1978

Progress Report No. 14

Biomedical Computer Laboratory

PROGRESS REPORT

No. 14

1 July 1977 — 30 June 1978

Biomedical Computer Laboratory

Washington University School of Medicine

700 South Euclid Ave.

St. Louis, Missouri 63110

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 14

JULY 1, 1977 - JUNE 30, 1978

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes activities during the period from July 1, 1977 through June 30, 1978. 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.

The vigorous development and evolution of specialized computer systems for use in the solution of research and clinical problems has continued to be the central focus of BCL activities. Several systems now in clinical use have seen a progression from exploratory pilot studies, to major developmental project, to local clinical trial, to clinical trials in multiple locations, to public availability through commercial manufacture. Perseverance in this sometimes tedious chain of development has found reward in the effective fielding of specialized computer systems to the medical community.

One class of computer applications requires strong coupling of the computer to its environment for digital signal processing. These applications typically involve the use of commercially available minicomputers and microprocessors in conjunction with specialized hardware designed and built locally. We have pursued many such applications by bringing signals from hospital wards and research laboratories to BCL by means of either analog or digital tape recordings or telephone lines and, more frequently, by taking the computers to the investigator's laboratory or the patient's bedside.

For those classes of applications dominated by information processing requirements, provisions have matured from telephone lines linking our minicomputers to the IBM System/360, Model 65 at the Washington University Computing Facilities, through development and support of a minicomputer based MUMPS system, to the establishment of an independent Medical Computing Facility to serve the local medical complex. Diverse needs continue to be met by these various options while collaborative work continues on more advanced information-processing developments.

Still another 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 BCL enjoys collaborations with over 15 departmental divisions within the medical school but also finds support and enrichment through close ties with other facilities throughout the University. These arrangements are of benefit both to the BCL and to graduate students who find projects and employment among the activities in the laboratory. The Department of Computer Science is under the direction of Dr. Jerome R. Cox, Jr., past Director of the BCL. Close collaboration with the department currently emphasizes the area of information systems. Strong ties with the Department of Electrical Engineering are sustained through its Biomedical Engineering Program and common interests in digital signal processing techniques. The Department of Electrical Engineering is chaired by Dr. Donald L. Snyder, past Associate Director of BCL.

The Washington University Computer Laboratories is a federation of two research laboratories and two working groups which brings together the interests and resources of major segments of the University. The Biomedical Computer Laboratory is a component of the Medical School. The Computer Systems Laboratory is organizationally directly under the Chancellor. Both BCL and CSL share staff members with the Medical School and the School of Engineering and Applied Science. The Information Systems Group is housed within the Department of Computer Science and the Systems Design Aids Group is housed within the Department of Electrical Engineering.

The Coordinating Committee for the Washington University Computer Laboratories is charged with the task of monitoring long-term interactions between programs. The present composition of the Coordinating Committtee is:

J. R. Cox, Jr., (Chairman) Principal Investigator for the Resource and Chairman, Computer Science
R. J. Benson, Director, University Computing Facilities and Assistant Vice Chancellor
S. B. Guze, Vice Chancellor for Medical Affairs
E. L. MacCordy, Associate Vice Chancellor of Research
J. M. McKelvey, Dean, School of Engineering and Applied Science
C. E. Molnar, Director, Computer Systems Laboratory
D. L. Snyder, Chairman, Electrical Engineering
L. J. Thomas, Jr., Director, Biomedical Computer Laboratory
D. F. Wann, Group Leader, System Design Aids

To aid in long-range planning of the health-related activities of the Washington University Computer Laboratories, a National Advisory Panel meets periodically with the Coordinating Committee. Particular attention is given to the confluence of important needs in biology and medicine with the technical advances capable of meeting these needs. Successful developments by WUCL may suggest implementation on a larger, perhaps national scale. The present composition of the National Advisory Panel is:

P. H. Abbrecht, Professor of Physiology and Internal Medicine, University of Michigan
H. L. Bleich, Associate Professor of Medicine, Harvard University
W. A. Clark, Consultant and former Director of CSL, Cambridge, Massachusetts
J. N. Gray, IBM Research Laboratories, San Jose, California
F. E. Heart, Bolt, Beranek & Newman, Cambridge, Massachusetts
D. M. Kipnis, Professor and Chairman, Department of Internal Medicine, Washington University
C. Mead, Professor of Electrical Engineering and Computer Science, California Institute of Technology
F. M. Richards, Professor of Molecular Biophysics and Chemistry, Yale University
J. M. Smith, Assistant Professor of Computer Science, University of Utah
E. A. Stead, Professor of Medicine, Duke University
H. S. Stone, Professor of Electrical Enginering, University of Massachusetts

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, Division of Research Resources.

RR 00396 A Resource for Biomedical Computing.

A research grant to study the relationship of arrhythmias and sudden death sponsored by the National Heart, Lung and Blood Institute has continued, in collaboration with the Department of Medicine and the Jewish Hospital.

HL 18808 Prediction and Prevention of Sudden Cardiac Death.

A subcontract was awarded by the American Heart Association under NHLBI Contract NO1 HV 72989 to develop a database for arrhythmia detector evaluation.

Another subcontract was awarded by the University of Rochester under NHLBI grant HL 22982 to support establishment of a Multicenter Postcoronary Risk Stratification Program.

NHLBI contract NO1 HV 72941 was received to establish a Holter Monitoring Core Laboratory to support a Multicenter Investigation of Limitation of Infarct Size.

Research efforts continued in support of activities for information exchange about MUMPS and MUMPS application transfers, funded by HS 01540, and grant HS 02760 was awarded to support Specification and Building of Ambulatory-Care Records which utilize the MUMPS software.

Collaborative research continues with St. Louis University, under NHLBI Contract NO1 HZ 62960, to establish a data management system, with the Jewish Hospital of St. Louis for research sponsored by their contract with Sandoz-Wander, Inc., and with the St. Louis Children's Hospital in establishing a perinatal database under a grant from the State of Missouri.

Collaboration with other investigators often involved work already supported by other grants.

Public Health Services grants.

AM 17904 Diabetes and Endocrinology Center,

CA 04483 Effects of X-Rays on Normal and Malignant Cells,

EY 00256 Factors Affecting Intraocular Pressure,

EY 00336 Glaucoma Clinical Research Center,

EY 02044	Automated Digital Processing of the Human Visual Field,
HL 07081	Multi Disciplinary Heart and Vascular Diseases,
HL 13803	Advanced Cardiac Valvular and Vascular Prosthesis,
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine,
HL 17646	Study of Ischemic Heart Disease,
HL 18144	Preprocessor System for Cardiograms,
HL 19537	Myocardial Injury with Ultrasound,
HL 21654	Autonomic Determinants of Arrhythmia Due to Ischemia,
HL 22517	Engineering Development of an Ultrasonic Ventilometer,
HS 00074	Technology and Health Care,
HS 01540	Pilot Project, MUMPS Users' Group,
HS 02760	Specification and Building of Ambulatory-Care Records,
HV 72941	Multicenter Investigation of Limitation of Infarct Size,
MH 31054	Mental Health in the Aged: Biomedical Factors,
NS 03856	Auditory Communication and its Disorders,
NS 06833	An Interdisciplinary Stroke Program,
NS 06947	Bioelectric Studies of Cerebral Cortex,
NS 11059	Brain Studies with Positron-Emitting Radiopharmaceuticals.

National Science Foundation grants.

APR 77-09776	Phase Cancellation Insensitive Receiver,
ENG 76-11565	Information Processing for Stochastic Point Processes,
ENG 76-16812	Controllability and Constraints in Non-Linear Systems.

III. PERSONNEL

EMPLOYEES

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

Director

Lewis J. Thomas, Jr., M.D., and Associate Professor in Anesthesiology, Physiology and Biophysics, Biomedical Engineering, and Electrical Engineering

Assistant Directors

G. James Blaine, III, D.Sc., and Senior Research Associate in Computer Engineering
V. W. Gerth, Jr., M.S.

Senior Research Associate

Jerome R. Cox, Jr., Sc.D., and Chairman, Computer Science, Professor of Computer Science, Electrical Engineering, and Biomedical Engineering in Physiology and Biophysics, and Associate, Division of Health Care Research

Business Manager

Virginia M. Bixon, B.S.

Research Associates

Robert J. Arnzen, Ph.D., and Computer Systems Laboratory
R. Martin Arthur, Ph.D., and Computer Systems Laboratory, and Associate Professor of Electrical Engineering
A. Maynard Engebretson, D.Sc., and Central Institute for the Deaf
William F. Holmes, Ph.D., and Associate Professor of Biological Chemistry
Kenneth B. Larson, Ph.D.
Thomas F. Martin, M.D., and Assistant Professor of Clinical Medicine
James G. Miller, Ph.D., and Associate Professor of Physics, and Associate Director for Biomedical Physics, Laboratory for Ultrasonics, and Research Assistant Professor of Medicine
Donald L. Snyder, Ph.D., and Chairman and Professor of Electrical Engineering
Bruce F. Spenner, D.Sc., and Lecturer in Electrical Engineering
Joan Zimmerman, D.Phil.

Research Assistants

H. Dieter Ambos, and Medicine (Cardiology)
Andrew L. Bodicky, B.S.
Gary H. Brandenburger, M.S.
Michael W. Browder, M.S.
Wen C. Chen, M.S.
Nian C. Cheng, M.S.
Kenneth W. Clark, M.S.
Stanley A. Garfield, B.S.
Robert H. Greenfield, D.Sc., and Research Assistant Professor of Ophthalmology
Ronald W. Hagen, M.S., and Surgery (Cardiothoracic Surgery)
Ross K. Hartz, M.S.
Barry R. Hieb, M.D., and Research Instructor in Medicine
Richard E. Hitchens, B.S., and Lecturer in Computer Science
Frank Hummel, M.S.
Janet A. Johnson, B.S.
Margaret C. Jost, M.S.
John R. Klepper, M.A.
Joanne Markham, M.S.
Charles N. Mead, M.D.
J. Philip Miller, A.B., and Instructor in Preventive Medicine (Biostatistics)
James K. Montrose, B.S.
Patricia Moore, Ph.D.
Nizar A. Mullani, B.S., and Research Associate in Radiology
Michael A. Province, B.A.
Sandra L. Rankin, B.S.
Kenneth L. Ripley, M.S., and Manager of Student Laboratory, Computer Science
J. Alan Ritter, S.B.
Sol M. Shatz, B.S.
Robert K. Stimac, B.S.
David K. Tao, D.Sc.
Nageswara R. Vemula, M.S.
Budimir Zvolanek, B.S.

Engineering Assistants

David C. Ficke, B.S.
Stanley R. Phillips
Don L. Rempel, M.S.
Wayne R. Roloff, B.S.
Marc L. Smith, M.S.
Timothy L. Weadon, B.S.

Technical Assistants

Katherine M. Bruce, B.A.
Alice A. Camuto, A.B.

Jing-Shiang Cheng, M.S.
Nicholas J. Colarelli
Gary R. Cook, B.A.
Joseph E. Denigan
Geraldine C. Hall
Russell E. Hermes, B.S.
Melissa A. Marlo
Patrick W. McLear
Susan E. Menner
Stephen M. Moore
Lorin D. Peterson, B.S.
Stephen J. Potter
David L. Shupe
Eufaula Thornton

Electronic Technicians

Theron R. Baird
George L. Bickmore
Louis F. Combrevis
Joseph H. Flacke
Thomas J. Marshall, B.S.
Remo Moroni, III
David T. Taylor
Jeffrey V. Winston, B.S.

Librarian

Beth E. Robinson, M.L.S.

Secretaries

Rebecca J. Bozesky
Elizabeth A. Dennis
Shirley A. Gonzalez-Rubio
Betty L. Hill
Clara E. Ingersoll
Sandra E. Katzen, B.S.
Celeste J. O'Rourke
Polly E. Raith

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

G. Charles Oliver, M.D., Associate in the Biomedical Computer Laboratory, Professor of Medicine and Chief, Cardiology Division, Jewish Hospital
Rexford L. Hill, III, M.S., Research Associate in the Biomedical Computer Laboratory and Assistant Professor of Computer Applications 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
Carol S. Higgins, A.B., Research Assistant in the Biomedical Computer Laboratory and Research Associate in Radiology

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

David A. Arnovitz
Paul J. Hasser
Charles E. James
Regis G. Lagler, M.S.
Ross D. Livengood, B.S.
Raymond E. Martin, Jr.
John R. Meuleman
Arthur Y. Ng
Eric O. Puronan
Jerry E. Rapert
John B. Schweitzer, B.S.
Jeffrey M. Shapiro, B.S.
John A. Spratt, M.S.
Jonathon F. Tait, A.B.
Sarah J. Thomas
Paul B. Webb

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.

J. Achtenberg, A.B., Medicine
W. E. Ball, D.Sc., Computer Science
L. J. Banaszak, Ph.D., Biochemistry
C. D. Barry, Ph.D., Computer Systems Laboratory
Y. Barsoum, B.S., Electrical Engineering
R. W. Beauchamp, Cardiothoracic Surgery
B. Becker, M.D., Ophthalmology
W. L. Becker, Ophthalmology
M. R. Bedford, B.S., Electrical Engineering
S. R. Bergmann, Ph.D., Medicine
R. J. Benson, J.D., Computing Facilities
L. A. Bernstein, B.A., Radiology
D. R. Biello, M.D., Radiology
S. B. Boxerman, D.Sc., Health Care Administration and Planning Program
J. D. Byrne, CPT, Medicine
M. E. Cain, M.D., Medicine
M. K. Campbell, R.N., Medicine
N. J. Caston, M.S., Radiology

D. Y. Chi, M.S., Neurology
G. L. Clark, M.D., Medicine
R. E. Clark, M.D., Cardiothoracic Surgery
L. A. Coben, M.D., Neurology
P. B. Corr, Ph.D., Medicine and Pharmacology
A. A. Ehsani, M.D., Medicine
J. O. Eichling, Ph.D., Radiology
D. L. Elliott, Ph.D., Systems Science and Mathematics
R. A. Ellis, M.S., Computer Systems Laboratory
R. G. Evens, M.D., Radiology
D. C. Ficke, B.S., Radiology
C. Frieden, Ph.D., Biochemistry
M. H. Gado, M.D., Radiology
P. E. Gallerstein, M.D., Medicine
G. G. Garcia, Barnes Hospital
E. M. Geltman, M.D., Medicine
S. A. Golden, B.S., Neurological Surgery
S. Goldring, M.D., Neurological Surgery
R. L. Grubb, Jr., M.D., Neurological Surgery
A. L. Gutovitz, M.D., Medicine
E. B. Hagelstein, B.S., Electrical Engineering
J. Hanaway, M.D., Anatomy and Neurology
W. M. Hart, Jr., M.D., Ph.D., Ophthalmology
A. Hernandez, M.D., Pediatrics
R. R. Heye, Radiology
J. Hirsch, B.S., Medicine
J. O. Holloszy, M.D., Preventive Medicine
J. T. Hood, B.S., Physics
C. P. Hughes, M.D., Neurology
S. Igielnik, Ph.D., Medical Computing Facilities
Y. Ikeda, B.S., Systems Science and Mathematics
A. S. Jaffee, M.D., Medicine
L. Jarett, M.D., Pathology
G. C. Johns, B.S., Computer Systems Laboratory
M. F. Johnson, Jr., M.L.S., Medical Library
E. G. Jones, M.D., Ph.D., Anatomy
S. A. Jones, M.D., Radiology
R. G. Jost, M.D., Radiology
L. I. Kahn, M.D., Health Care Research
M. A. Kass, M.D., Ophthalmology
E. W. Kiebler, Radiology
M. S. Klein, M.D., Medicine
A. B. Kliefoth, M.D., Radiology
S. J. Knaster, Ophthalmology
P. B. Kurnik, M.D., Medicine
B. E. Laux, B.S., Radiology
J. P. Livingston, A.B., Ophthalmology
P. A. Ludbrook, M.D., Medicine
R. E. Marshall, M.D., Pediatrics
M. M. Maurer, M.D., Pediatrics
M. L. McCartney, Sc.D., Electrical Engineering

M. M. McCrate, B.S., Biostatistics
J. W. Mimbs, M.D., Medicine
S. Mogelson, M.D., Medicine
C. E. Molnar, Sc.D., Computer Systems Laboratory
R. A. Moses, M.D., Ophthalmology
H. A. Neuwirth-Hirsh, B.S., Biomedical Engineering
S. M. Nordlicht, M.D., Medicine
R. E. Olson, B.S., Computer Science and Computer Systems Laboratory
J. M. Paine, B.A., Biostatistics
E. R. Passamani, M.D., Medicine
P. A. Penkoske, M.D., Medicine
C. A. Pérez, M.D., Radiology
G. T. Perkoff, M.D., Medical Care Group
T. C. Perry, M.S., Computer Systems Laboratory
L. D. Peterson, D.M.D., Ophthalmology
W. F. Pickard, Ph.D., Electrical Engineering
C. F. Pieper, M.S., Neurological Surgery
S. C. Prasad, Ph.D., Radiology
J. A. Purdy, Ph.D., Radiology
D. P. Ragan, Ph.D., Radiology
M. E. Raichle, M.D., Radiology and Neurology
R. T. Rassieur, Ophthalmology
R. Roberts, M.D., Medicine
F. U. Rosenberger, D.Sc., Computer Systems Laboratory
D. C. Sawyer, A.B., Radiology
W. R. Sherman, Ph.D., Psychiatry and Biochemistry
B. A. Siegel, M.D., Radiology
B. E. Sobel, M.D., Medicine
E. L. Spitznagel, Jr., Ph.D., Biostatistics
A. B. Sripad, D.Sc., Systems Science and Mathematics
H. D. Strauss, M.D., Medicine
S. P. Sutera, Ph.D., Mechanical Engineering
M. M. Ter-Pogossian, Ph.D., Radiology
T. J. Tewson, Ph.D., Radiology
A. J. Tiefenbrunn, M.D., Medicine
L. J. Tolmach, Ph.D., Anatomy and Radiology
B. J. Walz, M.D., Radiology
D. F. Wann, D.Sc., Electrical Engineering and Computer Systems Laboratory
A. W. Washington, M.B.A., Medical Care Group
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Cardiothoracic Surgery
R. Wette, D.Sc., Biostatistics
L. L. Wilson, B.A., Medicine
F. X. Witkowski, M.D., Medicine
F. D. Wolkow, Electrical Engineering
C. P. Zobkiw, B.S., Electrical Engineering

Baylor College of Medicine, Houston, Texas

D. H. Glaeser, D.Sc.

Central Institute for the Deaf, St. Louis, Missouri

A. P. Allen, B.S.
D. H. Eldredge, M.D.
N. P. Erber, Ph.D.
D. E. Hanpeter
A. F. Heidbreder, B.S.
I. J. Hirsh, Ph.D.
J. D. Miller, Ph.D.
R. B. Monsen, Ph.D.
A. F. Niemoeller, Sc.D.
D. A. Ronken, Ph.D.
A. P. Rueter, B.S.
R. M. Sachs, Ph.D.
J. W. Sharp

Baptist Memorial Hospital, Memphis, Tennessee

R. S. Gordon, B.A.

Creighton University, Omaha, Nebraska

F. M. Nolle, D.Sc.
A. Zencka, M.D.

Jewish Hospital, St. Louis, Missouri

F. D. Biggs, M.D.
L. L. Brandenburger, R.N.
M. Broderson
V. R. deMello, M.D.
B. R. Hieb, M.D.
J. R. Humphrey, R.N.
R. E. Kleiger, M.D.
R. J. Krone, M.D.
M. T. Mitchell
S. Thanavaro, M.D.
M. Wade

The MITRE Corporation, Bedford, Massachusetts

R. E. Zapolin, M.S.

Pennsylvania State University, University Park, Pennsylvania

D. B. Geselowitz, Ph.D.

St. Louis University, St. Louis, Missouri

S. M. Ayres, M.D.
L. Cusanelli

A. E. Deyer, R.N.
R. G. Evans, B.A.
S. A. Kaiser, R.N.
H. S. Mueller, M.D.

Stanford University Medical Center, Stanford, California

W. J. Sanders, M.S.

University of California, Davis, California

R. F. Walters, Ph.D.

University of Iowa, Iowa City, Iowa

R. C. Arzbaecher, Ph.D.

University of Massachusetts Medical Center, Worcester, Massachusetts

J. Rothmeier, Ph.D.

University of Missouri, Columbia, Missouri

W. Fairman, Ph.D.

University of Nottingham, England

A. L. Rector, M.D.

University of Wisconsin, Madison, Wisconsin

D. D. Gilboe, Ph.D.

Worcester Polytechnic Institute, Worcester, Massachusetts

C. L. Feldman, Ph.D.

Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year projects of joint interest have involved:

Artronix, Inc., St. Louis, Missouri - The OS/PC operating system.

