1975

Progress Report No. 11

Biomedical Computer Laboratory

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PROGRESS REPORT

No. 11

1 July 1974 — 30 June 1975

Biomedical Computer Laboratory
Washington University School of Medicine
St. Louis, Missouri
BIOMEDICAL COMPUTER LABORATORY
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 11

JULY 1, 1974 - JUNE 30, 1975
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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1974 through June 30, 1975. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine and its affiliated hospitals 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), a Programmed Console (PC) or other commercially available mini and microprocessors. We have pursued many such 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 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 is Robert J. Benson.

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 Associate Vice Chancellor for Research, the Director of the University Computing Facilities and the Associate Directors of both laboratories.

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, as well as specialized systems embodying commercially available processors often augmented by macro-modules, to problems in information processing and 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:

<table>
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<th>Title and Institution</th>
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<tr>
<td>W. A. Clark</td>
<td>Consultant and Past Director of Computer Systems Laboratory, Cambridge, Massachusetts</td>
</tr>
<tr>
<td>D. M. Kipnis</td>
<td>Busch Professor and Head of the Department of Medicine, Washington University School of Medicine</td>
</tr>
<tr>
<td>F. M. Richards</td>
<td>Professor in Molecular Biophysics and Chemistry, Yale University</td>
</tr>
<tr>
<td>R. S. Snider</td>
<td>Professor of Anatomy and Director of Center for Brain Research, University of Rochester</td>
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The Advisory Committee meets periodically with the WUCL Coordinating Committee to review developing projects and programs and to advise on 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

Support was also received by the laboratory for a training grant program in Health Care Technology from the Health Resources Administration:

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:

HV 12481	Relationship of Ventricular Arrhythmias to Sudden Death in Survivors of Myocardial Infarction

A research grant was awarded to support activities of information exchange about MUMPS and MUMPS application transfers:

HS 01540	Pilot Project, MUMPS Users' Group

Research was completed on a contract with the Picker Corporation for the development of advanced techniques for reconstruction of cross-sectional images of x-ray absorption densities by means of computerized transaxial tomography.

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

AM 13332	Metabolic Regulation and Interacting Enzyme System
AM 15531	Membrane Transport of Amino Acids
EY 00336	Glaucoma Clinical Research Center
GM 02016	Medical Scientist
GM 21357	Processing and Turnover of Human Cell Nuclear RNA
HL 12820	Lipid Protein Interactions in Blood Clotting
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine
HL 14147	Specialized Center of Research in Thrombosis
HL 17646	Study of Ischemic Heart Disease
HL 18144 Preprocessor System for Cardiograms
MH 19624 Behavioral Neuroendocrinology Chemical Correlates
MH 25571 Steady State Tricyclic Antidepressant Levels
MH 70734 Neuroendocrine Control Mechanisms Chemical Correlates
NS 03856 Auditory Communication and its Disorders
NS 05159 The Metabolism of the Inositol and Inositides
NS 06833 An Interdisciplinary Stroke Program
NS 11059 Academic Career Development Award
RR 05389 General Research Support

National Science Foundation:
ENG 74-07800 Information Processing for Doubly-Stochastic Poisson Processes

Alcohol and Drug Abuse Mental Health Administration:
AA 70180 Neurochemical Correlates of Drug Addiction in Animals
DA 00109 Morphine Tolerance and High Sensitivity Measurement
DA 00259 Drug Abuse Research Center
RM 00056 Bi State Regional Medical Program, Project # 50
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 Directors

G. James Blaine, III, D.Sc.
V. W. Gerth, Jr., M.S.

Administrative Officer

Edward L. MacCordy, M.B.A.

Research Associates

Robert J. Arnzen, Ph.D.
R. Martin Arthur, Ph.D., and Assistant Professor of Electrical Engineering
William E. Ball, D.Sc., and Professor of Computer Science
A. Maynard Engebretson, D.Sc.
Philip M. Fishman, D.Sc., and Research Instructor in Computer Sciences in Psychiatry
Barry R. Hieb, M.D., and Research Instructor in Medicine
William F. Holmes, Ph.D., and Associate Professor of Biological Chemistry
Sung-Cheng Huang, D.Sc.
Kenneth B. Larson, Ph.D.
Thomas F. Martin, M.D., and Instructor in Clinical Medicine
Floyd M. Nolle, D.Sc.
Donald L. Snyder, Ph.D., and Associate Professor of Electrical Engineering
Joan Zimmerman, D.Phil.

Research Assistants

H. Dieter Ambos
Philip S. Berger, M.S.
Andrew L. Bodicky, B.S.
Gary H. Brandenburger, M.S.
Brian E. Campbell, M.S.
Kenneth W. Clark, M.S.
Christine D. Coaker, B.S.
Thomas Ferriero, M.S.
William M. Fisher, Ph.D.
Stanley A. Garfield, B.S.
Robert H. Greenfield, M.S.
Ronald W. Hagen, M.S.
Richard E. Hitchens, B.S.
Janet A. Johnson, B.S.
Margaret C. Jost, M.S.
William A. Lavender, B.S.
Joanne Markham, M.S.
J. Philip Miller, B.A.
Nizar A. Mullani, B.S.
Kenneth L. Ripley, B.A.
J. Alan Ritter, S.B.
Jeffrey H. Rixleben, B.S.
Bruce F. Spenner, M.S.
Elizabeth Van Patten, B.A.
Nageswara R. Vemula, M.S.

Lecturer
Fred M. Domke

Technical Assistants

Donald R. Bassman, M.D.
Mary L. Dunne, B.S.
Robert L. Huck, A.B.
Andrew G. Kegel
Gail S. Kuthe
Deborah K. McDermott, B.S.
Charles N. Mead, M.D.
James B. Minard
Peter D. Norberg
Glen Roa
Emil D. Scheifler, B.S.
Robert W. Sheifler
John J. Schier, B.S.
Thomas F. Schuessler, B.S.
John J. Sueme, B.S.
Robert W. Sutherland, B.A.
David M. Ungar, B.S.
Budimir Zvolanek, B.S.

Electronics Technicians

Gary A. Appel
Theron R. Baird
Daniel J. Bax
George L. Bickmore
During the Spring 1975 semester Professor James M. Mozley was a visitor to the laboratory while on his sabbatical year at the Washington University School of Engineering and Applied Science.

The following staff members from other departments and divisions have joint appointments with the Biomedical Computer Laboratory to facilitate collaboration and enhance interdisciplinary research:

Carol S. Coble, B.S., Research Assistant in the Biomedical Computer Laboratory and in Radiology
Rexford L. Hill, M.S., Research Associate in the Biomedical Computer Laboratory and in Radiology
John W. Lewis, Ph.D., Research Associate in the Biomedical Computer Laboratory, Assistant Professor of Pathology and of Electrical Engineering, and Director of Laboratory Computing, Barnes Hospital
G. Charles Oliver, Jr., M.D., Associate in the Biomedical Computer Laboratory, Associate Professor of Medicine and Director, Division of Cardiology, Jewish Hospital
In addition, the following people worked at the laboratory for brief periods:

Barbara D. Eldredge
Markku T. Hakkinen
Edward H. Kovnar, B.S.
Eric H. Leder
Thomas C. Paino
Richard V. Sanders
James B. Sellinger
Carolyn Smelter
Daniel A. West
Philip G. Winger, B.S.

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:

P. O. Alderson, M.D., Radiology
G. Ahumada, M.D., Medicine
K. M. Baldwin, B.A., Medicine
W. E. Ball, D.Sc., Computer Science
R. A. Beauchamp, Surgery
M. R. Bedford, B.S., Electrical Engineering and School of Medicine
R. J. Benson, J.D., Computing Facilities
J. T. Biggs, M.D., Psychiatry
S. Boonvisut, M.D., Radiology
R. L. Boshans, A.B., Psychiatry
S. D. Boxerman, D.Sc., Health Care Administration
W. M. Buchholz, M.D., Medicine
E. M. Carlson, M.S., Medicine
T. J. Cicero, Ph.D., Psychiatry
R. E. Clark, M.D., Surgery
R. E. Coleman, M.D., Radiology
T. J. Coleman, M.S., Biomedical Engineering
D. G. Cooper, M.S.N., Ophthalmology
D. C. DeVivo, M.D., Pediatrics and Neurology
W. E. Dodson, M.D., Pediatrics and Neurology
J. O. Eichling, Ph.D., Radiology
J. D. Elliott, B.S., Electrical Engineering
R. G. Evens, M.D., Radiology
H. Fotenos, Radiology
M. A. Franklin, Ph.D., Electrical Engineering
C. Frieden, Ph.D., Biochemistry
M. H. Gado, M.D., Radiology
S. Goldring, M.D., Neurosurgery
R. L. Grubb, Jr., M.D., Neurosurgery
E. P. Gruendler, B.S., Electrical Engineering
P. J. Haas, M.A., Medical Care Group
B. K. Hartman, M.D., Psychiatry
A. Hernandez, M.D., Pediatrics
L. S. Hillman, M.D., Pediatrics
R. E. Hillman, M.D., Pediatrics
P. P. Hipps, Ph.D., Psychiatry
E. J. Hoffman, Ph.D., Radiology
W. H. Holland, A.B., Psychiatry
J. Hood, B.S., Physics
S. Igielnik, Ph.D., Medical Computing Facilities
C. M. Jackson, Ph.D., Biochemistry
L. Jarett, M.D., Pathology
G. C. Johns, Computer Systems Laboratory
J. H. Joist, M.D., Medicine
R. C. Jost, M.D., Radiology
I. N. Katz, Ph.D., Systems Science and Mathematics
M. J. Kenner, B.S., Medical Care Group
J. Ladenson, Ph.D., Pathology
M. H. Laird, M.S., Psychiatry
J. J. Lobick, M.S., Electrical Engineering
P. A. Ludbrook, M.D., Medicine
J. Marr, M.D., Pediatrics
R. Marshall, M.D., Pediatrics
T. F. Martin, M.D., Medicine
C. E. Molnar, Sc.D., Computer Systems Laboratory
R. J. Myrick, M.S., Electrical Engineering
G. D. Oliver, Ph.D., Radiology
P. M. Packman, M.D., Psychiatry
G. T. Perkoff, M.D., Medical Care Group
R. R. Pfeiffer, Ph.D., Electrical Engineering
M. E. Phelps, Ph.D., Radiology
W. F. Pickard, Ph.D., Electrical Engineering
S. M. Podos, M.D., Ophthalmology
S. V. Pollack, M.S., Computer Science
W. E. Powers, M.D., Radiology
D. P. Ragan, Ph.D., Radiology
M. E. Raichle, M.D., Radiology and Neurology
M. C. Rigden, B.A., Radiology
R. Roberts, M.D., Medicine
W. H. Rohr, M.D., Pediatrics
J. Rosenfeld, B.S., Biomedical Engineering
J. M. Rusche, B.S., Surgery
J. J. Schier, B.S., Surgery
D. Schlessinger, Ph.D., Microbiology and Immunology
A. Sen, D.Sc., Electrical Engineering
L. C. Sharpe, Ph.D., Psychiatry
L. A. Sherman, M.D., Medicine
W. R. Sherman, Ph.D., Psychiatry and Biochemistry
B. A. Siegfried, B.S., Surgery
B. E. Sobel, M.D., Medicine
M. G. Straatmann, M.S., Radiology
C. Tao, B.S., Electrical Engineering
D. Tao, M.S., Electrical Engineering
M. M. Ter-Pogossian, Ph.D., Radiology
L. J. Tolmach, Ph.D., Radiology
M. V. Vaca, Ph.D., Electrical Engineering
A. N. Weiss, M.D., Medicine
E. S. Weiss, M.D., Medicine
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Surgery
R. Wette, D.Sc., Biostatistics
S. F. Wolf, M.A., Microbiology and Immunology

Beth Israel Hospital, Boston, Massachusetts

R. F. Beckley, III, B.S.

Central Institute for the Deaf, St. Louis, Missouri

C. K. Burdick, M.A.
D. H. Eldredge, M.D.
I. J. Hirsh, Ph.D.
P. K. Kuhl, Ph.D.
J. D. Miller, Ph.D.
R. B. Monsen, Ph.D.
A. F. Niemoeller, D.Sc.
D. A. Ronken, Ph.D.
B. L. Scott, Ph.D.
J. W. Sharp
C. S. Watson, Ph.D.

College of Medicine and Dentistry of New Jersey, Newark, New Jersey

W. Perl, Ph.D.

Creighton University, Omaha, Nebraska

A. Zencka, M.D.

Jewish Hospital, St. Louis, Missouri

A. S. Geha, M.D.
Y. Hamuth, M.D.
B. R. Hieb, M.D.
R. E. Kleiger, M.D.
R. J. Krone, M.D.
B. A. Sandefur, B.A.
D. P. Wheeler

Methodist Hospital, Houston, Texas

M. E. DeBakey, M.D.
D. H. Glaeser, Sc.D.
Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year projects of joint interest have involved:


- Picker Corporation, Cleveland, Ohio - A reconstructive tomographic 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. The SPEAR PC in the Cardiac Catheterization Laboratory was replaced in 1973 by a new Artronix PC-1200 System housed in newly renovated space for Catheterization Laboratory Instrumentation, and in 1974, an Artronix PC-12/7 MUMPS System was installed at BCL to be used in a variety of projects in Health Care Technology and information 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. (A second IBM System/7 was added in November, 1973.) 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 ten 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 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.

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.

In May, 1973 a Texas Instruments TI 980 computer was acquired which is being used as a major element in a satellite patient monitoring system. A TI 980B computer system was added in December, 1974 to be used in program development, microprocessor support and booster cart system development.
Summary

The 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 and frequently to the design of specialized equipment. The laboratory's research program has traditionally been organized into several major project areas with many of the laboratory's staff grouped into teams whose interests focus in one of these project areas.

"Ischemic Heart Disease and ECG Analysis" replaces the former title, "Electrocardiographic Rhythm Monitoring," to reflect a broader range of related activities. These include the examination of non-ECG parameters of the natural history of ischemic heart disease, studies related to enzymatic quantification of myocardial infarct size, and the current emphasis on high-speed ECG analysis rather than monitoring per se. Former projects in communications for information processing and in health care technology have become closely allied and are therefore grouped together under "Information and Communication Systems" this year.

The internship program in Health Care Technology is not redescribed in this report. It should be noted, however, that it continues to thrive with the degree candidates still serving as welcome stimuli to all participants. Continued DHEW support beyond next year for this training grant as well as many others in the nation is again in serious doubt. Vigorous efforts to secure alternative sources of support are being made.

Ischemic Heart Disease and ECG Analysis. Production operation of the Argus/H System for high-speed analysis of tape recorded data for ambulatory subjects has continued throughout the year. Nearly 300 patients have been enrolled in the study of the precursors of sudden death. This study focuses on the analysis of arrhythmias recorded on Holter tapes from ambulatory patients recovering from proven myocardial infarctions. Of the nearly 2500 ten-hour tapes collected, approximately 1000 have been through full analysis, which includes Argus/H processing, human editing, and cardiologist review. In addition, demographic, clinical, and laboratory data have been collected from 1100 patients. Patient accrual was terminated on June 1, 1975 and the data are now being prepared for statistical analysis to develop and test prognostic indices. Other studies completed during the year include: correlations between enzymatically estimated infarct size and ventricular arrhythmias; the effect of steroid therapy on infarct size and PVC rates; the efficacy of anti-arrhythmic drugs; and the effect of coronary-artery by-pass surgery on PVC rates. Early results indicate the importance of early PVCs as prognostic indicators; thus, increased attention has been given to editor verification of QRS onsets and summary outputs including coupling-interval histograms.

Steady improvement of the analysis system has continued throughout the year with respect to both hardware and software. Algorithm developments recently completed but not yet incorporated, show promise for greatly improving system performance. These include contextual analysis
of the output cycle stream data for T-wave rejection and PVC editing by morphological sets ("family editing"). Evaluations completed during the year include: validation of Argus/H and Argus/Sentinal (corrected) along with a reconfirmation of the original real-time Argus; reproducibility testing of the high-speed analysis system; comparison of the latter with conventional manual scanning; an accounting of financial and time costs; review of editor performance; and an examination of detection accuracy. Observations relevant to practical utility are that the cost per ten-hour tape is less than $90 and that Argus/H with editing detects about 90% of total PVCs, PVC couplets, and PVC runs.

MUMPS for the IBM System/7 continues to be invaluable for data management. Reorganization of the files has improved maintenance of patient records of Holter recordings, analog tape manual scanning records, editing records, and results of cardiological review of tape folders.

Other related activities during the past year have included work on a multi-patient system for retrospective retrieval of two-hour ECG segments preceding serious arrhythmias; development of an annotated ECG data-base for algorithm testing and performance validation; formulation of plans for an Evaluation Group for Arrhythmia Detectors (EGAD) as a consortium with two other institutions; and studies of enzymatically (CPK) estimated infarct size including prediction from early data as well as development of a physiologically-based mathematical model to explain the observed time-course of serum CPK activity.

Tracer Kinetics. Our efforts in applying mathematical models for interpreting data from in-vivo dynamic studies have continued to yield important results, both in physiological research and in clinical practice. New insights have been obtained in studies of blood-brain barrier transport mechanisms and in the assessment of cerebral blood volume. The methods based on the models used to interpret data from these studies have been applied to the study in human patients of such pathologies as subarachnoid hemorrhage, subdural effusion, and pulmonary edema. Additionally, tracer methodologies in current use here and elsewhere have been subjected to critical examination and evaluation with the use of a physical flow system simulating the circulation.

The dual-processor Interdata computer-system installed in the Radiation Sciences Division has been interfaced to a new positron-emission tomograph that has been constructed for obtaining cross-sectional images throughout the body of human patients. The computer system is used both to control the scanning motions of the tomograph for data collection and to process the data for obtaining quantitative estimates of the distribution of radioactivity in the cross section. Approximately 23,000 data points are processed using a Fourier-based algorithm to compute the distribution. The result is displayed on a newly installed Ramtek display system. The tomograph is already being used for the study of cerebral and myocardial pathologies in humans. Extensive phantom, animal, and human studies have been conducted, and the results encourage us to believe this system will prove to be a valuable clinical tool.
Monitoring the Critically Ill. The digital computer system installed in the Cardiothoracic Surgical Intensive Care Unit (SICU) has completed its first two years of clinical trial, has performed well and has been effectively used by clinical personnel. Its reliability has continued to improve such that the mean time between all unintentional interruptions of patient monitoring has risen to 2100 hours. Nearly all such failures have been documented with their sources identified. Patient occupancy in the SICU has risen to 83% of capacity from 77% last year but with no increase in nurse staffing. Broadening activities in patient monitoring in other contexts are exemplified by an evaluation of pediatric monitoring instrumentation and the development of a color-video display for use in the operating room.

The satellite system for clinical physiologic research is now ready for use. This system brings a minicomputer to the bedside for processing eight analog and eight digital signals but capitalizes on the digital communication, video display generation, and mass-storage capabilities of the SICU system for support.

Efforts directed toward collecting relevant data of high integrity have drawn us into some transducer developments. These include a thermodilution system for cardiac output, an ultrasonic gas-flow instrument, a urine-output device, and a system for fiberoptic blood oximetry. Other device developments reflect collaborative efforts with the Department of Surgery in prosthetic heart-valve testing and extracorporeal perfusion.

Information and Communication Systems. During the past year, increasing attention has been given to the study and design of information systems and of supporting high-performance digital communication systems. The weaknesses of present-day information systems have been considered with a view toward remedy by the application of new technologies to system architectures emphasizing economy, simplicity, privacy, and reliability. The management of medical information is felt to be a particularly promising area in which biomedical computing can contribute to the quality and efficiency of medical care. The groundwork is now being done for major new efforts to capitalize on emerging mass-storage media and microprocessors which are both fast and inexpensive.

The study of data-base characteristics, usage patterns and needs in various contexts will be important not only to future applications of an advanced system but also to the continuing development of a system (MESCH) for expeditious tailoring to meet the needs of different environments. Several such studies have been initiated during the past year to include: a glaucoma patient registry (Department of Ophthalmology); an ambulatory care information system (Medical Care Group); and a system (CAPO) oriented to the physician's office. In addition, 18 hospitals in seven states were approached to establish outpatient appointment system needs prior to developing such a system for St. Louis City Hospital.
The expanding activities of the Office of the Executive Secretary of the MUMPS Users' Group (MUG) at BCL have served to heighten local awareness of the power of well designed information systems. During the past year, the Washington University Medical Computing Facility has been established. It will be initially addressed to meeting a broad range of information handling needs throughout the medical complex with close BCL interaction.

Cardiac Catheterization Laboratory. Upgrading and refinement of the cardiac catheterization laboratory computer systems at Jewish Hospital and Washington University have continued during the past year. The shortcomings of previous systems relative to the operational style at Washington University have been carefully identified and corrective design of a new-generation system has progressed smoothly. Transfer of the ventricular-volume system from Jewish Hospital has markedly increased interest and utilization of the Washington University system for both clinical and research purposes. The practical usefulness of this system was greatly enhanced by the addition of a disc drive.

The experimental Macromodular System for acquiring digitized video images obtained during angiography is now beginning to bear fruit. The records of ten patients have been acquired and are being used to explore techniques for image processing and ventricular function determinations.

Mass Spectrometry. The PDP-12 system for the acquisition and analysis of data from a mass spectrometer continues to be used heavily in this institution and in a number of others around the world. Program modifications to allow operation of a Finnigan quadrupole mass spectrometer were completed during the past year. These are now in use at the Research Triangle Institute in North Carolina. Widespread interest has stimulated development of a new computer system for gas chromatography/mass spectrometry applicable to both quadrupole and magnetic scanning instruments. A compact and inexpensive minicomputer, the Computer Automation LSI-2, was chosen for this system which is nearing completion. Multiple interfaces have been designed and programs are being written with consideration for ease of user modification.

The power of these systems as research tools is exemplified by the successful determination of levels of myo-inositol in tissue samples as small as five nanograms, the equivalent of a large single cell. Other applications in current use include blood assays of tricyclic antidepressant drugs, analysis of morphine brain levels in rats, kinetic studies of a local anesthetic (mepivacaine) and of anticonvulsants in newborn infants, and the identification of abnormal metabolites in the urine and serum of patients with inborn errors of metabolism.

Speech and Hearing. The speech and hearing computer system continues to be extremely useful for generating special sounds for use in speech perception studies done at the Central Institute for the Deaf (CID). These stimuli encompass a wide range of speech-like sounds that emphasize particular features of speech that would be difficult or impossible to generate without a computer. These synthetic sounds are reproduced in a wide variety
of experiments at CID using the Random Access Programmable Recorder (RAP). The RAP concept has proven invaluable as a research tool for manipulating complex auditory stimuli. To satisfy the growing demand on the present unit, construction of a second RAP has been started and is nearly completed.

The study of glottal waveforms in normally hearing adult subjects is a new effort begun this year. Also new is the development of improved tests to measure speech reception. Such tests are needed to evaluate new hearing aid designs and non-auditory speech reception aids for the deaf. An initial version of an interactive testing procedure using the speech and hearing computer system has been completed and is now being evaluated.

Studies with the linear predictor method of speech analysis are nearly finished. This method has been evaluated as a technique for estimating the cross-sectional area function of the vocal tract from the speech waveform. Along with the ability to measure glottal source functions, the linear predictor method may enable us to study articulation in normal and deaf subjects.

Work on the Cox-Lien model of the cochlea has progressed this year to a point where an algorithm suitable for hardware implementation has been developed.

Supporting Activities. As in previous years, mathematical, equipment or program development supporting two or more of the major programs of the laboratory or computer applications for users not related to any of the major programs are grouped together in this section. Of particular interest is the appearance of several systems based on microprocessors and a system for microprocessor development support. This new tool will assume a role of increasing importance in future systems development.
Individual Projects

A. Ischemic Heart Disease and ECG Analysis

A-I. Relationship of Ventricular Arrhythmias to Sudden Death: Clinical Data Gathering

Personnel:  G. C. Oliver, M.D., Medicine
H. D. Ambos, BCL
D. R. Bassman, BCL
S. E. Katzen, BCL
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
T. R. Martin, M.D., Medicine
J. P. Miller, BCL
B. A. Sandefur, B.A., Jewish Hospital

Support:  RR 00396
HV 12481
Barnes Hospital
Jewish Hospital
Washington University

Data gathering activities have continued in this investigation of precursors of sudden death (PR 10, A-I). We have been testing the hypothesis that patients destined to die suddenly can be identified before death by an analysis of clinical features and arrhythmias which can be detected by appropriate analysis of ambulatory ECG tapes (Holter tapes). The population studied has consisted of those patients less than 71 years old who were admitted to the Jewish or Barnes Hospital Coronary Care Unit with a proven acute myocardial infarction. To date 286 patients have enrolled in our study and 2444 tapes have been recorded. To the best of our knowledge, this is now the largest such data base of myocardial infarction patients accumulated by any one institution.

Each tape has been qualitatively analyzed by manual scanning techniques and an interpretation sent to the patient's physician. To facilitate data analysis, the analog tapes, records of manual scan results and copies of activity diaries of participating individuals are now stored at BCL. A MUMPS/7 data base, PLOG (A-14), was introduced last year to reduce the amount of manual labor involved in acquiring and processing of tapes. It has proven to be extremely useful and is part of the everyday operation of the clinical data gathering activities.

We have continued to collect demographic, clinical, and laboratory data on all patients with acute myocardial infarctions entering the coronary care units. Our file of clinical data on over 1000 patients is stored on disc for easy analysis on the IBM System/360 Model 65. We have continued to microfilm all patient charts for ready reference. These are currently being utilized to correct an error noted in the coding of congestive heart failure on certain patients. The forms on those patients coded as having heart fail-
ure are being retrieved, along with the microfilmed hospital chart, so that we can determine precisely what evidence the diagnosis of congestive failure rests upon.

Several other intimately related projects are entering their final phase. These include studies on antiarrhythmic drug therapy (A-8), coronary artery bypass surgery (A-9), and the influence of infarct size on arrhythmias (A-10).

A-2. Data Analysis on Acute Myocardial Infarction Patients

Personnel:  J. P. Miller, BCL  
J. R. Cox, Jr., BCL  
G. Ahumada, M.D., Medicine  
G. C. Oliver, M.D., Medicine  
R. E. Kleiger, M.D., Jewish Hospital  
T. F. Martin, M.D., Medicine  
L. J. Thomas, Jr., BCL

Support:  RR 00396  
HV 12481  
Jewish Hospital  
Washington University

Continued analysis of the data base which abstracts the clinical and laboratory features of each patient's stay during the acute phase of his MI continues (PR 10, A-2; A-1). Patient accrual was terminated on June 1, 1975 and the activities of the past year have been directed principally towards completing the data base so that various analyses can be performed. It is anticipated that over 1100 completed Myocardial Infarction Patient Information (MIPI) forms will be available for analysis.

