.
Carole S. Ripley, B.A.
Linda C. Smith, M.S.
Beatrice Y. J. Tan, M.S.
Vincent T. Yue, M.S.
Joan Zimmerman, Ph.D.

Biomedical Engineering
Medical Student
Applied Mathematics and Computer Science
Electrical Engineering
Medical Student
Psychology
Psychology
Medical Library
Biochemistry
Chemistry
BCL
VII. SEMINARS

During the year the following seminars were sponsored by the Biomedical Computer Laboratory:

"In-House Computer-Based Communications: Pros and Cons of Hardware, Software, and Systems"
Mr. Everett F. Menendez
Manager, Data Processing Department
Barnes Hospital
St. Louis, Missouri

October 25, 1972

"The Next (That is, Second) Generation Computer — Matching Semiconductor Technology to Computer Applications"
Mr. Ivor Catt
Author and Engineer
England

December 5, 1972

"Technology and Education"
Dr. George Bugliarello
Dean of Engineering
University of Illinois
Chicago, Illinois

December 14, 1972

"In Vivo Measurement of Glucose Metabolism in the Brain"
Dr. Marcus E. Raichle
Dr. Michael E. Phelps
Dr. Kenneth B. Larson
Washington University School of Medicine
St. Louis, Missouri

December 27, 1972

"The Reconstruction of an X-Ray Absorption Function From Its Projections"
Dr. Oleh J. Tretiak
Research Laboratory of Electronics
Massachusetts Institute of Technology
Cambridge, Massachusetts

January 25, 1973

"Using Extended Memory in the PC"
Mr. Dana Sawyer
Senior Programmer
Artronix Incorporated
St. Louis, Missouri

January 9, 1973

"Problem-Free Problem-Oriented Medical Record Systems and Computers"
Dr. Lawrence Weed
Department of Medicine
University of Vermont-College of Medicine
Burlington, Vermont

February 9, 1973
<table>
<thead>
<tr>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;A One Megabit Infrared Communication System&quot;</td>
<td>Mr. William R. Lang&lt;br&gt;Department of Electrical Engineering&lt;br&gt;Washington University&lt;br&gt;St. Louis, Missouri</td>
</tr>
<tr>
<td>&quot;The Case for Interpreters&quot;</td>
<td>Mr. A. Neil Pappalardo&lt;br&gt;Vice President&lt;br&gt;Medical Information Technology, Inc.&lt;br&gt;Cambridge, Massachusetts</td>
</tr>
<tr>
<td>&quot;A Mathematical Model of the Mechanics of the Cochlea&quot;</td>
<td>Mr. Monte Deh Lien&lt;br&gt;Department of Electrical Engineering&lt;br&gt;Washington University&lt;br&gt;St. Louis, Missouri</td>
</tr>
<tr>
<td>&quot;Computer-Based Ambulatory Medical Record Systems&quot;</td>
<td>Dr. Jerome Grossman&lt;br&gt;Massachusetts General Hospital&lt;br&gt;Boston, Massachusetts</td>
</tr>
<tr>
<td>&quot;Artificial Intelligence and Natural Stupidity&quot;</td>
<td>Dr. Leon D. Harmon&lt;br&gt;Head, Biomedical Engineering Department&lt;br&gt;Case Western Reserve University&lt;br&gt;Cleveland, Ohio</td>
</tr>
<tr>
<td>&quot;Some Aspects of Minicomputer Applications in Frame Testing&quot;</td>
<td>Dr. George D. Kraft&lt;br&gt;Bell Telephone Laboratories, Inc.&lt;br&gt;Naperville, Illinois</td>
</tr>
<tr>
<td>&quot;A 254- Probe Dynamic Gamma Camera for Measurements of Cerebral Blood Flow&quot;</td>
<td>Dr. Edda Sveinsdottir&lt;br&gt;University of Copenhagen and&lt;br&gt;Dr. Niels A. Lassen&lt;br&gt;Bispebjerg Hospital&lt;br&gt;Copenhagen, Denmark</td>
</tr>
</tbody>
</table>
VIII. PAPERS, PUBLICATIONS AND ORAL PRESENTATIONS


Bates, D. J. and Frieden, C., "Full Time Course Studies on the Oxidation of Reduced Coenzyme by Glutamate Dehydrogenase," submitted for publication to *the Journal of Biological Chemistry*.

Bates, D. J. and Frieden, C., "Treatment of Kinetic Data III. The Use of the Full Time Course of a Reaction, as Examined by Computer Simulation in Defining Enzyme Mechanisms," submitted for publication to *the Journal of Biological Chemistry*.


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Hoffman, E. and Phelps, M. E., "Production of Monochromatic X-rays from 8 to 87 KeV," accepted for publication in Physics in Medicine and Biology.