Mennen-Greatbatch, Clarence, New York and Hewlett-Packard, Waltham, Massachusetts - An arrhythmia monitoring system.

Picker Corporation, Cleveland, Ohio - A reconstructive X-ray tomographic system.

Sandoz-Wander, Inc., Hanover, New Jersey - A collaborative drug study.

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. During the past twelve years the laboratory space has been increased by 1526 square feet in the basement, 2762 square feet on the ground floor, and 3891 square feet on the second floor and 1257 square feet in the basement of the building just south of the original space. The added space includes 720 square feet created by enclosing a porch on the second floor of 700 South Euclid in the Spring of 1976. The gross total is now 18,000 square feet. Facilities for computational applications, laboratories, staff offices, and a WUCL reference room occupy the various BCL spaces. Other laboratory facilities include 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.

Frequently it is appropriate for computer systems to be housed physically near areas of clinical application. 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 was housed in 360 square feet of specially designed space within the unit. This system supported routine clinical monitoring and research until mid 1975 when it was replaced by a commercial version built by Mennen-Greatbatch, Inc. 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.

Throughout the years the laboratory has steadily increased its computational capabilities with the addition of new computer systems. At the time the laboratory was formed, 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 biological 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 and three prototypes were constructed to function as a combined stored-program digital computer and remote display console for the IBM System/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.) Thirteen Programmed Consoles were 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. 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 Artronix PC-1200 systems. The SPEAR PC in the Cardiac Catheterization Laboratory was replaced in 1973 by an 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 for use 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 high-speed analysis of electrocardiograms (a second IBM System/7 was leased from November, 1973 to November, 1975). 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.

In May, 1973, a Texas Instruments TI-980A 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, and two additional TI-980B computers were acquired in 1975, one to support patient monitoring software development and the other to serve as a component of an MMS-X graphics system.

In September, 1975, two CALDATA 135 computers and associated peripherals began service in the development of a system for high-speed ECG processing with functions similar to those of Argus/H implemented on the IBM System/7 but with improved performance at a lower cost. Another high-speed ECG processing system was developed at BCL based on two Digital Equipment Corporation PDP-11/34 processors and put into service in July, 1978.

A survey of computer systems installed at the Washington University Medical Center shows nearly one hundred minicomputer systems, with twenty different makes and models represented, applied to diverse clinical and research areas. In addition, microprocessors are being used in increasing numbers both in special instruments built at the laboratory as well as in commercial instruments.

V. RESEARCH PROJECTS

Introductory 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 traditionally has been organized into several major project areas with the staff grouped into teams whose interests are focused correspondingly.

As in past years project groupings have been modified to reflect evolving patterns of research activity. Work previously dominated by development of a computer-based cardiac catheterization system has moved on to emphasize research applications which are now reported under "Clinical Pathophysiologic Research Activities." Such is also the case for earlier work in the acquisition and processing of visual-field data. Because instrumentation applications in the area of laboratory biochemistry and a number of other generally supportive efforts have moved closer together in their emphasis on the use of microprocessors, these projects are now grouped together under the title, "Supporting Activities." Last year's developments in the various project areas are summarized in the following paragraphs.

Ischemic Heart Disease and ECG Analysis. Activities in high-speed ECG processing for studying the natural history of sudden death due to ischemic heart disease have changed direction during the past year. Enrollment of new patients into the study was discontinued as of March, 1978 in preparation for entering a data-analysis phase for which renewal funding was awarded in July. Detailed information has been collected in machine readable form for nearly 5500 patients admitted to coronary care units in Barnes and Jewish Hospitals. For this and five other studies the Argus/H computer system has been used in the past year to analyze over 750 Holter recordings for quantifying ventricular dysrhythmias. Meanwhile, programming of a more advanced system (Argus/2H), designed to accomodate dual-channel 24-hour recordings, has been completed. The prototype Argus/2H system also has been applied to the sudden-death study, but it has been especially important to a newly-funded nationally-directed project to develop an extensive database for evaluating arrhythmia detectors. This work, which is in collaboration with the American Heart Association (AHA) and funded by NIH, involves the solicitation of candidate recordings from international contributors, the selection of tapes by a committee of cardiologists, and the beat-by-beat annotation of half-hour segments by another committee of electrocardiographers. Both committees have been selected by the AHA ECG Committee from among nationally recognized experts. Digitization, preliminary analysis, editing, review, annotation, and documentation are all performed on the Argus/2H system at the Laboratory.

During the latter half of this report period a second-generation Argus/2H system was implemented to provide the additional high-speed processing capability necessary to the Laboratory's role in another newly-funded national-collaborative project, Multicenter Investigation of Limitation of Infarct Size (MILIS). For this study of the effects of two therapeutic interventions five clinical units in Boston, St. Louis, Dallas, and Burlington (Vermont) send Holter recordings to the Laboratory for detailed analysis. Still another multicenter (St. Louis, Buffalo, and New York City) study of risk-stratification has been recently (July, 1978) funded and will involve the Laboratory in a similar role. The fact that the second-generation Argus/2H system was brought into full operation less than six months after the equipment orders were placed, attests to the success of its design for ease of replication.

The past year also has seen substantial improvements in the ECG processing algorithms used in the Argus systems. Of particular note is the application of early work in frequency-domain analysis of physiologic signals which has rendered feasible the reliable discrimination of multiple PVC forms, a need in several of the new studies cited above. Also, a QRS detection algorithm previously developed for surgical intensive care unit monitoring has been modified and incorporated, along with other new work, to extensively revise the basic Argus algorithms. A preliminary evaluation shows a dramatic reduction in the number of missed PVCs and a greatly enhanced immunity to noise.

Other Argus-related projects include the implementation of an LSI-11 based real-time arrhythmia analyzer which has been completed and will be installed soon in a digital telemetry system in Barnes Hospital. Also, a PL/I program, SUMMARY, has been used to construct a SAS database from the Argus/H analysis results. Extended analysis of that database has been used to establish that Argus/H reprocessing variances for the measures of interest are an order of magnitude less than the corresponding inter-tape variances, thus confirming the usefulness of Argus/H processing results. Another study using the SAS database has yielded the important finding that a commonly assumed relation between heart rate and Q-T interval does not hold reliably within a given patient's recording.

Projects in instrumentation related to cardiology have resulted over the past year in improvements to a burst-analog sampling microprocessor system for real-time digital echocardiography, extensive evaluation of a microprocessor-based system for interactive digital acquisition of pediatric electrocardiograms, and a performance evaluation of Avionics and Oxford ambulatory ECG recorders.

Over the past year BCL collaboration in a SCOR program (HL 17646, Study of Ischemic Heart Disease) has continued in nine project areas: the development of mathematical models to describe the dynamics of enzyme (CK) release after myocardial infarction, the evaluation of interventions addressed to infarct size modification, the implementation of a SCOR computer system, electrophysiological and biochemical factors underlying the genesis of dysrhythmias due to myocardial infarction, ultrasonic cardiac imaging,

measurement of myocardial metabolism, left ventricular compliance studies, patient database studies, and the application of positron-emission transaxial tomography for non-invasive visualization of ischemic myocardium. The last three are reported elsewhere under other project-area titles.

Tomography Systems. Laboratory projects related to reconstructive tomography embrace three different modalities: ultrasound attenuation, x-ray transmission, and positron emission. Each of these conveys different information about the structures being imaged and, thus, each addresses a different class of research interests. The ultrasound-attenuation technique is in an early state of development, thus current work focuses on solving fundamental problems. X-ray transmission tomography is well established, but new developments show promise for substantial performance improvement. Emission tomography has proven its usefulness for both clinical and research purposes, but additional work is necessary to make it more practical in specific applications.

During the past year significant advances have been made in ultrasonic attenuation tomography. Phase cancellation in piezoelectric receiving transducers has been demonstrated to be the single most important error source. This demonstration is particularly significant because of the local availability of a phase-insensitive cadmium sulfide transducer which is based on the acoustoelectric effect. The acoustoelectric transducer results from work in the Department of Physics, with which the Laboratory's tomographic work collaborates. In addition, the frequency-dependence of ultrasonic attenuation, a parameter highly correlated with certain tissue pathologies, has been demonstrated to be important for the elimination of error due to transmission losses at discontinuities in ultrasonic impedance which are encountered in tissue specimens.

In the area of x-ray transmission tomography a recently initiated project is examining a novel approach to image reconstruction for the newer scanners which are implemented in a "fan-beam" geometry. The algorithm under development would allow the processing of each detector output independently as the source rotates. By using an emerging technology, adaptive charge-coupled devices, it appears that with the new algorithm, the image reconstruction can be accomplished promptly upon completion of the rotation. The possibility for achieving real-time reconstructions is exciting.

With regard to positron-emission tomography, its application to clinical research in cardiology has moved forward with the installation of the previously developed PETT IV system into the procedures room of the Cardiac Care Unit at Barnes Hospital. It is possible now to image the hearts of patients with acute myocardial infarctions and ischemia and to assess regional changes in myocardial metabolism acutely. Over the past year the utility of PETT IV for such studies has been enhanced by modifications to allow the collection of seven simultaneous cross-sections rather than the original four. Improved spatial resolution results from a shorter slice-to-slice distance. Also, reconstructions in sagittal and coronal planes are now provided. The design and mechanical construction of a new scanner, PETT V, was completed during the year. It is specifically

designed for rapid data collection, high sensitivity, and high spatial resolution for the study of regional dynamic processes (e.g., transport and metabolism) in the human brain. PETT V also will be applied to studies of regional cardiac metabolism in intact animals.

Clinical Pathophysiologic Research Activities. In January of 1978 operation of the computer system designed at BCL for the Cardiothoracic Surgical Intensive Care Unit (SICU) was turned over to Barnes Hospital personnel. Subsequently, minimal BCL support has been necessary for smooth functioning of the system, thus freeing Laboratory personnel for support of other digital-computer applications to pathophysiologic research. Although the SICU monitoring system is now over five years old and due to be retired in 1980, its functional design and human engineering considerations continue to have impacts on commercial systems, as has been evidenced recently in consultations by Laboratory personnel with a major vendor of medical instrumentation systems. Over the past year efforts have turned to the development of more generalized solutions to problems in applying digital computing techniques to acquiring, processing, displaying, and storing physiologic signals for research activities. Microcomputer-based programmable modules conveniently packaged and interconnected via the IEEE Standard 488 digital interface are being configured to meet applications needs flexibly. To date three modules based on MC6800 components have been built for initial use in hemodynamic studies in the Barnes Hospital Coronary Care Unit. Signal processing algorithms developed in other contexts are being implemented on the new modules.

In the cardiac catheterization laboratory the final algorithms for automated pressure-waveform analysis were completed and evaluated over the past year. The system now is capable of fully automated analysis of all waveforms ordinarily encountered in catheterization procedures. Physician review and edit of the analyses is encouraged through the provision of convenient and rapid routines for doing so. This major milestone was passed some six months ago and the system designers find considerable satisfaction in the sustained enthusiasm of the cardiologists who use the system daily. Other related work is now giving full attention to automatic ventricular boundary extraction from video-angiographic data. A closed-circuit TV video-image acquisition system has been completed and work is in progress to implement an augmented version of the algorithm developed at Latter Day Saints Hospital in Salt Lake City. A previously developed interactive system for acquiring ventricular contours and high-fidelity pressure waveforms synchronized to the angiographic frames is seeing continued use in studies of ventricular diastolic compliance.

Three instrumentation projects in support of pathophysiologic research have progressed over the past year. Work in collaboration with the Department of Electrical Engineering seeks a fundamental foundation for understanding the behavior of a previously designed acoustic ventilometer. Solution of a plane-wave model has been shown to be directly proportional to the observed behavior of the instrument but with a factor different from one. A point-source-array model is being examined with a view toward developing more confidence in the device before it is

put into clinical use. Thermodilution cardiac-output studies have confirmed the hazards of the popular bolus-injection method in the presence of significant physiologic perturbations, such as those due to intermittent positive-pressure ventilation. Animal studies performed in recent months suggest the feasibility of the limited-duration constant-infusion method using room temperature injectate. Although a steady state is not achieved under such conditions, it appears that an algorithmic correction for temperature drift due to recirculation may render the method practical. A microprocessor-based system for acquiring visual field data directly from a Goldman perimeter has been completed and is being packaged in preparation for trial in the Glaucoma Clinic. The accuracy of the computed Cartesian coordinates has been confirmed to be within $\pm$ 1 mm over the area of interest.

Databases for Disease Management and Research. Laboratory personnel are directly responsible for the design, maintenance, and utilization of five different clinical databases into which a total of approximately 9,500 patients are now entered. The databases and their approximate numbers of enrollees are tabulated below:

Database	Affiliation	No. Patients
Glaucoma Center Registry	Dept. Ophthalmology	1600
Sudden-Death Study	Cardiology-Jewish Hospital	5467
Propranolol Study	St. Louis University	1466
SCOR Patient Information	Cardiology-Barnes Hospital	450
Neonatology	Pediatrics	500

All but the last represent mature systems which are fully operational, are supporting their respective studies, and are showing continued growth. During the past year considerable progress has been made toward stabilization of the neonatology database system and it is now beginning to see use by the neonatologists for clinical studies. The complexity of the interactions between the multiple disease processes commonly encountered in the acutely ill newborn has presented challenges to the coding strategies employed. Also, the associated diversity of the types of data searches requested has raised special problems which have been addressed by the use of carefully structured inverted files. The durability of this solution will be tested as the database grows in size and usage.

All of the above systems are written in MUMPS and currently run either on an Artronix Modulex system located at the Mallinckrodt Institute of Radiology or on a PDP 11/34 emulation at the Medical Computing Facility which has been established within the Medical School to provide MUMPS service to those who do not desire to operate their own installations. During the past year a MUMPS facility at BCL was retired. It had been established to support training activities and investigations into database characteristics, but by the end of the current period remaining applications were deemed mature enough to migrate to the other available MUMPS facilities.

In September, 1977, the Executive Directorship of the international MUMPS Users' Group (MUG) was passed from Dr. Joan Zimmerman at the Biomedical

Computer Laboratory to Mr. Richard E. Zapolin at the MITRE Corporation. The vitality of MUG is evidenced by its current move toward self-sufficiency on the occasion of the termination of major federal funding. MUMPS User's Groups are active also in Japan and Europe, where three locally developed MUMPS applications were transferred, in addition to their wide distribution in North America.

Work continued last year toward development of a "MESCH" (Multi-Environment Scheme) questionnaire which will assist and educate group-practice personnel for the purpose of defining information-management systems which can be tailored to their needs. The questionnaire driver has been translated into Standard MUMPS and expanded to allow broader capabilities, including complex branching.

In keeping with the objective of allocating tasks to available resources according to their particular strengths, SAS on the University's IBM System/360 continues to be used heavily for analyses requiring the processing of large sets of patient data, for computationally burdensome statistical procedures, and for the production of large reports. Industry-compatible tape has been the primary mode of communication between the System/360 and the other database facilities cited above. However, a preliminary design has been completed to enable the Medical Computing Facility system to be connected directly to the System/360 for the submission of SAS jobs.

The Biomedical Computer Laboratory continues its participation, along with other Resource components, in work centered in the Information Systems Group, Department of Computer Science, for the development of an experimental high-performance information system. The experimental system consists of two user modules, two data modules, and a 2 × 2 crosspoint communication switch. It represents the minimal non-trivial configuration of the proposed system and thus provides a facility for cost (time and space) evaluations of multi-tasking software developments, as well as for system instrumentation experiments.

Speech and Hearing. Development of a hydromechanical model of the cochlea has been a major activity at the Laboratory in support of speech and hearing research both at the Central Institute for the Deaf (CID) and in the Sensory Biophysics Laboratory within the Department of Physiology and Biophysics. During the past year the model has been favorably compared with recent work by others. Work reported this year has used the model for parametric studies of the effects of changes in partition mass and partition damping. With a view toward implementing a new, more usefully interactive version of the model, various strategies for increasing the speed well beyond that of the current implementation are being examined.

The primary basis for collaborative work between the Laboratory and CID continues to be in the development of digital instrumentation required for a broad research program which addresses basic questions related to hearing and deafness. The psychophysical characteristics of electrocutaneous stimulation are being examined to explore the feasibility of capitalizing on this alternate sensory modality for profoundly deaf

patients. Early results indicate that among a number of stimulus variables tested, pulse width and burst rate appear to be the more useful for information coding. Work on the measurement of glottal source characteristics of normal and deaf talkers has been employing new instrumentation to study the phonation effects of deafness and of language differences. For psycho-acoustic studies of speech perception, simplified speech-like sounds, as well as exemplary speech sounds, have been generated and used for testing chinchillas and human adults and children. Preliminary work has been done to adapt the cochlear model for use in these speech discrimination studies. Since the model is physically based it will serve as a guide to the choice of appropriate scaling relations based on anatomical measurements.