The development of an appropriate method of constructing a prognostic index remains an important goal of this project. The large size of the data base from two separate institutions will allow us to utilize the data gathered in one institution for constructing a prognostic index and then validating the index on the data from the other institution thus avoiding the problems inherent in utilizing the same data for the learning set as for the test set. This type of replication has never been reported for prognostic indices for the identification of high-risk individuals within the coronary care unit.
A variety of statistical models including linear discriminant analysis, quadratic discriminate analysis, the Walker and Duncan procedure for estimating the optimum linear discriminant function via maximum likelihood criteria, and the non-linear interaction detection algorithms of the AID procedure will all be evaluated in this fashion. Computer programs to implement all of these procedures have been obtained and work has begun to implement those which are not currently available. The actual application of these methods awaits the complete closure of the data. Existence of the microfilmed versions of the charts has continued to be invaluable in the validation and verification of features abstracted on the MIPI forms.

Comparisons of the features recorded on the MIPI to the size of the infarct as estimated by the serial serum CPK infarct size index (PR 10, B-1) have been made for a sample of over 50 patients treated in the Barnes Hospital Coronary Care Unit. This analysis has confirmed many hypotheses concerning features associated with large infarcts. These include higher peak levels of standard daily serum enzyme levels; the development of complications indicative of pump failure e.g. congestive heart failure, pulmonary edema and cardiogenic shock; the higher incidence of both atrial and ventricular arrhythmias; and the appearance of first and second-degree heart block. The analysis did not confirm the hypothesis that infarcts on the anterior wall are larger than those on the inferior wall.


Personnel:  R. E. Kleiger, M.D., Jewish Hospital
           T. F. Martin, M.D., Medicine
           J. P. Miller, BCL
           G. C. Oliver, M.D., Medicine
           B. A. Sandefur, B.A., Jewish Hospital
           D. P. Wheeler, Jewish Hospital

Support:    RR 00396
           HV 12481
           Jewish Hospital
           Washington University

Analysis of manual scan data obtained on the post myocardial infarction patients has continued. Detailed analysis of 194 patients has been completed and 1417 ten hour tapes have been scanned for atrial and ventricular arrhythmias with all analyzed tapes graded according to the Lown and K classification for ventricular and atrial arrhythmias respectively. (1)

The results demonstrate that with repeated monitoring, more than 95% of patients show ventricular arrhythmias. Mortality is correlated
significantly with Lown class but most strongly with early PVCs. Higher Lown classifications are associated with the presence of early PVCs although early PVCs can occur with any Lown class except 0. Atrial arrhythmias which occur in about 12% of tapes are also correlated with high Lown classes. Over the period one month to two years, the distribution of Lown class remains the same with about 10% of tapes at any recording session showing couplets (L-4) or runs (L-5) and about a third exhibiting no PVCs. Furthermore, individual patients show remarkable stability in Lown class from one recording session to another with 85% remaining in the same or adjacent classes on subsequent recordings.


A-4. Processing of Holter Tapes Using Argus/H

Personnel:  
K. W. Clark, BCL  
H. D. Ambos, BCL  
J. R. Cox, Jr., BCL  
M. L. Dunne, BCL  
S. E. Katzen, BCL  
R. E. Kleiger, M.D., Jewish Hospital  
R. J. Krone, M.D., Jewish Hospital  
D. K. McDermott, BCL  
T. F. Martin, M.D., Medicine  
J. P. Miller, BCL  
F. M. Nolle, BCL  
G. C. Oliver, M.D., Medicine  
R. W. Sutherland, BCL  
L. J. Thomas, Jr., BCL  

Support:  
RR 00396  
HV 12481  
Washington University

Processing of ECG tapes for the study of ventricular arrhythmias and sudden death using the Argus/H system has continued since August, 1973 under the same procedure previously outlined (PR 10, A-4) except as noted below.

The demand for more exact and extensive clinical information concerning ventricular arrhythmias prompted major changes to the edit program (A-11) which in turn required a new editing protocol. The editor now forces or inserts PVC labels into the Cycle stream where none exist, but should, and ensures that onsets of each PVC and that of the preceding QRS complex are correct by manipulating such onsets if necessary. The editor is required to obtain a strip
of the earliest PVC in the record; the edit program has been amended to automatically display that PVC for the editor.

ECG strips are generated on fanfold paper via the Siemens recorder (A-12) at 4 times real time. The strips include Cycle-stream annotation with the waveform as well as tape and time identification.

Argus/H summary data with the cardiologists' review classifications (Lown and early, middle, late; see A-5) are no longer keypunched but entered directly into a MUMPS/7 data base called SUMMARY LOG (A-14) for later statistical analysis.

After a tape has been edited and a gross summary produced, the Cycle stream is written on magnetic tape with other Cycle streams. These are forwarded to the IBM System/360 for high-level statistical analyses of the individual Cycle streams. The data base of Cycle streams is also available for analyses of successive recordings for any one patient as well as analyses among patients. Though this data base is fairly recent, work has begun to extract pertinent information from each Cycle stream, including: tape ID; patient number; recording session number; length of tape; dates of edit and summary; data loss; numbers of normal beats, PVCs, couplets and runs; average QRS duration for normal beats and for PVCs; average heart rate; maximum and minimum 5 minute heart rates; peak PVC rate; frequency distributions of coupling intervals for isolated PVCs, couplets, and runs; average coupling intervals for isolated PVCs, couplets, runs, and the earliest PVC.

A-5. Ventricular Arrhythmias in the Early Post-Hospital Phase of Myocardial Infarction: Results of Argus/H Processing

Personnel: G. C. Oliver, M.D., Medicine
K. W. Clark, BCL
J. R. Cox, Jr., BCL
R. E. Kleiger, M.D., Jewish Hospital
T. F. Martin, M.D., Medicine
J. P. Miller, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HV 12481
Jewish Hospital
Washington University

We have recently evaluated arrhythmias which occur during the early post-coronary care unit phase of myocardial infarction (2 weeks - 3 months). A total of 689 tapes from 222 patients have been analyzed by Argus/H for quantitative evaluation of PVCs. For each tape, average PVC rate (PVCs per hour) was determined by dividing the total number of editor-verified PVCs on the tape by the length of the recording. The tapes were additionally
graded according to the Lown classification scheme where L-0 represents no PVCs, L-1 unifocal PVCs less than 10/hour, L-2 frequent unifocal PVCs greater than or equal to 10 per hour, L-3 multif orm PVCs, L-4 PVCs in pairs, and L-5 ventricular tachycardia (3 or more PVCs in a row). In addition, tapes were classified as early, middle or late, if they contained one or more PVCs meeting the early, middle or late criteria. An early PVC is one which is in or abuts the T wave of the previous beat, a middle PVC occurs within .04 seconds of the previous T wave and a late PVC is any other PVC. The results of this analysis are shown in Figure 1. One of the most striking changes occurs between two weeks and one month post MI in which there is a decrease in the proportion of patients in L-0 from 26% to 13%. The proportion of patients at one month in L-3, L-4, or L-5 shows a corresponding increase with the greatest change noted in the increased proportion of patients in L-5. From one month to three months there is no striking change in the proportion of patients in each of the Lown categories. Of 132 patients from whom recordings were taken at both two weeks and one month following infarction, 95 showed a change in Lown class with 68 showing an increase and 27 a decrease (p < 0.001).

Figure 2 shows the PVC rates obtained in these 222 patients during the same time period. Between 2 weeks and one month there is a marked increase in the percentage of patients having between 10 and 100 PVCs an hour with a corresponding decrease in the percentage of patients having no PVCs. Of 132 patients who had PVC rates determined at both two weeks and one month, 91 showed an increase in PVC rates with only 41 showing a decrease (p < 0.001). These results show that striking changes apparently take place between two weeks and one month in both the Lown classification and in the PVC rates of patients recovering from myocardial infarction. The cause of this phenomenon is not known but could be related to less adherence to antiarrhythmic medications once the patient returns home, or to increased activity.

Argus/H analysis reveals that there is a relationship between the Lown classification and the average hourly PVC rate (Figure 3). Patients classified L-1 showed average PVC rates of approximately 0.3 per hour whereas those in L-5 averaged approximately 50 PVCs per hour. Thus, there seems to be a clear association between the absolute frequency of PVCs and the occurrence of types of electrical instability such as couplets or runs of ventricular tachycardia.
Figure 1. Distribution of Lown Classes Post Myocardial Infarction

Months Post MI
0.5 1 2 3

Number of tapes
0 10 20 30 40 50 60 70 80 90 100

- 31 -
Figure 2. Distribution of PVC Rates Post Myocardial Infarction

Months post MI

No PVCs

<1/hr

1-10/hr

10-100/hr

>100/hr

Percent of tapes

Number of tapes

184 161 181 163
Figure 3. Relation between Lown Class and PVC Rates

Heavy vertical lines indicate means of log of PVC rates for each Lown class.
A-6. Quantitative Analysis of Ventricular Arrhythmias in a Population of Low-Risk Subjects

Personnel: J. P. Miller, BCL
K. W. Clark, BCL
R. E. Kleiger, M.D., Jewish Hospital
G. C. Oliver, M.D., Medicine
B. A. Sandefur, B.A., Jewish Hospital

Support: RR 00396
HV 12481
Jewish Hospital
Washington University

To place in perspective the ventricular arrhythmias observed in a population of post-myocardial-infarction patients, a group of subjects free of not only clinical heart disease but also of standard risk factors was studied. Individuals who had been screened by the St. Louis Heart Association and found to be free of the coronary heart disease (CHD) risk factors of hypercholesterolemia, hypertension, diabetes, cigarette smoking and ECG abnormalities were recruited for the study. Holter recordings were obtained from each subject, a standard 12 lead ECG was recorded, and a brief questionnaire administered. Subjects who currently reported clinical heart disease, diabetes, or smoking were excluded.

Forty-four subjects remained whose tapes were technically satisfactory for processing by Argus/H (A-4). The tapes were graded by the Lown scheme. The average age of the 37 men and 7 women was 50 with a range of 32-66. They all denied histories of heart disease, including angina pectoris, myocardial infarction, palpitations, abnormal ECG, shortness of breath and murmurs. They also denied histories of renal disease, stroke, diabetes, and abnormal chest X-rays.

The tapes were intermingled with the tapes of the post MI patients and processed in such a fashion that the difference was unknown to both the editors and the reviewers. The results of the processing were then compared to the ambulatory outpatient recordings obtained 1-3 months post infarction from 222 MI patients. The Lown classes resulting from the review process are compared in Table I.
Table I

Distribution of Lown Class (%)

<table>
<thead>
<tr>
<th>Lown Class</th>
<th>Low Risk Subjects</th>
<th>Post MI Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - no PVCs</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>1 - &lt;10/hr. unifocal PVCs</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>2 - &gt;10/hr. unifocal PVCs</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3 - multiform PVCs</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>4 - couplets</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>5 - ventricular tachycardia</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Although the patients with proven coronary heart disease more frequently demonstrated ventricular arrhythmias, 32% of the low risk group demonstrated ventricular arrhythmias more severe than occasional PVCs. Comparing the two groups of tapes (Table II) with respect to PVC rate shows a similar trend with 23% of the low risk subjects demonstrating a rate greater than 1/hr. against 55% of the post MI patients.

Table II

Distribution of PVC Rates (%)

<table>
<thead>
<tr>
<th>Rate</th>
<th>Low Risk Subjects</th>
<th>Post MI Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>no PVCs</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>0 - 1/hr.</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>1 - 10/hr.</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>10 - 100/hr.</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>&gt;100/hr.</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Three patients (all of whom were overweight) reported that in the past they had been told that they had high blood pressure. Another subject demonstrated left axis deviation on his 12 lead ECG at the time that the Holter recording was made. If these 4 subjects are eliminated from the analysis, the distribution of subjects according to Lown class changes only slightly with 48% demonstrating no ventricular arrhythmias. Whether the subjects who are free of any of the standard risk factors but demonstrate significant ventricular arrhythmias are at increased risk remains an unanswered question. The demonstration that 13 of 40 "risk free" subjects showed peak PVC rates greater than 10/hr., multiform PVCs, couplets or runs of PVCs raises the possibility that long term ECG monitoring may be useful for identifying individuals at increased risk of developing clinical CHD.
A-7. **Long-term Course of Ventricular Arrhythmias Following Myocardial Infarction**

**Personnel:**
- K. L. Ripley, BCL
- J. R. Cox, Jr., BCL
- M. L. Dunne, BCL
- D. K. McDermott, BCL
- J. P. Miller, BCL
- F. M. Nolle, BCL
- G. C. Oliver, M.D., Medicine
- R. W. Sutherland, BCL

**Support:**
- RR 00396
- HV 12481
- Washington University

Argus/H scans of 10-hour Holter tapes have been completed through the one-year post myocardial infarction (MI) recording for 20 patients. This represents 10 tapes per patient which were recorded monthly through six months post MI and then at three month intervals thereafter. Analysis of the mean hourly PVC rates (MHRs) as measured by Argus/H has revealed that certain patients demonstrate marked increases in MHR late during MI recovery. Of the 20 patients studied, 7 (35%) had characteristic increases in MHR which occurred at about nine months post MI. The 7 patients had four-month baseline MHRs averaging 22, but the maximum MHRs encountered for the remaining 13 patients averaged 49 and were evenly distributed throughout the one-year study period. Furthermore, the following criteria tentatively define the MINIMUM characteristics of these 7 patients:

1. The MHR peak contains at least 2 points and occurs after 3 months post MI.

2. At least one point in the peak must be greater than 75.

3. If the two points are consecutive, one must be greater than twice the baseline MHR and the other three times the baseline MHR.

4. If the two points are not consecutive both must be three times the baseline MHR.

Baseline MHR is defined to be the mean of two or more consecutive points which are both less than 60 and are prior to the first point after 3 months which is greater than 60.

Work is in progress to confirm this preliminary observation for a larger population, to delineate the characteristics of these late increases in MHR, and to determine what factors contrast the two groups. Although the
significance of these findings is not yet clear, this previously unreported increase in PVC rate could have major implications for patient management and administration of antiarrhythmic drug therapy.

A-8. A Study of Antiarrhythmic Drug Therapy Using Argus/H

Personnel: R. J. Krone, M.D., Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
J. P. Miller, BCL
G. C. Oliver, M.D., Medicine
R. W. Sutherland, BCL

Support: RR 00396
HV 12481
Jewish Hospital
Washington University

The ability of Argus/H to quantitate ectopic ventricular beats permits its use to evaluate the effectiveness of antiarrhythmic drug therapy. Accordingly, a protocol was devised to evaluate the results of treating patients with diphenylhydantoin, quinidine sulfate, procainamide and placebo in a double-blind randomized study. Twenty-four-hour Holter recordings were obtained after one week on each drug. In order to estimate day to day variability and to control for change in patient status, for the last eight patients, two Holter recordings were obtained on each drug and one additional recording was obtained after discontinuation of all drugs. Dosages chosen were those in common clinical usage, i.e. diphenylhydantoin 400 mg per day, procainamide 2 gm per day, quinidine sulfate 1.2 gm per day and placebo in four divided doses. A loading dose of 500 mg of diphenylhydantoin was also given, but no loading doses of the other drugs were utilized. Patients were selected from the population studied in the investigation of ventricular arrhythmias and sudden death and from the patients following coronary artery bypass surgery who demonstrated two or more recordings with 50-100 PVCs per hour and Lown classifications 3, 4, or 5. Twelve patients completed the protocol and preliminary data is available on nine. In two of these nine patients, diphenylhydantoin was terminated for non-cardiac side effects. With the Argus/H editing system, diurnal and day to day variations in ventricular arrhythmias could be distinguished from antiarrhythmic effect. In four patients, one or more antiarrhythmic agents reduced PVC rate by 75%. On five patients, one or more antiarrhythmic agents increased PVC rate by 35%. Couplets and runs were reduced by 75% by one or more antiarrhythmic agents in four out of six patients and were increased by two agents in one patient. All agents had beneficial effects on PVCs in some patients (Dilantin 3, Pronestyl 3, Quinidine 3) and deleterious effects on PVCs in others (Dilantin 1, Pronestyl 4, Quinidine 3). The data to date show that the antiarrhythmic agents have highly individualistic effects and that careful methodologic control with quantitative evaluation of response to treatment is required for their effective utilization.

Personnel:  R. J. Krone, M.D., Jewish Hospital
A. S. Geha, M.D., Jewish Hospital
Y. Hamuth, M.D., Jewish Hospital
G. C. Kaiser, M.D., St. Louis University
R. E. Kleiger, M.D., Jewish Hospital
J. P. Miller, BCL
G. C. Oliver, M.D., Medicine
R. W. Sutherland, BCL

Support:  RR 00396
HV 12481
Jewish Hospital
St. Louis University
Washington University

An intervention currently being used to alleviate angina pectoris in patients with severe coronary artery disease is coronary bypass surgery. This study was designed to evaluate the effect of this surgery on arrhythmias. Three 24-hour Holter recordings were obtained prior to surgery and compared with three recordings obtained two months to one year following surgery and an exercise test was obtained six months after surgery. The first 10 hours of the 24-hour tapes were analyzed via Argus/H and then reviewed by two cardiologists. All couplets and runs of PVCs were verified and counted.

Twenty-four patients completed the protocol but one was dropped from the study because of evidence of a cardiomyopathy. Of the 23 patients included, 17 had three-vessel disease (50% or more reduction in vessel diameter), 3 had two-vessel disease, and 3 had one-vessel disease. For 13 of the 23 patients, one or more of the diseased arteries were not treated (bypassed) surgically. Ten patients had no evidence of an infarct before surgery and four of these suffered infarcts post-operatively. Of the 13 with pre-operative infarcts, five had new infarctions after surgery.

At this writing, the data have not been fully analyzed but some preliminary generalizations seem warranted. Nine patients showed no clearly important change in PVC rates, i.e. neither a halving nor a doubling or, where pre-operative rates were low, a change of more than one PVC per hour. Twelve showed an increase by at least a factor of two, and only two showed a reduction to less than half their pre-operative PVC rates. In this context, the recordings showing the highest average PVC rates for the pre- and post-operative periods were compared since vulnerability to serious arrhythmias is the primary concern. Similarly, six patients revealed no change in Lown class, twelve increased, and only five decreased (frequently by more than one class for both).
This study thus fails to show any overall improvement in PVC rates or Lown class following coronary artery bypass surgery. It fails also to suggest that the procedure protects against subsequent myocardial infarction. It should be emphasized however, that it is premature to conclude from these observations that coronary artery surgery is not beneficial in the above respects since: (1) the intrapatient variance is large; (2) complicating factors are difficult to evaluate with such small subgroups; and (3) patient activity levels were likely increased after surgery as compared to the pre-operative period. The studies noted here do not, of course, address themselves to the primary intent of the surgery, i.e. the relief of angina.

**A-10. Infarct Size and Cardiac Electrical Instability**

**Personnel:** B. E. Sobel, M.D., Medicine  
H. D. Ambos, BCL  
J. R. Cox, Jr., BCL  
R. Roberts, M.D., Medicine

**Support:** RR 00396  
HL 17646  
HV 12481  
Washington University

During the past year, studies have been completed concerning the relationship between infarct size estimated enzymatically and electrical instability of the heart. In 25 anesthetized open-chest dogs, ventricular fibrillation threshold was determined before and after experimentally induced myocardial infarction and compared to infarct size estimated from serial changes in serum CPK activity, myocardial CPK depletion, and gross morphologic criteria. An additional series of dogs was used for determination of ventricular fibrillation threshold before and after coronary occlusion in experiments designed so that a series of occlusions could be produced without the need for reoperation. The extent of depression of the threshold to ventricular fibrillation 15 minutes after coronary occlusion correlated closely with infarct size as estimated by gross morphologic changes (r = .92). In addition, estimates of infarct size obtained enzymatically correlated with estimates obtained at necropsy (r = .90). Further findings indicated a substantial depression of the threshold to ventricular fibrillation after 24 hours of coronary occlusion and a significant correlation between the magnitude of depression of ventricular fibrillation threshold and myocardial infarct size.

In a second series of studies performed in the Barnes Hospital Cardiac Care Unit (CCU), the relationship between ventricular dysrhythmia and the extent of myocardial infarction estimated enzymatically was explored in patients. Patients selected were those with evolving acute myocardial infarction without shock. Infarct size index was estimated from hourly serum CPK and MB CPK enzyme changes. The incidence of ventricular dysrhythmia was quantified with the use of the Argus/H system by analysis of 20-hour continuous electrocardiographic recordings. Patients were divided into groups according to infarct size index as follows: Group 1, infarct-size index 1-24
CPK-g-eq (n = 12); Group 2, infarct-size index from 25-49 CPK-g-eq (n = 20); and Group 3, infarct-size index equal to or exceeding 50 CPK-g-eq (n = 18). Although the Norris prognostic index was significantly greater in Group 3 patients, indicative of a poor outlook based on clinical and demographic data, the value of the index in Group 1 and Group 2 patients was virtually identical. Serum potassium levels and arterial oxygen tensions were similar in all three groups. Premature ventricular complexes during the 20 hour interval of recording averaged 54±21 (S.E.), 99±33, and 635±258 for groups 1 to 3 respectively. The incidence of couplets or ventricular tachycardia combined, averaged 1.5, 4.3, and 9.9 respectively. All differences between groups were significant at the .01 level. These results indicate the severity of ventricular dysrhythmia early after myocardial infarction is related to the extent of myocardial injury manifested by enzymatic criteria of infarct size. They suggest that the efficacy and evaluation of antiarrhythmic agents in this setting may be influenced by the magnitude of ischemic injury sustained by the heart.

The Argus/H system has been used in additional studies recently completed in the Barnes Hospital CCU. In one series of 39 patients, the frequency of ventricular dysrhythmia was quantified, infarct size was predicted from projected serum CPK values using an empirical algorithm for curve-fitting and infarct size was estimated from serial 48-hour serum CPK changes. In the treated group of patients (n = 13) external circulatory assist was performed for 30 minute intervals with 15 minute rest periods for a total of 18 hours beginning immediately after prediction of infarct size. With this intervention, diastolic pressure was augmented by at least 30 mm Hg. The frequency of ventricular premature beats was decreased within one hour in all but one patient and the reduction was significant in comparison with changes in ventricular dysrhythmia in controls. However, during the remaining interval of external circulatory assist, the frequency of ventricular dysrhythmias did not remain depressed in comparison with controls and no evidence was obtained indicating salvage of myocardium on the basis of CPK changes. Thus, external circulatory assist decreases ventricular dysrhythmia transiently after its initiation in patients with myocardial infarction, but the effects are not persistent despite maintenance of circulatory assist and the intervention does not lead to detectable salvage of myocardium.

A second study recently completed was concerned with the use of methylprednisolone to limit infarct size in patients with myocardial infarction. Results in experimental animals have indicated potential benefit from this intervention, perhaps due to stabilization of lysosomes in myocardium. In the patient study conducted recently we administered methylprednisolone in single or multiple doses of 30 mg/kg beginning seven hours after the onset of serum CPK elevations and continuing in the case of multiple doses at six hour intervals for forty-eight hours. Ventricular dysrhythmia was quantified with the Argus/H system and myocardial injury assessed from serial serum CPK changes. Methylprednisolone did not affect the enzyme method as determined by independent experiments in-vitro and in conscious animals. Administration of single doses of methylprednisolone neither influenced the frequency of ventricular dysrhythmia nor altered the enzyme curves in comparison with those obtained in control patients. On the other hand, among patients treated with multiple dose methylprednisolone, observed infarct size exceeded that predicted prior
to the intervention by an average of 72% (p<.01) indicating progression and augmentation of myocardial injury. In addition, the severity of ventricular dysrhythmia was substantially greater after methylprednisolone treatment than in controls and MB CPK, the "myocardial" isoenzyme remained elevated in serum of treated patients much longer than in controls or patients treated with single dose methylprednisolone. The results of this study indicate that despite encouraging findings in animals, high doses of methylprednisolone administered in multiple dose regimens not only fail to protect jeopardized myocardium but exacerbate ventricular dysrhythmia and potentiate myocardial injury.

Results of these studies have been presented. (1 - 7)


A-11. Argus/H: Program Development

Personnel:  K. W. Clark, BCL
            J. R. Cox, Jr., BCL
            C. N. Mead, BCL
            J. A. Ritter, BCL
            R. W. Sutherland, BCL
            L. J. Thomas, Jr., BCL

Support: RR 00396
         HV 12481

The Argus/H system for rapid analysis of long ECG records consists of several programs accessible from an executive routine called ARGEXEC. ARGEXEC, together with other executive routines for handling assemblies, MUMPS programming, general file operations, tape and disc utilities, and hardware test utilities are all accessible from a master executive called UTILITY. UTILITY remains core resident for most individual programs; it includes all fundamental I/O routines, thus precluding the necessity of retaining object code for such routines in individual programs. All programs except the assembler and MUMPS/7 reside in a single IBM System/7 Disc Support System data set.

The programs related to ECG processing contained in ARGEXEC consist of three categories: high speed scan, interactive data review and edit, and generation of summary results. These are reported separately.

High-speed scan. The core routines of sample decode and display, Aztec, and Primitive have undergone no changes. The Cycle algorithm has been amended but not yet thoroughly evaluated nor implemented for routine operations to flag T-waves which might otherwise be falsely called PVCs. The T-wave detection is based on some contextual "learning" in that sequential, temporal, and morphological criteria must be met before the members of a feature-set ("family") are accepted as definite T-waves. Other potential or probable T-waves are then subsequently evaluated in terms of their similarity or sameness as per floating family-feature apertures. Multiple "definite-T-wave" families are allowable in order to cope with evolving morphologies. Early evaluation results indicate that false-positives due to large T-waves are nearly eliminated but without compromise of true-PVC detection. A broader evaluation is now in progress.

The Cycle stream generated by the Argus/H scan consists of Cycle data (beat kind and time identifiers plus serial number) and feature data (QRS duration, height, offset, and area). Features appear whenever a new family is born or whenever any feature maximum or minimum changes. Programs using the Cycle stream (edit, summary, and many developmental programs) have never used intermediate feature measurements, only the final features for any family. Thus, superfluous feature data in the midst of Cycle required that programs accessing the Cycle stream distinguish between Cycle and features,
an unnecessary and time-consuming operation. A "re-order" Cycle program was
written to separate the Cycle data from the features and, for the features, save only the final feature measurements for each family in the stream. The family population is also included in the stream. The re-order program executes following the Argus/H scan.

Interactive data review and editing. The edit program (PR 10, A-6) has been considerably amended to operate faster with the additional memory in the IBM System/7 (A-12) and to provide more accurate clinical information.

The edit program outputs selected ECG strips of 8 or 16 seconds on a Mennen-Greatbatch recorder at real-time (times one or X1) speed or on the Siemens recorder (A-12) at X4. Siemens output includes waveform, Cycle label and edit annotation, tape identification number, and time of strip.

The edit program now permits the editor to "force" corrected Cycle labels or to delete the label entirely. Where no Cycle label exists, one may be "inserted" into the Cycle stream. If PVC onsets are incorrect or/and onsets of QRSs prior to the PVCs are incorrect, those onsets may be "moved" with editor-assisted cursors to accurately reflect coupling intervals. Appropriate bits are set in the Cycle stream to record any force, insert, or move actions by the editor.

Before exit is made to ARGEXEC, the edit program presents the editor with the earliest true PVC of the edited tape. The editor may then make a strip if he has not already done so.

Editing is needlessly monotonous and repetitious where one must edit the same shaped waveforms again and again. Efforts are underway to offer a "family edit" in order to eliminate the repetition and to substantially reduce edit time. The family editing involves first defining a "search population" from the Cycle-stream data by selecting provisional PVC families with populations of non-normal beats larger than a specified threshold. Non-sequential examples from these selected families are then presented to the editor whose responses are noted and propagated to all other family members automatically. In addition, the features of the true-PVC families are compared with those of all other non-normal families for similar action on those deemed "close to" the true-PVC families. This results in the additional detection of PVCs from the same focus but which have been placed in different families due to sensitive Argus measurements and slight timing deviations.

Generation of summary results. For each tape edited, a PVC plot, heart rate plot, and gross summary (PR 10, A-6) are printed. The gross summary has been amended to include counts of force, insert, and move actions by the editor.

New printouts include a PVC coupling interval histogram and a listing of coupling intervals for individual couplets and runs. The Cycle stream for each tape is packed with other Cycle streams on magnetic tape for later higher level analysis on the IBM System/360.
Several programs not related directly to routine ECG processing but extremely valuable to developmental efforts have been written. One of these is the printing and displaying of the Cycle stream in a format more readable than its raw form. Another program summarizes two time-comparable Cycle streams by presenting a matrix of Cycle labels of one stream against the next; this kind of program has proven invaluable in testing the effects of any changes to the Argus algorithms.

Numerous other programs for communications, disc, and tape utilities as well as hardware test programs have been written as needs arose; they are not detailed here.

A-12. Argus/H: Hardware Development

Personnel: H. D. Ambos, BCL
R. E. Hitchens, BCL
J. A. Ritter, BCL

Support: RR 00396
HV 12481

Additional memory (8K) was installed in each IBM System/7. A 9600-baud Beehive Minibee terminal was installed on the leased System/7.

A Siemens Oscillomink high-speed liquid-jet chart recorder was installed. Because the recorder has a frequency range of 0 to 1000 Hz, ECG traces are perfectly legible at 250 mm/sec; however software generated QRS labels and identification characters are not legible at this speed. Typical operation is 100 mm/sec.

The printer and D/A driven high-speed oscilloscope and chart recorder are now operating with the BCL-designed IBM System/7 interface (H-11).
The digitizing and scanning aspects of ECG processing (PR 10, A-8) have undergone no significant changes except the replacement of the Avionics Model 650 Electrocardioscanner with a Model 660 capable of dual-channel playback.

Tapes edited during the year came from a variety of sources, predominantly from the study of ventricular arrhythmias and sudden death or "core project study" (A-1). Others were from the infarct size study (A-10), coronary bypass study (A-9), drug study (A-8), long-term follow-up study (A-7), low risk subjects (A-6), system evaluations (A-16), and annotated data base efforts (A-18). Total numbers of tapes processed since Argus/H became operational in August 1973 are core project: 900, infarct size study: 300, coronary bypass study: 138, drug study: 142, long-term follow-up study: 55, low risk subjects: 45, system evaluations: 81, annotated data base efforts: 19.

Lengths of records for the different studies vary but 10 hours is typical. Different studies have required different information to be extracted from a tape; for example, the infarct size study required the numbers of couplets and runs and when they occurred, while the drug study requires exact coupling intervals as well. Depending on the amount and kind of information needed, the time required to edit a tape may vary from study to study. For the core project tapes, over 70% took one-half hour or less to edit and less than 11% required more than one hour. Drug study tapes, in contrast, on the average require 1.75 hours/tape editing time.
Patient records of Holter recordings, analog tape manual scanning records, editing records, and results of cardiological review of tape folders have continued to be maintained in MUMPS/7 data bases (PR 10, A-11; PR 10, A-19). The logs are called PATIENT LOG (PLOG), EDIT LOG, and SUMMARY LOG.

Initially, the three logs were maintained on separate tape files since the evolution of MUMPS/7 had been a tape oriented system. Each tape contained the MUMPS/7 interpreter, the data base, and related programs. For the three logs, three tapes were required. However, in the core project study of ventricular arrhythmias and sudden death (A-1), it soon became necessary to cross reference the 3 data bases or logs in order to follow the flow of individual tape processing, to perform some quality control functions on data entry, and to be able to print meaningful summary information for management perusal. A first attempt to merge the three files proved unwieldy since the files were still maintained on tape and merged only for programs requiring cross referencing. Multiple tape loads to disc and disc copies were required. The second attempt resulted in the present disc system which is devoid of magnetic tapes. All three logs plus the MUMPS/7 interpreter plus MUMPS/7 programs requiring access to the logs are maintained on a single disc cartridge. The amount of data includes recording session data on the 286 patients in the core study, the manual scan results for the 2444 Holter tapes collected, and the log of editing operations and summary statistics for some 900 computer processed tapes.

A master summary, called the Core Project Status Log (CPSL), provides a well ordered printout of all currently stored information in the three logs by patient and, for each patient, by recording.

The success of the MUMPS/7 disc version of the three merged logs prompted the creation of an analogous system for the Coronary Bypass Study (A-9). This system contains information for 33 patients and 138 analog and edited digital tapes.
As part of a detailed evaluation of the performance of the Argus/H Holter-tape processing system, a study of the reproducibility of the final report data was undertaken (PR 10, A-9; A-11). Forty-three 10-hour tapes were selected at random from the nine-month processing period August 1973 through April 1974. The original digital tapes were removed from storage and blank tapes with identical markings substituted. Each tape was then designated as needing redigitization and reprocessing. Such events occur normally in the analysis procedure. Regular personnel then handled these tapes in their normal fashion without any knowledge of the reason for their redigitization. The completed folders were intercepted after completion of the review process and the data were compared with those generated by the original processing. Three measures of reproducibility were made on each tape: Lown class assignment (0-5), PVC coupling-interval assignment (early, middle, late) and mean hourly PVC rate.

Comparison of the Lown class assignments for the first and second processings show that this assignment did not change in 81% (35/43) of the cases. Six of the remaining eight cases showed a change in Lown class of only one step and the last two had a change in Lown class of two steps. Although this result was felt to be quite satisfactory, a detailed analysis was made of the sources of errors in each of the eight cases where a change in Lown class occurred. This analysis indicated that the errors were fairly evenly divided among the reviewer (3), the editor (4) and the computer (4). It should be noted that a given change may have more than one source of error.

Comparison of the PVC coupling interval (CI) results from the two processings of each tape showed a satisfactory level of reproducibility for PVC-PVC CI classifications: of fourteen tapes with two consecutive PVCs, 9 showed no change. Of the five that did, all were one-step changes. However, the reproducibility of the non-PVC to PVC coupling interval assignment was somewhat poorer. Of the 36 tapes with PVCs, 25 had no changes in CI assignment, while 11 did. These changes were frequently of the early-to-late or late-to-early type. Although more variability was expected in CI classification than in Lown class assignment, the variability observed for non-PVC to PVC CI assignments was felt to be too high. Hence, a detailed error analysis was made of those tapes which showed a two-step change in CI classification. Here the error sources were mainly the editor (4) and the computer (4); the reviewer had caused only a single error. These errors on the part of the editor and the computer were primarily omission errors, i.e.
appropriate data was not available for the reviewer to make an accurate decision. These kinds of errors prompted changes to the edit program (A-11).

The final index studied was the mean hourly PVC rate (MHR). Of the forty-three tapes, twenty six had MHRs $\geq 1$. The average percentage change in MHR for these twenty-six tapes was 18% with MHRs of small magnitude showing more variation than those of large magnitude. Five tapes had MHR changes greater than 25%. These tapes were again studied in detail to determine any sources of error. As might be expected, the computer was the major error source (5) while the editor caused two errors and the reviewer none. The computer errors are probably due in part to variation in gain settings between the two processings, noisy records, and a large number of normal-appearing PVCs.

**A-16. Argus/H: Evaluation Efforts**

**Personnel:**
- F. M. Nolle, BCL
- K. W. Clark, BCL
- J. R. Cox, Jr., BCL
- R. E. Kleiger, M.D., Jewish Hospital
- R. J. Krone, M.D., Jewish Hospital
- T. F. Martin, M.D., Medicine
- J. P. Miller, BCL
- G. C. Oliver, M.D., Medicine
- K. L. Ripley, BCL
- L. J. Thomas, Jr., BCL

**Support:**
- RR 00396
- HV 12481
- Washington University

Evaluation of the present system for production analysis of Holter tapes with Argus/H must involve procedures for measuring both human and machine performance. The four processing steps of digitization, high-speed scan, edit, and review must all be performed properly to obtain reliable and consistent results. Of these steps, all but the high-speed scan rely mainly on human ability. Several evaluation efforts have been underway to measure over-all system performance as well as characteristics of individual processing steps.

**Validation.** A set of 34 segments of ECG data with a total duration of about 10 hours comprise the only certified validation data set for the Argus algorithms (PR 7, B-1). Validation of Argus/H using this data set is reported separately elsewhere (A-17).
Reproducibility. A completed study which measures the stability and reproducibility of the complete Holter processing system is reported elsewhere (A-15).

Manual Scan Comparison. To determine how many significant ventricular arrhythmias were being missed by computer processing, a comparison was made of computer Lown classification results with those of manual scanning. To reduce the effect of cardiological review, the manual scan records used for the test were first subjected to additional independent reviews to replicate the Lown classification procedure used for computer analysis. Of 98 records analyzed by both procedures, the computer generated Lown classifications were at least as high as those by manual scanning in all instances but one. The single record in which manual scanning was superior showed one PVC on the manual scan report whereas none was detected by computer analysis. The Lown classifications by computer were greater than those of manual scanning in 44 of the 98 records.

Processing Time. In our current system, digitizing is performed off line using special purpose hardware and operates at 60 times real time, or one minute per hour of ECG, excluding set-up time.

Processing time distributions for the automatic high speed scan have been previously reported (PR 10, A-8). The average analysis time required was 1.34 minutes per hour of ECG data measured on 50 tapes from 50 different subjects.

The time required to edit a tape is much more variable than the time required for digitizing and scanning. It is recorded to the nearest quarter hour in a log of editing operations (PR 10, A-11). For the first 658 tapes from the core study (A-1), averaging 9 hours in length, the minimum edit time of one-quarter hour was recorded for 299 tapes or 45.4%. Over 70% required one-half hour or less to edit. Less than 11% of the tapes required more than one hour of editing time. Editing of drug study (A-8) tapes is a longer process primarily because each tape is quite rich in PVC content. For the first 104 drug tapes processed, editing time averaged 1.75 hours per 12-hour tape. In summary, editing time has been proven to be greatly dependent on the average number of total Argus/H identified PVCs per tape; efforts to reduce this edit time are underway (A-11).

Editor Evaluation. Forty previously edited computer ECG tapes were re-edited using a special program to call attention to editing discrepancies. Less than 1% of some 20,000 Argus/H flagged PVCs were misedited which would indicate that the editing process is quite reliable.

Detection Accuracy. While the editing process virtually eliminates false-positive PVCs flagged by the Argus/H scan, the problem of false-negative PVCs (true PVCs missed by Argus/H) remains. Although a recent version of the editing program (A-11) permits the editor to "insert" a PVC label if he or she notes a missed PVC, this procedure does not capture false negatives not seen by the editor. Nineteen tapes were examined on a beat-by-beat basis and a total of 5006 PVCs were observed out of approximately 900,000 beats.
The Argus/H program correctly detected 3768 PVCs (75%). When those PVCs missed by the computer but noted by the editor were included, however, the total number of PVCs detected by the system was increased to 4452 or 89% of the 5006 PVCs observed in the beat-by-beat examination. In addition, a total of 43 couplets or runs of PVCs were present in the tapes and the computer/editor combination detected 39 (91%) of these. This study has shown that the PVC detection accuracy of the Argus/H system may be significantly increased by the editing process but additional work is needed to further reduce the incidence of false-negative PVCs.

The nature of missed PVCs is not yet completely evaluated, though preliminary efforts indicate the reasons are not different from those of the real-time Argus system (PR 7, B-1).

Cost. Table I below illustrates the approximate cost of processing a single 10-hour Holter recording from the point of scheduling the patient through final summary and documentation. The major cost item is the task of digital tape processing and editing in the supplies/equipment column ($33.10). The major components of this category are lease of the IBM System/7 plus amortization of purchased peripheral equipment ($20.00) and purchase of the magnetic tape ($11.00). The other significant item is overhead ($18.68). Figures in this table are based on the processing of 1500 tapes over a one year period at 1974-1975 wages and prices.
Table I. Cost Components per Holter Tape Processed

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<th>Time (minutes)</th>
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<th>Total</th>
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<td>Analog Tape Processing</td>
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<td>7.33</td>
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</tbody>
</table>

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Personnel: K. L. Ripley, BCL  
R. M. Arthur, BCL  
K. W. Clark, BCL  
J. R. Cox, Jr., BCL  
F. M. Nolle, BCL  
M. C. Rigden, B.A., Radiology  
J. J. Sueme, BCL  
I. Teicher, B.A., Mennen-Greatbatch Electronics, Inc.

Support: RR 00396  
Washington University

The PVC detection capability of three different implementations of Argus has been measured by allowing each version, original Argus or Argus/Original (Programmed Console), Argus/Sentinel (PDP-11) and Argus/H (IBM System/7), to process the same ECG data base and then comparing on a beat-by-beat basis the labels generated by each computer with those of a cardiologist. Argus/Original was previously evaluated using an annotated data base consisting of 15-minute segments of ECG on each of 38 patients collected while they were in the Barnes Hospital Coronary Care Unit. This same data base was used to carry out the present three-version evaluation of Argus.

Prior to the PVC evaluation of Argus/Sentinel, a significant effort had to be invested into correcting several program-timing and pointer-management errors which produced seriously degraded quality of operation. A 12-bit communication pathway was established between the Argus/Sentinel and the LINC-8 computers, both residing in the Barnes CCU. Programs were written to convert the Aztec data collected during the first Argus/Original evaluation back to sampled data and this data was processed by Argus/Sentinel. A new operating system was designed and overlayed on the Argus/Sentinel programs to allow precise controls of software operation. The Aztec, Primitive and Cycle data streams generated by Argus/Sentinel were sent back to the LINC-8 and listed on a printer. These data streams were manually compared with the Argus/Original data streams and discrepancies in the Argus/Sentinel output data were traced and corrected where necessary (PR 9, B-1; PR 10, VI; PR 11, VI).

Following correction of these basic processing errors in Argus/Sentinel, Cycle data streams were collected from all three Argus computers and fed to the System/7. Cardiologists' annotations were entered on the System/7 via the display terminal. All four data streams were merged using the MUMPS/7 language (PR 10, A-19) with the time of occurrence associated with each data stream entry used for time alignment. MUMPS/7 was then used to generate a four-dimensional matrix of comparison statistics. These statistics indicate that the PVC detection rates and false-positive rates were as follows:
<table>
<thead>
<tr>
<th></th>
<th>PVC Detection</th>
<th>False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argus/Original</td>
<td>78.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Argus/Sentinel</td>
<td>80.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Argus/H</td>
<td>80.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

The re-evaluation results on the Argus/Original are exactly the same as those collected previously. Argus/Sentinel and Argus/H show a 2% improvement in PVC detection with essentially no increase in false positives. Hence, both new versions were concluded to be satisfactory implementations of the original version of Argus.


A-18. Progress Towards a Data Base of Annotated ECG Waveforms

Personnel: T. Ferriero, BCL
           K. W. Clark, BCL
           F. M. Nolle, BCL
           A. Zencka, M.D., Creighton University

Support:   RR 00396
           HV 12481

As computer scanning algorithms and editing and review protocols change, evaluations of the performance of the Argus/H processing system are necessary. In order to perform such evaluations, an annotated data base is being constructed and an automatic comparison program has been written. The annotated data base is being constructed from short records selected from various tapes and digitized and scanned by Argus/H in the usual fashion. An initial test set of tapes consists of 19 one-hour segments from 19 ten-hour tapes; the hour from each tape covers the time period of maximum PVC rate. The test tapes were then edited beat-by-beat using some of the newer special features of the editing program (A-11) to relabel PVCs erroneously classified by the computer and to delete labels from waveforms such as artifact spikes which were falsely called QRS complexes. T-waves falsely called QRS complexes were relabeled as T-waves. The questionable PVC label was also used to identify uncertain waveforms. No
attempt was made to change QRS labels such as normal, borderline, abnormal or artifact if the QRS was not considered to be a PVC or questionable waveform.

To obtain cardiological overread of the records, the ECG is written continuously on paper along with the corrected labels using the Siemens high speed ECG writer operating at 4 times real time. The variations in non-PVC labels are suppressed; T-wave labels are not shown; and only the notations of V, ?, and *(QRS not a PVC) are placed on the records. A few intentional errors are also introduced to measure the alertness of the reviewers. The reviewers separately prepare exception lists for those waveforms considered to be erroneously labeled, differences are resolved, and the results are then used for final corrections to the data base. Presently, all 19 one-hour records have been collected and sent to the reviewers. Their results are expected soon and, with them, final work on the trial set can be completed.

A program to compare Cycle data streams for the annotated test set was initially written in the MUMPS language to facilitate investigation of the effect of different editing passes and different Argus/H scanning algorithms. Eventually, the program was rewritten in assembly language to obtain fast operation in high volume tests. The final program compares 2 Cycle data streams on a beat-by-beat basis and prints the results of its comparison in a matrix as well as totals for each row and column. The program thus allows quick and easy evaluation of the effects of any change made to Argus/H.

A-19. Evaluation Group for Arrhythmia Detectors

Personnel: J. R. Cox, Jr., BCL  
E. L. Alderman, M.D., Stanford University Medical Center  
C. L. Feldman, Ph.D., Worcester Polytechnic Institute  
T. F. Martin, M.D., Medicine  
J. P. Miller, BCL  
G. C. Oliver, M.D., Medicine

Support: RR 00396  
Jewish Hospital  
Washington University

Plans to process a set of ECG test tapes for evaluation of monitoring systems through a three-institute consortium consisting of Worcester Polytechnic Institute, Washington University and Stanford University Medical Center (PR 10, A-16) have been prepared and submitted to the NIH for financial support.

At the American Heart Association Meetings in the fall of 1974, the AHA Committee on Electrocardiography established contact with this evaluation group and discussed ways in which recommendations could be developed for the
evaluation of arrhythmia monitoring systems. Among the recommendations were
that specifications should be drawn up for three classes of systems: (1) analog
monitoring devices, (2) rate meter devices with so called "PVC detectors", and
(3) computer systems.

A-20. A Mathematical Model for an Evaluation Methodology

Personnel: J. R. Cox, Jr., BCL
T. Ferriero, BCL
Support: RR 00396
HV 12481

Good evaluations of arrhythmia detection systems are few in number and
flawed by insufficient data and questionable annotation. EGAD (A-19) has
as its goal the generation of a well documented test tape, but the method
of comparing results on this test tape is an open question.

A model of the evaluation process that suggests a method of comparison
is shown in Figure 1. The model shows patient j with a rate parameter \( \lambda_j \) and
a pattern difficulty measure \( q_j \) indicating how well the system does on a par­
ticular waveform. The computer system detects PVCs from the time-windowed ECG
signal. For a particular patient the system succeeds with probability \( q_j \) and
misses with probability \( 1 - q_j \). The result can be modeled as a point process
with a fraction of the PVCs deleted from the output. We want to compare the
input stream and the output stream of detected PVCs to get an estimate of how
well the system performs. Early data indicate that the distribution of the
rate parameter for PVCs in outpatients is log normal with an average for our
population of about 30 PVCs per hour.

The probability of a hit by the detection system is not uniform over
all patients. In fact, it varies widely from patient to patient. Some
patients have extremely difficult waveforms because, for example, the P or
T wave may be as big or bigger than the QRS or because a PVC may be projected
onto the recorded lead as if it were a normal. This variation in performance
with patient waveform has been included in the model.

Maximum likelihood estimation of the parameter describing the distribution
\( P_q \) provides a measure of system performance. In two cases we have analyzed, the
results seem more accurate than the ratio of the total number of PVCs detected
by the system to the total number of PVCs recognized by the electrocardiographer.

(1) J. R. Cox, "One-Dimensional Signal Analysis: Electrocardiographic Rhythms,"
in Biomedical Signal Analysis, L. D. Harmon, ed., Report of a Workshop held at
Case Western Reserve University, Cleveland, Ohio, January 12-14, 1975.
Figure 1.

Personnel: K. L. Ripley, BCL
J. R. Cox, Jr., BCL

Support: RR 00396
Washington University

A multi-patient monitoring system is being developed which will provide the facility to retrospectively capture two-hour segments of ECG data on up to eight patients in a coronary care unit (PR 9, B-13; PR 10, A-17). The system will continuously monitor eight patients and save ECG data in two-hour circular buffers on one of two disc drives. When an event of interest has occurred the machine is signalled and the desired buffer is "frozen" and placed in a permanent file without interrupting the monitoring of other patients. After the transfer is complete, monitoring is resumed on this patient. Normally the total sixteen hours of ECG data (2 hours from each of 8 patients) would require 144 megabits of storage assuming 250 samples/second and 10-bit samples. However, by Huffman encoding of the ECG data (1) a factor of three reduction in storage space may be obtained without any loss of accuracy. Since the cost of the storage device is a major part of the total cost of such a system, a considerable reduction in cost may be obtained by using this technique. In addition, the quality of the ECG data obtained is considerably better than would be obtained using analog tape. Furthermore, the data is stored in a format readable by Argus/H for subsequent arrhythmia analysis (PR 9, B-11).

At the present time, the multi-patient encoding and decoding algorithms have been written and tested. The disc storage routines are currently being tested and initially a three-patient system will be implemented on one disc drive. A second disc drive is expected to be installed within a month, following which the system will be expanded to the full eight patients. Work is in progress to install sense lines to switches in each patient room in the Barnes Coronary Care Unit where the system is installed. These switches will be used by medical personnel to signal the computer when a given patient exhibits some form of cardiac distress, whereupon the preceding two hours of ECG data on that patient will be permanently saved on a separate disc platter designated for this purpose. This data will later be analyzed by Argus/H for premonitory ventricular arrhythmias. Plans are also being made to use this system to collect three-channel surface lead recordings from patients simultaneously with His bundle recordings made in the special procedures room of the CCU. These recordings will allow verification of PVC labels made by both the cardiologist and Argus/H and may serve to enhance the Argus criteria for PVC detection.

The infarct size estimation programs (PR 10, B-1) have been used to analyze serial serum CPK data from approximately 80 selected patients and 40 dogs during the past year. Observed infarct size, based on the actual serum CPK values, was compared to predicted infarct size, calculated by projection of the CPK curve from a least-squares fit to CPK values obtained during the first five to seven hours after enzyme levels in the blood began to rise above normal. The results of these comparisons indicate that, on the average, observed and predicted infarct size correlate well, although for individual cases there may be a large discrepancy between the two values. Consequently, predicted infarct size may provide a useful tool in evaluating the effect of therapeutic interventions on infarct size in groups of patients.

A detailed user's guide had been prepared for the infarct prediction program. In addition to listings of the program and test data cases, the guide also describes the procedures used to obtain initial parameter estimates for the curve-fitting algorithm, to correct the CPK data for background serum levels, and to select the first CPK data value to be used in the infarct size analysis.


A-23. Physiologically Based Mathematical Models for Estimation of Myocardial Infarct Size

Personnel: J. R. Cox, Jr., BCL
E. M. Carlson, M.S., Medicine
K. B. Larson, BCL
J. Markham, BCL
R. Roberts, M.D., Medicine
D. L. Snyder, BCL
B. E. Sobel, M.D., Medicine
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 17646
Washington University

The extent of tissue damage resulting from myocardial infarction can be estimated quantitatively from the time course in blood serum of the enzyme creatine phosphokinase (CPK) released into the circulation from ischemic myocardium. (1) Such a measurement has a demonstrated utility in the clinical management of patients with ischemic heart disease, (2) (A-22).

Previously reported efforts (PR 10, B-2) to widen the area of applicability of the method have continued. In general, we are seeking to identify and characterize biological processes accounting for the release of CPK from the ischemic myocardium, to verify assumptions regarding these processes experimentally, and to characterize measurement errors so that reliability of infarct size determinations can be ascertained within definable confidence intervals. To this end, the diffusive transport model devised (PR 10, B-2) to explain the observed time course of serum-CPK activity has been further refined (2) and tested against clinical data. (3, 4) Four parameters enter into the model: total CPK appearing in the circulation, a characteristic diffusion time, the fractional rate of clearance of CPK from the blood, and the infarct onset time. The fits obtained by use of an iterative least-squares parameter-estimation technique implemented on the IBM System/360 Model 65 are generally good for widely disparate infarct sizes and curve shapes, and values estimated for the parameters agree well with independent measures.


B. Tracer Kinetics


Personnel: J. J. Lobick, M.S., Electrical Engineering
K. B. Larson, BCL
M. E. Phelps, Ph.D., Radiology
D. L. Snyder, BCL

Support: RR 00396
HL 13851
Washington University

The previously described studies (PR 10, B-10) using a physical flow system to investigate the performance of various mathematical models (1,2,3) in the analysis of residue detection data have been concluded and the results have been reported. (4) The objective of the studies was to assess the reliability of methods based on the models for measurement of relative flow and compartmental model parameters under conditions of rigorous control achievable neither in the physiology laboratory nor in clinical practice.

The flow system was employed both in non-recirculating and in recirculating configurations. In each case, excellent correlations were found between flows as measured by a flowmeter and flows determined indirectly from residue-detection data processed according to algorithms based on the appropriate mathematical model. Less success was achieved in estimating the four parameters describing the system when operated in a two-compartment, tracer-recirculation mode. The explanation advanced (4) for the observed discrepancies is that tracer transport in the flow chambers was not characteristic of that in a true compartment, i.e., tracer in the chambers was insufficiently dispersed.

The principal conclusion from these studies is that values of relative flow deduced from appropriate residue-detection models (1,2,3) are relatively insensitive to variations in the physical characteristics of the flow system under investigation. For this reason, it would appear that considerable confidence can be placed on results based on these models when they are used in physiological and clinical studies for measuring relative blood flow. Some caution is indicated, however, when using the methods to obtain parameters conjectured to represent the tracer transport processes in a region of interest.