Other work carried on during the past year addresses lip-reading studies which use computer-synthesized mouth outlines, model-based determinations of vocal-tract area function during phonation, the development of aids for hearing-aid design, and the establishment of a library of routines for speech-synthesis studies.

As an outgrowth of the longstanding CID-BCL collaboration, the Research Department of CID has completed installation of a central computer system (Eclipse) which is shared by several laboratories. Two simpler but compatible minicomputer (Nova) systems are deployed also in the department for use in on-line data collection and stimulus control. A third satellite system is scheduled for completion early in the next report period. Several major application programs have been completed and a few others are currently under development. These CID supported systems have provided welcome relief from the previously heavy demands on the BCL speech and hearing system.

Central Nervous System Diseases and Encephalogram Analysis. Laboratory research efforts in application of computers and mathematical models to CNS disease and EEG analysis have expanded to include two new project collaborations with the Departments of Neurology and Anatomy. The visual evoked response (VER) is to be used as an indication of cerebral physiology in a temporal study of patients with senile dementia. Collaborative efforts this year have included a pilot study to develop experimental protocol, design of a microprocessor-based two-channel VER acquisition system, and algorithm development for computer-assisted feature extraction. Studies were initiated for an improved image-processing system for Neuroanatomy. The system, which is to be used to support automatic analysis of autoradiographic specimens, is to offer increased speed, flexibility, and exportability by utilizing a distributed architecture. An initial system design has been completed.

Work has continued on regional in-vivo brain metabolism studies, using positron-emitting radio-isotopes and the positron-emission tomograph PETT IV. The generality of the underlying mathematical model has been successfully demonstrated for widely varying conditions of blood flow, blood pH, and altered brain-blood barrier permeabilities.

Experiments using the MMS-X graphics system to achieve three-dimensional display of cerebral ventricles were continued. Procedures for obtaining actual cerebral ventricle cross-sectional outlines from CT image data have been developed.

In support of work on seizure localization, development and construction of an EEG-electrode switching matrix has proceeded. A digital communication link has been designed to provide data transfer between the epileptic patient's bedside and a computer for recording EEG activity during seizures.

Supporting Activities. BCL projects which contribute to the advancement of more than one of the major laboratory programs or which are in stages of early formulation and do not yet fit logically within established categories are grouped here. These projects can usually be classified as biomedical applications, system development aids, or digital hardware designs.

The principal activities in the biomedical applications grouping are radiation treatment planning and physiologic signal processing. The mathematical model which is the basis for our absorbed dose calculations in the presence of inhomogeneities for radiation treatment planning has been validated against published experimental results from simple phantoms. In addition, validation work has begun, using the more realistic RANDO phantom with CT scan data and an empirical electron density correlation. The efforts in physiologic signal processing have been directed toward characterizing ECGs in the frequency domain. The success of this activity has already enhanced the operation of the Argus system for arrhythmia detection. Other biomedical applications include studies for a system to measure corneal pressure and a microprocessor-based time-lapse cinemicrography system.

Our microprocessor support capability continues to be heavily used in a variety of projects. Our cross-assembler, FOCRAS, has been augmented to include relocatable assembly and linking which increases our ability to handle larger programs. Three intelligent consoles are now in use at BCL and a fourth has been built by Electrical Engineering for teaching and research. A number of significant improvements have been completed in the system software for the PC-1200s which continue to support a variety of BCL projects.

A number of hardware designs have been completed in support of multiple projects. The Universal Storage Device (USD) has been improved with respect to its disk error-performance and replication is now in progress.

Individual Projects

Biomedical Computer Laboratory

A. Ischemic Heart Disease and ECG Analysis

The projects reported in this section continue longstanding work in real-time and high-speed ECG analysis. Many of the clinical studies detailed below are natural outgrowths of the ECG analysis work, as are the strong interests in the evaluation of automated arrhythmia detectors. Modeling and signal-processing endeavors in the field of cardiology have taken the form of collaborations which address other aspects of ischemic heart disease, such as the kinetics of enzyme release, myocardial metabolism, and the electrophysiologic characterization of abnormal myocardial depolarization. Digital techniques applied to clinical echocardiography are reported here, whereas other ultrasonic work applied to tomography is considered in section B.

Argus/H is a high-speed version of the real-time computer-based arrhythmia monitoring system Argus, which was in operation in the Barnes Hospital Coronary Care Unit (CCU) from 1969-1975 and replaced in 1975 by "Argus/Sentinel," a commercially available version developed through collaboration with the Mennen-Greatbatch Company. Work on Argus/H was begun in 1971 and it has matured to a heavily used system for processing 24-hour recorded ECGs at sixty times real time. Although the principal application of Argus/H continues to be the study of ventricular dysrhythmias in ambulatory patients who have survived a myocardial infarction, there are rapidly increasing interests here and elsewhere in utilizing such systems for therapeutic trials of antiarrhythmic agents, as well as for evaluation of interventions designed to protect the ischemic myocardium. Argus/H is especially valuable for such studies because of its ability to yield precise quantitative measures of significant ventricular arrhythmias.

Argus/H employs specialized hardware (macromodules) to encode ECG data sampled at 15,000 samples per second. Software and appropriate peripherals expedite review and edit of computer results which are saved for subsequent statistical analysis via the University's IBM 360/65. Extensive evaluations have verified the integrity of the analysis algorithm, proven the value of the quantified results as compared to conventional manual-scanning techniques, and confirmed the consistency of results on reprocessing. Recent work has developed a post-Argus processing stage which uses more contextual information to substantially improve system efficacy. As an outgrowth of that work, plus new activity in frequency-domain signal analysis, the basic Argus algorithms are undergoing extensive revision. A new system, Argus/2H, is designed to capitalize more fully on new algorithms to provide for dual-channel processing and to allow graceful exportation of the system. Argus/2H will be applied to production processing of Holter ECGs for a local study of the natural history of sudden death and for a national multicenter clinical trial of interventions to limit infarct size. It will provide the power and flexibility necessary for work on new signal-processing strategies and it will serve the analysis and documentation needs of other nationally-directed work to generate an annotated digital database for the evaluation of automated arrhythmia detectors.

A-1. Argus Algorithm Development

Personnel: C. N. Mead, BCL
K. W. Clark, BCL
S. M. Moore, BCL
S. J. Potter, BCL
J. A. Ritter, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808
HV 72941

During the past year algorithmic development on the Argus/H and Argus/2H systems has centered in two main areas: 1) investigation of waveform processing algorithms which utilize frequency-domain information, and 2) a major revision of each of the three stages of the original Argus algorithms (Aztec, Primitive, and Cycle). The immediate goal of the first area of endeavor was to aid in the extraction of data regarding the presence of multiform premature ventricular contractions (MPVCs). The Argus rewrite, which will be an on-going project during the coming year, has as its ultimate goal a substantial improvement in total system performance through the incorporation of experience in waveform processing gained at this and other institutions during the past several years.

Frequency-Domain Analysis of PVCs (PR 13, G-7). The identification and quantification of MPVCs is of considerable clinical and research interest. Historically the Argus/H and Argus/2H systems have allowed for the identification of MPVCs only by means of direct observation by a human editor. As automated editing strategies gain prominence (PR 13, A-3) reliance on human detection of MPVCs becomes less desirable. Furthermore, even when the detection of MPVCs by a human technician is known to be accurate (i.e., the tape was not processed by Machine Edit), no attempt has been made previously to quantify PVCs by morphological form. Work to date has centered around development of an algorithm to reliably and automatically classify editor- or machine-labeled true-PVCs by form, thus allowing for the collection of timing and contextual data on PVCs of a given morphology.

Each QRS detected by the Argus system is classified as a PVC or non-PVC by means of four time-domain-based "features:" duration, height, offset, and area. Because all but the first of these parameters is dependent upon local signal amplitude, and because changes in this amplitude over time, as well as additional changes in the electrical projection of the heart, may substantially affect the time-based feature measurements of beats of clinically similar form, clusters of PVCs defined solely on the basis of these four measurements tend to be redundant from a clinical point of view. A search for one or more frequency-domain parameters which could be used to augment the time-domain-based cluster analysis led to consideration of the first spectral moment (FSM). The FSM, a derived parameter corresponding to the "center of gravity" of the power spectrum, satisfies the requirement of being a quickly computed, generalized "shape"

parameter. For use in this context it is calculated at 5 Hz intervals in the range 5-25 Hz. We have found it to be extremely useful in identifying "redundant" time-domain-based clusters. Further consideration of the 5- and 10-Hz phase angles allows for the separation of unique time-domain clusters whose FSMs are similar.

To date the Detection Algorithm for Multiform PVCs (DAMP) has been applied to twenty 24-hour tape recordings on which MPVCs were known to exist. DAMP correctly identified the presence of MPVCs and the correct number of such forms for each tape in all cases. Classification of forms was done using a 6-tuple of both time- and frequency-domain information (QRS height, area, and offset; FSM of family center and its associated 5- and 10-Hz phase angles). More importantly, DAMP was able to classify greater than 80% of the true-PVCs on each tape into one of the forms detected. The unclassified beats represent editor-defined true-PVCs with a signal-to-noise ratio which makes interpretation of the frequency-domain information unreliable. Such beats are automatically excluded from analysis by DAMP. A further evaluation is underway and, in addition, portions of DAMP are being tested for use in an automated strategy for the detection of false-negative PVCs.

Argus Revision. The basic Argus algorithms, originally developed for application in the real-time environment (PR 6, B-2) and subsequently adapted for high-speed Holter tape analysis (PR 9, B-7), have remained essentially unchanged since their inception. Digital sample data are converted into a series of slopes and bounds characterizing the analog ECG signal with a data compression ratio of approximately 10:1 (Aztec), a QRS detector delineates each QRS complex which is then measured to extract four morphological features (Primitive), and finally, beats are placed into groups called "families" and are classified as PVC, Normal, etc., based on their feature measurements and minimal timing information (Cycle). The excellent performance of a QRS detector with an adaptive automatic gain control (AGC) in the SICU monitoring system,[1] coupled with the realization that many of the mistaken beat classifications in Argus were fundamentally related to inaccurate QRS detection and/or delineation, led to the decision to rework the QRS-detection section of Primitive. Experience with the increased use of timing and context data in the Machine-Edit algorithms (PR 13, A-3) suggested that the performance of the beat classification logic (Cycle) could be enhanced significantly. Furthermore, work by other investigators[2] on feature extraction from the ST-T segment of the ECG indicated that utilization of such data might be helpful in certain beat-classification situations. Therefore, a major revision of Argus is currently underway.

To date the SICU QRS detector has been extensively modified to perform as a delineator as well as a detector. The modifications left intact the AGC function, as well as the original concept of the detector as a finite state machine. However, extensive logic was required to deal with P-wave rejection and delineation of biphasic and notched QRS complexes (bundle-branch block). Additionally, the various finite states had to be restructured when the conceptual change was made from a detector that processed sample data one point at a time to one which processed Aztec

data which, by definition, spans a variable length of time per Aztec datum. The new detector/delineator presently is undergoing an extensive evaluation. The Argus rewrite will proceed in a sequential fashion through each of the sections and subsections of the original program. Each modification will be compared to the original Argus program for its effect on processing. Additionally, later stages will be compared to Argus in concert with all preceding changes as the revised system evolves.

(1)C. F. Pieper, L. J. Thomas, Jr., "QRS Detection for the SICU," BCL Monograph 222, February 1974.

(2)D. E. Lovelace, S. B. Knoebel, D. P. Zipes, "Recognition of Ventricular Extrasystoles in Sedentary Versus Ambulatory Populations," Proceedings of the Conference on Computers in Cardiology, St. Louis, Missouri, pp. 13-18, October 1976.

A-2. High-Speed ECG Processing: Hardware

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

Support: RR 00396
HV 72941

A modified version of the Argus/2H prototype system (PR 13, A-2) has been built to provide Holter-tape processing for the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study (A-21). Emphasis in the design of the system was placed on using currently available standard components whenever possible in order to improve maintainability and exportability of the Argus/2H system. The major differences between the new Argus/2H and its prototype are the use of PDP 11/34s instead of Cal Data 135s, commercially available data acquisition hardware instead of specially built equipment, and Hewlett-Packard 78172 2-channel chart recorder with alphanumeric annotation instead of the Siemens ink-jet recorder. The system is compatible with existing Argus/2H software (A-3) except for routines used to service the new chart recorder and data acquisition hardware.

A-3. High-Speed ECG Processing: Software

Personnel: K. W. Clark, BCL
R. E. Hitchens, BCL
C. N. Mead, BCL
S. M. Moore, BCL
S. J. Potter, BCL
S. L. Rankin, BCL
J. A. Ritter, BCL

Support: RR 00396
HL 18808
HV 72941

During the year software on the Argus/2H systems for the processing of dual-channel 24-hour ECGs underwent substantial refinement as the experience of the first recordings through the systems closed the feedback-loop and exposed areas of needed improvement. While none of the refinements merits lengthy discussion, the effort, in toto, was no trivial matter. New efforts focused on hard-copy summary generation, the storage (on-line and archival) of digitized waveforms, and automatic editing.

Hard-copy summary generation. Summaries produced after processing of a Holter recording have changed only slightly (PR 13, A-3). An additional sheet tabulates heart rate, PVCs, couplets, runs, bigeminal complexes, and data loss by hour, and this summary typically is mailed to the patient's physician. Minor software changes were needed for the ECG strip-recording generation routines in the edit program to accomodate the new chart recorder for the second Argus/2H system (A-2). The recorder's annotation mechanism permits characters at strip's edge via thermal print head. No similar mechanism exists for the ink-jet recorders on the Argus/H and first Argus/2H systems where any annotation is strictly under software control of the galvanometers. The latter mechanism, however, permits annotation anywhere within the range of the galvanometers, not just at the paper's edge.

Storage of waveforms. Recent algorithm development (A-1; PR 13, A-1) necessitated on-line, random access to the entire digitized dual-channel waveform of a 24-hour Holter ECG recording. For expeditious retrieval the first and second channels are digitized onto disk and appear as straight 10-bit (sign-extended to 16-bit) samples in alternate words. For magnetic tape archival purposes a packing scheme affords a 2:1 data compression from the disk storage mode. First differences between samples in each channel are computed and the differences of the two channels are stored in adjacent bytes. Processing programs will accept raw or packed waveforms.

Automatic Editing. The algorithms for automated confirmation as true-PVC of selected Argus-labeled PVCs (Machine Edit, PR 13, A-1) have been put into routine use in the processing of 24-hour dual-channel Holter tapes on the Argus/2H systems. During the course of algorithm translation

several major processing changes were made, which significantly increased the execution speed of the routines without in any way degrading their performance. Because the increase in speed is of several orders of magnitude Machine Edit can now be "tried" on virtually every tape analyzed by the system, the penalty in processing time for a "failure" (i.e., a tape on which the machine fails to "learn" enough to establish a true-PVC cluster) being trivially small. The end result of the new version of Machine Edit is, therefore, a more rapid processing of an increased number of tapes.

Machine Edit operates as a sequence of two separate programs, Set-Up and Edit. Changes in processing strategy were made in both portions. During Set-Up a list of all Argus families containing PVCs is generated (PVC Catalog) and ordered by population. Each family in the catalog is then examined, member-by-member, to determine if a sufficient percentage of the family members appear in stable and appropriately timed context and are likely true-PVCs. If a true-PVC family is identified a cluster is formed around the family, utilizing fixed extensions of its morphological feature measurements. Since the PVC catalog is examined beginning with the largest families (by population), families within a given cluster always contain the same or fewer members than the family around which the cluster is formed. Both the generation of the PVC catalog and the family-by-family "learning" process require multiple passes through the beat-by-beat, time-ordered "Cycle data stream" generated by Argus during routine tape processing. This Cycle stream typically contains 100,000 - 150,000 QRS complexes for a 24-hour tape (approximately 1.5 megabytes of disk storage). Since only a small fraction of the total number of QRS complexes usually have been labeled PVC by Argus, and since the Machine Edit routines need to analyze only those Argus-labeled PVCs which are preceded and followed by non-PVCs, the creation of a temporary "squashed" Cycle stream as the first step in Set-Up greatly reduces the processing time in both the remainder of Set-Up and the subsequent Edit phase.

Further gains in execution speed have been realized by reorganizing the PVC catalog following true-PVC cluster identification. The catalog now is passed to the Edit program ordered by cluster (largest first) rather than simply by family population. Iterative editing passes through the squashed Cycle stream then are made in 8-family chunks for a given cluster. When the percentage of beats edited on a given pass is small compared to the previous pass the Edit routine exits the cluster and begins editing the next cluster. Compact clusters thus may be completely edited in a single pass, while more dispersed clusters may require multiple iterations. The cluster-ordered PVC catalog is saved with the Cycle Stream and the PVC clusters so identified are analyzed further during post processing summarization (A-6). It should be emphasized that many times the clusters are redundant with respect to PVC form. Attempts to coalesce redundant clusters utilizing frequency domain information are currently underway (A-1).

Processing time for the entire Machine Edit sequence varies depending on the PVC content of the tape, but is now routinely in the range of 1-5 minutes (worst case 8 minutes, most tapes under 2 minutes), whereas the original algorithms operated in the range of 15-60 minutes with difficult tapes requiring 3-4 hours of processing time.

A-4. Holter Tape Processing

Personnel: K. W. Clark, BCL
H. D. Ambos, BCL
K. M. Bruce, BCL
P. B. Corr, Ph.D., Medicine and Pharmacology
A. A. Ehsani, M.D., Medicine
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
M. A. Marlo, BCL
P. W. McLear, BCL
S. E. Menner, BCL
J. W. Mimbs, M.D., Medicine
S. M. Moore, BCL
S. J. Potter, BCL
J. E. Rapert, BCL
P. B. Webb, BCL

Support: RR 00396
HL 17646
HL 18808
HV 72941
Sandoz-Wander, Inc.

Holter tape processing facilities now include three complete systems. The original system, Argus/H, remains a system for single-channel Holter processing. Within a year we hope to convert this system to dual-channel capability with the addition of sorely needed on-line random-access mass storage. The other two systems, Argus/2H -- serial numbers 1 and 2, process 24-hour dual-channel Holter recordings.