These studies confirm that deductions from a specific mathematical model of tracer transport in a flow system depend for their validity only upon adherence to the explicit assumptions on which the model is based. Any deviation between values observed independently for the parameters and values estimated from the data on the basis of the model are more likely to have their explanation in a lack of correspondence between actual conditions and model assumptions than in logical flaws in deductions from the model.
B-2. **Mathematical Modeling for In-Vivo Studies of Blood-Brain Barrier Transport**

**Personnel:** M. R. Bedford, B.S., Electrical Engineering  
K. B. Larson, BCL  
M. E. Raichle, M.D., Neurology

**Support:**  
RR 00396  
GM 02016  
HL 13851  
NS 11059  
Washington University

The present work is an outgrowth of previous efforts in the development of a model for the interpretation of data from experiments employing $^{11}$C - labeled glucose to study cerebral glucose metabolism in-vivo. The previously reported studies (1,2) (PR 9, C-1, C-2, C-3; PR 10, B-12) employed intravenous injections of radiopharmaceuticals and had as their objective the development of a relatively non-invasive technique for in-vivo measurement of glucose utilization rates in brain. The technique that was developed worked well for measurement of net flux across the blood-brain barrier. For obtaining unidirectional fluxes, however, the method proved to be less useful due to compounding of uncertainties in the necessary calculations involving multiple arithmetic operations with the three estimated parameters.

The work reported here is being undertaken in an effort to circumvent the difficulties experienced in the measurement of unidirectional fluxes, and differs from the previous work in several respects.
First, direct intracarotid artery injections are employed. Second, blood radioactivities need not be monitored continuously. Third, a spatially distributed tracer transport model, rather than a compartmental model, is being used to interpret the data. We expect that these modifications will enable us to measure unidirectional fluxes with enhanced precision.

The new technique, as developed up to the time of the previous Progress Report (PR 10, B-7, B-12) for in-vivo measurement of blood-brain barrier transport, was limited by the problem of tracer recirculation. Therefore, to refine the technique for measuring capillary extraction, we have developed a mathematical model that explicitly accounts for recirculation. The model is an extension of a previous model developed by Larson and Snyder (3,4) for measuring blood flow per unit volume and transit-time distributions by external monitoring when recirculation is not a late event and must be taken into consideration. Central to the model is the use of two injections: one upstream (carotid artery) and one downstream (jugular vein) of the region of interest. From the resulting two residue curves, the transit time distribution during the first 30 seconds can be derived, as required by our technique for estimating a capillary extraction fraction.

The basic equation of the recirculation model, which is a direct result of Larson and Snyder's mathematical formulation of the recirculation problem, reads as follows:

\[
 r(t,\theta) = r_a(t) + \int_0^t \frac{dr(T,\theta)}{dT} r_v(t-T)dT.
\]

Here,

- \( r_a(t) \) = residue response for arterial injection;
- \( r_v(t) \) = residue response for venous injection;
- \( r(t,\theta) \) = "first pass" (i.e., no-recirculation) residue response; and
- \( \theta \) = parameters of the transport model.

This is a Volterra integral equation which is solved numerically by successive approximations, employing Gauss-Newton non-linear regression at each iteration of the algorithm. This method also utilizes a specific transport model, dependent on the compound being traced, to characterize the first-pass residue response as a parameterized function. The capillary extraction is estimated as one of these variable parameters.
The parameter estimation algorithm has been tested using computer-simulated data arising from first-pass and subsequent radiotracer recirculations. Simulated Poisson noise due to radioactive decay was added to the arterial and venous detector responses. Application of the parameter estimation algorithm to the simulated data revealed that the known parameters of the underlying first-pass residue response could be recovered. Performance characteristics of the algorithm have been established to set bounds on the expected errors for the estimated parameters.

The algorithm has also been validated experimentally by applying the method for an intravascular tracer, C$^{150}$-hemoglobin-labelled red blood cells. The method obtained the same mean transit time as the conventional Larson-Snyder method.$^{(3,4)}$ In addition, it was revealed that the tail of the transit-time distribution for an intravascular tracer was well described by a power-law relation, in agreement with predictions of a previous theoretical study.$^{(5)}$

Current experimental studies employing the new model are being undertaken to investigate the relation between the forward flux of glucose and its concentration in arterial blood. Since the transport of glucose across the blood-brain barrier is known to be mediated by a mechanism of passive facilitated diffusion, fitting of the Michaelis-Menton rate equation to the data will allow us to estimate the parameters $K_m$ and $V_{max}$. Comparison of our estimates for these parameters with literature values obtained from in-vitro studies$^{(6)}$ will enable us to make judgments concerning the validity of our methodology.

Other substrates that may lend themselves to labeling with positron emitters, and whose transport behavior in the blood-brain barrier are at present not known with precision, also offer the potentiality of being studied by our method. Such compounds include acetoacetate, fructose, phenylalanine, tyrosine, lactate, and deoxyglucose.


Personnel: K. B. Larson, BCL
W. Perl, Ph.D., College of Medicine and Dentistry of New Jersey at Newark
D. L. Snyder, BCL

Support: RR 00396
Washington University

In using tracer methods for in-vivo measurement of flow or volume of distribution of traced substances, the information sought is the density, \( h(t) \), of transit times through the vasculature of interest, or more commonly, the first moment, \( t \), of this density. (1, 2) When tracer does not recirculate or when tracer recirculation is a late event, this information can be obtained in a direct way from the response of the system of interest to a single injection of tracer. However, when tracer recirculation is an early event, recirculating tracer obscures the primary response that would have been observed without recirculation. In this case, the density \( h(t) \) can still be obtained provided multiple tracer injections or multiple sampling sites are employed. (3) This expedient has been applied successfully in both outflow-detection and in residue-detection experiments for the measurement of blood flow and volumes of distribution of traced substances. (4, 5) In such experiments, the computational procedure employed has been to recover the density, \( h(t) \), in its entirety by means of numerical solution of expressions involving
convolution integrals or of other integral equations. By this means, the mean transit time, $\bar{t}$, can be obtained using its definition, $\bar{t} = \int_0^\infty th(t)dt$. In turn, this has permitted relative blood flow or volumes of distribution to be evaluated by appeal to the Central Volume Principle. (2)

A major difficulty with the procedure just outlined arises from the instability commonly encountered in numerical deconvolution or in numerical solution of integral equations, especially with noisy data. However, when the objective of a tracer study is the measurement of blood flow or of volume of distribution, determination of the first moment, $\bar{t}$, of $h(t)$ suffices, and information concerning the detailed shape of $h(t)$ is superfluous. Larson and Snyder (6,7) have shown that when tracer recirculation interferes in residue-detection experiments, the first moment, $\bar{t}$ (as well as higher moments) of $h(t)$ can be computed directly by purely numerical means from dual-injection data without the intermediate step of recovering $h(t)$ itself. Their method has been used successfully for measurement of $\bar{t}$ in heart (8) and brain (9,10) studies.

Larson, Perl, and Snyder have since applied mathematical techniques similar to those used in obtaining $\bar{t}$ in residue-detection experiments (6,7) to situations in which the data are obtained by outflow detection. The resulting equations have been employed to obtain the distribution volume of water in a study of pulmonary edema. (11) As in the residue-detection case, these equations permit the mean transit time of traced substance to be obtained directly from dual-injection outflow data when tracer recirculation invalidates the single-injection technique. Thus, for outflow studies, the new method bypasses the difficult and uncertain step of obtaining $h(t)$ by numerical deconvolution.

Mathematical simulations of outflow-detection data obtained in single-injection, dual-blood-sampling experiments for measuring brain-blood flow in the presence of tracer recirculation are presently being carried out. The objective of these simulation studies is to evaluate the performance of algorithms based on the above-described method under the potentially disadvantageous conditions encountered in practice, such as the presence of noise in the data, the practical necessity of data truncation, the effects of catheter dispersion and delay, and the use of protracted tracer injections.


B-4. Solution of Maximum-Likelihood Function for Tracer Kinetic Data

Personnel: J. Markham, BCL
J. R. Cox, Jr., BCL
B. D. Eldredge, BCL
D. L. Snyder, BCL

Support: RR 00396
ENG 74-07800
HL 13851
Washington University

Two programs which implement a new optimization algorithm for solution of the maximum-likelihood function for Poisson-distributed tracer data with a multiexponential intensity have been completed (PR 10, B-3).(1) One program was written for the Interdata Computer in the Radiation Sciences Division of the Department of Radiology; the second is a more general purpose program written in FORTRAN for the IBM System/360 Model 65. A user's guide which includes listings of the program and test data has been completed for the general purpose program.(2)


B-5. Limitations on the Number of Views Required in Computerized Tomography

Personnel: D. L. Snyder, BCL
J. R. Cox, Jr., BCL

Support: Washington University
Picker Corporation

The fundamental mathematical relations of computerized tomography require an infinite number of projection measurements for exact reconstruction of an unknown density. However, only a finite number of projections will be available in any practical implementation of a reconstructive tomographic apparatus. The implication is that the unknown
density cannot be reconstructed exactly in practice even in the absence of any other sources of error. We have studied the limitations introduced by a finite number of projections. (1) We find that if the measurements of a density of maximum radius $r_{max}$ are preprocessed to limit the maximum spatial frequency to $P_{max}$, and if the number of projections is at least $2\pi r_{max} P_{max}$, then the density can be reconstructed to within an error that depends only on spatial frequencies greater than $P_{max}$ in the unknown density. If the bandlimited measurements are sampled at the Nyquist rate to produce $N_t$ transverse samples of the unknown density at each projection angle, and if projections are obtained at $N_\theta$ angles, then the density can be reconstructed to within the above error if $N_\theta = (\pi/2)N_t + 1$.


B-6. Radiation Sciences Division Computer System

Personnel: N. A. Mullani, BCL
C. S. Coble, A.B., Radiology

Support: RR 00396
HL 13851
HL 14147A
HL 17646

The dual processor Interdata computer-system for the Radiation Science Division (PR 9, C-15 and PR 10, B-9) has been expanded to include separate disc drives and disc controllers for each processor. The two processors now run independently but still share the other peripherals. The teletypes which were used as systems consoles have now been replaced by Beehive terminals for faster and quieter operation.

The new PETT III (B-8, B-9) scanner has been interfaced to the computer system and extensive software developed for data collection, reconstruction of images, and display of images on a Ramtek display system.
B-7. Positron Emission Transaxial Tomography

Personnel: M. E. Phelps, Ph.D., Radiology  
C. S. Coble, A.B., Radiology  
R. E. Coleman, M.D., Radiology  
J. R. Cox, Jr., BCL  
E. J. Hoffman, Ph.D., Radiology  
N. A. Mullani, BCL  
B. A. Sobel, M.D., Medicine  
D. L. Snyder, BCL  
M. M. Ter-Pogossian, Ph.D., Radiology  
E. S. Weiss, M.D., Medicine  
M. J. Welch, Ph.D., Radiology

Support: RR 00396  
HL 13851  
HL 17646  
NS 06833

Studies with a prototype positron emission transaxial tomograph (PETT-II) (1-3) demonstrated the high resolution, contrast, efficiency, and accuracy of this technique (PR 10, B-13). The experience gained from phantom and animal studies with the prototype PETT-II led to the design and construction of a larger system suitable for human studies, PETT-III. (3-8) Three types of studies have been conducted and are described below.

(1) The performance characteristics of the system have been evaluated with phantom studies. The maximum count rate capabilities, effect of random or accidental coincidences, spatial resolution, statistical noise, image contrast, and distortions due to angulation errors in the data collection were all studied. (4-5) Further studies in this area are planned to develop a better understanding of the capabilities and limitations of this technique.

(2) Animal studies have been carried out in conjunction with the Cardiovascular Division of the Department of Medicine. These studies have employed $^{11}$C-palmitic acid, $^{15}$NH$_3$ (index of perfusion), $^{11}$CO-hemoglobin (blood tracer), and $^{11}$C-glucose (metabolic substrate) for transaxial tomographic studies to evaluate the capabilities of this system for the detection and imaging of myocardial infarction and ischemia. (6-7) These studies are presently carried out in dogs and, after sufficient validation, will be performed on humans. Animal studies using dogs have also been conducted in collaboration with the Nuclear Medicine Division of the Department of Radiology to evaluate this technique in the liver and pancreas using $^{15}$NH$_3$, $^{68}$Ga-macroaggregated albumin, and $^{11}$CO-hemoglobin.
(3) Human studies have been carried out in normal volunteers and patients with selected cerebral pathologies. The objective of the studies in volunteers was to define the imaging capabilities for different organs (specifically the brain, heart, liver, pancreas and spleen) in the human. (8-11) The parameters that have been investigated are radiation dose requirements, statistical quality of the imaging, examination time, spatial resolution, and the effect of these factors on the delineation of different anatomical structures of the body. Patients with cerebral lesions (stroke and tumors) have also been studied to demonstrate the unique features of this system in the detection of lesions through the use of physiological variables such as regional blood perfusion, blood volume, and metabolism. (9-11)

Encouraging results were obtained in all the above studies, and more detailed studies are now in progress.


PETT-III Scanner

Personnel: M. E. Phelps, Ph.D., Radiology
C. S. Coble, A.B., Radiology
E. J. Hoffman, Ph.D., Radiology
J. Hood, M.S., Physics
N. A. Mullani, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851

A whole-body computerized transaxial tomograph has been designed and constructed (B-7). It is presently being evaluated with phantom, animal, and human studies. This system consists of a hexagonal array of forty-eight 5 x 7.5 cm NaI(Tl) detectors. There are 8 detectors per side of the hexagon. The output of each detector is routed to individual preamplifiers (each having a 500 mHz bandwidth and a gain of 10) and one-shot leading-edge discriminators (250 mHz) for timing and energy discrimination. The forty-eight digital outputs of the discriminators are routed into the interface described in B-9. The interface contains coincidence circuits, buffers, and a data selector for the controlled transfer of data to an Interdata Model 80 minicomputer. Each detector on a side of the hexagon is connected in coincidence (20 ns resolving time) with all the detectors on the opposing side for a total of 64 coincidences per pair of opposing sides. Thus there are a total of 192 coincidences for the system. The coincidence technique establishes an "electronic" collimation for the detection of the annihilation radiation (two 511-keV photons emitted simultaneously in 180° opposition) from positron-emitting radionuclides which lie in a well-defined region between two detectors connected in coincidence.

Two motions are performed during data collection. First, stepping motors are used to scan all 6 detector banks synchronously in a linear fashion in 1-cm steps over a total distance of 5 cm. Then the gantry supporting the hexagonal array rotates 3° and the linear scan is repeated. This sequence is continued through a 60° angle of rotation. The data, consisting of about 23,000 data points, are processed using a convolution-based algorithm in order to reconstruct the cross-section distribution of positron activity in a transaxial plane through the body. Presently, the minimum scanning time is 2 minutes. Typically, scan times between 2 to 8 minutes are employed.

The scanning motions and data collection are under the control of an on-line Interdata Model 80 minicomputer (B-6). After data collection, the minicomputer is used to reconstruct the tomograph image, which is then displayed on a Ramtek (256 x 256 x 64) television monitor display system and stored on magnetic tape or disc (B-6).
The center section of the PETT-III scanner has a 50-cm diameter hole through which the patient is passed for selection of the transaxial level to be scanned. This hole is sufficiently large that any section of the human body can be scanned. During data collection, the patient lies still on a bed, and the tomograph scans around the examined cross section.

This system, in conjunction with the non-invasive administration of radiopharmaceuticals labeled with positron-emitting radionuclides (\(^{15}O, ^{13}N, ^{11}C, ^{18}F, \text{ and } ^{68}Ga\)), allows three-dimensional imaging of metabolic and hemodynamic processes of organs of the body to be accomplished in normal physiological and in pathological states.


The new PETT-III scanner (B-8) consists of forty-eight NaI crystal detectors arranged in a hexagonal array and grouped 8 to a side. A block diagram for the PETT-III interface electronics is shown in the figure below. The output from each detector is a negative-going pulse varying in maximum height from 0 to 30 millivolts depending on the energy transferred from the γ-ray to the crystal and the high voltage applied to the photo-multiplier tube. This pulse is amplified by a gain of 10 and sent to a low-level discriminator which serves two purposes:

1. it discriminates against low-level noise pulses and undesirable low-energy pulses;

2. for the pulses that are accepted, a variable width and constant height pulse is generated for coincidence counting.

Coincidence timing is determined by the width of a pulse which can be varied from 7 to 100 ns. Coincidence resolving time is defined by the relation: coincidence resolving time = (2 x pulse width) - minimum overlap time, where the minimum overlap time is the minimum pulse width of a coincidence gate output required to activate the counting circuit following it. For the PETT-III interface, which uses Schottky nand-gates for implementing the coincidence gates followed by Schottky flip-flops for buffering the coincidence information, this resolving time is of the order of 5 ns.

Cross-coincidence data are collected for detectors on opposing sides of the hexagon to improve the detection efficiency of the scanner. The two sets of eight signals from the opposing sides are sent to a bank of coincidence gates arranged in an 8 x 8 matrix and followed by an 8 x 8 matrix array of buffer flip-flops. There exist three such sets of gates, latches, and counters, but only one set will be described here.

The outputs of the flip-flops are interrogated cyclically by the counting circuit. This comprises control logic, which generates the timing and control signals, four 16-bit up-counters, and a dual 64-word, 16 bits/word solid-state memory. Each possible coincidence is allocated a memory location to minimize the total interrogation time. The flip-flop outputs and the counters are split into four banks of 16 each. All four banks operate simultaneously thus reducing the total interrogation time by a factor of four.
The control logic cyclically interrogates the outputs of each flip-flop and, at the same time, reads into the up-counter the contents of the memory location corresponding to that flip-flop. If the latch being interrogated is set, the up-counter is incremented by one, and the new count is written back into that memory location. The latch is then reset, and the control logic initiates another interrogation cycle. Each interrogation cycle takes 500 ns. The total time for reinterrogation is 16 μs.

Figure B-9.
Dual memories are included in the interface to allow for selective data collection during a certain phase of physiological cycles such as respiration and heartbeats. An external signal, provided by the user, controls the channeling of data into either memory bank.

A real-time clock is imbedded within the interface to control the data collection periods, to initiate the scanning motion of the detectors, and to interrupt the computer for data transfer from the interface to the computer memory.

Data are only transferred to the computer when a specified integration time is completed. The time required to transfer all of the PETT-III memories to the computer is approximately 2 ms. Therefore, the computer is free during most of the data collection time to process and reconstruct the image.

B-10. Kinetics of Chronic Subdural Effusions

Personnel: D. C. DeVivo, M.D., Pediatrics and Neurology
J. Markham, BCL

Support: RR 00396
NS 06833
Washington University

The compartmental model developed to describe the kinetics of proteins present in subdural effusion fluid has been thoroughly tested with the two most complete sets of data we have available (PR 10, B-4). The model appears to be a good representation of the movement of albumin into and out of the blood and the subdural space. However, the fact that albumin movement is such a slow process made it difficult to obtain reliable estimates of the transfer rates involved. The model appears to be compatible with six other experimental studies, although the data from these studies are not adequate for complete analysis with the model.

For all eight studies, a one-exponential fit to the first day's subdural washout data was obtained. The decay rate estimated by this fit was compared to the total clearance rate for the subdural compartment calculated from the model for the two complete sets of data. The rates obtained by the two methods were very close, and future work will concentrate on relating the decay rates estimated by the one-exponential fit to a clinically useful index. There is evidence to suggest that the rates may reflect the vascularity of the outer subdural membrane. For clinical practice, it may be possible to obtain useful information concerning the movement of proteins from the subdural space by a simpler experiment in which a few subdural samples are taken within 12 to 24 hours following injection of a tracer.
B-11. Quantitation of Left-to-Right Cardiac Shunts in Children Using Area Ratio Techniques

Personnel: P. O. Alderson, M.D., Radiology
R. G. Jost, M.D., Radiology
S. Boonvisut, M.D., Radiology
J. Markham, BCL

Support: RR 00396
HL 17646
Washington University

A comparison of several reported methods for detection and quantitation of left-to-right shunts by radionuclides was performed in 50 children (PR 10, B-5). Count ratio (C2/Cl) techniques were compared with the exponential extrapolation and gamma-function area-ratio techniques. C2/Cl ratios accurately detected shunts and could reliably separate shunts from normals, but there was a high rate of false positives in children with valvular heart disease. The area-ratio methods provided more accurate shunt quantitation and a better separation of patients with valvular heart disease than did the C2/Cl ratio. The gamma function method showed a higher correlation with oximetry than the exponential method, but the difference was not statistically significant. For accurate shunt quantitation and a reliable separation of patients with valvular heart disease from those with shunts, area-ratio calculations are preferable to the C2/Cl ratio.

B-12. Nuclear Metabolism of Ribosomal RNA in Growing and Puromycin-Treated HeLa Cells

Personnel: S. F. Wolf, M.A., Microbiology and Immunology
D. Schlessinger, Ph.D., Microbiology and Immunology
J. Markham, BCL

Support: RR 00396
GM 21357
RR 05389
Washington University

The flow of $^3$H labeled methyl groups into successive precursor and product rRNA species was followed in suspension cultures of growing and puromycin-treated HeLa S3 cells. At various intervals from 5 to 180 minutes after the addition of $^3$H-methyl methionine, RNA was extracted and analyzed by gel electrophoresis in conditions that minimized degradation and aggregation. The quantities of label in the individual pre-rRNA and rRNA species were assessed from the gel patterns, and the data analyzed on
the IBM System/360 Model 65 using the SAAM (Simulation, Analysis and Modeling) program written by Berman and Weiss. Estimates of the rates of incorporation of the label into the individual species were obtained by assuming a compartmental model for the data.


Personnel: W. M. Buchholz, M.D., Medicine  
R. E. Coleman, M.D., Radiology  
J. H. Joist, M.D., Medicine  
L. A. Sherman, M.D., Medicine  
J. Markham, BCL

Support: RR 00396  
HL 14147A  
Washington University

Thrombocytosis has been associated with a high incidence of thrombo-hemorrhagic events (THE). In order to discriminate those patients at risk for THE, subjects were evaluated with a series of coagulation and platelet function tests as well as platelet and fibrinogen kinetic studies. Platelet survival was analyzed on a PDP-12 computer using a FOCAL program which fitted three different models to the data: linear (senescent removal), exponential (random removal), and combination (both senescent and random removal). The only variable which consistently identified patients at risk for THE was the platelet mean life span. A platelet survival study in which the data were best described by either an exponential or a combination model also consistently identified patients at risk for THE.
We have continued to refine our previously reported technique (1) (PR 10, B-8) for in-vivo tracer assessment of cerebral blood volume (CBV) and have applied it to a study of subarachnoid hemorrhage in humans.

Using as a control the dual-injection method based on the mathematical model of Larson and Snyder (2,3) to measure vascular mean transit time in rhesus-monkey brain, we have critically examined the effects of any supposed departures in our experiments from the theoretical conditions demanded by our technique. These conditions have been well satisfied for the range of CBV values investigated. (1,4)

We have employed our technique (1) to measure regional cerebral blood volume (rCBV) in 21 human patients with subarachnoid hemorrhage. Additionally, in-vivo tracer methods were employed to measure regional cerebral oxygen utilization (rCMO₂) (5) and regional cerebral blood flow (rCBF) (6) in these patients. The average results of the regional studies in each patient were then divided into groups based on three factors: (1) neurological status; (2) presence or absence of cerebral vasospasm; and (3) pre-operative or post-operative state.

Pre- and post-operative patients with no neurological dysfunction (Class I) and no cerebral vasospasm had normal rCBF, rCBV, and rCMO₂ values. Pre- and post-operative patients with varying degrees of neurological dysfunction (Classes II-V) and without cerebral vasospasm had a moderate decrease in rCBF, a mild but not significant increase in rCBV, and a normal rCMO₂. The most striking changes were seen in patients with cerebral vasospasm, both pre- and post-operatively. All had some degree of neurological dysfunction (Classes II-V) correlating with the degree and location of the vasospasm. In the area of vasospasm, rCBF was moderately decreased, and was accompanied by a marked decrease in rCMO₂ and a marked increase in rCBV. These data demonstrate for the first time a clear and predictable relationship between rCBF, rCMO₂ and cerebral vasospasm. The accompanying paradoxical increase in rCBV (20-45% greater than normal) remains unexplained but suggests dilation in some segment of the cerebral vasculature.


Blood-Brain Barrier Permeability Studies Employing $^{15}$O-labeled Water and $^{11}$C-labeled Alcohols

Personnel:
M. E. Raichle, M.D., Neurology
C. S. Coble, A.B., Radiology
J. O. Eichling, Ph.D., Radiology
R. L. Grubb, Jr., M.D., Neurosurgery
K. B. Larson, BCL
N. A. Mullani, BCL
M. G. Straatmann, M.S., Radiology
M. M. Ter-Pogossian, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

Support:
RR 00396
HL 13851
NS 06833
NS 11059
Washington University

We have continued our previously reported studies (PR 10, B-7)\(^{(1)}\) on the blood-brain barrier (BBB) permeability of $^{11}$C-labeled alcohols and $^{15}$O-labeled (1,2,3) water. In confirmation of our earlier finding that the fractional extraction of the three lowest alcohols was positively correlated with chain length, we have determined that the fractional extractions of butanol and benzyl alcohol are greater (in fact, ~100%) than that of isopropanol.

These data provide for the first time an accurate estimate of the relative BBB permeabilities of the four short-chain alcohols and confirm our earlier observation of the BBB permeability limitations of water. They demonstrate a clear association between lipid solubility (lipid solubility increases with carbon chain length) and the BBB permeability for the alcohols, supporting the hypothesis that the barrier to diffusion is the membranes of the endothelial cells forming the capillary walls. Our data would suggest the use of butanol or a longer-chained alcohol rather than ethanol as an internal standard when evaluating the BBB passage of other substances or when measuring CBF. Finally, our findings demonstrate the feasibility of accurately measuring the BBB permeability of a variety of highly diffusible substances using a single injection technique in conjunction with the external detection of biologically significant compounds labeled with cyclotron-produced positron emitting isotopes. The potential for such a technique for studies in animals as well as humans is obvious.


C. Monitoring the Critically Ill

C-1. SICU: Overview and Evaluation

Personnel: L. J. Thomas, Jr., BCL
R. E. Clark, M.D., Surgery
R. W. Hagen, BCL
T. F. Schuessler, BCL

Support: RR 00396
Barnes Hospital
Washington University

The cardiothoracic surgical intensive care unit (SICU) system continues to perform well after more than two years of literally continuous use. The efforts described in the following subsections have been directed toward the further development of this cost-effective computer-based system for improving the care and study of the critically ill. Over the past year, additional experience has been gained in identifying and finding solutions for both technical and "human factor" problems. A major effort has been directed toward completion of a "satellite" cart for extending the SICU data-gathering capabilities to other clinical settings (C-6); and the necessary software development for its initial implementation in an SICU annex is nearing completion (C-3). These programming efforts and the experience gained with the Texas Instruments TI 980A computer serve to also lay the groundwork for subsequent expansion of the SICU system to service eight beds, a need which has developed sooner than anticipated. Plans are to bring the cart up to full clinical utilization in the SICU setting. This will not only help to relieve the pressure for additional monitoring capability in the care unit but also expedite trouble-shooting by virtue of proximity to the supporting SICU system with which it communicates. Subsequent applications will include monitoring and control of a pulsatile perfusion pump (C-15) as well as study of circulatory function in the Barnes Hospital Coronary Care Unit.

Planned research activities in the SICU have been frustrated by technical difficulties in the development of needed transducers. Examination of the relation between changing metabolic demands and circulatory instability in the post-operative period awaits completion of the ultrasonic gas-flow device (C-8); successful resolution of the signal-to-noise problem with the reflectance oximetry device (C-10); and completion of the thermodilution system for automated cardiac output (C-7). The recent introduction of Swan-Ganz catheters on a routine basis at this institution has stimulated plans to examine the validity of a model predicting discrepancies in acid-base status between mixed-venous and systemic arterial blood samples as a function of cardiac output. The natural clinical courses seen in the SICU patient population offer unusual opportunities to study such pathophysiological interactions; however the need to gather reliable data expeditiously and to avoid interference with responsible clinical
management places serious demands on the necessary transducers. Slow but definite progress is being made.

An engineering evaluation of the SICU monitoring system has continued since its installation and the first eighteen months' experience has been reported. Noteworthy observations were that the mean time between unintentional interruptions of patient monitoring (hard failures) showed a progressive increase and exceeded 2100 hours in the third six-month period. The corresponding figure for soft failures (failure of any system function, no matter how trivial, but not causing any interruption of patient monitoring) was 432 hours. The total "down time" was less than 48 hours for the entire 1.5 years.

Utilization of the four-bed SICU has increased progressively since the computer system was installed in late March, 1973 and the average length of stay has decreased as shown below.

<table>
<thead>
<tr>
<th>5 months beginning:</th>
<th>Occupancy as % of capacity (24-hr. day; 7-day week)</th>
<th>Average length of stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan. 1973</td>
<td>76</td>
<td>3.2</td>
</tr>
<tr>
<td>Jan. 1974</td>
<td>77</td>
<td>2.6</td>
</tr>
<tr>
<td>Jan. 1975</td>
<td>83</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Meanwhile, the shortage of nursing personnel has not abated and has actually become more severe in the past six months. Since an increased admission frequency has likely affected the length of stay, it is not justified to conclude that the computer system has contributed to shorter stays.

Heavier clinical demands on the system have begun to interfere with efforts to thoroughly document every failure encountered. A higher population of critically ill patients and the increasing dependence on the system by the limited clinical personnel have required that documentation be waived for clinical priorities more frequently. Vigorous efforts are now required to maintain the integrity of our continued engineering evaluation. Maintenance of the prototype system at BCL for testing, development, and back-up components is more critical than ever.

Some perspective in considering future directions for computer-based patient monitoring has been gained from the opportunity of one of the authors to participate in preparation of a review on this subject.


C-2. SICU: Hardware

Personnel: T. F. Schuessler, BCL
R. W. Hagen, BCL

Support: RR 00396

Since the prototype or engineering system at BCL was to be used for hardware and software development as well as hardware backup for the clinical system in use at Barnes Hospital, it was necessary to make all components interchangeable. Modifications of the Bus Monitor, PC-1200 interface, cards, cables, and bedside logic file needed to accomplish this goal have been completed.

Because software development has reached a point where it is difficult to pinpoint multiple bed interactions on a single bed system, expansion of the engineering system to three beds has been undertaken. All the necessary logic cards and cables have been constructed and only completion of the video module packages is yet to be done. This expansion will provide complete hardware and software troubleshooting capability.

Installation of the optical isolators and bedside power supplies allowed redesign of the Patient Communications Digital Interface board. It has been reduced from twenty-one packages to eight packages. These isolators have eliminated problems caused by defibrillator interference (PR 10, C-1).

Integrated circuit package failures had been negligible until the past month. Three failures have been directly attributable to pin corrosion of the Texas Instruments ICs in dual-in-line sockets. Replacement of the packages in question corrected the failures. Removal of the corrosion and testing of the packages in question showed that they were still good and only the corrosion of the silver leads had caused the problem. Texas Instruments has indicated that they are aware of the problem and are working on a solution. In the interim, however, approximately one-hundred TI ICs are being replaced with other brands that do not use silver leads.
C-3. SICU: Software

Personnel:  L. J. Thomas, Jr., BCL
            J. A. Johnson, BCL
            T. A. Lavender, BCL
            J. J. Schier, B.S., Surgery
            E. Van Patten, BCL

Support:    RR 00396
            Washington University

Programming activities relevant to patient monitoring have been in
three areas: modification of existing system, research cart development
and implementation, and thermodilution cardiac output development (C-7).
The research-cart software is included here since for reasons of accessi­

bility and convenience its first application will be in the SICU.

In the area of modifications of the existing system, three major
changes have been made. The desirability of making trend data available
at the bedside displays has been previously noted (PR 10, C-1) and was
rendered practical by the addition of a Pertec disc and controller late
last year. The modified program now provides a static graphic display
of the last two hours of trend data on the bedside video display for any
monitored parameter by means of a single key-stroke. Examples of normal
and trend-mode displays are shown in Figure 1. Reallocation of display­
package buttons was done by software so that no hardware changes were
necessary.

The rapid access to trend data stored on the disc also stimulated
revision of the trend displays at the doctors' discussion station to improve
their format, time resolution, flexibility and speed. An example of the
revised display is shown in Figure 2.

Since the above changes required a different data-storage format, it
was necessary to revise the programs for off-line plotting which had used
a Houston digital plotter interfaced to a Spear PC (PR 10, C-4 and C-9).
Significant improvements in speed and quality were achieved by re-writing
the programs for a Versatec matrix plotter which had been acquired. An
example is shown in Figure 3.

In support of the thermodilution cardiac output efforts, a number
of programs have been written in FORTRAN for the PC-1200. These provide
the capabilities to flexibly display and plot the waveforms, process
temperature and flow calibration signals, analyze large numbers of deter­
minations using easily modified algorithms, and to digest the results
thereof via linear regression and correlation statistics. When an optimal
processing strategy is established, an assembly language version will be
incorporated into the patient-monitoring system.
Figure 1a: Routine video-monitor display. Displays of ECG (upper trace) and arterial pressure waveform (lower trace) are of non-fade moving-scroll format. Time-of-day (hours, minutes and seconds) is given at the upper right and two lines are available for alphanumeric patient information at the bottom. The calibrated arterial pressure trace is automatically scaled and appropriately annotated (upper line 100 and dashed line 50 mm Hg, shown here). The vertical lines on the arterial waveform indicate QRS detection by the computer. Any "alarms" are displayed as flashing messages (bed and parameter) near center-screen and appear on all monitors throughout the care unit.

Figure 1b: Video-monitor display with trend data. A single key-stroke replaces the usual arterial pressure waveform with a static display of the last two hours of data for any selected parameter (mean arterial pressure, shown here), the corresponding name and current value are shown on the alphanumeric display just below the video monitor. The scale lines are relabeled appropriately for the trend data.
Figure 2. Trend data displayed on storage scope in doctor's discussion station. Any 2-, 4-, 8-, or 16-hour segment starting up to 36 hours ago can be selected for any two parameters. Systolic, mean and diastolic values are given for arterial pressure. The current date and time-of-day are included at the lower right. Hard copy of the display is immediately available.
Figure 3. Off-line plot of patient data showing a six-hour segment from a 36-hour plot of a patient's course in the care unit. The 7-minute perturbations resulted from "sighs" imposed by a mechanical ventilator. The transient dips in temperature were caused by cold suppositories placed near the temperature probe.
In the area of the TI-PC remote research cart software system, three developments have been made. They are concerned with hardware testing, program development tools, and patient monitoring and research.

Following the completion of the remote cart hardware interfaces, seven programs were written to test their accuracy and reliability. These include tests for:

1. Keyboard -- KBDTEST.MS tests the various status modes of the TI keyboard and displays characters typed on the cart video screen.
2. Digital output interrupt -- CNTRL.MS tests setting and reading the status of the digital output interface as well as the decoding of the interrupt by the computer.
3. Strip chart recorder -- CHART.MS tests the output of the fourteen modes of the strip-chart recorder.
4. Analog input -- ADVAL.MS checks the accuracy of conversion of a DC input voltage between -2.5 and +2.5 volts.
5. Digital input and output -- DDECHO.MS tests digital inputs and outputs by comparing what is written to one of the two output channels to what is read from one of the eight input channels.
6. Communications -- ALLTESTS.MS tests the reliability of the communications card interface by echoing data from PC to TI.
7. Synchronization -- Run concurrently with the communications test, the sync test checks to see that neither machine misses a clock interrupt.

Work in the area of program development tools consisted of the creation of a PC FORTRAN program called TIPCI, TI-PC Intercommunication. Since the TI 980A in the remote cart system does not have the usual interactive peripherals for writing, editing and debugging programs, this software package was written to utilize these features of the PC-1200. The package includes subroutines for sending TI programs from the PC disc to the TI and sending TI object code and assembler listings back to the PC for display and storage. TIPCI allows the programmer to type programs on the PC keyboard and save them on the PC disc. Then by loading TIPCI and following the instructions displayed on the PC scope, the programmer can load the object program from the PC disc to the TI for execution. To communicate between the TI and the PC, TIPCI uses the TI 980 teletype interface card and PC asynchronous serial interface card which makes each machine look to the other like a local I/O device.

Using TIPCI, work has begun on a patient monitoring/clinical research system. The QRS detection and arterial pressure calculation algorithms from the PC-1200-based SICU monitoring system have been translated into TI 980 assembler code and tested. A preliminary system incorporating the QRS detector and the arterial-pressure program as well as video display and heart-rate calculation is presently being tested.
C-4. SICU: Mechanical Systems

Personnel: T. F. Schuessler, BCL
R. J. Arnzen, BCL
A. L. Bodicky, BCL
R. W. Hagen, BCL

Support: RR 00396
Barnes Hospital

To more conveniently accommodate the addition of a disc and disc controller to the SICU computer system, the desk and shelf area in the discussion station have been removed. A second five-foot rack has been added and now houses some of the monitoring hardware and disc components. Relocation of the a.c. power outlets and addition of a new computer power supply remain to be done before this change will be considered complete.

Unintentional violation of the SICU grounding system has prompted rewiring of all grounds in the unit. This has been completed on two of the patient areas but due to the heavy patient load, remains to be done on the other two patient areas. Ground tests are being conducted and methods of detecting when ground violations occur and what is causing them are under consideration.

Because of the increase in the patient load and utilization of the facility, a doorway connecting to a three-bed annex has been constructed. The annex serves as a graduate facility and all beds in the original SICU are devoted to acute care. Defibrillator/cardioverters have been added to beds 1 and 2. Monitoring in the graduate areas now employs conventional analog devices.

Due to damage inflicted by x-ray machines and beds, a raised platform has been installed around each transducer manifold pole. Damaged transducer platforms have been replaced and no additional damage has occurred in the past six months.

On the prototype system at BCL, the communications bus has been completely wall-mounted for easy accessibility, compactness, and damage-immunity. The bedside monitoring hardware has been placed in a five-foot rack. A disc and disc controller have been added to allow continued software development on this system. Five additional bedside video modules are under construction in our machine shop. Two will be used to expand the prototype system to three "beds" in order to expedite the testing of station interactions. The other three will be required for expansion of the system to include full instrumentation of the three-bed annex to the SICU.

After a year of heavy use, the Gould OEM strip-chart recorders in the SICU system required complete overhaul. This included replacement of the paper-drive rollers, cleaning or replacement of the ink-feed tubing,
replacement and alignment of the pen-drive bands, replacement of several ink-plunger diaphragms, and general cleaning of the instruments. Recording pens have been replaced several times due to damage inflicted by hospital personnel.

Testing has been conducted on various stopcocks available for use in the catheter-transducer system (PR 10, C-6). The main considerations were availability, ability to withstand high pressure without leaking, type of bore, and the ability to be flushed free of air bubbles. The Medex, Monojet, and the Sherwood six-way stopcocks all trapped bubbles which could not be completely removed. The Medex and Monojet showed a high susceptibility to leaking or uncoupling. The bore of the Pharmaseal stopcock is smaller than desired for our system, but it was nevertheless selected for use since it was found to be more satisfactory in other respects. As other stopcocks become available, they will be tested as possible replacements for those now in use.

C-5. SICU: Personnel Training

Personnel: T. F. Schuessler, BCL
Support: RR 00396

Since the rapid turnover of the SICU nursing staff has not decreased significantly, the program of in-service training and orientation has continued. In addition to the medical student already assisting in the off-hour technical coverage of the unit, a freshman biomedical engineering student has been trained in this capacity.

Due to recent and in-progress implementations of various hardware and software changes, revision of the User's Manual and writing of the Technician's Manual have not been completed.
C-6. Clinical Physiologic Research Cart

Personnel: B. E. Campbell, BCL
          G. J. Blaine, BCL
          R. W. Hagen, BCL
          J. A. Johnson, BCL
          T. F. Schuessler, BCL
          L. J. Thomas, Jr., BCL

Support: RR 00396

The design, implementation, testing and engineering evaluation of the clinical physiologic research cart has been completed during the past year. The general design objectives have included mobility, hardware and software flexibility, hardware cost under $16,000, and power load less than 15 amperes at 120 volts. These had been met at the design level as previously reported (1) (PR 10, C-7). In the course of subsequent implementation, testing, and evaluation efforts, a number of deficiencies were uncovered and corrected but none required compromise of the original objectives.

The satellite cart system is composed of modules that can be independently modified with minimal constraints. The system includes a dedicated mini-computer (Texas Instruments 980A) and can monitor eight analog and eight digital channels. The eight analog channels consist of amplifiers that can accommodate an ECG and seven other patient signals. The dedicated mini-computer performs all necessary data formatting and analysis. All alphanumeric display requirements are met with a single closed-circuit television monitor which, in addition to a two-channel chart recorder, can provide desired graphic displays. Permanent record of any video image is provided by a video hard-copy unit. Additional outputs from the minicomputer are available for control of external devices. All user-to-processor communication is accomplished using a full-function keyboard. Data sampling and conversion is initiated and controlled by external hardware independent of, but synchronized with, the computer sampling schedule. Digital values are made available via buffers to the computer for data transfer.

Video information generation and mass storage of data are provided to the satellite system through serial communication with the SICU at a considerable cost saving. The serial link is capable of full duplex operation, and consists of two transmitter/receiver modules which plug into the TI 980A I/O chassis and the SICU bus, and a two-twisted-pair cable. (2) The principal mode of operation is to transmit data from the cart to the SICU disc on a scheduled basis. This is accomplished by slaving both systems to the same clock source, which is the vertical sync signal from the SICU video display system. The TI 980A can be loaded from the SICU system using the Teletype bootstrap loader available in the TI 980A.
The engineering evaluation included the short-term accuracy and noise characteristics of the analog section of the data-acquisition interface, the frequency response of the analog inputs and outputs, error rates of digital inputs and outputs, error rates of the communication system, long-term synchronization of the two system computers (TI 980A and PC-1200), operating temperatures of the local computer, acoustic noise of the total package, and mechanical stability. The details and results of these evaluations as well as design changes have been reported and documented(3).

Parallel software efforts for testing and evaluation as well as clinical application are detailed elsewhere (C-3). Use of the cart in a clinical area will begin within the next few weeks once the first set of application programs is finalized. In the meantime, the cart is in use with real patient signals cabled to BCL from the Barnes Hospital Cardiothoracic Surgical Intensive Care Unit.


C-7. Cardiac Output Via Thermal Dilution

Personnel: J. J. Schier, B. S., Surgery
R. E. Clark, M. D., Surgery
R. W. Hagen, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
Washington University

The objective of this effort is to develop a system for automated cardiac output determinations via thermodilution in the clinical environment. In order to minimize operator intervention, system complexity, and data processing overhead, the plan is to use ordinary maintenance fluids for the injectate at room temperature with temperature sensing via an ultra-linear device requiring no bridge balancing or corrections for non-linearity over a wide temperature range (10°C).
As previously noted (PR 10, C-12), evaluation of the original bridge/amplifier instrumentation revealed that non-linearities inherent in thermistors and bridge circuits present serious limitations. Careful error analysis of the instrumentation alone showed that worst-case errors in cardiac-output could be as high as 17% and that in order to reduce the maximal instrumentation error to less than 1%, the slope-deviation of the sensor should not exceed 0.5% over the full 10°C range. These requirements were met by adding an analog linearizing circuit which applies a correction approximating a third-degree polynomial. Other simpler and more conventional strategies such as adding fixed resistance in parallel with the thermistor were tried but found to be inadequate for a variety of reasons. The necessary correction could have been accomplished by the computer which will process the output but then the data-processing overhead would be burdensome and the device could not be used in a stand-alone configuration.

Over the past several months, efforts have been directed toward exploring the practical requirements for reliable cardiac output determinations. Minimally adequate injectate volume (at room temperature), injection site, catheter position, and the details of data analysis are the issues of concern. Large (>25 Kg) dogs are subjected to interventions which vary cardiac output from less than one to over six liters per minute. True instantaneous flow is recorded from a calibrated electromagnetic flow-probe placed at the root of the aorta and the output of the temperature sensor is recorded to the nearest 0.003°C on a second channel using a portable analog-to-digital tape recorder (H-6). Results are monitored on-line via a two-channel strip-chart recorder. The digital data are then manipulated and analyzed off-line using a PC-1200 at BCL with conveniently flexible programs (C-3) to test various processing algorithms.

Early results indicate that a 5 ml injection of room-temperature saline into the right atrium is marginally adequate (e.g. $r = 0.939$). A 10 ml injectate can give distinctly better results (e.g. $r = 0.993$) but would permit determinations to be made only half as often. At least some of the variability appears to result from incomplete mixing as well as transient variations in stroke volume at the time of injection. The latter has been confirmed by examining the integrated flow signal at various times relative to injection. A different type of catheter which should diminish these vagaries is now on order.

C-8. **Ultrasonic Gas-Flow Instrument**

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

Support: RR 00396

The development of a suitable respiratory gas-flow instrument, reported in PR 10, C-13, has continued. In order to improve the instrument's
zero-flow stability numerous transducer configurations were tested. The most promising configuration provides an improved stability to 0.25% of the flow range. Additional testing is required to evaluate the performance of this transducer configuration in the clinical environment. It is expected that the device will meet most clinical needs as presently designed.

C-9. Urine-Output Device

Personnel: R. W. Hagen, BCL
A. L. Bodicky, BCL
L. J. Thomas, Jr., BCL
D. A. West, BCL

Support: RR 00396

A device to automatically measure the urine-output of patients in the SICU has been designed, constructed and tested. This pneumatically operated system utilizes a 1 cc syringe to quantize the volume of urine produced by a patient. It is designed for use with a disposable urine drainage set manufactured by Pharmaseal Inc. Clinical evaluations will begin soon.

C-10. Fiberoptic Blood Oximetry

Personnel: R. W. Hagen, BCL
G. J. Blaine, BCL
A. L. Bodicky, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

In-vivo monitoring of blood oxygen saturation for certain patients in the surgical intensive care unit is clinically feasible (BCL Monograph 260). Blood oximetry units utilizing analog processors are manufactured by Physio-Controls Corporation. A gain in utility could be accomplished by interfacing the unit to the digital-computer-based monitoring facility of the surgical intensive care unit. Both display at the bedside and nurse's console, as well as recording of trend data could be provided.

A Physio-Controls optics module has been purchased, and the circuitry to drive the light-emitting diodes constructed. Preliminary results indicated a low SNR on the signals available from the optics module. (The SNR was confirmed by Physio-Controls.) The sampling technique of the analog processor results in signal averaging which reduces error due to noise. During the next
period, efforts will be directed to establish a valid model for comparison of parameter estimation techniques to process the reflected signals. This should give a quantitative basis for the choice of an analog preprocessor or digital signal processing.

C-11. A Color Non-Fade Display for Operating Room Monitoring

Personnel: V. W. Gerth, Jr., BCL
R. E. Clark, M.D., Surgery
K. L. Kunkelmann, BCL

Support: RR 00396
Barnes Hospital
Washington University

The Operating Room display system described in PR 10, C-14 has been completed and is in daily operation. The video processors and control electronics are mounted in a rack which includes the analog signal conditioners and a chart recorder. The rack is located near the table and can be conveniently used by either the anesthetist or perfusionist, however, most surgical procedures do not require any interaction after initial calibration.

The system employs four video display packages to provide convenient viewing. Two of the display packages include 19" color monitors mechanically integrated with digital displays and suspended from the ceiling in gimbal mounts which allow both rotation and tilt. A 9" black-and-white monitor is mounted in the equipment rack to aid in calibration and another is mounted in the induction room with remote ECG and pressure input cables to allow monitoring during that phase of a procedure.

During system checkout at BCL prior to installation, it was felt that the positional stability of the pressure calibration lines was barely adequate so this section was redesigned using a 25 MHz crystal oscillator as the reference. This change provided the desired stability and is now incorporated in the final system.

The system has been in actual use for more than six months with no failures. User response has been enthusiastic with most of the comments relating to the large, bright display with different colors which allow traces to be easily interpreted even when overlap occurs due to large ECG baseline shifts. Calibration is handled by the perfusionists who were able to manage the system skillfully after only a short orientation period.
C-12. Evaluation of Pediatric Monitoring Instrumentation

Personnel: E. P. Gruendler, B.S., Electrical Engineering
          R. M. Arthur, BCL
          R. Marshall, M.D., Pediatrics

Support:  RR 00396
          HS 00074
          Mennen-Greatbatch Electronics Graduate Student Assistantship

Monitoring instrumentation has become an integral part of the environment and routine of neonatal and pediatric intensive care units. Unfortunately, documentation describing desirable configurations, minimal performance characteristics, reliability and clinical efficacy of this class of equipment is quite limited. In the first phase of this two-part study, a comprehensive plan for evaluating pediatric monitors was developed. In the second phase, which is nearing completion, the plan itself is being tested in the evaluation of three monitors: the Abbott CA-8 with heart rate and apnea alarms, the KDC IM-300 AR, and the Mennen-Greatbatch 402/A.

The initial version of the evaluation protocol was created after consideration of 1) pertinent literature, 2) views of a variety of users and of medical product evaluators at the Emergency Care Research Institute in Philadelphia, and 3) construction practice and maintenance records of representative pediatric monitors. The protocol has three components. The first is a thorough visual inspection. The second includes a series of tests conducted with standard equipment and signals to determine electrical characteristics. The third series of tests attempts to define clinical behavior. It uses as input a set of waveforms collected from patients in the St. Louis Children's Hospital Neonatal Unit.

The visual inspection checklist contains 85 items. Most of the items can be answered yes or no. Mechanical and electrical construction practices were noted. Operating features, including display quality and organization of controls, were tabulated. Also considered were the nominal parameters describing or limiting performance of both the circuitry and the cable and connectors. Finally, documentation was checked for completeness and ease of use. Measurements included safety tests and determination of input impedance, noise contribution, common mode rejection, linearity, frequency response, accuracy of calibration levels, and baseline stability. Ratemeter range and accuracy and radio frequency susceptibility were also assessed.

Each system studied was configured to monitor an ECG and respiration. Consequently, the clinical component of the evaluation was designed specifically to exercise the circuitry which operated on these signals. Test signals were recorded from the preamplification stages of the KDC unit for playback to the detection stages of all three monitors. Cardiac ratemeter performance was studied over 15, 30, and 60 second intervals; the respiratory ratemeter, over
30 and 60 second intervals. Rate determination and artifact susceptibility were evaluated over either three or four minute intervals at each of ten threshold settings for cardiac and respiratory meters, respectively. Finally, alarm limits and delay settings were systematically examined.

C-13. **Prosthetic Heart-Valve Tester**

**Personnel:**
- R. J. Arnzen, BCL
- R. E. Clark, M.D., Surgery
- R. W. Hagen, BCL
- J. M. Rusche, B.S., Surgery
- J. J. Schier, B.A., Surgery
- B. A. Siegfried, B.S., Surgery

**Support:** RR 00396
Washington University

Throughout the past year continued research into the fatigue-failure modes of prosthetic aortic valves has kept the valve tester located in the surgical research laboratory at Barnes Hospital in frequent use. To date over 2 billion cycles representing the testing of nine different valve types have been completed by the tester and will be reported.\(^1\) Presently, all monitoring and associated electronic equipment is functioning satisfactorily and no difficulties have been experienced over the year.

With respect to the mechanical hardware of the tester it seems appropriate at this time to implement some modifications to the hydraulic circuit. These modifications stem mainly from the poor control and interdependence of pressure and flow characteristics exhibited by the existing circuit components. It is felt that a more desirable approach to the hydraulic problem would be an arrangement as illustrated in the figure below.

```
\begin{center}
\begin{tikzpicture}
  \node[draw, circle] (P_U) at (0,0) {$P_U$};
  \node[draw, circle] (P_D) at (2,0) {$P_D$};
  \node[draw, circle] (flow) at (0,-1) {FLOW SOURCE};
  \node[draw, circle] (pressure) at (2,-1) {PRESSURE SOURCE};
  \node[draw, circle] (test) at (1,0) {TEST VALVE};

  \draw[->] (flow) -- (P_U);
  \draw[->] (P_U) -- (test);
  \draw[->] (test) -- (P_D);
  \draw[->] (P_D) -- (pressure);

  \node at (0.5,-1.5) {$P_U < P_D$};
\end{tikzpicture}
\end{center}
```

During simulated systole, the flow source would be connected through a rotating valve to the valve under test. This flow source could be a positive displacement pump whose output is varied by means of a variable...
speed drive. The volumetric output of this device is, ideally, independent of the downstream resistance. Following systole the rotating valve would uncover a passageway to the pressure source indicated as Pu in the figure. This pressure source together with the downstream constant pressure source PD would maintain a constant pressure difference across the valve during the diastolic phase. These pressure sources could be adjustable and the closing differential pressure \( \Delta P = P_D - P_U \), maintained throughout tests.

Planning is currently in progress to implement this approach within the framework of the existing system.


C-14. **Automated Perfusion System**

**Personnel:**  
R. W. Hagen, BCL  
R. A. Beauchamp, Surgery  
R. E. Clark, M.D., Surgery

**Support:**  
RR 00396  
Washington University

Nine pump controllers were constructed and installed in the perfusion pumps used by the Division of Cardiothoracic Surgery. A description of the controller as well as the clinical use of the automated perfusion system has been reported. (1) The systems are functioning satisfactorily and work is continuing on a circulatory support system for infants.

C-15. Pulsatile Perfusion Pump

Personnel:  R. W. Hagen, BCL
            R. E. Clark, M.D., Surgery
            K. L. Kunkelmann, BCL

Support:  RR 00396
          Washington University

It has been postulated that by carefully controlling the blood pressure and flow developed by the peripheral perfusion circuit during long-term perfusions, certain negative effects of such procedures can be reduced. Therefore the design of a flexible system which will enable control of these parameters as desired has been initiated. The system will utilize the physiologic research cart (PR 11, C-6) to monitor selected variables and control the operation of the roller pumps. Appropriate stepper motors have been selected to drive the roller pumps. The motor/pump assembly is currently being constructed.
D. Information and Communication Systems

D-1. Information Systems Studies

Personnel: J. R. Cox, Jr., BCL
G. J. Blaine, BCL
F. M. Domke, BCL
W. F. Pickard, Ph.D., Electrical Engineering

Support: RR 00396

Present day information systems are too expensive, inflexible and unreliable to gain acceptance except in centralized operations. Relatively small, semi-autonomous groups with heavy information handling needs (for example, medical group practice) require information systems which emphasize economy, simplicity, privacy and reliability.