During the year the Argus/H system processed approximately 400 24-hour tapes for the natural history study of sudden death (PR 12, A-1). Additionally, from the study of ventricular arrhythmias and sudden death (PR 11, A-1) several hundred 10-hour tapes, which were processed under an incomplete protocol, have been "re-edited" under a new protocol -- most tapes were in digital form so that complete reprocessing was not necessary. The system also processed tapes from the studies of interventions designed to protect the ischemic myocardium immediately after infarction (PR 13, A-18), as well as four additional investigations which are summarized below.

Differentiation of coronary-occlusion and reperfusion dysrhythmias in man. Since many patients autopsied after sudden cardiac death do not show pathological evidence of complete coronary occlusion, vasospasm of coronary arteries with phasic alteration in regional coronary flow is considered to be a possible progenitor for malignant dysrhythmias. Furthermore, since both coronary occlusion and reperfusion initiate severe ventricular dysrhythmias in experimental animals, we investigated whether distinct electrophysiological differences underlie these two types of dysrhythmias. In studies performed in the feline preparation the two types of dysrhythmias appear to depend on entirely different mechanisms

(A-15). Holter recording of the surface electrocardiogram in the cat during the two types of ventricular dysrhythmias, with subsequent Argus/H computer analysis, revealed that two distinct populations of coupling intervals were evident during each dysrhythmic phase (n=8). During the dysrhythmia induced by coronary occlusion the majority of premature beats occurred with a R-R' interval of 200-224 msec, in contrast to the dysrhythmia induced by reperfusion where the initial premature beat (R-R') usually occurred at 100-150 msec. In an attempt to verify whether these findings could be applicable to man and possibly useful in differentiating diverse electrophysiological mechanisms in man, patients undergoing coronary bypass surgery were Holter recorded since this kind of surgery usually induces ventricular dysrhythmia associated with known times of both coronary occlusion and/or subsequent reperfusion. Although results to date are not yet conclusive two distinct populations of coupling intervals were seen, suggesting that this type of approach may have predictive value relative to therapeutic intervention in man.

Treatment of ventricular dysrhythmia associated with mitral-valve prolapse: a double-blind study of propranolol. Although propranolol is often used to treat ventricular dysrhythmia associated with mitral valve prolapse (MVP) its efficacy has not been defined. Accordingly, we have studied 9 patients (mean age = 40 years) with MVP documented by angiographic or strict echocardiographic criteria. Each patient was randomly assigned in double-blind manner to therapy of 2 weeks placebo followed by 2 weeks oral propranolol (maximal dose of 160 mg/day) or vice versa. Verification of therapy was obtained by plasma propranolol level on at least one occasion during each 2-week interval. Ambulatory Holter recordings (24 hour) were obtained at 5 and 13 days of each 2 week therapy interval and analyzed with the Argus/H computer system. Results of Holter data obtained on maximal propranolol dose compared to results from both Holters obtained during placebo revealed: 1) decreased mean heart beats/min (76 to 63), 2) decreased mean VPC/hr (199 to 108), and 3) decreased mean couplets/24 hr (58 to 35). In 2 patients with ventricular tachycardia, episodes were obliterated in 1 (8 to 0/24 hr) and insignificantly decreased in the other (18 to 17/24 hr). These results are preliminary and suggest the need for additional data in order to make definitive conclusions about the efficacy of propranolol for treatment of ventricular dysrhythmia in mitral-valve prolapse.

Correlations between late ventricular dysrhythmias and infarct size. Enzymatically estimated infarct size index (ISI) appears to be a determinant of ventricular dysrhythmia within the first ten hours and of mortality within one month after acute myocardial infarction. To determine whether ISI is also related to later events we followed 63 patients with enzymatically estimated infarct size, $\leq$ 60 years of age, who had sustained an initial infarction uncomplicated by an extension during the initial admission and who survived for at least five days. ISI in survivors was 22 ± 2 (mean $\pm$ SE) CK-g-eq/m^2 BSA compared to 71 ± 7 in the five patients who succumbed ($p < .001$). The frequency of premature ventricular complexes (PVCs) in 28 patients (none of whom had sustained additional infarctions) assessed by Argus/H analysis of 24-hour Holter tapes obtained between 2

and 12 months after infarction averaged 241 $\pm$ 117/24 hours in patients with small infarcts (ISI < 15) compared to 1292 $\pm$ 840 in patients with large infarcts (ISI $\geq$ 15) ($p < .05$). These results indicate that among relatively young patients with initial infarction enzymatically estimated infarct size presages not only ventricular electrical instability during the acute episode, but also the severity of ventricular dysrhythmia as long as one year after myocardial infarction.

Efficacy of LB-46 (Prindolol), a cardio-selective beta adrenergic blocking agent. Sixteen patients of twenty anticipated have completed participation on the evaluation of LB-46, a beta-blocking agent produced by Sandoz-Wander, Inc. (PR 12, A-7). The study is designed as double-blind crossover, lasting four weeks for each patient. A patient with a PVC rate in excess of 50 PVCs per hour over 48 hours is given a placebo or LB-46, 5 mg four times a day, for one week. The alternate is given during the third week with drug tapering during weeks two or four. Holter recordings are obtained prior to the first week and again at days 6 and 7 of each drug/placebo week. The recordings are processed by Argus/H or Argus/2H. Grouped data on 14 of the 16 patients indicate that LB-46 has no significant effect on reducing the average PVC rate, nor on reducing the incidence of salvos of two or more PVCs. However, LB-46 does have the effect of prolonging slightly the coupling intervals of PVCs which are not salvo-PVCs. Since early-cycle PVCs have been shown to place persons recovering from myocardial infarction at high risk of sudden death the effect may prove to be beneficial.

The first Argus/2H system has been primarily dedicated to algorithm and program development (A-1, A-3) and to database development for the evaluation of arrhythmia analysis systems (A-8). However, several tens of 24-hour tapes for the natural history study of sudden death (PR 12, A-1) have been processed on this system.

The second Argus/2H system (A-2), only recently installed, will be dedicated to the processing of recordings from the Multicenter Investigation for the Limitation of Infarct Size (A-22).

A-5. LSI-11 Argus/RT

Personnel: J. A. Ritter, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808
Washington University

The Argus/RT arrhythmia monitoring system prototype was completed in May, 1978. Bench testing confirmed the proper functioning of the arrhythmia monitoring algorithms and also demonstrated some minor problems with the user-interaction keyboard.

An expanded keyboard has been interfaced with the system. System installation awaits the completion of support programs to program the monitoring software into EPROMs, using the Intelligent Console EPROM programming feature (G-1).

The components for a second Argus/RT system have been purchased. This system will be used initially for algorithmic refinement. It will be packaged as a portable unit to enhance the utility of the system.

A-6. Extended Analysis of Argus/H-Quantified Ventricular Ectopic Activity

Personnel: J. P. Miller, BCL
K. W. Clark, BCL
G. C. Hall, BCL
C. N. Mead, BCL
P. Moore, BCL
G. C. Oliver, M.D., Medicine
J. M. Paine, B.A., Biostatistics
S. J. Potter, BCL
M. A. Province, BCL
J. A. Ritter, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808
HV 72941

Following the processing and editing of Holter tapes by Argus/H or Argus/2H (A-4) the beat-by-beat annotation of the 10- or 24-hour recordings (Cycle streams) are accumulated on industry-compatible tape and transported to the IBM System/360 for bulk processing of the Cycle streams in order to extract salient features of the ventricular ectopic activity (VEA).

Summary (PR 12, A-2), the PL/I program which runs on the S/360 to reduce the beat-by-beat annotation of the Holter tape to variables of interest, was updated to handle the Argus/2H cycle streams which had been expanded to more fully annotate the ECG. Also constructed was a special version of Summary which produces for each PVC a record which summarizes salient features concerning the environment of that PVC, e.g., its coupling interval, family number, Argus features, several averages of heart rate preceding the PVC, and the labels of the two beats preceding the PVC. The output of both versions of Summary are in turn utilized to construct a SAS database (D-12) for further analysis.

The extended analysis of the Argus quantified VEA continued to be of use in the analysis of the results of antiarrhythmic agents (PR 13, A-6).

For the evaluation of LB-46, an experimental beta-blocker developed by Sandoz-Wander, Inc. (VI-C), it was discovered that the major effect of the drug was to reduce the number of isolated PVCs with short coupling intervals (under 400 ms) and to lengthen the average PVC coupling interval. The standard deviation of the 5-minute heart rates proved to be a sensitive indicator, demonstrating that the drug was achieving beta-blockage.

The special version of Summary is being utilized to characterize the distribution of coupling intervals for isolated PVCs with a particular QRS morphology. The standard version of Summary[1] produces a frequency distribution of PVCs, grouping the isolated PVCs into 12 different bins according to their coupling intervals. Previous attempts to fit a statistical distribution to this frequency distribution have been frustrated by both the coarseness of the bins and by the confounding of the distributions, a situation most profoundly noticed in tapes with multiformed PVCs in which a bimodal distribution is noted. By utilizing the clustering algorithms developed to speed automatic editing (A-3) it has been possible to group PVCs according to morphological forms. It is hoped that standard statistical distributions then may be fit to the coupling interval frequency distribution from these morphologically homogeneous PVCs and a few parameters extracted which characterize the distribution. These extracted parameters then will have utility as potentially more stable and meaningful characterizations of the coupling intervals in the evaluation of drug studies (vide infra) and as risk markers for sudden death (A-7).

Several special analysis studies have been undertaken in order to facilitate the characterization of coupling intervals and to provide information of use in the development of new Argus processing algorithms (A-1). The QT interval is of particular importance in the evaluation of the "earliness" of a PVC since it is reflective of the repolarization of the ventricle. Animal research has implicated its importance in the relative refractory period for the initiation of ventricular fibrillation. Interpreting the coupling interval of the earliest PVC in light of the estimated QT interval was found previously (PR 13, A-6) to improve the prediction of cardiologists' judgments about whether the PVC's onset is within or adjacent to the T wave of the previous beat. The estimated QT interval was based on a mathematical relationship between heart rate and QT interval commonly cited in the literature.[2] The relationship was estimated from resting ECGs <u>across</u> a population of patients whose ECGs were read as normal. We attempted to replicate the study to determine if the relationship held <u>within</u> a single patient's Holter recording. Tapes from 20 patients were examined and a special program allowed the editor to manually adjust the QT interval according to the 2-channel ECG displayed at varying heart rates. Nonlinear regression techniques were utilized to examine the relationship. While the data of some patients closely followed the Ashman formula, other patients demonstrated a total independence of heart rate and QT interval.

In order to adapt Argus for the identification of areas on the Holter tape which might contain supraventricular arrhythmias, in support of the MILIS study (A-22), an analysis was undertaken to determine the best method of estimating the coupling interval of the next normal beat, given a sequence

of preceding normals. Previous research of others had indicated the utility of a linear function of the preceding beats. Selected periods with long sequences of normal beats were extracted from 16 tapes processed by Argus/2H. Attempts to estimate such relationships met with a number of obstacles, the most significant of which was the presence of sinus arrhythmia, the heart rate of the individual oscillating in synchrony with his respiration. The strength of this influence appears to vary considerably from patient to patient and no simple statistical model was found which could be incorporated into the Argus processing system easily.

Of continuing interest for studies which utilize multiple Holter recordings on the same patient is the reproducibility of the various indices of VEA extracted from the processed Cycle streams. One component is the reproducibility of Argus/H itself. As part of the regular processing of Argus/H some of the recordings are reintroduced into the processing queue in such a fashion that it blinds the editors and reviewers to the fact that it is a reprocessing operation. An initial analysis was performed on 50 tapes which were processed in this manner. Table I shows the variance between processings for several measures commonly extracted for analysis. In order to place the magnitude of this reprocessing variance into perspective, estimates of the inter-tape variances are shown, based on 1060 24-hour recordings from the sudden death study. The intraclass correlation coefficient represents, then, the correlation between processings for each measure. A more complete analysis, which takes into account the day-to-day biological variability as well as the accuracy with which Argus/H identifies the ECG features, is being completed, based upon a model originally developed for the evaluation of diagnostic concordance in psychiatric followup studies.[3]

(1) J. P. Miller, J. A. Ritter, K. W. Clark, L. J. Thomas, Jr., and G. C. Oliver, "Extended Analysis of Argus/H Quantified Ventricular Ectopic Activity," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 165-170, October 7-9, 1976.

(2) R. R. Ashman, "The Normal Duration of the Q-T Interval," American Heart Journal, vol. 23, pp. 522-534, 1942.

(3) C. R. Cloninger, J. P. Miller, R. Wette, R. L. Martin, and S. B. Guze, "The Evaluations of Diagnostic Concordance in Follow-up Studies: I. A General Model of Causal Analysis and a Methodological Critique," Psychiatric Research, in press.

Table I

MEASURE	INTERTAPE VARIANCE	REPROCESSING VARIANCE	INTRACLASS CORRELATION
Heart rate (/min)	131.350	.603	.998
Log_{10} PVC rate (/hr)	1.274	.038	.985
Average NV coupling interval (ms)	9606.348	733.838	.961
Earliest NV coupling interval (ms)	8685.870	785.191	.954
Length (min)	23059.150	1709.890	.963
Data loss	.0049	.0004	.961

A-7. The Natural History of Sudden Death

Personnel: G. C. Oliver, M.D., Medicine
F. D. Biggs, M.D., Jewish Hospital
L. L. Brandenburger, R.N., Jewish Hospital
K. W. Clark, BCL
V. R. deMello, M.D., Jewish Hospital
J. R. Humphrey, R.N., Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
T. F. Martin, BCL
J. P. Miller, BCL
P. Moore, BCL
M. A. Province, BCL
L. J. Thomas, Jr., BCL
E. Thornton, BCL

Support: RR 00396
HL 18808
Barnes Hospital
Jewish Hospital

We continued to recruit patients into the natural history study during the past year and have collected detailed information on 5467 patients who were admitted to the Coronary Care Units of Barnes or Jewish Hospitals. Exactly 1072 patients had definite myocardial infarctions and approximately 200 had probable myocardial infarctions. Precisely 441 patients were actively enrolled in the monitoring study at the end of March, 1978.

This year marks the beginning of a new phase in which emphasis shifts from patient enrollment and data collection to extensive data analysis. Because the substantive number of patients already enrolled seems adequate for answering the original questions posed at the start of the study, we ended enrollment of new patients in March, 1978. Those currently enrolled will continue to be followed until March, 1979.

Although final analysis of the data must await completion of patient follow-up, important information has been obtained from preliminary data analyses. We compared the in-hospital mortality of patients with transmural versus nontransmural myocardial infarction. Controversy exists over the prognosis of the latter, with some investigators finding they do as poorly as patients with transmural infarctions, but others disagreeing. We found that if correction is made for the fact that patients with nontransmural myocardial infarctions have smaller infarcts no substantial difference in mortality between the two groups is demonstrable.

We have investigated the relationship between clinical features observed during the acute phase of myocardial infarction and subsequent arrhythmias. Results show that the height of serum enzyme rise is an

important predictor of arrhythmias, such as couplets and ventricular tachycardia, for as long as twelve months after onset of myocardial infarction. The site of the myocardial infarction appears to be less important in determining which patients will have these high-grade ventricular arrhythmias.

Intensive efforts to complete patient follow-up have continued. The follow-up of all patients enrolled in an earlier monitoring study has been completed. In addition, a follow-up of an important group of patients who suffered a myocardial infarction but who were not enrolled in our monitoring study has been started. The majority of such patients have been located and their statuses are known. The next two years will be spent in completion of patient follow-up and an intensive analysis of the data which have been collected.

A-8. Development of the American Heart Association Database for Arrhythmia Detector Evaluation

Personnel: K. L. Ripley, BCL
J. E. Denigan, BCL
D. B. Geselowitz, Ph.D., Pennsylvania State University
R. E. Hermes, BCL
G. C. Oliver, M.D., Medicine

Support: RR 00396
HV 72989

This project, in operation since September 30, 1977, has as its primary goal the development of a database for the evaluation of automatic ventricular arrhythmia detectors (PR 13, A-11). A major activity during this initial portion of the activity has been the selection of key personnel to serve on two committees, the Committee of Expert Electrocardiographers and the Tape Selection Committee. Every effort has been expended to select individuals of outstanding reputation who are respected by their peers. The Tape Selection Committee chooses the tapes which will become part of the final database. The committee members are: Dr. Robert C. Arzbaecher, The University of Iowa; Dr. Nancy Flowers, University of Louisville; Dr. J. Thomas Bigger, Jr., Columbia University; and Dr. Suzanne Knoebel, Indiana University.

The Committee of Expert Electrocardiographers is charged with the task of reviewing, on a beat-by-beat basis, every QRS complex that will be involved in the final database and deciding whether or not the beat is of ventricular origin. The committee is charged also with grading the noise content of the signal and classifying the background rhythm in which ventricular arrhythmias may be embedded. The committee members are: Dr. Charles Fisch, Indiana University; Dr. Borys Surawicz, University

of Kentucky; and Dr. Richard Langendorf, University of Chicago. Members of this committee have received, annotated, and returned examples of the target arrhythmias.

Considerable activity has been directed also toward obtaining recordings from contributing institutions. These institutions will supply us with two-channel 24-hour ambulatory recordings from which portions will be selected for the final database. We are maintaining constant contact with interested institutions and are doing everything possible to encourage them to submit recordings as soon as possible. As of July, 1978, 126 tapes had been submitted from seven institutions as follows:

Contributor	Tapes Contributed
Dr. G. Charles Oliver, Washington University	81
Dr. Allen Zencka, Creighton University	24
Dr. Lawrence Hinkle, Cornell University	9
Dr. Philippe Coumel, Lariboisiere Hospital	2
Dr. Bernard Chaitman, Montreal	5
Dr. Nigel Roberts, University of California	4
Dr. Damgaard Andersen, Copenhagen	1
TOTAL	126

Of these, 69 have been reviewed by the Tape Selection Committee with the following results:

Arrhythmia Class	Tapes Selected	Tapes on Hold	Tapes Rejected	
No PVCs	6	1	8	
Isolated Uniform PVCs	6	-	4	
Isolated Multiform PVCs	3	-	4	
Bigeminy	5	1	3	
R-on-T	-	-	2	
Couplets	7	-	6	
Ventricular Tachycardia	3	1	9	
Ventricular Fibrillation	-	-	-	
Totals	30	3	36	69

Tapes for the R-on-T class have been difficult to obtain. The Tape Selection Committee seeks tapes which have a significant number of PVCs with onsets clearly within the previous T-wave. Tapes reviewed so far show very few such beats. Tapes for the class ventricular fibrillation are to be collected primarily from CCU recordings using the MECCA system (A-9) to be installed at Jewish Hospital.