New technological advances in digital communications, memories and processors make possible the specialized design of systems optimized for information storage, retrieval and processing. Particularly important are the developments of

- fast access (10 µs), moderately-sized (10 Mbyte) memory
- inexpensive ($10/Mbyte), large (100 Mbyte) rotating memory
- inexpensive ($500), high-speed (100 µs) microprocessors.

These developments lead to system designs that emphasize parallelism and functionally differentiated organizations.

Designs studied over the past two years (PR 10, H-4) have been directed toward a more effective system architecture. Several innovations have recently been identified. Most important are:

1. A complete transaction log is proposed. This, because of its simplicity, offers the potential of extremely reliable operation. The rapidly decreasing cost of on-line storage provides the opportunity for a large fast-access index, thereby facilitating the use of a complete transaction log.

2. An improved general-search capability is anticipated from the introduction of implicit record linkage utilizing descriptors associated with each record name rather than a network of hard-to-maintain pointers.

3. Multiple processors will provide the parallelism necessary for the dynamic reorganization of files in order to reduce the number of accesses to rotating storage. Files that could benefit by such reorganization will be identified by inspecting the complete transaction log for recurrent patterns of access to rotating storage.
Our design studies will continue, utilizing the tools of simulation and modelling. The goal of these studies is the initial design of an information system with high performance that will be implemented in hardware based on restructured macromodules. System performance will be compared with the results of the planned simulations, providing meaningful data for the continued design process. The hardware implementation will make system tests possible in a realistic, real-time environment.

D-2. Characteristics of Clinical Data Base Files and Their Usage

Personnel: R. H. Greenfield, BCL
W. E. Ball, D.Sc., Computer Science

Support: RR 00396
HS 00074

The characteristics of computer data bases in the medical field have not yet been well studied. There is a general lack of and need for information regarding the static and the dynamic structure of data bases in use or in the process of design. Such needed information about "typical applications" includes:

- the length of character strings or records be they of fixed or variable length;
- the frequency and temporal distribution of data access, modification, and deletion;
- the ratio of access to modification;
- the logical structure of the data base in both a static and a dynamic sense;
- the measure of security required for the particular application.

Any set of applications which exhibits a clustering of the above characteristics we define to be a "primitive" application.

It is very difficult to measure the efficiency and the degree of optimization of a system without a set of metrics such as the above. Furthermore, without a knowledge of the above characteristics of an application type, it is very difficult to design an efficient file system for it; for example, a linear file could not be efficiently used to implement an inherently random-access mode of operation.
Work towards the objective of characterizing clinical data bases and their uses has proceeded with the creation and study of two data bases, a bibliographic data base which is being used to support this research and the Glaucoma Patient Registry which is reported elsewhere (D-3). The bibliographic data base currently contains 330 citations to journal articles. This data base is being used to study:

- The sizes of the test strings for authors, titles, and sources;
- The alphabetic distribution of authors' names, and a comparison with the distributions obtained from the Soundex and the Davidson codes;
- The effects of a redistribution of MUMPS subscripts between the first and second levels of a global file.

Dynamic usage studies are not being currently contemplated on this data base.

The Glaucoma Patient Registry is steadily growing in size. It now has 338 patients with approximately 85 items of information per patient. This data base is expected to grow to about one thousand patient entries. When an improved version of MISAR (D-3) is available the amount of information for each patient will probably be increased to facilitate research studies by the Department of Ophthalmology. MISAR has been locally provided with a skeleton program for monitoring the dynamic usage of its various modules, which is currently not being used, however we plan to expand and use it. A static data-base analysis has been done for approximately the last two-and-a-half months, which has documented the growth of the data base.
D-3. Activities with the Glaucoma Center

Personnel: R. H. Greenfield, BCL
D. G. Cooper, M.S.N., Ophthalmology
C. A. Kulikowski, Ph.D., Rutgers University
J. L. Persky, B.A., Ophthalmology
S. M. Podos, M.D., Ophthalmology
S. M. Weiss, Ph.D., Rutgers University

Support: RR 00396
    EY 00336
    HS 00074
    MB 00161 (Mt. Sinai - Rutgers Health Care Computer Laboratory, Mt. Sinai Hospital and Rutgers University)
    RR 00643 (Rutgers Research Resource for Computers in Biomedicine, Rutgers University)
    RR 00785 (Support for Computing Facility, Stanford University)

Two projects currently active at Ophthalmology's Glaucoma Center involve BCL personnel. These projects are a glaucoma diagnosis and research project and a Glaucoma Patient Registry.

Rutgers University is developing a computer program to automatically diagnose and recommend therapy for the glaucomas. This program is being developed on Stanford University's SUMEX-AIM TENEX PDP-10. Washington University, Johns Hopkins University, the University of Illinois, and the Mt. Sinai Hospital (in New York) are providing clinical input to Rutgers. BCL is managing the technical details of computer usage at the Glaucoma Center as well as providing human-factors input to Rutgers to facilitate their program modifications for improved ease of use in a medical environment.

Concurrently, BCL is implementing a Glaucoma Patient Registry for Ophthalmology in order to facilitate research studies on the Glaucoma Center's patient population and to help manage the Center's records. MISAR, the Miniature Information Storage and Retrieval system (1) developed at the Beth Israel Hospital in Boston, was imported from Beth Israel Hospital via the MUMPS Users' Group and translated to operate on the Artronix PC-12/7 at BCL. This version of MISAR is essentially the same as that running at Beth Israel except that some small extensions which are required here were made. These were easily implemented on the very powerful version of MUMPS provided by Artronix. MISAR, which is demographically oriented, is not the ideal solution to the data handling problems of the Center, being poor in handling multiple values for a particular attribute. It is, however, a very substantial start. We expect that Beth Israel will shortly have a more powerful version of MISAR which we may use. Local modifications to MISAR have so far been minimized in order not to duplicate the work at Beth Israel. If Beth Israel does not soon upgrade MISAR to improve its handling of multiple values, appropriate changes will be
made locally. We will attempt to maintain as much compatibility with the current version of MISAR as possible. Washington University is currently developing MISAR documentation. The Glaucoma Patient Registry and the usage statistics developed from it are to be used to help support the study of the characteristics of clinical data base files and their usage as reported elsewhere.


D-4. Medical Care Group Information System

Personnel: F. M. Domke, BCL
            M. J. Kenner, B.S., Medical Care Group

Support:   HS 00074
           Bi-State RMP Project No. 50
           Medical Care Group

The Medical Care Group (MCG) data base continued to be used in order to further explore the effectiveness of MUMPS as a tool for medical information systems. During the year, the MCG data base was transferred from the original single-user MUMPS system (PR 10, H-3) to the commercially available multi-user Artronix MUMPS-PC on the PC-12/7, with a 60 Mbyte disc. Data and code were transferred by asynchronous serial transmission between computers under MUMPS control. Due to syntactical differences in the MUMPS dialects on the two systems, some translation was necessary and this was accomplished automatically in MUMPS.

The system has been extensively redesigned and augmented in order to fit the changing and expanding needs of MCG and to increase the efficiency of data retrieval. The patient demographic files were merged into a single file which contained both individual and family information. Programs which use this file include data entry, error checking and editing facilities. Other programs print the data in a compressed format for microfiching. Subsets of the data base may be printed by family or individual. Numerous searches and summaries may be generated, including summaries of the population by insurance carrier and employer, age and sex, family size, geographical distribution, and termination from the pre-paid health-care plan.

The encounter-data file has also been merged into a single file. The Densen tables have been replaced by a group of generalized search
programs. A universal one-dimensional-table program can summarize the occurrence and frequency of any recorded visit parameter for any or all payment groups for any number of months. There is also a program for two-dimensional tables which can cross-correlate any two parameters.

In order to facilitate peer review by physicians, detailed and summary physician profile programs have been implemented. These profiles describe the patient load of each physician and the lab tests, procedures, immunizations and injections, and disposition for their visits and allow any physician to compare his profile to those of the average MCG internist or pediatrician.

An automated problem-coding system has been developed in order to relate treatment to problem, facilitate research, and automate protocol studies. The goal of this system is to accept the physicians' diagnoses in his own English and encode this in a 16-digit systematized nomenclature of pathology (SNOP) code to be used for data retrieval. This system was developed with the assistance of the Medical Care Group staff, especially Dr. L. I. Kahn and Dr. L. Berland. It is now successful at coding 90% of all diagnoses encountered at MCG. Retrieval of patients with a specific disease entity or any combination of disease attributes is readily accomplished due to the hierarchical structure of SNOP. Analysis of visit data in relation to problems and a mini-history of patients are implemented.

In the process of developing this system, much has been learned about the data needs of an ambulatory care facility. Furthermore, the effectiveness of MUMPS as a data base management system for such an application has been shown.

D-5. MESCH (Multi-Environment SCHeme) for Ambulatory Care

Personnel: J. Zimmerman, BCL
F. M. Domke, BCL

Support: HS 00074
HS 01540

There are growing needs for effective data manipulation in ambulatory care. This results primarily from increasing nationwide concerns over improved health care provider awareness of each patient's total health status, improved utilization of health care providers and facilities, and reduced administrative (billing, scheduling, etc.) costs. A few developed data systems for ambulatory care have been shown to cost less to run than manual systems, and to offer additional features that manual systems would not include. However, such systems require extensive
modification before transfer from one ambulatory care group to another, owing to inter-group differences in population size, how patients are identified, what demographic data are collected, what medical data are collected, and how the data are utilized. The cost of modifying one of the few existing ambulatory medical record systems to serve another institution appropriately is usually prohibitive; and, in fact, when money is available to establish such a system, the temptation to develop a new one rather than to transfer and modify an existing program is often overwhelming.

We are therefore creating a unified approach to the problem of ambulatory care data base systems. This is called the MESCH (Multi-Environment SCHeme) approach, introduced previously (PR 10, H-8) under the preliminary title "universal package". The intent of the ambulatory care MESCH is to provide "any" ambulatory care group with an apparently infinite framework within which the group may specify its data environment. These specifications define the data that are manipulated, and the ways in which they are used. The created definition is used as the basis for the generation of a customized file structure and program set which are optimal for the environment which has been defined. The accomplishments thus far are in the three key areas of:

- defining the framework of choices: a comprehensive series of menus is being completed which lists the various data manipulation capabilities that different ambulatory care groups have been found to possess.

- establishing a sophisticated interactive capability through which an environment may be defined: a specially tailored questionnaire driver is being used as the initial tool by which an environment may be defined.

- creating the necessary programs to convert each environment definition to a tailored data base system: studies of data base structures and of automated programming and file design are in progress to allow us to optimize the data base systems that we will create.
An extensive research and design project in outpatient appointment systems is currently under way. This is conceived in three phases:

- Analysis of outpatient appointment systems throughout America;
- Design, writing (in MUMPS) and testing of an experimental outpatient appointment system for the St. Louis City Hospital clinics;
- Generalization of this package via MESCH (PR 10, H-8; D-5) for easy transferability to other institutions.

The first phase began with observations and data collection in City Hospital's outpatient clinics, to discover how existing appointment procedures affected patient care and attitudes. The collected data, in conjunction with information gathered from the literature, showed that a wide variety of benefits for patients, medical and paramedical staff, and administration could be achieved through computerized appointment systems. Benefits include: reduced waiting time; improved continuity of care; enhanced rapport among patients, doctors, and clinic staff; better chart availability; reduced paper work; more balanced loads; fewer no-show patients; and increased revenues for the hospital.

After surveying other approaches to outpatient systems, we determined the most useful functions to automate, and designed the system. Programming in MUMPS began in December 1974, and was substantially completed in May 1975. Documentation has been written. A two-to-four month test at the hospital will start shortly, and we expect to use the results of this test to suggest improvements in the package. Two demonstrations have been given, and support of the existing package has been expressed by the medical and clerical staff. We are working with the hospital to develop a conversion plan of the package from MUMPS on a PC-12/7 to COBOL on the UNIVAC 9480, and the outline of this plan should be clear before the trial begins.

The work on generalizing the outpatient appointment system begins with the data collected on eighteen outpatient departments in seven states which were visited during autumn of 1974. Their existing procedures, devices, problems, plans, and attitudes towards automation were discussed at length. As a result, a comprehensive insight into the scope of appointment systems was attained, and the potential tasks to be included in a MESCH package were more clearly defined. More detailed information is currently being obtained.
The MESCH specifications are scheduled for completion in the autumn.


D-7. **CAPO Program Translation**

**Personnel:** J. Zimmerman, BCL  
B. E. Campbell, BCL

**Support:**  
HS 00074  
HS 01540

The CAPO (Computer Aids in the Physician's Office) material is a set of code and data which has the potential of expediting the delivery of health care to ambulatory patients in the practitioner's office. This material was developed under an HEW contract (HSM 110-71-244) with Bolt, Beranek and Newman Inc., and was made available to the MUMPS Users' Group (PR 10, H-5; D-9) in 1974 following the conclusion of that contract. The machine-readable data and code that were made available were a large number of histories and two history drivers. The code was in the MIIS dialect of MUMPS, so that translation into the MUMPS-PC dialect was necessary. Furthermore, the material was on DECTapes, and was transferred to LINC tapes by means of special PDP-12 hardware and software; it then had to be organized into a 1-character-per-word format which would be acceptable to MUMPS-PC as normal input. The transferred code was translated from MIIS to MUMPS-PC. Most of the translation was performed automatically, with questionable items flagged for inspection and possible manual modification. The transfer and translation processes are being documented. (1)

The resulting transferred and translated histories contain copious errors. These appear to be due primarily to faults in the MIIS code and data rather than to errors we have introduced. We plan to correct most of the faults during the coming months.

(1) B. E. Campbell and J. Zimmerman, "The Transfer and Translation of Applications in MIIS on DECTapes to MUMPS-PC on a PC-12/7," BCL Monograph No. 275, to be published.
D-8. Application Program Transfer

Personnel: J. Zimmerman, BCL
          G. S. Kuthe, BCL
          J. H. Rixleben, BCL

Support: RR 00396
         HS 00074
         HS 01540

Our concerns over application transfer (PR 10, H-5 and H-8) have led us to consider further the total spectrum of application transfer. This spectrum ranges from the creation of:

- Transfer-oriented applications, and
- Administrative-level documentation,

through the definitions of:

- Technical documentation,
- Media of transfer,
- Inter-dialect translation, and
- Application modification procedures,

to

- Assignment of responsibility for the application content.

We have made progress in all of these areas. In particular, we are currently designing and implementing:

- A general mailing address package,
- A package of utilities for editing, documenting, and further manipulating MUMPS code and data,
- "SIMSTAT", a simple statistics package.

Each of these packages is created with the intention of being readily transferable to other institutions, being designed either to be non-institution-specific or to be readily adaptable to institutional individualities. Furthermore, the MUMPS-PC code is written in a form that is fairly compatible with Standard MUMPS. For each of these packages, administrative-level and technical documentation is in progress or will be started shortly.
D-9. MUMPS Users' Group (MUG) and MUMPS Development Committee (MDC)

Personnel: J. Zimmerman, BCL
R. F. Beckley III, B.S., Beth Israel Hospital, Boston, Ma.
J. R. Cox, Jr., BCL
G. S. Lodwick, M.D., University of Missouri, Columbia, Mo.

Support: RR 00396
HS 00074
HS 01540

The activities of MUG have expanded from those reported last year (PR 10, H-5). Some of the most important achievements are:

- Unified MUMPS application programs (PR 10, H-6) have been completed for the collection and maintenance of the MUG mailing list, the MUG institution profiles, and the MUG Application Abstracts Library. Various documents (1) have been generated from the accumulated data.

- The 1974 MUG Meeting was organized and the proceedings (2) published. The 1975 MUG Meeting is currently being organized.

- The first draft of an advanced MUMPS programming manual (3) has been completed and is being distributed to a restricted group for assessment. A manual on introductory MUMPS is partially complete.

- Numerous articles on MUMPS have appeared in scientific and popular literature in the last year, and the visibility of MUMPS has been thereby increased. The direct result of this has been that our mailing list has approximately doubled in the past year, and is now about 1600. Enquiries for MUMPS material are received daily from new people.

- Our concern with the transferability of computer packages (PR 10, H-8) has led to the projects summarized elsewhere (D-5; D-7; D-8) and investigations (4) of the success and running costs of application transfer through various application libraries.

- The continued publication of the quarterly MUMPS News. (5)

The MDC (PR 10, H-7) has produced the first MUMPS Language standard, and the specifications of a "Level 1" standard which defines the current limits of such features as string length and number range for application portability. A manual on MUMPS documentation has also been completed and distributed.
D-10. Digital Telecommunications Study

Personnel: R. J. Benson, J.D., Computing Facilities
           G. J. Blaine, BCL
           M. A. Franklin, Ph.D., Electrical Engineering
           S. Igielnik, Ph.D., Medical Computing Facility
           A. Sen, D.Sc., Electrical Engineering

Support: RR 00396
          Washington University

A study was conducted to ascertain technical feasibility, availability and price for a two-way high-speed digital communications link between the Washington University Medical Computing Facility (MCF) and the Washington University Computing Facility (CF). The link would connect the planned MCF MUMPS system to the CF IBM System 360/65 system to provide services such as microfiche, high-quality plotting and high-speed/high-capacity tape processing to the users of the MUMPS system and data concentration for minicomputers which currently utilize 1200-baud leased lines for teleprocessing (D-11).

The principle constraints included a 1 to 5 Mbit/sec data rate requirement in both directions, and a distance of 2.25 miles (3.6 km) between the facilities. Existence of a clear line-of-sight path allowed optical and microwave links as well as telephone company services to
be considered.

A brief comparison of products judged to satisfy the requirements at minimum cost follows:

<table>
<thead>
<tr>
<th>Optical</th>
<th>Radio/Microwave</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS Laser Link</td>
<td>Norden 226HZ</td>
<td>Telephone Co. 551A CSU</td>
</tr>
<tr>
<td>$10,000</td>
<td>$26,500</td>
<td>$2,400 monthly rental</td>
</tr>
</tbody>
</table>

The laser optical link has been proposed for implementation. The optical link offers the advantages of no FCC licensing requirements and lower cost. The ALS laser operates in the near-infrared spectrum with output power well below limits prescribed by the proposed Federal laser regulations for eye safety (<0.2 microjoules per pulse). Impairments due to atmospheric attenuation and noise due to background radiation are to be evaluated. A low-speed telephone line is proposed as a back-up to enhance system reliability.

D-11. Teleprocessing Networks

Personnel: R. H. Greenfield, BCL
A. L. Bodicky, BCL
K. L. Kunkelmann, BCL
E. Van Patten, BCL

Support: RR 00396

The interactive teleprocessing activity between the IBM System/360 Model 65 computer and the remote computers (BCL Monograph 260) has been undergoing an evolutionary decline. As minicomputers become more powerful, with larger on-line storage devices and more sophisticated operating systems, the need for host support is decreasing.

Documentation of work reported on in the previous year (PR 10, 1-14) was completed in November 1974. Revised and updated versions of BCL Monographs No. 95 and No. 104 were released. In addition to a new chapter describing the "PL/I Subroutines for PC Files," changes were made to reflect the reduced number of communications links (from four to two), and other minor modifications.

In the Fall of 1974, the Computing Facilities requested BCL to reduce its core-storage requirements from 20K to 16K. The lower usage then existing on the network easily permitted this. The reduction
was made by dropping support of two communications links to the medical school (leaving two links in service) and thus releasing the requested 4K of core storage. Only a minor re-assembly of the buffer module was required. The data communications cross-bar switch at BCL required minor wiring changes to implement its reduced capacity. While this was being done some minor maintenance changes were made. The transition to a lessened capacity was smooth and uneventful.

In the Spring of 1975 a reallocation of space in BCL's basement required the movement of the cross-bar switch. The unit was out of service for one day while telephone company and BCL personnel effected the move.

Currently, computers in Radiation Oncology, the Coronary Care Unit, Biological Chemistry and one BCL computer are connected to the network. Although current utilization of the network is low (approximately 15%), the network remains a vital asset for those applications requiring the collaborative computing support of the large system.

D-12. MUMPS on the IBM System/360

Personnel: R. H. Greenfield, BCL
W. E. Ball, D.Sc., Computer Science

Support: RR 00396
HS 00074

Since our last report (PR 10, H-11), we have turned from the development of an intermediate-code generating system to the creation of a model of the MUMPS global-array structure on the IBM System/360 using PL/I and direct-access I/O. This model can read, write and kill global variables, each global reference being interpreted in the same manner as in MUMPS. The model also reports statistics on the number of reads and writes required to access or create a data item in the global file.

After trace data streams have been gathered on the characteristics of clinical data base files (D-2), the MUMPS model will be used to study variations of the present MUMPS filing structure. At this time it is unclear whether such trace data on global accesses will be sufficient to drive this model, or whether the intermediate-code generating system will be needed to drive the model directly from MUMPS code.
Over the past year the Jewish Hospital macromodular video data acquisition system has been expanded to work directly with the Pertec disc unit of the PC 12/7. This was made possible with the completion of the macromodule-to-disc controller interface in the second half of 1974. Since that time a macromodule system has been installed and utilized in the cath lab for the real-time acquisition of video data occurring during radio opaque injection in the left ventricle. Records of ten patients have been acquired through the use of this system. These records will provide raw material for future work concerning image processing and ventricular function determination.

With the current system configuration a total of 256 frames (or 8.5 sec) of video information may be sampled and stored directly on one bank of the Pertec disc which is equivalent to 2048 LINC tape blocks. Each video frame is sampled at 4096 points. Each point intensity is sampled and converted into a six-bit binary representation. Two such samples are packed together to comprise a twelve-bit word for compatibility with the disc and PC systems. Only the odd field of each video frame is sampled. Samples may be drawn from a "window" 64 points wide and 64 lines high. Every other line of the odd field and 64 out of 128 points along any given line are available as samples. This "window" may be manually positioned to encompass a region of interest to efficiently utilize the disc storage capacity.

Following its capture on the disc, the data are formatted and available in the form of two double-length LINC tapes. Each frame of video information then occupies eight 256-word blocks, each block containing 8 lines of data.

A literature survey of image processing methods applicable to the ventricular-contour edge-detection problem is nearly complete. Several edge detection algorithms are presently used for X-ray image detection. These and other more general edge-detection methods offer possible starting points for the development of an edge-detection system applicable to the video data acquired by the Macromodular Video Digitizer. This literature survey includes descriptions for many of the algorithms from which programs can be written and evaluated.

A grey level display device has been developed for the PC 12/7 (E-4). The new display will facilitate qualitative evaluation of the digitized video as well as providing a display of the video image over which the computer-generated edge contour may also be displayed.
The existing machine language version of the cardiac cath lab system (CACLSYS) was modified to permit addition of FORTRAN programs to perform specialized functions. This was done by providing a "jump-out" option. The jump-out module stores appropriate parameters in buffers in the unused portion of memory, corresponding to "COMMON" used by FORTRAN. The module then transfers control to the appropriate FORTRAN overlay using absolute block reads. At the current time two major jump-outs have been completed.

The first jump-out program evaluates the quantity \((dP/dt)/P\) for left ventricular pressures. This module is used to evaluate changes in left ventricular (LV) contractility. The overlay is invoked immediately after conventional pressure analysis has been performed on a left ventricular pressure tracing. The program calculates the quantity \((dP/dt)/P\) for each pair of points on the systolic upstroke portion of the left ventricular pressure tracing. A plot of \((dP/dt)/P\) versus pressure is then generated for each beat in the pressure data. The program performs a least squares fit to the initial portion of the \(dP/dt\) curve and extrapolates this back to a pressure of zero to obtain the quantity \(V_{max}\), a measure of LV contractility. In addition, the program calculates the quantity \((dP/dt)/P\) for a pressure of 40 mmHg (millimeters of mercury) using the least squares fit equation. The information for each of the individual beats is then displayed in graphic and tabular form on the oscilloscope. After all of the beats have been calculated, a summary graph is generated showing the data points for all of the beats on a single graph and a single least squares fit using all of the data points. This least squares fit is used to calculate an "average" \(V_{max}\) and \((dP/dt)/P\) evaluated at 40 mmHg.

All of the above measurements are obtained using absolute ventricular pressures. At this point the program determines the developed ventricular pressures (absolute pressure minus end diastolic pressure) for each of the beats and redispays the entire sequence of events described above using developed pressure in place of absolute pressure. If desired, tabular data are listed on the printer, and hard copy records of the graphic data are produced.

The second major jump-out performs dye dilution curve analysis. For this particular jump-out the operator must position arrows on the injection spike and the appearance time of the dye curve to be analyzed. The FORTRAN analysis program is then called via the jump-out routine.
The FORTRAN program first performs a gamma-variate analysis of the dye-curve data by performing a least squares fit of a function, related to the gamma function, to the upstroke of the dye curve. Appropriate indices are then calculated including the area under the least squares-fit curve, the cardiac output, and the cardiac index. Calibration factors are also displayed. After this display has been produced, the program performs a Stewart-Hamilton analysis of the dye data. Beginning with the peak value of the digitized dye data the Stewart-Hamilton program calculates the exponential decay constant for successive groups of points on the down slope of the dye curve data. The decay constants are plotted on the display. After all the decay constants have been calculated the program performs a linear least squares fit to the graph of the decay constants in an attempt to find a series of decay constants with a nearly zero slope, minimal variance, and values which are less than 1. If such a group of points can be found, the group is averaged to form an average decay constant and the exponential portion of the dye curve is extrapolated using the average decay constant. If no such decay constant group can be found, the system requests manual selection of the appropriate decay constant and then uses that constant to perform the exponential fit. In either event, the program then displays appropriate indices as mentioned above. Copies of the analysis display can then be obtained following which the program returns to the cath lab system data directory.


E-3. Washington University Cardiac Catheterization Laboratory System

Personnel:  G. H. Brandenburger, BCL
           B. R. Hieb, BCL

Support:   RR 00396

Evaluation of the existing Washington University Cardiac Catheterization Laboratory System (Cath Lab System) has been completed. The Cath Lab System in its present form is inadequate for use at the Washington University unit without operational assistance from BCL. Much valuable information about the requirements for a new Cath Lab System has been learned from the operation of the existing system, and this information has been applied in the re-design efforts (E-4).
During the construction and testing phase of the new system, the PC-12/7 computer system has been upgraded. An adaption of a semiautomatic cineangiographic ventricular volume analysis system developed at Jewish Hospital has been in use for several months. More recently, a floating point unit and matrix line printer have been added. Both devices will be used in the new system, and are currently used by the ventricular volume system. The PC-12/7 power supply has been replaced with several standard Lambda power supplies for increased reliability.

E-4. A New Generation Catheterization Laboratory Data Acquisition and Analysis System

Personnel: G. H. Brandenburger, BCL
S. A. Garfield, BCL
B. R. Hieb, BCL
P. A. Ludbrook, M.D., Medicine

Support: RR 00396

The plans for the new Cardiac Catheterization Laboratory system resulted from observations and evaluations made at the Washington University and Jewish Hospital Cath Labs. The principal goals realized in this new system's development are:

1. A system requiring little operator attention, particularly during the catheterization procedure when computer-caused interruptions cannot be tolerated.