In summary, all collaborators have been selected, equipment necessary for the operation of all phases of the work has been purchased and tested, and protocols and procedures have been developed and

exercised for most operations. A major protocol awaiting specification is that for reconciliation of electrocardiographers' beat-by-beat annotations. Discussion of this topic is scheduled for the next meeting of the AHA Committee on Electrocardiography.

A-9. MECCA

Personnel: K. L. Ripley, BCL
R. E. Hermes, BCL
R. D. Livengood, BCL

Support: RR 00396
HV 72989

Modification of the MECCA system (PR 12, A-19; PR 13, A-14) for its use for The American Heart Association Arrhythmia Database (A-8) has continued at a reduced pace throughout the last year. The need to develop software to process incoming recordings for that database has postponed the MECCA installation until this fall. Plans to improve the on-line and off-line displays have been completed, allowing the user to view any data saved by the system rather than just the data currently being acquired. Programs have been implemented to reformat and transfer Huffman encoded data from the MECCA system to the Argus/2H system in sample data form. A number of improvements also have been made in speed and storage requirements. Algorithms have been developed and partially implemented to synchronize the Huffman encoded data with real time and to incorporate delays in the "episode capture" routines. A third interrupt level has been added to the system to allow sample buffering. This enables the system to monitor eight ECG channels rather than the previous six channels.

The major tasks yet to be accomplished are:

1) Extend the current system from ten-bit samples to twelve-bit samples,
2) Convert the system from one ECG channel per patient to two ECG channels per patient,
3) Add a delay (5 to 15 minutes) after pressing the alarm button to capture more of the alarm episode,
4) Install MECCA at Jewish Hospital.

The last of these four tasks includes installation of signal connectors, alarm buttons, and associated cables from fifteen bedsides to the computer site, extension of the data acquisition system from 8 to 32 channels (with ability to select any 8), nurse training on the use of MECCA, and actual installation and verification of the MECCA computer system.

A-10. Feasibility Evaluation of the Esophageal-Lead ECG

Personnel: K. L. Ripley, BCL
R. C. Arzbaecher, Ph.D., University of Iowa
J. R. Cox, Jr., BCL
G. C. Oliver, M.D., Medicine
L. J. Thomas, Jr., BCL
F. D. Wolkow, Electrical Engineering

Support: RR 00396
HL 18808

Preliminary work has been done to evaluate the utility and patient acceptance of esophageal electrodes (PR 13, A-15) for long term ambulatory recordings. The staff of the Jewish Hospital Department of Medicine has agreed to collaborate in this study and has obtained human subjects' experimentation approval for recording both in- and out-patients. Dr. Arzbaecher, the developer of the esophageal "pill" electrode, has held a special training session at Jewish Hospital on the use of the electrode and has agreed to supply us with electrodes for the study.

Three preliminary recordings were made from patients at Jewish Hospital using the two-channel Avionics recorder, one channel being used for the esophageal electrode and one channel for a standard surface lead. These recordings presented problems due to low signal amplitude on the esophageal channel, but they were still interpretable by humans. Better application techniques may be required in order to obtain signals suitable for machine processing. Patient acceptance was good in all three cases.

A three-channel recorder (Oxford Medilog) has been leased for the purpose of simultaneously recording two surface leads in addition to the esophageal signal. These data will be presented to several cardiologists, two leads at a time, in order to assess the relative merits of the esophageal-surface combination compared to conventional two-surface-lead recordings.

A-11. Mathematical Models for Estimation of Myocardial Infarct Size

Personnel: J. Markham, BCL
G. L. Clark, M.D., Medicine
R. Roberts, M.D., Medicine
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646

In this project we have examined factors which influence plasma CK activity levels after myocardial infarction with the aim of more accurately defining the relation of CK released into the blood to infarct size. In previous studies we have shown that plasma CK time-activity curves obtained after bolus injections of purified CK conform more closely to a double-exponential than to a single-exponential curve, thus suggesting that CK distributes in extra- as well as intra-vascular pools (PR 13, A-16).[1] Other studies have shown the importance of lymph as a pathway for transport of CK from tissue to blood following myocardial infarction (A-12). In addition, we have found that native, circulating CK disappears more slowly than CK purified or extracted by muscle press from myocardial tissue, thus accounting, at least in part, for the observed slower disappearance of plasma CK after myocardial infarction as compared to the disappearance after bolus injections of CK. Continuing release of the enzyme from the heart long after the post-infarction plasma-CK peak appears to account for some of the observed differences in disappearance rates.

Characterization of the distribution of CK and its removal from plasma enables us to compute the release function of CK into blood following myocardial infarction in animal experiments. Preliminary experiments using CK infusion to simulate CK release following infarction in an animal have not been successful because of the rapid degradation of the enzyme.[2-13]

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[2] B. E. Sobel, J. K. Kjekshus, and R. Roberts, "The Quantification of Infarct Size," in Enzymes in Cardiology: Diagnosis and Research, D. J. Hearse and J. De Leiris, eds., John Wiley and Sons Limited, Chichester, in press.

[3] R. Roberts and B. E. Sobel, "The Inactivation and Clearance of Enzymes," in Enzymes in Cardiology: Diagnosis and Research, D. J. Hearse and J. De Leiris, eds., John Wiley and Sons Limited, Chichester, in press.

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(7) B. E. Sobel, "Evaluation of Jeopardized Ischemic Myocardium and Infarction in Man," in Proceedings of the Conference on Acute and Long-Term Medical Management of Myocardial Ischaemia, Copenhagen, September 1977, in press.

(8) G. L. Clark, R. Roberts, and B. E. Sobel, "The Influence of Creatine Kinase (CK) Transport in Lymph on Plasma CK Curves After Myocardial Infarction," Clinical Research, vol. 25, p. 213A, 1977 (abstract).

(9) R. Roberts, A. A. Painter, and B. E. Sobel, "The Relation Between Clearance of Creatine Kinase Enzyme Activity and Turnover of Enzyme Protein Assessed by Radioimmunoassay," Clinical Research, vol. 25, p. 249A, 1977 (abstract).

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(11) B. E. Sobel, "Biochemical Estimation of Infarction," presented at the International Symposium of the European Society of Cardiology, Vienna, June 1977 (abstract).

(12) A. A. Painter, B. E. Sobel, and R. Roberts, "The Dependence of Clearance of Creatine Kinase on Removal of Protein," Circulation, supplement III, vol. 56, pp. III-86, 1977 (abstract).

(13) R. Roberts and B. E. Sobel, "Clearance of Creatine Kinase Activity Versus Turnover of Enzyme Protein Assessed by Radioimmunoassay," Annals of the Royal College of Physicians and Surgeons of Canada, vol. 11, p. 29, 1978 (abstract).

A-12. Radioactive Tracer (I-125) Evaluation of Lymph Flow

Personnel: G. L. Clark, M.D., Medicine
D. C. Ficke, BCL
J. Markham, BCL
B. A. Siegel, M.D., Radiology
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 07081
HL 17646

In completed studies we have developed methods to provide enzymatic estimates of the effect of myocardial infarction in vivo based on plasma CK (creatine kinase) time activity curves.[1,2] Work in this project is concerned with the role of cardiac lymph as a component of the distribution volume of CK released from the regions of infarction. We have shown that complete obstruction of cardiac lymph flow in the canine preparation alters plasma CK time-activity curves markedly and, therefore, affects enzymatic estimates of infarct size.[3] Accordingly, modifications of estimates based on incorporation of factors taking into account lymph flow assessed quantitatively should provide useful refinements in estimates of infarct size based on the CK plasma time-activity curve method developed in our laboratory.

We have established that interstitial fluid in the left ventricular anterior wall drains almost exclusively to the cardiac lymph node which lies between the superior vena cava and innominate artery in the dog.[4] Cardiac lymph flow was measured by cannulation of the afferent lymphatics to the node and found to be 1 to 3 ml/hr.[5] The ultimate goal of this project is to measure cardiac lymph flow non-invasively without cannulation of the lymph vessels in intact canine preparations and possibly in patients.

The indirect method for estimation of lymph flow which we are applying to the cardiac node site is one developed by J.J.P. de Lima,[6] who measured lymph flow across the popliteal lymph node in the hind limb of dogs with the use of "step pulse injection" theory, briefly described as follows: Two detectors are used to record the activity at an inlet labyrinth and the total activity in the lymph node following a step-pulse injection of radioactivity at the entrance of the labyrinth. Detector 1 is positioned over the inflow to the cardiac node in the open chest animal and records the radioactivity curve

$$A_1(t) = K_1 H_1(t) \qquad (1)$$

where K_1 is a proportionality constant which depends on the efficiency of the detector and the amount of radioactivity injected and $H_1(t)$ is the step-pulse response function of the inlet labyrinth. Detector 2 is positioned directly over the cardiac lymph node and records $A_2(t)$. If

$h_2(t)$ is the unit impulse response function for the node and K_2 the proportionality constant for detector 2, then

$$A_2(t) = K_2 \int_o^t [H_1(t) - H_1(t) * h_2(t)]dt, \qquad (2)$$

where * denotes convolution, i.e., the mass of tracer in the lymph node at any time is the difference between the total mass of tracer which has entered and the mass which has left up to that time.

Because $H_1(t) * h_2(t) = H(t)$ is the response of the series system formed by the afferent lymphatics and the lymph node to a unit step pulse, equation (2) can be rewritten as

$$K_2 \int_o^t H(t)dt = K_2 \int_o^t H_1(t)dt - A_2(t). \qquad (3)$$

The curve

$$A_3(t) = K_2 \int_o^t H_1(t)dt \qquad (4)$$

can be obtained from integration of $A_1(t)$ and the scale factor K_2/K_1 which can be computed by making use of the fact that there is a finite delay between the input and output of the node. After an initial delay the two curves, $A_3(t)$ and $A_3(t) - A_2(t)$, form two parallel lines so that the time delay between the two lines is the mean transit time ($\bar{t}_2$) through the cardiac lymph node.[6]

Assuming that flow through the node is constant, the total flow (F) can be calculated by the equation derived by Meier and Zierler,[7]

$$F = V/\bar{t}_2, \qquad (5)$$

if the volume (V) of the labyrinth of the node can be determined.

We applied this method to detection of lymph flow through the cardiac node of the dog as follows:

1. A left lateral thoracotomy between the 2nd and 3rd ribs was performed with the dogs under halothane anesthesia with assisted ventilation. The lungs were retracted to expose the superior vena cava and innominate artery just above the aorta. The cardiac node was located by the use of cardio-green dye injected at the apex of the left ventricle through a separate incision.

2. Two focused collimators were positioned in the chest cavity, one at the inflow to the cardiac node and one over the cardiac node. The scintillation probe detectors then were placed in these focused collimators to detect radioactivity after injection of 0.2 cc (40 μ Ci) ^{125}IHSA into the left ventricular apex. The dual-channel scintillation counter was connected online to an Interdata computer.

To obtain total node volume V_t we removed the cardiac node from each animal, after tying off the afferent and efferent lymphatic channels, and measured its length and width (for area calculations) and applied an elipsoid of revolution equation to these parameters. The labyrinth volume was obtained by aspirating the node and centrifuging to obtain the fractional volume of the supernatent.

Preliminary results of indirect estimation of lymph flow (1.56 ml/hr, average) agree well with lymph flow measured directly (1 to 3 ml/hr) after cannulation of the afferent to the cardiac node.

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A-13. Modification of Infarct Size

Personnel: R. Roberts, M.D., Medicine
H. D. Ambos, BCL
M. K. Campbell, R.N., Medicine
G. L. Clark, M.D., Medicine
P. E. Gallerstein, M.D., Medicine
E. M. Geltman, M.D., Medicine
J. Markham, BCL
S. Mogelson, M.D., Medicine
S. M. Nordlicht, M.D., Medicine
E. R. Passamani, M.D., Medicine
B. E. Sobel, M.D., Medicine
A. J. Tiefenbrunn, M.D., Medicine

Support: RR 00396
HL 17646

Studies were performed in the Cardiac Care Unit at Barnes Hospital to assess the effect of selected pharmacological agents on infarct size, ventricular dysrhythmia, and hemodynamics in patients with myocardial infarction. Infarct size was estimated from serial plasma creatine kinase (CK) changes during a 72 hour interval. Infarct size was predicted from CK values projected by least squares approximation to the log-normal curve best fitting data obtained hourly for 7 hours after the initial plasma CK elevation. The difference between infarct size predicted and infarct size observed was compared to that observed in control matched by predicted infarct size. All Holter tapes were digitized and processed by the Argus/H computer system (A-4). Hemodynamics, including cardiac output, were determined by Swan-Ganz thermodilution technique and the effect of the drug assessed by comparing hemodynamics before and after administration.

Studies initiated in 1975, to evaluate the effects of acebutolol in patients with myocardial infarction, were completed in 50 patients with acute myocardial infarction. Acebutolol is a cardio-selective beta blocker which has marked chronotropic effects with minimal inotropic effects. Acebutolol (10-50 mg every four hours) was administered intravenously to 25 patients for 24 hours and results were compared to 25 concomitant controls who did not receive acebutolol. Acebutolol did not significantly change the wedge pressure, peripheral resistance, or systemic pressure. Cardiac output decreased from 5.1 L/minute $\pm$ .2 (mean $\pm$ S.E.M.) to 4.4 $\pm$ .2($p<0.05$), heart rate decreased from 82 $\pm$ 2 beats/minute to 71 $\pm$ 3 ($p<0.05$), and hourly PVC rate decreased by 60% compared to controls ($p<0.05$). These favorable effects occurred without changing overall infarct size (88 $\pm$ 13 CK-g-eq) compared to controls (71 $\pm$ 13). Thus, acebutolol decreased heart rate and ventricular dysrhythmia without elevating wedge pressure or increasing enzymatically estimated infarct size in patients with evolving myocardial infarction.

Results of a study completed in 1976, assessing the effect of dobutamine in patients with acute myocardial infarction, showed dobutamine to be a potent inotropic agent with minimal chronotropic effect. Dobutamine significantly increased cardiac output and decreased the wedge pressure without deleterious effect on infarct size or ventricular arrhythmias. However, in order to obtain adequate data for prediction of infarct size, dobutamine was not administered until 12 hours after the onset of chest pain. Another study is now in progress to assess the effect of dobutamine in patients with myocardial infarction when administered immediately upon admission to the Coronary Care Unit. Results of dobutamine on infarct size and ventricular arrhythmias will be compared to those observed in concomitant controls. Forty patients with acute myocardial infarction have been entered into the study and results so far are similar to those obtained in the previous study showing beneficial effects on hemodynamics without deleterious effects on heart rate, ventricular arrhythmias, or infarct size.

A randomized trial is now in progress to assess the effect of intravenous nitroglycerin on infarct size and ventricular arrhythmias in patients with acute myocardial infarction. The intravenous infusion of nitroglycerin is titrated so that the systolic blood pressure does not fall below 100 mm Hg and the heart rate does not increase by more than 10 beats per minute. The drug is initiated immediately after the patient is admitted to the Coronary Care Unit and results on infarct size and ventricular arrhythmias will be compared to those of the concomitant randomized controls. So far 46 patients with acute myocardial infarction have been entered into the study. Patients have tolerated the drug well without any significant side effects and in patients, particularly those with cardiac failure or pulmonary edema, marked improvement in hemodynamics has been observed without any significant increase in heart rate. It is too early to determine the effect on infarct size and arrhythmias, but the overall trend suggests a beneficial effect on infarct size.

Studies initiated in 1977, to assess the effect of aprindine in patients with acute myocardial infarction, have been completed. Aprindine was administered to 25 patients with acute myocardial infarction and results compared to 25 concomitant controls. Aprindine is an anti-arrhythmic agent with quinidine-like properties but with a half-life of 12-16 hours. Aprindine 2-5 mg/minute (200 mg initially and 100 mg 1 and 12 hours later) was given I.V. to 25 patients with acute myocardial infarction. Overall infarct size was similar in treated and controls (51 ± 10 CK-g-eq and 60 ± 11), as were heart rates and blood pressure. Cardiac output (4.7 ± 0.8 and 4.8 ± 0.5 L/minute) and wedge pressure (10 ± 3 mm Hg and 10.8 ± 2) were not affected by aprindine. In treated patients during control intervals (3-4 hours after onset of infarction) PVC rate was 2.8 per minute, but decreased 85% to 0.4 per minute after 300 mg of aprindine ($p<0.02$). During a subsequent 16 hour period the effect was sustained. In contrast, PVCs decreased only 58% during corresponding intervals in controls ($p>0.1$). Thus, aprindine effectively supressed PVCs for prolonged periods (12 hours) in patients with infarction without compromising cardiac function.

To determine the relationship between prognosis, infarct size, and ventricular arrhythmias we prospectively studied 314 patients. Sixty-nine patients suffered non-transmural myocardial infarctions (NTMI) and 245 had transmural infarctions (TMI). Infarct size index (ISI) in patients with transmural infarction was 25.1 $\pm$ 2 CK-g-eq per m^2 compared to 11.7 $\pm$ 1 ($p<0.001$) in non-transmural infarction with a mortality (1 month) of 17% vs 4% ($p<0.02$). Average PVCs per 10 hours were similar (51 $\pm$ 1 vs 40 $\pm$ 2, $p>0.5$). The actuarial survival rates (%) for patients with initial non-transmural myocardial infarction was 94 vs 77 for transmural infarction at one year ($p<0.001$) and 78 vs 62 at 3 years ($p<0.001$). However, if patients with previous infarction are included, survival rates for NTMI and TMI were similar at 1, 2, and 3 years. ISI associated with NTMI is smaller than with TMI. Acute and long-term prognosis in patients with initial NTMI is much better than with initial TMI, but similar if previous infarctions occurred. Thus, overall infarct size is a predominant determinant of mortality whether infarction is subendocardial or transmural.

To determine the effect of site of infarction on infarct size and mortality we prospectively studied 258 patients with acute transmural infarction with the site of infarction determined electrocardiographically (anterior in 116 and inferior in 142 patients). Mean age (62 and 61 years), heart rate (71 and 73 beats per minute), and systemic blood pressure (138/82 and 137/79 mm Hg) 8 hours after the onset of pain were similar in patients with anterior and inferior infarction. Infarct size index was 24.8 $\pm$ 1 CK-g-eq per m^2 for patients with anterior vs 23.4 $\pm$ 2.2 for those with inferior infarction. Thus, despite the conventional view that the increased mortality associated with anterior compared to inferior infarction reflects myocardial damage, infarct size was similar in patients with anterior or inferior infarction. The higher mortality associated with anterior infarction may, in part, be related to all the damage occurring in the left ventricle as opposed to its distribution in both ventricles with inferior infarction.