2. A system flexible enough to meet different cardiologists' requirements, as well as different laboratory hardware requirements.

3. Correctability of operator errors both during and after data acquisition, with provisions for missing, incorrect, and incomplete data to be typed in manually when necessary.

4. Provisions for the cardiologist to specify his own analysis scheme for unusual data (such as shunt pressures and unusual anatomical sites encountered in pediatrics).

5. Automated waveform pattern recognition (with operator override capability) for standard pressure and dilution analysis when desired by the cardiologist.
6. A "user's operating system" permitting research and experimental data analysis programs to be easily added to the cath lab software, with all software and data overhead handled by the operating system.

7. Merging of the new cath lab system and the Jewish Hospital ventricular volume analysis system (E-3). Combined pressure-volume analysis overlays are planned for the merged software system.

8. Provision for a high-speed sampling (one kilohertz) pressure data acquisition overlay for \( \frac{dP}{dt} / P \) and \( V_{\text{max}} \) calculations. For efficient data acquisition, sampling is synchronized to the ECG and only the pressure pulse upstroke is sampled.

9. Software modification and exportability simplification through the use of a higher-level language and software modularity.

More than one-third of the cath lab software has been written and tested. Flowcharts for most of the remaining software are complete. A prototype \( \frac{dP}{dt} / P \) and \( V_{\text{max}} \) program has been implemented and is being evaluated (E-2).

All initial hardware design is complete. This includes:

1. A data acquisition control panel. Through the "panel", the operator supplies information to the computer such as anatomical site, amplifier channel number, patient condition, pressure scale, sampling rate, and data acquisition status. The physical layout of the panel is designed to simplify computer operation so that little operator intervention is ever required, especially during the procedure. To further simplify operation, frequently occurring data acquisition sequences (procedure "protocols") may be entered from the panel prior to the cath procedures. During a procedure, the selected protocol sequence flashes lamps in the panel keys; if the operator agrees with the computer's choice, no keys need to be pressed. The protocol can be overridden by simply hitting an anatomical site key.

2. The PC-12/7 display has been upgraded using a PEP 400 R video scan converter. The advantages of the scan converter over the conventional Tektronix 611/613 display are:

   a) The increased contrast and brightness of the standard video monitors used.

   b) Sixteen grey-level image capability.

   c) Multiple remote displays using inexpensive video monitors and a single coaxial cable.

   d) Selective point erasure.

   e) Increased writing speed when disrupted viewing is permissible during writing.
3. A hardware, multiplexed, sixteen channel, 20 µs A/D converter-interface. The multiplexer is expandable to 64 channels.

4. An extension of the PC-12/7 data bus. The data bus has room for one additional interface card as a result of the latest system upgrading (E-3). The new bus extension, "B-BUS", can accommodate eleven additional interface cards and provides an interruptable auto-wait-if-busy feature not available with the commercially available PC-12/7 bus extension.
F. Mass Spectrometry

F-1. Mass-Spectrometry Program for a Quadrupole Mass Spectrometer

Personnel: B. L. Shore, BCL
           W. F. Holmes, BCL
           D. W. Rosenthal, Ph.D., Research Triangle Institute

Support: RR 00396
         State of North Carolina

The PDP-12 programs originally designed for use with an LKB-9000 magnetic scanning mass spectrometer have been extended to operate a Finnigan quadrupole mass spectrometer (PR 10, F-2). The new programs have been operating for the past nine months at the Research Triangle Institute in North Carolina. Adaptation to quadrupole instruments from other manufacturers should be straightforward. Mass spectra can be acquired by two modes of scanning: peak detection and integer mass detection. The peak detection mode is a digitized version of the continuous-scanning method in standard use with magnetic instruments. The mass is incremented by 0.1 mass unit intervals while the ion intensity is monitored for the occurrence of peaks. This method provides reliable information on the mass and intensity of each fragment ion, which is necessary to establish a calibration curve and to monitor drift. In most applications, the nominal integer mass of each fragment ion provides sufficient information for identification. Thus continuous scanning by 0.1 mass unit increments results in 90% of the acquired information being discarded. Therefore, if the mass range is scanned by 1.0 mass unit increments, it should still be possible to detect the peak intensity of each fragment ion, providing calibration is maintained. This method results in increased scanning speed as well as increased sensitivity, both most useful for GC/MS analysis of small quantities of biological material.

A multiple ion detection (MID) program was written to record fragment ion intensities at selected masses (PR 9, G-2), where increased precision and sensitivity is needed for the analysis of known compounds. Quadrupole mass spectrometers are more flexible than magnetic instruments in this application, since the full mass range can be covered in one second or less. In related developments, PDP-12 interfaces for MID analysis with magnetic instruments using electrostatic scanning (PR 8, G-2), have been constructed at two outside laboratories. The Stanford Research Institute has a functioning installation, while the Fish and Wildlife Service at Columbia, Missouri, is installing the interface for use with a Perkin-Elmer 270.
F-2. Interactive Program for Mass Spectrum Processing

Personnel: R. W. Scheifler, BCL
W. F. Holmes, BCL

Support: RR 00396

Continuous scanning of gas chromatograph effluent creates hundreds of spectra from a single analysis, which would require a lengthy period for one-by-one evaluation. A program has been written that generates from the spectra a reconstructed total ion current (TIC) signal as a function of time, similar in appearance to a GC detection curve. Each TIC time point represents a complete spectrum, whose intensity approximates the amount of material entering the mass spectrometer at that time. The user can then examine this GC curve for peaks, which usually correspond to separated compounds. A movable pointer allows designation of any TIC point. The corresponding spectrum can be viewed immediately. The user can also select a series of spectra for storage into a file. Individual background spectra for subtraction may also be specified. Usually a background spectrum is selected from the adjacent peak minimum, however, partially resolved components create many situations where human judgement is preferable to a totally automated procedure. The file of selected spectra can then be plotted, or searched against a reference file of known spectra (PR 10, F-3).

F-3. Adaption of the PDP-12 Mass Spectrometer System to the LSI-2 Computer

Personnel: P. D. Norberg, BCL
P. S. Berger, BCL
W. F. Holmes, BCL
R. W. Scheifler, BCL

Support: RR 00396

The PDP-12 system (PR 10, F-1) is being adapted and extended for use with a new low-cost computer system. The basic hardware consists of an 8 or 16K Computer Automation LSI-2 computer, a dual platter Pertec disc (F-5), a display controller with character and vertical line generators (F-4), a control console, and a data acquisition interface. A high-speed eight-bit parallel data transmission interface has also been constructed for communication between the LSI-2 and the PDP-12. The interface has allowed us to use the disc and high-speed printer on the PDP-12, in conjunction with the LSI-2 assembler, for writing programs. This
provided an effective disc-oriented operating system at an early phase of system development. Over the long term, the communication lines will allow transfers of data collected by the PDP-12 and LSI-2 systems. The computer hardware is intended to provide equal or superior capacity to commercial mass spectrometry systems at approximately one-third the cost. The software is organized as an open system so that users of the programs can modify them and add new ones. In this way, experienced mass spectrometrists will have a method of directly contributing to program development. Considerable savings in memory space have been realized during program conversion, allowing substantial improvements within the basic 8K system, which is expected to be fully operational this summer.

F-4. A Display Interface for Use in Mass Spectrometry

Personnel: P. S. Berger, BCL
G. A. Appel, BCL
W. F. Holmes, BCL

Support: RR 00396

A compact, multifunction oscilloscope display interface has been implemented with features optimized for the display of mass spectra without substantial flicker. The device, driven by a Computer Automation LSI-2 minicomputer (F-3), is capable of generating points, vertical lines and a set of 64 alphanumeric characters. An internal character generator accepts 6 bit ASCII-coded character inputs, translates them into a character dot matrix and displays the dots in a single computer output instruction. A vertical line of any height, composed of a set of closely spaced dots, can likewise be produced by a single instruction, allowing readable displays of mass spectra containing several hundred fragment ion peaks. Automatic indexing between characters and along the graphical x-axis further simplify the display of labelled spectra.

The generator will drive a Tektronix 602 Display (8 cm x 10 cm screen) or a Tektronix 604 Display (4 in. x 5 in. screen) with good visual clarity. A display time of 2 μs/dot is used. Four intensity levels, and fifteen dot spacings for characters and vertical lines can be selected under computer control.
F-5. A Disc Interface for the LSI-2 Computer

Personnel: P. S. Berger, BCL
G. A. Appel, BCL
R. W. Scheifler, BCL

Support: RR 00396

The general-purpose BCL disc controller (PR 8, J-15) has been interfaced to a Computer Automation LSI-2 minicomputer to control a Pertec D3000 series dual platter disc. The system is software compatible with that of Finnigan Corporation which markets a computer system for gas chromatography mass spectrometry. In addition to this software compatibility, the interface will accept other commands such as formatting, variable block length designation, and status reporting for error diagnostics. The system can be interrupt driven or operated in a software testing loop to sense controller ready or error status. A general purpose disc test program has been written for formatting of new disc platters, location of bad disc sectors, and diagnosis of hardware malfunctions.

F-6. An Amplifier System for Monitoring and Recording Data from a Stopped-Flow Spectrophotometer

Personnel: P. S. Berger, BCL
G. A. Appel, BCL
C. Frieden, Ph.D., Biochemistry
W. F. Holmes, BCL
Support: RR 00396
AM 13332

A stopped-flow mixing device coupled to a spectrophotometer has been used for several years to analyze millisecond response enzyme kinetics. The system uses a storage oscilloscope as a visual monitor, and an FM recorder (PR 8, G-5). The recorded data is introduced off-line into a PDP-12 computer with a floating point processor for analysis by an interactive kinetic simulation program (PR 8, G-4). The original setup used the storage oscilloscope itself as the primary amplifier of the absorbence signal, with the output at the deflection plates then attenuated and fed into the recorder. This provided the closest possible correspondence between visual monitoring and the recorded signal. However, quantitative computer analysis has shown that a small, variable transient is superimposed on the kinetic signals by the oscilloscope. To correct this problem, the amplifier system has been completely redesigned to bypass the oscilloscope, which is now used only for qualitative monitoring.
and nulling the signal against a variable reference voltage. To accommodate the wide signal range, the new amplifier has precision gain settings from 1 to 200, with corresponding settings for the variable reference voltage.

F-7. A Microprocessor Controlled Monitor for a Liquid Chromatograph

Personnel: P. S. Berger, BCL
          C. A. Appel, BCL
          W. F. Holmes, BCL
          C. M. Jackson, Ph.D., Biochemistry

Support: RR 00396
         HL 12820
         HL 14147

With the recent advent of microcomputers, one is able to cost effectively dedicate a sophisticated processing element to a laboratory instrument for the purpose of acquiring, translating and processing raw data. Many jobs once considered appropriate for minicomputers can be performed by microprocessors, leaving the larger computers free to perform more complex processing, especially that requiring costly peripherals.

A microprocessor-controlled monitoring system was implemented and connected to a Varian Techtron spectrophotometer, which is used to monitor a liquid chromatograph. The microprocessor acquires data, translates to ASCII format, and drives a Teletype paper-tape punch. The small cabinet houses an Intel 4004 microcomputer chip set, input/output electronics, clocks and power supplies.

An internal 8-bit A/D converter samples the analog signal from the spectrophotometer. This sample value is converted to binary coded decimal for a numeric display, and the corresponding 8-bit ASCII codes are punched onto paper tape. The user may enter the sampling interval (in seconds) from front-panel thumbwheel switches along with a 5-digit code identification number used for cataloging. The analog input-voltage range is 0 to 1 volt; the digital output range is 0 to 255 decimal. The unit can be modified to accommodate four input channels by altering the microprocessor software, which is stored in reprogrammable ROM. The paper tape output is to be used as an input to an offline WANG 600, a programmable calculator with paper-tape input, magnetic tape cassette storage and a printer/plotter for output.
Measurement of myo-Inositol in Nanogram-Size Rat Brain Tissue Samples

Personnel: W. R. Sherman, Ph.D., Psychiatry and Biochemistry
M. H. Laird, M.S., Psychiatry
P. M. Packman, M.D., Psychiatry
R. L. Boshans, A.B., Psychiatry

Support: NS 05159
MH 19624
MH 70734

A study has been underway for the past year on the feasibility of determining tissue levels of myo-inositol in samples of brain on the order of 5 to 50 nanograms dry weight (PR 9, G-9). Samples of this size are dissected under a microscope and weighed by a quartz-fiber balance. These sample sizes encompass single large cells, at the lower weights, to portions of hypothalamic nuclei, and other brain regions with larger samples. The hypothalamic samples are being studied in different estrous states in the hope of observing changes in inositol levels with peptide hormone release (myo-inositol may be produced as a product of phosphoinositide hydrolysis in cellular functional states).

The method being used is direct derivatization of the dry tissue with a small volume of trimethylsilylating reagent containing deuterated myo-inositol. The samples are later subjected to multiple ion detection (MID) analysis.

The results of these analyses are puzzling. In an experiment to determine linearity of response of the instrumental set-up to varying amounts of tissue, a range of cerebellar granular layer samples from 5 to 50 ng dry weight were examined. The plot was linear, with $r = 0.92$, and intersected the myo-inositol weight axis at 0.4 picograms, certainly near zero for our purposes. The concentration of myo-inositol agreed well with previously and subsequently run macro-analysis samples, and, on three separate occasions, the micro-analysis was consistent. However, in hypothalamic regions the scatter of data is great, although precision remains at a level of about $\pm 5\%$. The parameters involved are too complex to review here, but the results seem to be explicable in two ways: either a real and sizable regional variation in concentration, or some uncontrolled variable in the analysis. It is clear that, working at the limits of the instrumentation, problems arise that are not seen in other situations. We are presently methodically examining possible sources of experimental variation.
F-9. Tricyclic Antidepressant Studies

Personnel: J. T. Biggs, M.D., Psychiatry
W. R. Sherman, Ph.D., Psychiatry and Biochemistry

Support: RR 00396
MH 25571

One of our initial objectives was the development of a rapid and accurate gas chromatographic-mass fragmentographic assay for all the tricyclic antidepressants marketed in the United States. This has been accomplished, so that at present we have the capability to assay 120 samples in an 8 hour period. While developing the assay method for tricyclic measurements, routine patient plasma analysis have been carried out. Exact data regarding optimal therapeutic range for the tricyclic drugs is not known, however, the routine measurement of tricyclic antidepressants levels has been useful in checking compliance in patients who fail to respond to therapy. The measurement of over 600 patient samples has proven that such measurements are practical on a routine basis. At present out-patient studies are under way to determine the optimal plasma range for amitriptyline and nortriptyline antidepressant therapy. Patients are initially carefully screened to determine an accurate diagnosis of either primary or secondary affective disorder. Patients are then treated with a level dose of one of the two drugs and evaluated weekly for the first 6 weeks and subsequently at monthly intervals for 6 months. At present 15 patients have been studied. Blood levels have been measured in patients ingesting tricyclic antidepressant overdoses. Measurements are made each 8-12 hours for up to 144 hours and careful clinical evaluation is made at each plasma sampling. The initial purpose of the study has been to determine if any of the usual clinical symptoms said to be associated with tricyclic overdoses are reliable predictors of the seriousness of the overdose. At present, 20 subjects have been studied. The duration of the QRS interval appears to be the only specific predictor of the severity of a tricyclic overdose. Such information is of practical use to the emergency room physician in evaluating a patient said to have ingested tricyclic antidepressants.
F-10. Morphine Analysis in Rat Brain Tissue

Personnel: P. P. Hipps, Ph.D., Psychiatry
W. R. Sherman, Ph.D., Psychiatry and Biochemistry
T. J. Cicero, Ph.D., Psychiatry

Support: AA 70180
DA 00109
DA 00259

An analysis of morphine as its bis-O-trifluoroacetyl derivative was developed using the multiple ion detector (MID) with our LKB-9000/PDP-12 computer. The analysis utilizes N-CD₃-morphine as internal standard. This confers excellent accuracy and precision on the method. Sensitivity for pure samples of morphine extends to below 2 picograms (S/N ratio at this level is about 8:1). The method has been used to correlate morphine brain levels with analgesic effect through a six-hour period. The results agree with earlier studies, confirming them with greater specificity for morphine than has previously been possible. This procedure also shows a greater correlation (r = 0.923) between brain morphine level and degree of analgesia than earlier studies. Current studies are aimed toward a determination of regional brain levels of morphine after an acute dose. The method combines sensitivity and drug specificity to a degree not previously available.

F-11. Pharmakinetics in the Neonate

Personnel: W. E. Dodson, M.D., Pediatrics and Neurology
L. S. Hillman, M.D., Pediatrics
R. E. Hillman, M.D., Pediatrics

Support: RR 00396
The National Foundation
Washington University

The metabolism and routes of elimination of mepivacaine have been studied in newborns intoxicated with this drug (PR 10, F-5, F-13). The drug was administered as local analgesia to the children's mothers. Studies have demonstrated that the drug is most efficiently removed in the urine. Tissue and brain section levels were measured in one infant who died. Kinetic studies of anticonvulsants in neonates are also in progress.
GLC and GLC-MS have now become routine means of evaluating patients with inborn errors of metabolism (PR 10, F-6). In the past year, one new case of maple syrup urine disease, 3 cases of propionic acidemia, and two cases of non-ketotic hyperglycinemia have been diagnosed. In addition, two cases of phenylketonuria have been confirmed. Samples have been analyzed from several other universities outside the St. Louis area including University of Pennsylvania, Johns Hopkins, University of Toronto, State University of New York at Buffalo, and the Royal Children’s Hospital in Melbourne, Australia.
G. Speech and Hearing

G-1. RAP Development

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
J. W. Sharp, Central Institute for the Deaf
B. F. Spenner, BCL

Support: RR 00396
NS 03856

RAP (PR 10, G-1) (Random Access Programmer for Complex Sounds) continues to be used extensively as a stimulus source in speech experiments at Central Institute for the Deaf. A second version of RAP, mRAP, that will be shared by the signal detection laboratory and the physiology laboratory is nearly finished. This abbreviated version of RAP is designed to be interfaced with existing computer systems in these laboratories. With the addition of a control console and peripherals, mRAP can be used as a stand alone system similar to RAP. Tentative plans call for the construction of at least one more mRAP unit this next year to satisfy increasing laboratory demands.

We have found that the original RAP disc format (5000 words per track) is awkward to use with the speech and hearing computer system. Excessive memory space is wasted to provide buffering for the 5000 word disc transfers. This nonstandard format was originally chosen to utilize the entire storage space on each track. The design of mRAP provides for operation with either a RAP formatted disc or a more standard block formatted disc (16-256 word blocks per track). The standard block format results in about a 20% loss in storage capacity on the disc. However, it is expected that the increased ease of programming with the standard format will cause most users to change over in the future.

Considerable design effort has been expended to isolate the mRAP analog system power and ground from the power supplies for the main logic, memory, and disc unit. Separate power supplies, photo-isolators, and shielding are used to minimize analog system noise caused by ground currents and capacitive coupling from the logic circuitry.
C-2. A Mathematical Model of the Mechanics of the Cochlea

Personnel:  B. F. Spenner, BCL
            J. R. Cox, Jr., BCL

Support:    RR 00396

Current effort centers around refinement and implementation of the mathematical model (1) reported previously (PR 9, H-2). Methods of calculating the Green's function have been reviewed, and an improved calculation procedure has been developed that provides a closed form solution to the infinite series. The revised Green's function is calculated n times assuming n discrete pressure sources along the membrane length. The result provides a representation of the fluid coupling between the discrete elements.

Digital techniques are used to perform the simulation with digital integration and matrix multiplication being the predominant simulation functions. Digital integration techniques are being explored to find a sufficiently accurate technique requiring a minimum number of iterations per time step. Presently a third-order Milne method, used in a Predictor-Modifier-Corrector (P-M-C) mode, is being examined. The P-M-C mode has the advantage of providing error control while requiring only two iterations per time step. Secondly, matrix multiplication techniques and matrix characteristics are being examined to find means to reduce the number of constants requiring storage, and to increase multiplication speed. Parallelism inherent in the required calculations provides a means for increasing the simulation execution speed. This parallelism will be taken advantage of by implementing the digital functions with a parallel-structured macromodule system (2).

Another facet of the modeling effort has been to produce a check solution satisfying the cochlea boundary conditions. The check solution was derived using techniques independent of the solution obtained using Green's theorem. The check solution which assumes a constant membrane impedance and sinusoidal excitation, will be compared with results of the Green's theorem model having sinusoidal excitation.


G-3. The Speech and Hearing Computer System (Status and Usage)

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
J. R. Cox, Jr., BCL
W. M. Fisher, BCL and Central Institute for the Deaf
S. A. Garfield, BCL
M. T. Hakkinen, BCL
J. D. Miller, Ph.D., Central Institute for the Deaf
D. A. Ronken, Ph.D., Central Institute for the Deaf
J. W. Sharp, Central Institute for the Deaf
B. F. Spenner, BCL
N. R. Vemula, BCL

Support: RR 00396
NS 03856

Major usage of the speech and hearing computer system (PR 10, G-3) continues to be for the development of programs to analyze and synthesize speech signals and for the support of various research activities at Central Institute for the Deaf. The study of the linear predictor method of speech analysis is continuing (G-6) and more general analysis methods are being developed (G-5, G-6).

A phone-line communication link has been added between the system at BCL and the LINC computer in the physiology laboratory at Central Institute for the Deaf. Programs have been modified so that the system can now be used on-line during cochlear microphonics (CM) experiments to generate calibrated stimuli and to analyze the CM data as it is collected.

The speech and hearing system continues to be most useful for tailoring and manipulating natural sounds that have been recorded on RAP (PR 10, G-7) and for accurately generating various speech-like sounds for use as stimuli in speech perception studies with animals, babies, and adults. The stimuli are designed to emphasize different aspects of natural speech sounds.

Numerous subroutines of general interest have been added to the software library. New additions include FORTRAN programs for solving a set of simultaneous linear equations, for fitting a polynomial to data in a least-squares sense, for displaying variable density line segments, and a general purpose program for finding the minimum of an arbitrary function of N variables. Graphic display subroutines have been written which: 1) display a data curve with choice of scale factors, symbols for data points, and interpolating lines between data points; and 2) calculate and plot histograms (bar-graphs). Utility programs have also been written to display and play back individual RAP tracks, to play back consecutive RAP tracks, to test RAP discs for errors, to copy entire RAP disc packs, and to copy consecutive RAP disc tracks. A program for the time expansion and compression of speech sounds stored on RAP discs is also available.
For OS/PC users, commands were written for changing LINC/SIM banks, for copying between banks, and for modifying files. Programs were written to dump files, create bootstrap-loadable program tapes and to change index names. New functions and subroutines include those for sensing or setting the LINC/SIM bank, program chaining, tape write-protection testing, index creation, file management, block input/output, plotting scope display, graphic tablet input, RAP input/output, file creation, recording and play back of sounds, numerical methods, complex arithmetic, FFT for the new floating point unit, pushdown stacks, question and answer buffer dumps, array moving, character conversion, rounding, uniform random number generation and Gaussian random number generation.

Equipment changes this year include the installation of a FORTRAN compatible floating point unit so that FORTRAN compiled programs would run faster. However, some of the more elaborate speech-synthesis models still require long computational times.

A sound booth has been installed this year adjacent to the speech and hearing system. The sound booth will be used initially with the MEGS test (G-7).

Design of the new audio system has begun and construction should be finished by the end of August. The new system will have 16 inputs and 8 outputs that are equally divided between two independent ADC-DAC channels. The number of outputs can be expanded up to 16 as future needs arise by plugging in additional circuit boards. The system will have its own programmable clock so that sampling times are precisely determined without jitter, and improved audio filters and amplifiers.

G-4. Variable Characteristics of the Normal Male Glottal Wave

Personnel: W. M. Fisher, BCL and Central Institute for the Deaf
R. B. Monsen, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf

Support: RR 00396
NS 03856

The study of glottal waveforms in normally hearing adult subjects is a new effort begun this year. Glottal waveforms from a number of subjects for a variety of conditions of pitch, stress, and inflection, have been recorded through a reflectionless tube and analyzed with the computer system for differences in waveshape and spectrum (1). This research will provide a basis for comparison with the glottal waveforms of deaf subjects to be studied in the future.
G-5. An Interactive Speech Wave Examiner System

Personnel: W. M. Fisher, BCL and Central Institute for the Deaf

Support: RR 00396
NS 03856

Programming has been completed on the basic version of this system, and it has been used productively in the analysis of glottal waves (G-4). Options to play back and record signals on-line and to automatically set the analysis window limits to zero crossings of the signal have been added. A BCL monograph under preparation will document the system and serve as a user's guide.

G-6. A Study of Linear-Predictor and Related Methods of Speech Analysis

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

Support: RR 00396
NS 03856

Various errors that arise from the use of Linear Predictor (LP) methods to estimate vocal tract area functions have been examined. The procedure has been described earlier (PR 10, G-6) and involves analyzing the acoustic impulse response of idealized physical models of the vocal tract for which the dimensions, the termination at the lips and the input excitation at the glottis are precisely known. The area function and transfer function obtained from the LP coefficients are compared with the known shape and the measured frequency response of the acoustic models.

Errors introduced by the following factors have been studied in detail: 1) sampling rate, 2) quantization noise, 3) the number of LP coefficients, 4) the number of samples chosen, and 5) the glottal source characteristics. In addition it has been verified that the lossless, plane-wave approximation used in deriving the LP model is valid up to about 3 kHz for the physical models tested. Above 3 kHz the measured and theoretical curves deviate in a systematic way. The largest discrepancies occur near the resonant peaks of the system.
Simulation studies of quantizing error and additive random noise have been done to verify that these sources of error are not significant for the conditions of the tests (12-bit samples, 40 dB S/N).

The number of LP coefficients and the number of samples analyzed interact in a complicated way to introduce error in the area function estimate. If the "window" is too short, the system is not adequately defined by the sampled data. The effect of "window" size on the results can be seen by comparing the z-transform of the "windowed" data evaluated along the unit circle to the measured frequency response curves of the system under test. The more samples that are included, the closer is the correspondence between the two curves. Similar comparisons can be made using different "window" functions.

In practice, the number of LP coefficients is generally chosen to be much smaller than the number of samples analyzed. As the number of LP coefficients is increased, the correspondence improves between the LP transfer function and the z-transform evaluated on the unit circle.

The greatest error in the LP transfer function often occurs in the region of the first resonance or formant. This apparently is a consequence of the linear weighting over frequency of the error that is minimized by the LP procedure. When averaged over frequency, large errors can exist over a small range of frequencies such as that occupied by the first formant, without contributing significantly to the overall error averaged over the entire signal spectrum (in our case 10 kHz). The error tends to be in the direction that results in larger estimated bandwidths of the first formant. The effect on the area function is to increase the size of the narrow portions of the acoustic tube models.