A-14. Ischemic Heart Disease SCOR Computer System

Personnel: J. Markham, BCL
H. D. Ambos, BCL
D. C. Ficke, BCL
T. L. Weadon, BCL

Support: RR 00396
HL 17646

A second 10 Mbyte disk drive was added to the SCOR Interdata computer system to provide fast-access storage for tomographic data generated by the PETT IV (PR 13, B-5) which was recently moved to the Cardiac Care Unit. Software developed by the Radiation Sciences Division (PR 13, B-4) for the collection, analysis, and display of tomographic data has been

implemented on the SCOR computer. Extensive calibration procedures have been performed on the PETT IV to ensure that the photomultiplier tubes and the 48 detectors are properly balanced.

Initial studies of patients with acute myocardial infarction indicate that synchronization of data collection with the patient's heart cycle will be necessary to prevent excessive blurring of the reconstructed images due to heart motion. While such blurring is minimal in normal subjects and patients with older myocardial infarctions, the disruption of cardiac rhythm associated with acute myocardial infarction can result in distorted cardiac images.

A-15. Electrophysiological and Biochemical Factors Underlying the Genesis of Dysrhythmias Due to Myocardial Infarction

Personnel: P. B. Corr, Ph.D., Medicine and Pharmacology
M. E. Cain, M.D., Medicine
P. A. Penkoske, M.D., Medicine
S. R. Phillips, BCL
B. E. Sobel, M.D., Medicine
F. X. Witkowski, M.D., Medicine

Support: RR 00396
HL 17646
HL 21654
Missouri Heart Grant-In-Aid

During the past year several techniques have been developed and utilized to record subepicardial intracellular action potentials in vivo simultaneously with the previously reported (PR 13, A-20) epicardial, mid-myocardial, and endocardial extracellular bipolar electrograms in a feline preparation exhibiting reproducible ventricular dysrhythmia early after coronary occlusion as well as after coronary reperfusion.(1) An automated analysis system uses a PDP-12 computer to permit pulse-by-pulse determination of the minimum and maximum amplitudes, rise time, pulse width, and dV/dt prior to and at selected intervals after coronary occlusion and subsequent reperfusion.(2) Initial results utilizing intracellular recordings indicate that just prior to the onset of the ventricular dysrhythmia induced by ischemia, profound changes in ischemic-zone action potentials occur, including: 1) decrease in maximum rate of rise of voltage of phase 0, 2) decrease in the resting membrane potential, 3) decrease in overall amplitude, as well as the positive overshoot of phase 0, and 4) shortening in action potential duration.

As reported last year we have demonstrated that distinct electrophysiological differences underlie the two types of severe ventricular dysrhythmias associated with coronary occlusion and reperfusion in experimental animals. Concurrent with these studies the influence of the sympathetic nervous system(3) on the electrophysiological derangements resulting from ischemia was assessed by simultaneous measurement of regional cyclic AMP content of ischemic and normal myocardium, used as one index of regional adrenergic activity.(1,2) In contrast to the increased concentrations of cyclic AMP seen during coronary occlusion, coronary reperfusion(4) results in an immediate (30 sec) decline in the cyclic AMP content, reaching a nadir within 2.0 minutes in both ischemic and normal myocardium. Furthermore, animals developing ventricular fibrillation associated with reperfusion failed to show an increase in cyclic AMP content in either normal or ischemic zones. Since cyclic AMP content is not decreased 50 minutes after coronary occlusion without reperfusion, it is likely that the decrease in myocardial cyclic AMP after reperfusion does not result from loss of integrity of the adenylate cyclase system. Although enhanced washout of cyclic AMP could be responsible, this seems unlikely since the cyclic nucleotide penetrates cell membranes so slowly that

rapid washout within 30 seconds after reperfusion does not seem to be probable. Thus, the influence of the adrenergic nervous system on these two types of dysrhythmias may vary appreciably.

Since results of the initial studies demonstrating a decrease in cyclic AMP content immediately after coronary reperfusion, associated with the development of ventricular dysrhythmias, might have been caused by α-adrenergic stimulation, studies were performed in animals pretreated with phentolamine to induce α-receptor blockade. Alpha-receptor, but not β-receptor blockade (propranolol), eliminated the dysrhythmia induced by coronary reperfusion (361 $\pm$ 62) to 14 $\pm$ 10 PVCs, $p<.001$, entirely prevented the development of ventricular fibrillation (25% to 0%, $p<.01$), and prevented the increase in idioventricular rate normally seen with coronary reperfusion, suggesting that α-blockade afforded protection by decreasing the enhanced ventricular automaticity seen after reperfusion. Furthermore, the protective influence of α-receptor blockade was not due to more favorable redistribution of coronary blood flow as determined by the use of radioactive (^{141}Ce, ^{85}Sr and ^{95}Nb) microsphere injections. α-adrenergic receptor stimulation appears to produce deleterious electrophysiological alterations during coronary reperfusion and ultimately may be important in therapeutic management of sudden death in man.

Recently we have detected accumulation of lysophosphoglycerides, catabolites of phospholipids, in ischemic myocardium early after coronary occlusion, as well as in effluents from isolated perfused hearts under hypoxic conditions. Comparable concentrations (.75 to 3.0 mM) of lysophosphoglycerides bound to albumin markedly and reversibly altered action potentials of isolated canine Purkinje fibers *in vitro*.[5,6,7] An automated system for analysis of intracellular action potentials was developed to allow precise quantification of the changes induced by lysophosphoglycerides which included: 1) decreases in the resting membrane potential, overshoot of phase 0, V_{max} of phase 0 and action potential duration, 2) fractionation of the action potential into several components, unresponsiveness to external stimulation, and enhanced automaticity at normal and reduced membrane potentials at the higher concentrations (2.0 and 3.0 mM), 3) a rightward and downward shift in the membrane response curve (V_{max} vs resting membrane potential), 4) 40 fold prolongation of conduction time, and 5) an increase in the ratio of effective refractory period to action potential duration so that the effective refractory period persisted beyond action potential duration, resulting in post repolarization refractoriness. These electrophysiological alterations were entirely reversible after 70 minutes of perfusion without LPC with the exception of persistent depression in the V_{max} of phase 0. Lysophosphatidyl ethanolamine (LPE) elicited alterations in action potentials identical to those elicited by LPC. Since lysophosphoglycerides accumulate early after myocardial ischemia and since concentrations equivalent to those occurring *in vivo* induce electrophysiological alterations resembling those seen in ischemic myocardium *in vivo*, lysophosphoglycerides may be of major importance as biochemical mediators of malignant dysrhythmia induced by ischemia.[5,6,7] Clarification of factors affecting lysophosphoglyceride accumulation in ischemic tissue may be useful in developing new and effective approaches for the control of early malignant ventricular dysrhythmias associated with myocardial ischemia.

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A-16. Ultrasonic Cardiac Imaging

Personnel: J. W. Mimbs, M.D., Medicine
D. A. Arnovitz, BCL
M. K. Campbell, R.N., Medicine
P. B. Kurnik, M.D., Medicine
P. A. Ludbrook, M.D., Medicine
J. Markham, BCL

Support: RR 00396
HL 17646

Characterization of myocardial function by noninvasive ultrasonic techniques has become an important experimental and clinical activity. The purpose of this project is the utilization of a system designed by Digisonics, initially for identification of abnormalities of cardiac wall motion and ventricular dimension, and subsequently for characterization of myocardial physiologic properties by quantitative ultrasonic indices. During the past year activities have been devoted to establishing the capabilities of the system. Characterization of the Digisonics hardware demonstrated: 1) calibration of the recording equipment revealed <0.5% error for arm potentiometer voltages, and 2) definition of phantom targets revealed 3% error in determination of distances on a range of 10 to 120 mm utilizing both a 12 cm and 20 cm scale. Approximately twenty patients were studied, utilizing this two-dimensional sector-scanning imaging system, over the past six months for the purpose of investigating potential modifications in the data processing and reconstruction of images. As presently performed, 24 images are reconstructed from equally divided intervals of a single archetypal heartbeat. The data input to generate the 24 images represents approximately 8000 ultrasonic scans (or beam paths) obtained over a 5 to 10 minute interval. Data from these studies were processed by computer using two different reconstruction algorithms. Results of these studies revealed the need to expand cell size from the current 100 × 256 array in approximately 14 × 14 cm, and the need to optimize computer processing, including specifically omission of the lowcut filter and data rectification steps and the omission of the interpolated data column. In addition to these activities, initial trials of a novel design for transducer configuration employing a receiver based on the acousto-electric effect have been performed.

A-17. Real-Time Digital Echocardiography

Personnel: R. M. Arthur, BCL
A. L. Gutovitz, M.D., Medicine
C. P. Zobkiw, B.S., Electrical Engineering

Support: RR 00396
HL 18144

Instrumentation for the acquisition and digital processing of ultrasonic echoes (PR 13, A-22) has been improved and algorithms for automatic depth compensation have been devised and tested. The digital echocardiograph combines burst-analog sampling circuitry using serial analog memory with a dual Motorola 6800 microprocessor network.(1) Analog samples are acquired at a high rate during the 300 μs echo from an ultrasonic pulse and are accessed slowly for analog-to-digital conversion in the 5 ms period before the next ultrasonic pulse.

Improvements include keyboard entry of control functions, addition of the gain function and depth vs time markers to A-mode and M-mode displays respectively, and a high-speed link to a TI-9800 for real-time storage of echo signals. Several data-reduction schemes and a moving-target-indicator algorithm have been studied on the TI-980B. An alternative to serial analog memory for sampling has been implemented and evaluated. We operated a charge coupled device at sample rates to 20 MHz.

A major effort has been directed at defining and automatically controlling the depth compensation function, i.e., the gain applied to the echo signal versus time. The gain function is designed to compensate for loss of signal strength due to attenuation and refraction. Our echocardiograph allows manual setting of the gain function in a manner similar to that in conventional instrumentation except that the gain function is stored and generated by one of the microprocessors. In addition, an analog AGC circuit can control gain. Finally, one of the microprocessors can automatically establish the gain function. These methods are being compared to assess their relative merits in compressing the dynamic range of the echo signal into 8-bit samples.

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A-18. Interactive Digital Acquisition of Electrocardiograms

Personnel: R. M. Arthur, BCL
E. B. Hagelstein, B.S., Electrical Engineering
A. Hernandez, M.D., Pediatrics

Support: RR 00396
HL 18144
Washington University

A microprocessor-based (Intel 8080) ECG cart previously designed and implemented to test signal quality of three simultaneous leads (PR 13, A-23) was used to study 708 pediatric vectorcardiograms stored on FM analog tape. The two-part study included an evaluation of test algorithms and an assessment of pediatric ECG signal quality. Signal out-of-range, transient content, presence of a QRS complex, baseline shift, and noise content were checked. Tests were intended to screen multiple-lead ECGs for signal quality and not necessarily to fix precisely any particular waveform parameter.

Determination of baseline shift and noise content utilizes histogram techniques which are faster than traditional feature-extraction methods and, therefore, more suitable for real-time operation. The baseline was set by the peak of the 8-bit sample-value histogram, i.e., the most common value in the R-R interval. Each 6-second pediatric record was plotted with the baseline superimposed on each beat for inspection. Baseline placement was not within about 0.1 mv of the TP or PR segments for 0.2% of the beats. Noise content was determined from the first-difference histograms. For 10-bit samples the noise measure was the sum of the number of first differences equal to -1, 0, and 1 divided by the number of samples in the R-R interval. This quantity varied between 0 (large rapid changes) and 1 (constant input). The noise measure was generalized and calculated as a function of gain and sample precision for frequencies from 10 to 200 Hz. It was calibrated with this ECG cart using known sinusoidal inputs. Noise content of each ECG beat was quantified by computing the RMS value in the S to P segment after alternating frequencies to 40 Hz with a 23-point filter designed using the Remez exchange algorithm. With a high frequency content above 30 μv considered noisy, a noise measure of 0.5 gave an 80% correct detection rate with a false positive rate of 2%. Determination of both baseline shift and noise content took about 260 μs per sample in the 8080 implementation. The speed of the tests made it possible to calculate baseline shift and noise content for at least three leads in real time at sample rates to 500 per second.

Quality of the records was studied by generating distributions of baseline shift and RMS noise content as functions of age both by beat and by record. Baseline shift of more than 0.5 mv was found between 6% of the beats and in 37% of the records. Noise content of more than 30 μv vms was found in 1% of the beats and 6% of the records. When out-of-range and transients were included and the above criteria used for baseline shift and noise content, 49% of the 708 records had technical difficulties during acquisition.

The implementation for the FM tape study contained a CRT for interactive alphanumeric and graphic displays. The cart had, however, no high-gain ECG amplifiers and no mass storage. ECGs were stored and processed on a TI-980B connected to the cart via a serial link. Eight channels of amplification have been designed and will be added to permit simultaneous acquisition of the standard 12-lead set. Sample precision has been increased from 10 to 12 bits. Messages are shown on a 16-character self-scan display. A three-channel strip-chart recorder will provide graphic outputs. A floppy-disk controller and drive are being added for mass storage. Integrated circuit count was reduced by substituting the latest 8080-family chips for much of the existing circuitry.

A-19. A Database for Analysis of Patient Diagnostic Data

Personnel: H. D. Ambos, BCL
P. Moore, BCL
R. Roberts, M.D., Medicine
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646

To assess data on selective diagnostic techniques in relation to patient turnover in a large volume of patients a MUMPS database was established (PR 13, D-7) in the Barnes Hospital CCU. Patient data were entered on 1,733 patients presented within 24 hours of chest pain with a diagnosis of suspected myocardial infarction (MI) by electrocardiogram and history. The primary goal was to determine the specificity and sensitivity of ^{99m}TC pyrophosphate scintigrams and ECGs compared to plasma CK isoenzymes for MB CK analysis in the diagnosis of MI. The diagnosis of infarction was established on the basis of elevated plasma MB CK.

Results of data analysis showed that 1,059 patients did not sustain infarction, the other 674 patients exhibited infarction as determined by elevated plasma MB CK activity. Of the 674 MI patients 84% exhibited a positive scintigram as opposed to only 5% of the 1,059 non MI patients. However, a minimum of 24 hours after onset of symptoms is required for reliable interpretation of pyrophosphate scintigrams opposed to only 6 hours for reliable MB CK interpretation.

Serial ECGs (from admission to 72 hours) gave a diagnosis of MI in 66% (1144) of the patients. Nonspecific ST changes were present in 90% of the patients with a documented MI, but similar changes were noted in 61% of the patients without a proven MI. The average length of stay in the CCU for patients with an MI was 6.3 days, as opposed to 3.4 days for patients without an MI. Thus, plasma MB CK determinations provide

a rapid diagnosis and rapid turnover with more proper utilization of expensive Intensive Care facilities. Pyrophysphate scintigrams, as a qualitative diagnostic procedure, are most helpful in patients who present more than 24 hours after the onset of symptoms, a time when plasma MB CK is returning to normal.

A-20. Measurement of Myocardial Metabolism

Personnel: B. E. Sobel, M.D., Medicine
H. D. Ambos, BCL
S. R. Bergmann, Ph.D., Medicine
J. O. Eichling, Ph.D., Radiology
M. S. Klein, M.D., Medicine
K. B. Larson, BCL
M. E. Raichle, M.D., Radiology and Neurology
T. J. Tewson, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

Support: HL 07081
HL 13851
HL 17646

This project is designed to provide the information needed for external assessment of regional cardiac metabolism to improve detection and assessment of heart disease and its response to therapy. During the past year we have utilized ^{11}C-palmitate in ischemic myocardium in isolated perfused hearts,[1] and subsequently extended the observations to intact dogs and patients by quantifying the distribution of myocardial infarction in man with ^{11}C-labeled palmitate detected by positron emission transaxial tomography.[2-8] Since we have shown in the isolated perfused rabbit heart system that ^{14}C-labeled palmitate is distributed primarily into an intracellular neutral lipid pool during normal aerobic metabolism with proportionately less radioactivity incorporated into a stable phospholipid fraction, we postulated that the slowly metabolizing neutral lipid fraction resulting in release of CO_2 from the field of detection might permit quantification of metabolism based on the rate of clearance of ^{11}C-fatty acids determined from time-activity curves. Accordingly, isovolumically beating isolated rabbit hearts were perfused with Krebs-Henseleit solution and a bolus of ^{11}C-palmitate injected into the perfusate. Determinants of cardiac work were selectively altered during an eight-minute interval after extracellular tracer had been washed out, and positron emission from the heart was measured with the use of two sodium iodide crystals. Elevation of left ventricular diastolic pressure from 1 to 20 mm Hg produced a 1.5 to 3-fold increase in the rate of disappearance of counts from the heart compared to disappearance under control conditions in the same hearts. With pressure held constant acceleration of heart rate from 90 to 220 beats/minute increased clearance rates by 2-fold. Cardioplegia induced by potassium chloride resulted in a virtual ceasing in clearance

of isotope despite constant flow conditions. Paired ventricular pacing, utilized to substantially augment myocardial metabolism, increased the rate of clearance of tracer by 3 to 5-fold. External detection of these marked changes in metabolism suggest that positron emission transaxial tomography will permit assessment of regional metabolism in vivo.

Since conventional perfusates, such as Krebs-Henseleit solution containing palmitate and albumin, do not contain hemoglobin and, therefore, have limited oxygen-carrying capacity, flow rates required are significantly greater than those prevailing under physiological conditions in vivo. Accordingly, for evaluation of perfusion externally development of a different system was required. To facilitate characterization of myocardial metabolism and perfusion by residue detection of tracers we developed a sanguinous, perfused isolated heart preparation with flow and substrate extraction maintained within the physiological range. Isovolumically beating rabbit hearts, paced at 180 beats/minute, were perfused retrograde at 60 mm Hg at 37° with non-recirculating Krebs-Henseleit buffer (KH) containing .4 mM albumin and .6 mM fatty acid with or without washed sheep red blood cells (Hct = 25 or 40: KH-RBC_{25}, KH-RBC_{40}) with the perfusate filtered through a 13 μm Swank filter to obviate microaggregation. LV systolic pressure averaged 63 $\pm$ 4 (mean $\pm$ S.E.M.) mm Hg with KH (n = 7), 78 $\pm$ 5 with KH-RBC_{25} (n = 28), and 97 $\pm$ 6 with KH-RBC_{40} (n = 8). Corresponding values of peak dP/dt and LV pressure time index averaged 663, 851, and 1,232 mm Hg/sec, and 1,705, 2,149, and 2,949 mm Hg/sec ($p<.05$ for all differences). MVO_2 and fatty acid uptake increased linearly with increased left ventricular pressure ($r = .88, .76$, $p<.05$). Although a coronary flow of 4.6 ml/g/min was required with KH, only 1.5 ml/g/min was required in hearts perfused with RBC-enhanced media. All hearts were stable for at least two hours. Isolated hearts perfused with erythrocyte-enhanced media provided a more useful preparation for the study of cardiac function and metabolism than hearts perfused with buffer alone. Time-activity curves resulting from injection of ^{11}C-palmitate into the perfusate of this preparation closely resembled curves obtained in vivo. The rate of ^{11}C-palmitate oxidation, calculated from time-activity curves, correlated with $^{14}CO_2$ production from prelabeled neutral lipids in isolated heart preparations.

To determine whether myocardial metabolism could be evaluated in vivo as well as in vitro, rabbits were given intra-atrial ^{11}C-palmitate injections and cardiac time-activity curves monitored with two sodium iodide crystals with colinear fields of view encompassing the heart. In the same animal, under constant physiological conditions, the rate of decline of cardiac ^{11}C-palmitate counts remained constant (.099 $\pm$ .002 (SE) log counts/minute). In contrast, monoexponential clearance reflecting oxidation varied directly with tension time index (range = 1,000 to 2,850 mm Hg second, $r = .96$) and peak dP/dt (1,000 to 5,550 mm Hg/second, $r = .84$) among different animals. Furthermore, the decline of counts from blood was rapid compared to the rate of decline in the heart. Hence, persistent circulating tracer did not distort results. These data indicate that external detection of cardiac ^{11}C-palmitate metabolism reflects myocardial oxygen requirements in vivo, and may permit assessment of regional

metabolism in man with disappearance of tracer monitored by positron emission transaxial tomography.

The close correlation between tension time index and peak dP/dt with the monoexponential portion of time-activity curves in vivo was obtained initially with injection of tracer into the left atrium of anesthetized open-chest rabbits. Preliminary data with right atrial injections in the same system suggest that analogous relationships hold. Therefore, it is likely that administration of isotope via a Swan-Ganz catheter placed in the right atrium in patients will permit quantification of cardiac metabolism on a regional basis with detection achieved with positron emission transaxial tomography.

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A-21. Multicenter Investigation of Limitation of Infarct Size (MILIS)

Personnel:
B. E. Sobel, M.D., Medicine
H. D. Ambos, BCL
D. R. Biello, M.D., Radiology
K. W. Clark, BCL
E. M. Geltman, M.D., Medicine
R. E. Hitchens, BCL
A. S. Jaffe, M.D., Medicine
M. S. Klein, M.D., Medicine
C. N. Mead, BCL
J. P. Miller, BCL
R. Roberts, M.D., Medicine
B. A. Siegel, M.D., Radiology
L. J. Thomas, Jr., BCL
L. L. Wilson, B.A., Medicine

Support:
RR 00396
HV 72941
Washington University

During the past 18 months Washington University, in collaboration with four other centers participating in the collaborative clinical trial of therapy to protect ischemic myocardium, has developed protocols, operations manuals, and procedures required for implementation of phase II of the project as of August 1, 1978. The overall goals of the project include objective evaluation of the efficacy of administration of hyaluronidase and of propranolol in limiting the extent of infarction among patients with acute myocardial infarction and in modifying prognosis. Data will be acquired from five clinical centers, including Washington University, Massachusetts General Hospital, The Medical Center Hospital of Vermont, Parkland Hospital in Dallas, and the Peter Bent Brigham Hospital in Boston. Each of the clinical units plans to enroll patients during a three-year interval to provide an overall sample size sufficiently large to statistically test the hypotheses being explored. During the planning for the project (phase I) a series of meetings was held, during which operations manuals for each of the core laboratories were developed (see below) along with a final protocol pertaining to the performance of the clinical studies themselves. Both the manuals and the protocol necessitated in-depth consideration of data collection, hierarchy of the study's endpoints, possible conflicting and non-conflicting concurrent studies in each center, logistics, and technical considerations.

In addition to the five clinical units participating in the study, a series of core laboratories will be utilized so that objective analysis

of data obtained from each unit can be performed in a blinded fashion. These core facilities include a CK Reference Laboratory (at Washington University), a Holter Recording Analysis Reference Laboratory (also at Washington University), an Electrocardiographic Reference Laboratory (at the Peter Bent Brigham Hospital), a Myocardial Infarct Scintigraphy Laboratory (at Parkland Memorial Hospital in Dallas), and a Radionuclide Ventricular Function Laboratory (at the Massachusetts General Hospital). During phase I the Washington University Reference Laboratories were equipped with the necessary analytical biochemical and computer equipment (A-2). In addition, personnel were trained in procedures needed for analyzing the large number of samples that will be acquired during the course of the study. Data from each core laboratory will be forwarded to the Data Coordinating Center (Research Triangle Park, North Carolina) so that objectivity in data management and statistical analysis can be assured.

The Washington University components of this project comprise the Clinical Investigation Unit itself, directed by the Clinical Unit Coordinator, Dr. Allan S. Jaffe, the CK Reference Laboratory, directed by Dr. Robert Roberts, and the Holter Reference Laboratory, directed by Dr. Lewis J. Thomas, Jr. During the planning phases of the project necessary biochemical analytical techniques were verified with samples obtained from other institutions and needed developments in software for the Holter Reference Laboratory were undertaken.

The final protocol, developed after multiple drafts had been reviewed during the planning sessions, defines studies among patients with suspected myocardial infarction identified as early as possible after arrival at each clinical unit and specifically within 18 hours of the onset of acute symptoms leading to admission. The diagnosis of infarction will be established with the use of electrocardiographic criteria, as well as clinical indices, and confirmed with the use of enzymatic criteria. Patients to be excluded are those with cardiogenic shock, those aged 75 years or more, and those with other significant illnesses or conditions that may effect their response to therapy. Therapy comprising either administration of placebo, propranolol, or hyaluronidase will be administered in randomized fashion. For purposes of randomization patients will be initially divided into two groups based on the presence or absence of possible contraindications to propranolol. Management of patients participating in the study will comprise a standardized treatment regimen developed during the planning phases, designed to provide maximum safety to the patient and to avoid potentially conflicting effects of other unnecessary medications. Medical management of each patient will remain the responsibility of his own personal physician, and adjunctive emergency measures will, of course, be instituted whenever indicated.

A series of endpoints will be utilized to assess the effects of therapy on the extent of infarction and on prognosis. These include enzymatic estimation of infarct size based on analysis of serial changes in plasma creatine kinase activity, the extent of infarction assessed from

the number of electrocardiographic leads in which initial ST-segment elevation is followed by development of criteria of transmural infarction, the distribution and extent of impairment of ventricular function assessed from radionuclide ventriculograms, the severity and persistence of dysrhythmia assessed from Holter recordings, and the distribution of infarction assessed from ^{99m}technetium pyrophosphate scintigrams. Additional endpoints will include exercise tolerance tests six months after the episode of infarction, as well as clinical follow-up recorded on standardized forms developed during the planning phases of the project. Radioventriculograms will be obtained three months after infarction, along with a 24-hour Holter recording. Six months after infarction myocardial infarct scintigrams will be obtained, along with a repeat 35-lead precordial electrographic map and 24-hour Holter recording. Provisions have been made for pathology studies among patients who expire during the acute or follow-up phases of the study for whom autopsy permission can be obtained.

The extensive participation contemplated at Washington University involves participation of faculty members from several departments within the Medical Center. Much of the endpoint data to be used in the cooperative trial are based on concepts and verifications of the relationships of endpoints to morphological estimates of infarct size pursued in investigations conducted at Washington University during the past several years. Work at this Medical Center and many other institutions has demonstrated the feasibility of influencing the course of infarction in experimental animals with the use of appropriately selected interventions. The planned collaborative trial now getting underway offers the opportunity for definitive, objective assessment of the efficacy of two interventions which have exhibited considerable promise in experimental animal preparations among patients experiencing spontaneous acute myocardial infarction evaluation studied under rigorously controlled conditions.

A-22. Evaluation of Ambulatory ECG Recorders

Personnel: R. M. Arthur, BCL
Y. Barsoum, B.S., Electrical Engineering

Support: RR 00396
HS 00074

The performance of automatic arrhythmia detectors is, of course, dependent upon the measurement system used to obtain the ECG to be analyzed. A critical element in the measurement system for ambulatory subjects is the battery-powered recorder typically worn for 24 hours. In addition to frequency response, linearity, noise values, and other factors used to characterize ECG amplifiers, variations in tape speed and signal strength during recording and playback may significantly influence the waveforms obtained.

We studied speed and amplitude variation in 9 Avionics (reel-to-reel) and 1 Oxford (cassette) recorders. A fixed amplitude and frequency pulse was recorded in bench tests for units powered both by laboratory supplies and by batteries and in field tests with battery powered recorders worn for 24 hours. Recordings were played back on scanners designed by the respective manufacturers for hour-by-hour measurement of pulse rate. Argus/H was used to analyze the pulse trains to provide detail on both amplitude and speed variations. Histograms of pulse amplitude and pulse interval were generated on a PC from the Argus/H Cycle streams. Results indicate both long term and pulse-to-pulse variations of a few percent for new or fully recharged batteries and variations of up to 50% with marginal batteries. The significance of the effect of signal changes due to the recorder on the performance of automatic arrhythmia detectors is yet to be determined.

B. Tomography Systems

Stimulated by the clinical impact of the EMI transmission tomographic scanner in 1973, experimental studies were initiated in collaboration with the Division of Radiation Sciences to evaluate positron coincidence-detection as a method for emission reconstruction tomography. This collaborative activity resulted in a prototype scanner called PETT (Positron-Emission Transaxial Tomograph). A series of modifications following preliminary studies led to the development of a clinically usable scanner called PETT III. This development was facilitated by the application of specialized digital technology for coincidence detection and scanner control. A back projection algorithm, based on a convolution approach, was implemented in a mini-computer to effect reconstructions of radioisotope activity from coincidence detections. Extensive studies in patients and animals were conducted subsequently with the PETT III scanner in collaboration with the Division of Neurology and Cardiology. A new scanner, called PETT IV, was then designed and constructed. This new scanner utilized concepts developed with its predecessor, PETT III, but incorporated a novel technique for the simultaneous collection of four tomographic slices from a single set of detectors so that the total scan time was reduced substantially. PETT IV has been modified so that seven tomographic slices are now collected simultaneously from a single set of detectors. This seven slice scanner is now located in the Cardiac Care Unit for use in the SCOR project for the quantification of regions of myocardial ischemia and infarction *in vivo* in experimental animals and patients.

Although ultrasound has proven to be a useful source of diagnostic information, results of examinations based on current ultrasonic methods are primarily qualitative and pictorial. In contrast, the development of ultrasonic computerized tomography offers promise of providing quantitative information in addition to a picture. Each matrix element of the reconstructed image contains the local value of the ultrasonic parameter of interest. This should allow the investigator to make measurements of a more localized nature than is now possible without structural damage to the tissue, making possible the use of ultrasound for detailed characterization of tissue. The feasibility of ultrasonic reconstructive tomography has been demonstrated using either attenuation or phase velocity as the ultrasonic index.

A collaborative effort with the Physics Department has been undertaken to develop ultrasonic computerized tomography into a clinically useful tool. Research in at least two areas is needed. First, methods for ultrasonic computerized tomography itself must be improved. Progress during the last year has resulted in the suppression of the serious distortions that arise due to phase cancellation effects. This has been achieved through the development of a new receiving transducer, as reported below. Second, the results of quantitative ultrasonic measurements must be correlated with independent indices of tissue pathology so that the results of an ultrasonic computerized tomography image can be meaningfully interpreted. Research on the use of ultrasound for quantitative tissue characterization is proceeding rapidly in a number of institutions, including our own. Thus, we anticipate that information relating quantitative ultrasonic indices to tissue pathology will be available for use in conjunction with ultrasonic computerized tomography.

B-1. Ultrasonic Tomography

Personnel: G. H. Brandenburger, BCL
J. R. Cox, Jr., BCL
J. R. Klepper, BCL
J. G. Miller, BCL
D. L. Snyder, BCL

Support: RR 00396
APR 77-09776
Washington University

State-of-the-art clinical ultrasonic imaging systems have continued to find expanded successful application in cases where information about tissue edge geometry and movement is clinically useful. However, these systems provide little quantitative information about localized ultrasonic properties such as attenuation. In contrast, indices based upon the attenuation of ultrasound appear to be suitable for use as quantitative indicators of tissue pathology (PR 13, B-1). The efforts described here are directed toward development of tomographic methods capable of localized quantitative assessment of various ultrasonic indices, such as attenuation, in tissue.

Potential applications for ultrasonic tomography include:

a) localized quantitative measurement of tissue attenuation, phase velocity, and reflectivity for use in ultrasonic tissue characterization studies *in vitro*;

b) quantitative imaging of certain tissues *in vivo*, e.g., breast tissue.

Historically, ultrasonic tomography was first demonstrated at the Mayo Clinic in 1974.[1,2,3] Tomographic reconstruction of acoustic velocity has been carried out successfully by several groups,[3,4,5] but indicators derived from ultrasonic velocity have shown only limited correlation with tissue pathology. Tomographic reconstructions of attenuation-based indices carried out prior to the work described here were compromised by serious errors due to methodological problems, especially phase cancellation.

During this year the following significant advancements have been made by our group in attenuation tomography:

1) Phase cancellation, an instrumental error resulting in frequent over estimation of apparent attenuation measurements with piezoelectric receiving transducers (PR 13, B-2), has been identified as the single largest error source in attenuation tomography.[6] A receiving transducer based upon the acoustoelectric effect in cadmium sulfide is capable of making acoustic intensity measurements uncompromised by phase cancellation error.[7] The results below represent the first application of an acoustoelectric receiver to ultrasonic attenuation tomography. With reference to Figure 1, the reconstructions of a cylindrical castor oil phantom made

from both piezoelectric and acoustoelectric receiving transducer measurements demonstrate the improvement presumably due to elimination of phase cancellation error. Phase cancellation will cause a significant over estimation of attenuation when portions of the acoustic beam traverse paths of different acoustic velocity. A typical projection from the scan of the castor oil in Figure 1 clearly depicts large over estimation at the edges where the beam follows paths both through water and through varying thicknesses of oil. The acoustic velocity in castor oil differs from water by about 1%. The projection measured with an acoustoelectric receiver exhibits no such error and well approximates the projection for a theoretical uniform cylinder. The resulting reconstruction from piezoelectric measurements exhibits substantial edge artifact and inaccurate attenuation values. The acoustoelectric measurements yield average attenuation values accurate to within 5% of independent measurements. The acoustic impedance of castor oil is near that of water (.97 relative to water); hence, the non-unity transmission coefficients discussed below present relatively small error.

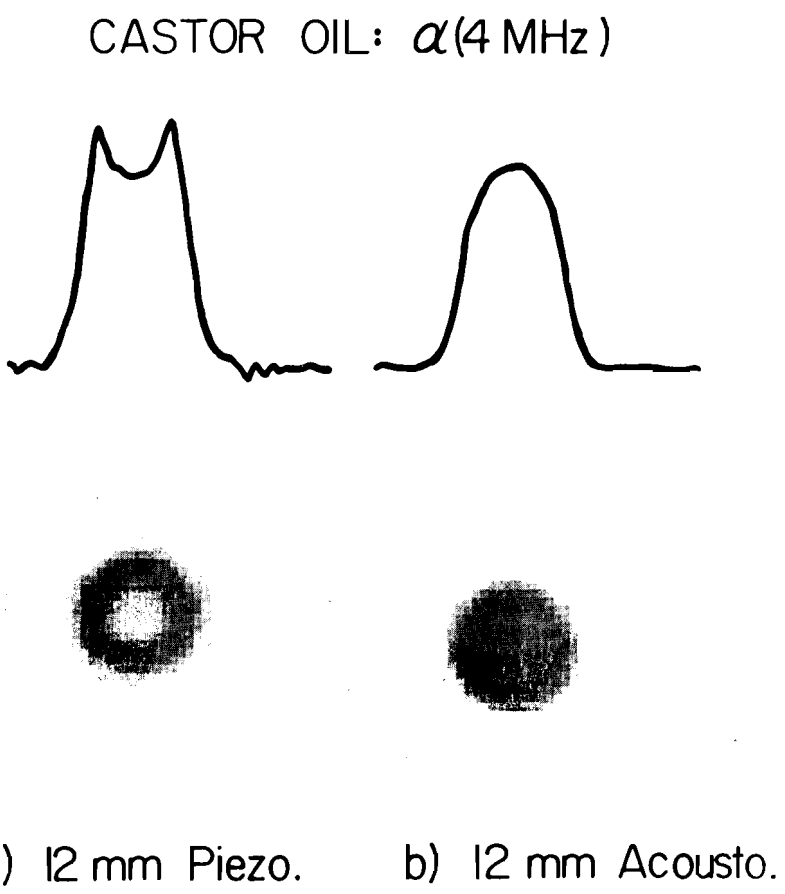


Figure 1. Phase Cancellation Effects: Projections and reconstructions of the attenuation of a cylinder of castor oil from measurements obtained using a) a piezoelectric receiving transducer, and b) an acoustoelectric receiving transducer.

2) The frequency dependence of ultrasonic attenuation, a parameter highly correlated with certain tissue pathologies (PR 13, B-1), was demonstrated to be of importance in the elimination of tomographic reconstruction error due to transmission losses at ultrasonic impedance discontinuities in *in vitro* tissue and laboratory phantoms. Because these non-unity transmission coefficients are nearly constant with respect to frequency, whereas homogeneous tissue attenuation exhibits a nearly linear frequency dependence, the inferred measurement of attenuation "slope" with respect to frequency is largely independent of the transmission coefficients. Refraction of the beam away from the receiver, due to non-unity index of refraction, is responsible also for a largely frequency independent measurement artifact whose effect on tomographic reconstruction is reduced by reconstructing the slope of attenuation. Figures 2 and 3 demonstrate the improvement realized by reconstructing the slope of attenuation. In Figure 2 the attenuation coefficient projection from the scan of a finger cot filled with olive oil, when measured at a single frequency, demonstrates the over-estimation error presumably due to substantial reflection at the cylinder edges. At oblique incidence angles, such as at the edges, an acoustic impedance discontinuity will give rise to large reflection, manifested here as a non-unity transmission coefficient. The acoustic impedance of olive oil (.89 relative to 1 for water) differs from water more so than castor oil, causing larger error than was evident in Figure 1. The difference between apparent attenuations measured at two frequencies is largely free of the frequency independent transmission coefficient but suffers a decreased signal-to-noise ratio. Measurements were made at eight frequencies and the added information makes possible a least-squares slope estimation with significantly lower noise than for the simple difference. Figure 3 shows the image enhancement realized with the slope for an excised dog heart. While the single frequency shows considerable detail, reconstructed attenuation values are incorrect, and slope reconstruction, while noisier, yields average left ventricle slope values within 10% of independent measurements.