The sources of error that have been described above can be dealt with, at least theoretically, by choosing appropriate values for sample rate, "window" size, number of LP coefficients, etc. A more difficult problem continues to be the sensitivity of the LP method to the spectral characteristics of the excitation waveform. With natural speech, the glottal excitation is not known with any degree of accuracy and therefore cannot be compensated for exactly. However, a 6 dB/octave rising compensation seems to work reasonably well for many natural speech sounds. Additional simulation studies are underway to investigate this problem.

Portions of this work were presented at the Fall 1974 Acoustical Society Meeting. (1)

G-7. MEGS: A Speech Reception Test

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
S. A. Garfield, BCL
B. L. Scott, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

In dealing with problems of the deaf, it is important to be able to evaluate the patients' ability to understand speech. In addition, as auditory and non-auditory speech aids are developed, it is important to be able to measure the improvements gained with these aids. The number of different speech sounds in most languages is so large that exhaustive tests are lengthy and tedious for the patient and simpler tests may not include important sounds. The MEGS system (1) was developed to accommodate large sets of speech sounds, but then to quickly focus on a smaller subset of sounds that are frequently confused by the patient.

The testing algorithm works in the following way. Test sounds are presented to the subject in random sequence. Initially all sounds are presented with equal probability. Sounds that are correctly identified are assigned to an "out" list from which items are chosen less frequently. Sounds that have been incorrectly identified remain assigned to the "in" list and are presented more frequently. If a sound from the "out" list is incorrectly identified, that sound and the one that it was confused with are reassigned to the "in" list. As the test proceeds, speech items are thereby sorted into two groups. Since items from the list of incorrect responses are presented more frequently, most of the testing time is spent on sounds that are troublesome for the subject.

The MEGS system uses most of the features of the speech and hearing computer system. Individual programs which comprise the system each require the full 16K of memory; 4K for data storage, 2K for buffer space, and 10K for program space. Extensive use of program overlay is made. The unit 0 tape contains the individual system programs that are copied automatically to a scratch area on the disc when the tape is loaded. The system operates from this scratch area to take advantage of the disc access speed. The unit 1 tape is used for storing the results of the test. Stimulus sounds are stored in 12-bit, digitized form on the removable disc. Program options and test information are entered on the keyboard and echoed on the storage scope. The storage scope is also used to display messages and information as the tests are run. Lists of sounds, test results, analyses, and confusion matrices are produced on the printer. Single, combined, or averaged test results are produced in graphical form on the digital plotter.
During the test, all stimulus-response pairs are recorded in sequence. These data can be displayed graphically to show the number of "in" items as a function of the number of trials. This type of display shows at a glance the approximate difficulty of the test and the number of trials necessary to achieve asymptotic performance. Since all of the test data are saved, post-test analysis programs can be written to examine in detail the sounds that are difficult for the patient to discriminate. By examining the properties of these sounds it should be possible to better delineate the problem area. Although the MEGS test is being developed for use with the deaf, similar methods appear to have a wide range of applications such as the evaluation of data reduction schemes for speech transmission and the evaluation of automatic pattern recognition systems.


G-8. Programs for Inverse Synthesis of Speech

Personnel: W. M. Fisher, BCL and Central Institute for the Deaf

Support: RR 00396
         NS 03856

An effort was initiated to program the automatic determination of parameter values for a given synthesizer model so that the output of the synthesizer would match a given segment of a speech wave. A direct search algorithm for minimizing a function of N variables was used. The N variables are the synthesizer parameters and the minimized function is a measure of the difference between the output of the synthesizer and the given signal, either in terms of wave shape or spectrum. In the frequency domain the convergence is less good, but may be improved with further work. Testing of this system showed that the algorithm converges well in the time domain.
H. Supporting Activities

H-1. Random Point Processes

Personnel: D. L. Snyder, BCL
           J. R. Cox, Jr., BCL
           P. M. Fishman, BCL
           J. Markham, BCL
           M. V. Vaca, Ph.D., Electrical Engineering

Support: RR 00396
         ENG-74-07800

Previously described efforts (PR 10, I-10) on the mathematical study of random point processes have continued. A textbook (1) and several papers (2 - 10) have been completed.


H-2. Interactive Digital Acquisition of Electrocardiograms

Personnel: J. D. Elliott, B.S., Electrical Engineering
R. M. Arthur, BCL
A. Hernandez, M.D., Pediatrics
W. H. Rohr, M.D., Pediatrics
D. G. Wantzelius, M.S., Electrical Engineering
A. N. Weiss, M.D., Medicine

Support: RR 00396
HL 18144
HS 00074
Washington University

Automatic morphologic analysis of resting-adult ECGs is commonplace. Successful adult programs are quite sophisticated, yet limited in their ability to measure pediatric ECGs. One reason is that it is much more difficult to obtain good technical quality pediatric records, because it is often impossible to get patient cooperation. An attempt to use an existing adult routine to measure pediatric VCGs(1) resulted in a rejection rate due to artifact of more than 25%, even after careful manual editing of analog tape records. Automatic selection of the segment to be measured, in accordance with precise technical criteria could considerably reduce the number of records rejected or disturbed by artifact in subsequent processing.
Control of signal quality is one aspect of an interactive clinically-based acquisition system which could also be used to test for procedural errors and to obtain limited preliminary analysis for immediate comparison to other clinical findings. Two ECG acquisition systems have been developed. Each collects complete patient identification data in addition to the ECGs.

Algorithms were developed on a uLINC to test three simultaneously recorded ECG leads for: 1) signal out of range, 2) baseline shift, 3) excessive noise, 4) short duration pulses, and 5) no QRS. When the digitized signal fails one of the tests, the data-collection phase is restarted. Algorithms operate on ECG records from analog tapes. Test thresholds are relaxed if no acceptable segment is found in the tape record. A file management system has been created to simplify retrieval and subsequent analysis of digital records now numbering about 100. Conversion of another 450 records stored on analog tape is in progress. A trial analysis routine has also been written which selects and measures six key features from each QRS complex in a six-second Frank vectorcardiogram.

A second implementation based on a microprocessor, the Intel 8008, was undertaken to permit direct clinical acquisitions of ECGs and to explore alternative algorithms for performing the tests indicated above. These algorithms, which tested sample and first difference distributions, were designed to be specific to acquisition tasks, i.e. without regard to subsequent analysis requirements. The system included an 8-channel A/D converter, CRT display and keyboard, and 12K bytes of RAM for ECG storage. Programs were contained in 2K bytes of PROM. The system was tested on analog tape records and directly on 12 patients in the ECG clinic at St. Louis Children's Hospital. Results indicated that the tests eliminated significant technical flaws in the ECG records, yet did not pose an undue burden on either patients or staff. Patient age ranged from 6 weeks to 15 years. Four records were accepted on the first try; the average number of tries was four. The worst case, a two year old, required fifteen tries. Even for this case, acquisition and testing took only four minutes.


Reflection of ultrasonic energy (2-10 MHz) from interfaces between
tissues of differing acoustic properties permits noninvasive construction
of images of internal structures. Image quality is limited by the fact
that there are usually many other echo producing structures in the area
being investigated besides the one of interest. It can be very difficult
to locate, identify, and isolate the desired information from the resulting
clutter. Also annoying is the loss of data when the target structure
moves in and out of the ultrasonic beam. Other limitations include re­
strictions in both range resolution and lateral resolution.

Many signal processing schemes have been proposed as partial
remedies for shortcomings of present echocardiographic systems. Among
the most promising are digital techniques which not only allow the appli­
cation of sophisticated noise reduction and image enhancement algorithms,
but also are well-suited to automatic feature extraction and parameter
derivation. Unfortunately, progress has been hindered by constraints on
digital acquisition methods.

At least four methods for digital acquisition of ultrasonic signals
have been proposed. Among these methods, only high-speed analog-to-digita­
(A/D) conversion can be employed in real-time. This method, somewhat
limited by the cost and complexity of high-speed A/D units, is restricted
primarily by the problems of handling a digital data stream produced at
rates exceeding direct memory access capability. These disadvantages
are largely overcome by burst analog sampling which has previously
not been feasible.

Analog samples are stored in a series of sample-and-hold circuits.
During the interval in which echoes are observed, samples are stored
at a high rate. During the period before the next ultrasonic pulse, the
samples are accessed slowly for conversion by a standard A/D converter.

Analog memory is in essence a series of high-performance sample­
and-hold circuits in a single package. The Reticon SAM-64 analog memory
was evaluated for its suitability in burst analog sampling. (1) Although
two major design oversights indicated that this application was not in­
tended for this unit, the tests did demonstrate that it is possible to
use analog memory for burst sampling at a sample rate of at least 7 MHz.
with an equivalent accuracy of at least 5 bits over a 45 dB dynamic range. The time-base expansion factor obtained was greater than 400:1 which allows A/D conversion with conventional, general purpose units.

A digital acquisition system based on the burst-analog-sample technique was constructed with three objectives in mind. One was to demonstrate the feasibility of real-time operation with no analog detection circuitry. The second was to optimize the processor role in and control over ultrasonic data acquisition. The third was to implement a basic set of algorithms to generate and store chirp envelope (A-mode) and interface position versus time (M-mode) displays from raw echo signals.

Burst analog sampling circuitry was combined with a conventional analog-to-digital (A/D) converter and a minicomputer (μLINC 300) to form a digital echocardiograph. An effective sample rate of 7 MHz was obtained with an actual A/D rate of 70 KHz. At this rate the 256 analog samples provided a 2.8 cm window in tissue. The A/D rate can be varied by the processor to make analysis context dependent. Gain can be altered under processor control for depth compensation and to optimize dynamic range. The system operated in real time at 100 ultrasonic pulses/sec. It has been tested in A-mode and time-motion studies of cardiac structures.


H-4. A General Purpose Disc Controller

Personnel: B. F. Spenner, BCL
            G. A. Appel, BCL

Support: RR 00396

Two additional disc controllers (PR 10, I-5) have been constructed and tested. These two controllers and their associated disc drives, fulfill the mass storage needs of the two LSI-2 computers interfaced to the Mass Spectrometer (F-3). An interface connecting the disc controllers to the LSI-2 has been implemented and is operational (F-5).
H-5. Macromodular Disc Interface

Personnel: B. F. Spenner, BCL
B. R. Hieb, BCL
R. V. Sanders, BCL
R. W. Wodicker, BCL

Support: RR 00396

The need for a macromodular-compatible mass storage element became evident when it was necessary to store digitized video (E-1) and speech (C-3) data, processed by macromodular systems. The mass storage interface, operating through the PC-1200 disc interface (PR 10, I-6), provides 51,968 accessible blocks of data, each block containing 256 12-bit words. The selection of a block is controlled by a 16-bit macromodular address supplied to the interface by the macromodular system. During an operation, 256 words are either stored or retrieved at a 1.52 M-bit per second rate, using the selected block. Data stored or retrieved is transferred through a macromodular-compatible write or read port respectively. Macromodular systems control the operation of the disc interface through macromodular-compatible control ports. Initiate and complete control ports are provided for both store and retrieve operations.

H-6. A Digital Recording System for Analog Signals

Personnel: R. W. Hagen, BCL
J. L. Robinson, BCL
J. J. Schier, B.S., Surgery
B. F. Spenner, BCL

Support: RR 00396

A portable system for recording digitized analog signals on LINC tape has been designed and constructed. It is currently being used to record blood flow and thermal dilution signals during cardiac output studies (C-7). The system utilizes a LINC tape transport, a LINC-4 tape controller (BCL Monograph No. 149) and an A/D conversion control console.

This recording system functions much like a conventional strip chart recorder except that the output is a digitized representation of the input analog signal stored on magnetic tape. The A/D conversion control console offers the user four discrete signal sampling rates ranging from 30 to 240 samples per second, one or two analog input channels, a Run/Pause control, tape block number readout and A/D converter readout. The Run/Pause control allows an operator to initiate and interrupt signal recording as desired. The tape block number, associated with each
recorded segment, is displayed on the console. Each LINC tape stores from 18 minutes (at 240 sps) to 145 minutes (at 30 sps) of digitized data with 12 bits of precision. It is anticipated that this system will provide a convenient method for sampling, digitizing, storing and retrieving a variety of physiological signals.

H-7. A Microprocessor-Based Optical Scanner for Diagnostic Radiology

Personnel: M. C. Jost, BCL
R. M. Arthur, BCL

Support: RR 00396
Mallinckrodt Institute of Radiology

Preliminary work has been done toward development of a computer-based system for use in diagnostic radiology to monitor patient flow and to track the movement of film folders. (1) Such a system will provide an effective way for radiologists to study accurately the operation of their department over a long period of time and to improve its efficiency.

A survey of codes, manufacturers, and products indicated that hand-held pen or wand reader-decoder units operating on black and white bar codes would be logical building blocks for such a system. No generally accepted methods for evaluating pen reader system components or for developing sampling and decoding algorithms were available. Consequently, a computer system for developing algorithms and evaluating system components was developed on the PDP-12 minicomputer using FOCAL-12. An Interface Mechanisms hand-held optical pen reader and signal conditioning module were used to sense the bar code patterns. Two user-defined subroutines incorporated into FOCAL-12 control the analog-to-digital converter and the real-time clock of the PDP-12 and thereby acquire and store values representing the widths of the bar-code bars and spaces. A package of programs written in standard FOCAL-12 commands has been prepared for use in data analysis, data processing, and bar-code decoding. This minicomputer system has been used to develop sampling and decoding algorithms for several black and white bar codes and to evaluate the characteristics of the Interface Mechanisms hand-held pen reader.

In order to provide a prototype pen reader unit which could be used to demonstrate the use and capability of the proposed computer-based tracing system, sampling and decoding algorithms for a suitable black and white bar code have been implemented using a four bit microprocessor system. This prototype pen reader unit is capable of scanning and decoding white two-out-of-five code labels printed on a Diablo HyType printer. These labels may contain a bar code representing a nine-digit patient information number, a single-digit check character, and start and stop codes. The unit (1) requires no special start procedure in order to begin a sweep; (2) per-
mits the user to sweep at a wide range of sweep speeds and pen tilt angles; (3) provides an LED display of the decoded characters and an audible acceptance signal; and (4) provides an LED error signal upon detection of certain of the possible error conditions. The unit can be modified to sense and decode any black and white bar code simply by changing the program stored in the reprogrammable read-only memory. The pen reader is presently a stand-alone unit. Input and output lines have been provided, however, to permit future use of a keyboard for manual entry of patient identification and function information and to permit serial ASCII output of the decoded characters to a central control computer.


H-8. A System for Microprocessor Development Support

Personnel: G. J. Blaine, BCL
R. M. Arthur, BCL
B. F. Spenner, BCL
D. M. Ungar, BCL

Support: RR 00396

Although microprocessors were introduced only three years ago, they represent a new technology with a potentially significant impact on a variety of clinical systems. Their low cost, small size and implementation flexibility open new areas for the application of technology in the diagnostic laboratory, in direct acquisition of patient data, and in patient information manipulation, storage, and retrieval.

Several projects have been undertaken which demonstrate this potential. The Intel 4004 has been used to implement a multichannel analyzer for blood cell sizing (PR 10, I-7), a controller for a liquid chromatograph (F-7) and an optical bar code scanner for diagnostic radiology (H-7). An interactive ECG acquisition system was based on an Intel 8008 (H-2). A close relative, Intel's 8080 was the central processing unit of a data logging system for microbiology (H-9). The patient interview terminal in a system to broadcast medical history questionnaires is designed around the Motorola 6800 family. These examples are only a fraction of the number of projects now in the planning stage.

The ultimate advantage of a microprocessor, that is feasible to include a digital processor in a dedicated, special purpose device, is a disadvantage during development. On the one hand it is more efficient and economical to configure the system specifically for its application.
On the other hand such a system is almost never capable of supporting program development.

Commercially available development systems have had important drawbacks. Perhaps the most severe is that each is capable of supporting only one processor. Thus a new development system must be purchased for each type of microprocessor. In addition there has usually been considerable lag between the introduction of a microprocessor and the availability of adequate hardware and software support.

Rather than duplicate the one-microprocessor-one-development-system approach, our effort has been directed toward the design of an intelligent console. This console is envisioned to have the flexibility to support a variety of microprocessors. It will exhibit the usual console features, such as single step and breakpoint plus display of key registers. It will also serve as a port to load programs into the microprocessor. Programs will be written on a TI 980 computer which will be connected to the intelligent console via a serial link. Data transferred will also include the programming for the console itself, i.e. the routines needed to configure the console for interface to a given microprocessor.

A cross assembler and a core image assembler for the Motorola 6800 have been written to run on a TI 980. Design of the intelligent console is in progress. The initial implementation of the console will focus on the problems of Motorola 6800 support. Later, both the cross assembler and the console will be extended to serve additional microprocessors.

H-9. A Microprocessor-Based Data Logging System for Microbiology

Personnel: J. W. Lewis, Ph.D., Pathology  
J. Ladenson, Ph.D., Pathology  
J. Marr, M.D., Pathology  
C. Tao, B.S., Electrical Engineering

Support: HS 00074  
Washington University

Characteristic patterns of metabolite production as a function of time in bacterial cultures are being studied. Up to six ion-specific electrodes are monitored for each culture over twelve to eighteen hours at intervals of two to fifteen minutes. It is highly desirable that the data be logged in machine-readable form for later analysis. To aid in this study, an inexpensive data logging device based on the Intel MCS-4 microprocessor system is being constructed. The initial configuration will permit variation of electrometer settling time, logging interval, and number of channels under front-panel control and will drive a teletype (for punched tape output) or a Texas Instruments ASR733 cassette system.
Studies on Instrumentation for Analysis of Cell Size Distributions in Clinical Hematology

Personnel: J. W. Lewis, Ph.D., Pathology
J. Rosenfeld, B.S., Biomedical Engineering

Support: HS 00074
Brunswick Foundation
Washington University

For both platelets and erythrocytes, the distribution of cell sizes in an individual is a very useful indicator of certain disease states. For example, the commonly used Coulter "S" (R) blood counter provides an estimate of the mean cell volume (MCV); in bimodal anemias, however, a severely pathological condition may exhibit a normal MCV. Platelet size distribution studies are becoming increasingly more significant as knowledge of hemostasis and thrombosis grows. For both purposes, it is desirable to have an inexpensive pulse height analyzer which can collect size distribution information, perform simple statistical calculations on the data to extract shape parameters, and display or record the size distribution curves.

The microprocessor-based pulse-height analyzer (PR 10, I-7) constructed previously has been improved with respect to signal processing electronics and interfaced to the Texas Instruments 980A computer in the Division of Laboratory Medicine. This allows more flexible data analysis and display.

Currently, data are being accumulated on the correlation between moments of the erythrocyte size distribution and reticulocyte count. Preliminary results have been encouraging. Further, the microprocessor-based pulse-height analyzer constructed previously will go into routine operation in the Barnes Hospital Hemostasis and Thrombosis Laboratory in the near future.

IBM System/7 I/O Channel Interface

Personnel: R. E. Hitchens, BCL
J. A. Ritter, BCL

Support: RR 00396
HV 12481

An interface to the Direct Control Channel has been installed in BCL's first IBM System/7. The interface is connected through the D Enclosure Attachment Feature and includes a multiplexer for up to six
modules, which emulates the IBM D Multiplexer. The purpose of the interface is to replace the 5012 Multifunction Module and also provide for cycle-steal data transfers and for additional peripheral devices.

The interface will accommodate three different module types:

1) Non-Interrupt Module

2) Cycle-Steal Module

3) Interrupt Module

The Non-Interrupt Module can service up to 16 devices not presenting interrupts. Currently, a single module is controlling a high-speed CRT, chart recorder, and line printer. An asynchronous communication device has also been designed for this module.

The Cycle-Steal Module will service a single device presenting cycle-steal requests. This module has been designed and two will be built to control 45 IPS, 800 BPI and 75 IPS, 800/1600 BPI tape drives.

The Interrupt Module will service up to four devices presenting interrupt requests. Design of this module is partially completed. A CRT-terminal interface will be designed for this module.
VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Progress being made in this important phase of the laboratory's activities is summarized below.

Two collaborative activities with Artronix which were mentioned last year were successfully concluded prior to this report period. The Radiation Treatment Planning System is now fully established and is completely supported by Artronix. Our earlier activities in small information systems (MUMPS for the Programmed Console) had concluded with the development of a multi-user system by Artronix, which assumes full responsibility for its maintenance, documentation and further development.

A. Arrhythmia Monitoring. Formal evaluation procedures have been completed during the past year for the Mennen-Greatbatch Argus/Sentinel computer system, a six-patient monitoring system based on the Argus algorithms (PR 8, B-7). Following the correction of several hardware and software errors detected during the evaluation process, the Washington University Argus/Sentinel System has been found to be a satisfactory duplicate of the original Argus algorithms (A-17). A written statement to this effect has been forwarded to Mennen-Greatbatch. In addition, the corrections have been reported to Mennen-Greatbatch for installation in all Argus/Sentinel systems. In return for the significant evaluation effort made by BCL personnel, Mennen-Greatbatch has consigned to Washington University the Argus/Sentinel system used for the evaluation. This system had recently been updated with all new hardware and installed for clinical use in the Barnes Hospital Coronary Care Unit. Acceptance tests are presently in progress, following which the system will undergo clinical evaluation by the Coronary Care Unit personnel. (BCL personnel: R. M. Arthur, J. R. Cox, Jr., K. L. Ripley, F. M. Nolle)

B. Reconstructive X-Ray Tomography. Work has continued during the past year in collaboration with the Picker Corporation (PR 10, VI-D). The objective of this work is to develop an advanced apparatus for rapidly obtaining quantitative, high-resolution images of the x-ray absorption-density in planar cross-sections through the body of human patients. In the technique being developed, called computerized transaxial-tomography, a beam of x-rays is used to scan the planar section under study. Measurements of the attenuation of the x-ray flux are used to reconstruct the desired absorption density by any of several algorithms that have been developed for this purpose. Our efforts have been directed toward developing efficient methods for implementing the required computations, studying fundamental and practical limitations of the method and the means to compensate for these, and evaluating the particular implementation of interest to the Picker Corporation. We are presently preparing the final report of our efforts on this project. The Picker Corporation has taken respon-
sibility for the remaining design and the actual construction of the apparatus. (BCL personnel: R. J. Arnzen, J. R. Cox, Jr., V. W. Gerth, Jr., P. M. Fishman, R. E. Hitchens, J. A. Ritter, D. L. Snyder)
VII. TRAINING ACTIVITIES

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

Programming for Medical Information Systems

An interpretive language (MGH Utility Programming System - MUMPS) designed for medical information systems was presented with programming examples from hospital and ambulatory care settings. The course was taught by Fred Domke. Attending the course were:

Fall, 1974
H. D. Ambos BCL
G. J. Blaine, D.Sc. BCL
A. L. Bodicky, B.S. BCL
L. M. Calcaterra, M.A. BCL
C. S. Coble, B.S. Radiology
R. L. Fox Computer Science Student BCL
V. W. Gerth, Jr., M.S. BCL
B. L. Hayes Computer Science Student BCL
B. L. Hill BCL
R. E. Hitchens, B.S. BCL
S. E. Katzen, B.S. BCL
M. J. Kenner, B.S. Medical Care Group
R. G. Kleinman Medical Student BCL
J. Markham, M.S. BCL
N. A. Mullan, B.S. BCL
J. L. Persky, B.A. BCL (now Ophthalmology)
B. F. Spenner, M.S. BCL
L. J. Thomas, Jr., M.D. BCL

Spring, 1975
D. M. Beasley, A.B. Health Care Administration Student
S. B. Boxerman, D.Sc. Health Care Administration
J. Carver, B.A. Health Care Administration Student
R. R. Gebhardt, A.B. Health Care Administration Student
K. A. Gritzke, B.A. Health Care Administration Student
A. Hartman, M.B.A. Health Care Administration Student
C. W. Jones, A.B. Health Care Administration Student
T. Price, B.S. Health Care Administration Student
J. Privett, B.S. Health Care Administration Student

Introduction to Programming the Laboratory Computer, Spring, 1975

Digital computer concepts including a generalized description of logical design, octal and binary number systems, structured programming
techniques, assembly language programming and an introduction to higher level languages provide a solid foundation for researchers interested in computer applications. Laboratory exercises conducted on the PC-1200 minicomputer provide "hands-on" experience. The course was taught by Fred Domke. Attending the course were:

A. L. Bodicky, B.S.  
J. Johnson, B.S.  
L. D. Koen, B.S., M.B.A.  
M. H. Laird, M.S.  
A. Rasheed, Ph.D.  
F. Reed  
M. Schreiber, B.S.  
J. W. Wetzel, B.A.  

BCL  
BCL  
Medical Student  
Psychiatry  
Psychiatry  
Cardiology  
Medical Student  
Radiation Oncology
VIII. SEMINARS

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

"Computerized Terabit Data Bases: Comments on the State of the Art"
July 12, 1974

Dr. Mark Franklin
Dr. William Pickard
Department of Electrical Engineering
Washington University
St. Louis, Missouri

"Reflections on MUMPS"
September 6, 1974

Dr. Jeffrey Rothmeier
Thayer School of Engineering
Dartmouth College
Hanover, New Hampshire

"Some Recent Techniques in Automatic Speech Recognition"
November 15, 1974

Dr. William M. Fisher
Central Institute for the Deaf
and
Biomedical Computer Laboratory
Washington University Medical School
St. Louis, Missouri

"Washington University Computing Facilities in 1975"
January 13, 1975

Mr. Robert J. Benson
Computing Facilities
Washington University
St. Louis, Missouri

"The Reconstruction of Multidimensional Signals from Their Projections"
January 29, 1975

Dr. Russell M. Mersereau
Department of Electrical Engineering
Massachusetts Institute of Technology
Cambridge, Massachusetts

"Current Developments in Nuclear Imaging Instrumentation"
March 18, 1975

Dr. Gerald J. Hine
Department of Medicine and Surgery
Veterans Administration
Washington, D. C.

"A Problem in Optimal Bilinear Control" (jointly sponsored by the Department of Systems Science and Mathematics)
April 10, 1975

Mr. John Baillieul
Aiken Computational Laboratory
Harvard University
Cambridge, Massachusetts
"Reconstruction of Coronal and Sagittal Anatomic Data from Computerized Transaxial Tomographic Systems"

June 4, 1975

Dr. William V. Glenn
Department of Radiology
Massachusetts General Hospital
Boston, Massachusetts
IX. PUBLICATIONS AND ORAL PRESENTATIONS


Greenfield, R. H., "An Introduction to MISAR. The Miniature Information Storage and Retrieval System Developed at the Beth Israel Hospital, Boston," seminar presented at the Department of Computer Science, Washington University, St. Louis, Missouri, March 1975.


Zimmerman, J., "The MESCH (Multi-Environment Scheme) Approach to the Creation of All Ambulatory Care Record Systems," presented to the Association for Health Records, Rochester, Minnesota, June 24, 1975.


The Biomedical Computer Laboratory's Monograph Series was established to systematize the many informal reports, reprints, program descriptions and other documents written at BCL or supported by some of the laboratory's facilities or staff. Following is a list of the monographs published by BCL during the past year. Copies of the complete index to the Monograph Series are available on request.

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