3) Additional error occurs when the angle of incidence for a beam passing between media with differing indices of refraction exceeds the critical angle given by Snell's law. Total beam reflection occurs and no meaningful measurement is possible. The transmitted beam width usually exceeds most of the uniform portions of the generally irregular media-boundaries in tissue; hence, total loss of received signal occurs infrequently. Reflection and refraction losses do, however, degrade the signal-to-noise ratio for attenuation-slope measurements. A partial remedy is the matching of the water-bath acoustic velocity to that of the tissue specimen. Experiments with 6.5% saline and dog heart and kidney specimens have demonstrated enhanced edge definition in the reconstructions.

Alternative methods for increasing the water-bath acoustic velocity while preserving isotonic salinity are being sought.

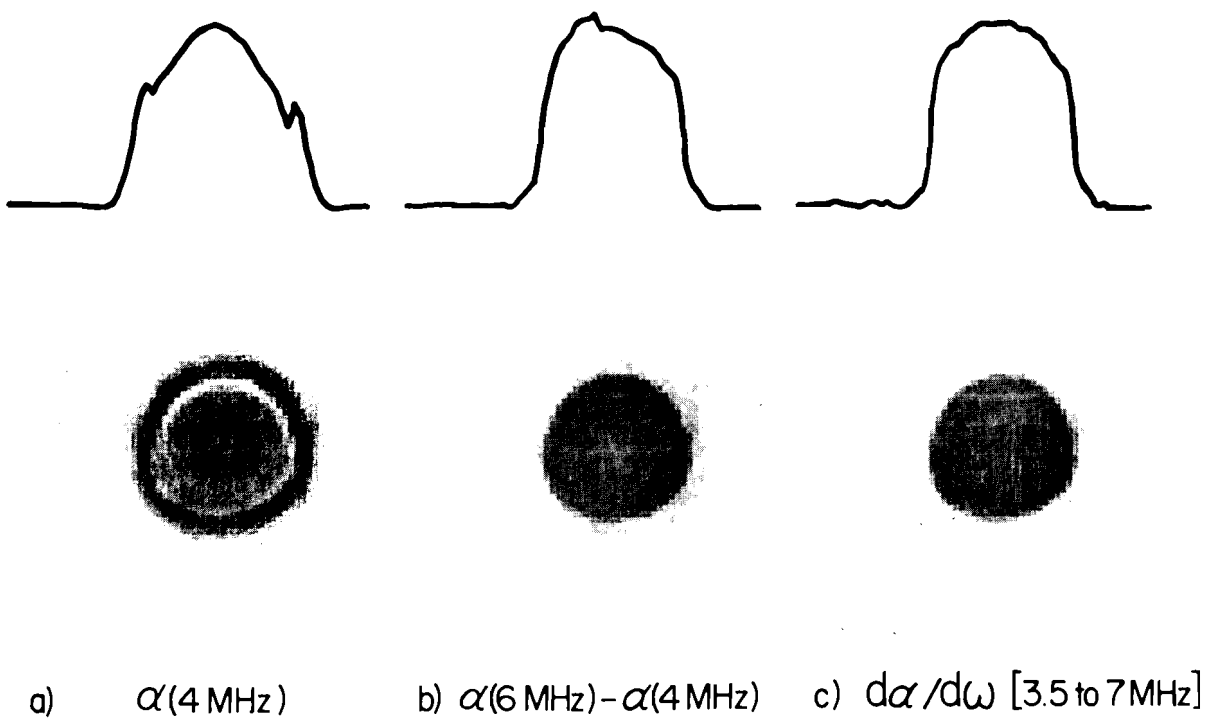


Figure 2. Reflection and Refraction Effects: a) the attenuation coefficient at a single frequency, b) the difference between the values of the attenuation coefficient at two frequencies, and c) the slope of the attenuation versus frequency curve.

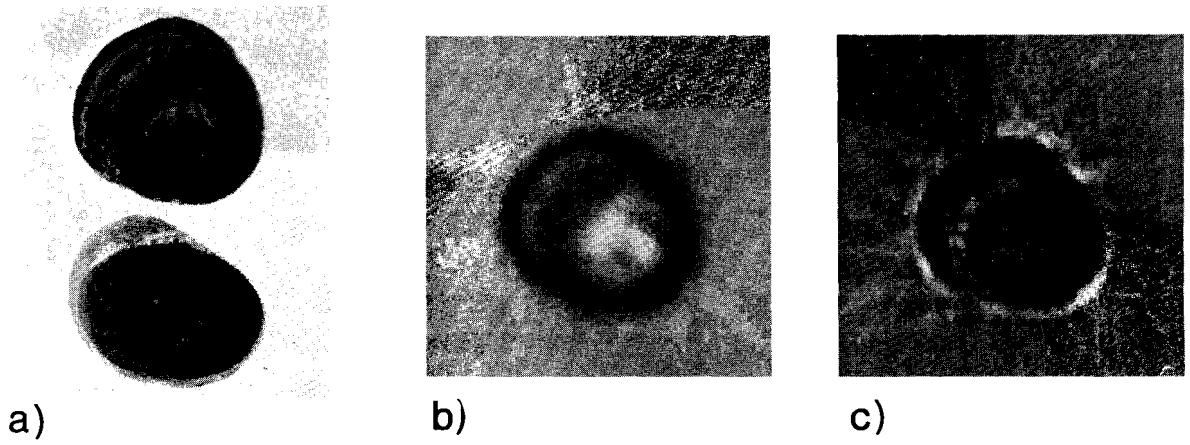


Figure 3. Cross sections of an excised dog heart showing: a) photographs of apical and basal views of the imaged region, b) a reconstruction of the attenuation coefficient at 6.5 MHz using the 12 mm acoustoelectric receiver, and c) reconstruction of the slope of the attenuation from 4 to 7 MHz using the 12 mm acoustoelectric receiver.

Refraction, as depicted for a cylindrical object in Figure 4, may cause the acoustic beam to be deflected from its straight-line path. While use of the slope of attenuation can reduce the error due to the finite width beam partially missing the receiver, beam profile frequency dependence and reduced measurement signal-to-noise ratio limit the effectiveness of the method. Figure 4 demonstrates the over estimation error due to refraction and the successful reduction of the error obtained by using a spatially extended receiver to capture more widely deflected beams.

The computation of attenuation-slope with respect to frequency from apparent attenuation measurements at several frequencies also yields an "attenuation-intercept" parameter. It is believed that, in the absence of refraction and variation of beam shape with frequency, the intercept is related to the logarithm of the product of transmission coefficients. Transmission coefficients in turn are related to the reflections that give rise to pulse-echo images. Further, in the absence of the above and the transmission coefficients' angle-of-incidence dependence, it may be possible to model the intercept as a line integral measurement capable of being tomographically reconstructed. Actual reconstruction (Figure 5) of the intercept (the above not withstanding) produces an image qualitatively delineating specimen edges. The intercept reconstruction can be thought of as an average difference between the single frequency reconstructions and the slope reconstruction. The intercept reconstruction is, therefore, related to the error due to non-unity transmission coefficients and refraction that was removed to produce the slope reconstruction.

The transmission coefficients are "anisotropic" quantities by virtue of their angle-of-incidence dependence. The anisotropic nature of the transmission coefficient is analogous to the suspected anisotropy in certain muscle tissue (PR 13, B-2). The intercept measurement provides added impetus for further work in analytically modeling and deriving corrections for the reconstruction of anisotropic quantities.

A cadmium sulfide acoustoelectric receiver was fabricated this year, particularly for use in the CUTAR scanner (PR 13, B-3). The CUTARSYS (PR 13, B-3) software has been substantially upgraded and has taken full advantage of operating system improvements (G-2). New algorithms for attenuation slope computation, noise reduction, and semi-automatic calibration have been implemented. Figure 6, a cross-sectional view of a dog kidney, was made using tissue-water velocity matching and the above improvements. The crystal face is 1.4 cm wide (horizontally), providing sufficient receiver aperture to intercept most refracted beams. A silver-doped epoxy backing was used to reduce backwall reflection. A new gated analog peak detection method was developed to circumvent received signal triggering uncertainty. The new detector provides a reliable peak measurement despite widely varying received pulse shape and arrival time. Significant improvement in resolution was achieved by replacing the planar transducer with a moderate f-number (f-8), spherically focused transmitting transducer.

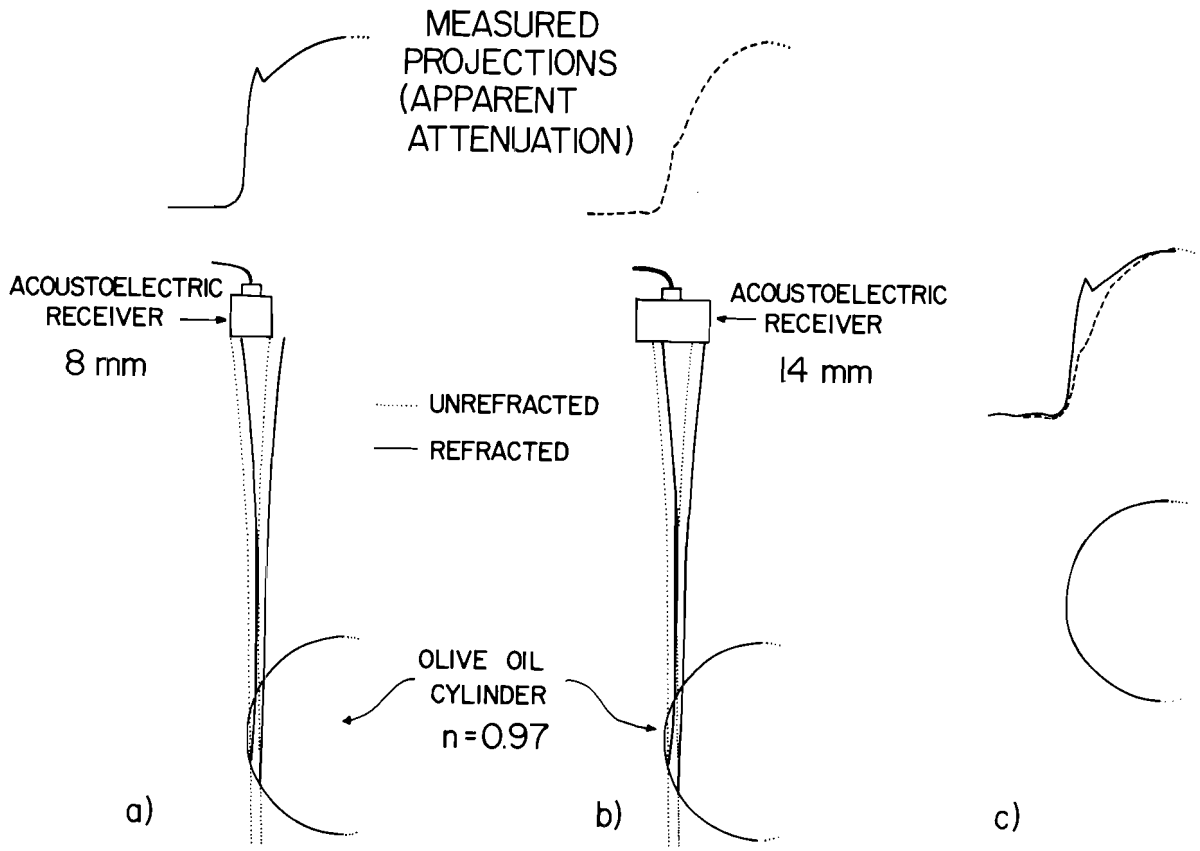
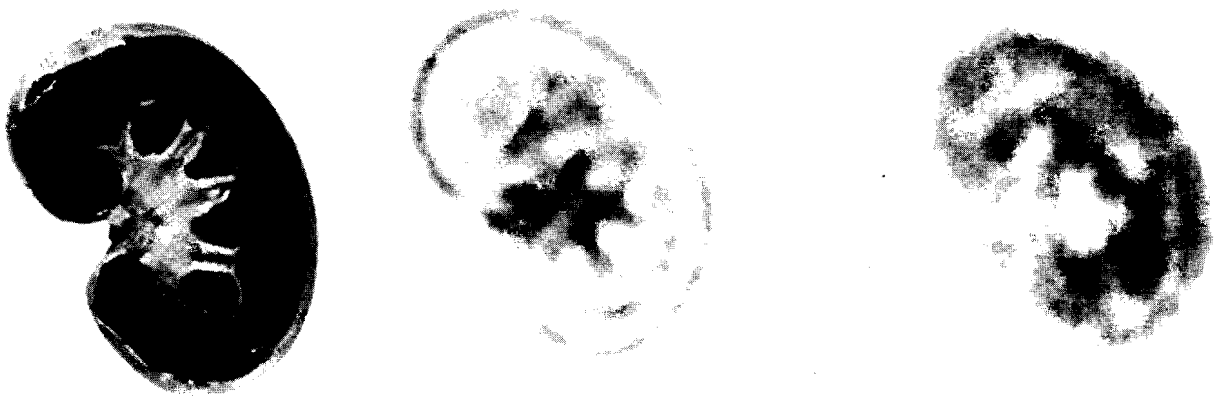


Figure 4. Results of measurements carried out on a cylindrical specimen of olive oil using acoustoelectric receivers of 8 mm and 14 mm lateral dimension. The apparent attenuation estimated from measurements made with the smaller receiver are presented in panel a), and with the larger receiver are presented in panel b). In panel c) the measured parallel ray projections are superimposed.

a) b)

Figure 5. Images of an excised dog kidney. Panel a) is a photograph of the approximate plane imaged. The image in panel b) is the reconstruction of the (zero frequency) intercept of the least squares line fit to the apparent attenuation over the range 5.0 to 6.5 MHz.



a) b) c)

Figure 6. Images of an excised dog kidney. Panel a) is a photograph of the approximate plane imaged. The image in panel b) is the reconstruction of the apparent attenuation coefficient at 5 MHz. The image in panel c) is the reconstruction of the slope of the attenuation versus frequency estimated from the slope of a least squares line fit to measurements carried out at 5.0, 5.5, 6.0, and 6.5 MHz.

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B-2. External Detection and Tomography of Ischemic Myocardium

Personnel: B. E. Sobel, M.D., Medicine
M. S. Klein, M.D., Medicine
J. Markham, BCL
R. Roberts, M.D., Medicine
M. M. Ter-Pogossian, Ph.D., Radiology
T. J. Tewson, Ph.D., Radiology
T. Weadon, BCL
M. J. Welch, Ph.D., Radiology

Support: RR 00396
HL 13851
HL 17646
HL 19537

Research in this project is designed to quantify the distribution and extent of myocardial injury and rates of regional myocardial metabolism externally in order to improve detection and assessment of ischemic heart disease, as well as other cardiomyopathic states, and to evaluate their response to therapy. During the past year the positron emission transaxial tomograph (PETT IV, B-4) was installed in the Procedures Room of the Cardiac Care Unit. This equipment permits imaging of patients with acute myocardial infarction and myocardial ischemia for assessment of changes in regional cardiac metabolism.

Results from completed studies in this project[1-7] indicate that identification of the distribution of ischemic myocardium and the extent and locus of acute myocardial infarction are possible with the use of ^{11}C-palmitate injected intravenously. Use of the PETT IV system permits acquisition of seven cross-sectional images of the heart from apex to base simultaneously. Plans have been implemented to provide gating capabilities for this instrumentation so that measures of ventricular function, such as ejection fraction, can be acquired with the use of positron-emitting vascular pool tracers such as ^{11}C-hemoglobin. The present equipment provides resolution of approximately 1.5 cm and requires scanning in the range of six to eight minutes. Equipment presently under construction (PETT V) will utilize a circular array of detectors with a "wobbling" motion with a predicted resolution capability of 7 mm and a scan time as brief as several seconds (B-5). This system, used primarily for cerebral studies, will be employed also for studies of cardiac metabolism in animals. Based on results obtained in this project with isolated hearts and rabbits *in vivo*, with ^{11}C-palmitate, the rate of disappearance of tracer incorporated into triglycerides is a direct reflection of myocardial fatty acid oxidation and, therefore, regional, oxidative metabolism.[8-14] Detection of clearance rates with "fast" tomographic instrumentation should make this approach applicable *in vivo* with the use of positron tomography.

Since we have found that extraction and metabolism of ^{11}C-palmitate ceases quickly in myocardial tissue subjected to either ischemia without necrosis or infarction,[1,8-14] the two entities cannot be clearly delineated

by a single ^{11}C-palmitate image. They can be differentiated, however, by serial studies, since impaired ^{11}C-palmitate extraction associated with ischemia alone is transitory. Nevertheless, to determine whether positive images of reversibly ischemic myocardium could be obtained, based on persistence in tissue of pyruvate after conversion to lactate (thus permitting differentiation between ischemic versus necrotic myocardial tissue), isolated rabbit hearts were perfused with buffer containing labeled pyruvate for five minutes at controlled (20 ml/min) or low (2 ml/min) flow.(15) Although tissue radioactivity immediately after labeling was 40% higher in controls because of increased delivery of the tracer, after perfusion with unlabeled buffer for an additional 15 minutes, radioactivity in ischemic hearts was 433% greater than in controls (6,244 vs 1,433 dpm/g). Residual radioactivity correlated with total lactate in TCA extracts of the left ventricle (r = .81). In addition, when labeled pyruvate was injected via the left atrium immediately after coronary artery occlusion in open chest rabbits, two to three-fold more radioactivity persisted in ischemic compared to normal zones after 15 minutes. Based on these results, persistence of label introduced in pyruvate within ischemic myocardium in the form of labeled lactate offers promise for positive delineation of zones of transitory ischemia using positron emission transaxial tomography and facilitating delineation of zones of ischemia from zones of infarction.

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B-3. Algorithms for Tomography Systems Having Fan-Beam Geometries

Personnel: D. L. Snyder, BCL
N. C. Chang, BCL
Y. Ikeda, B.S., Systems Science and Mathematics

Support: RR 00396
ENG 76-11565
Washington University

Because of the potential for more rapid data collection, newer scanners for reconstructive tomography are implemented in a "fan-beam" geometry. In these implementations there is a source that emits a fan-shaped pattern of radiation. A detector located on the opposite side of the scanned object provides data that depends on the attenuation density of the object integrated along a ray in the fan joining the source and detector. Increased speed is realized by the use of not just a single detector but, rather, a circular array of detectors that collect data simultaneously along several rays in the fan. Original procedures for constructing tomographic sections from fan-beam data rely on the use of existing algorithms for parallel-beam data, which can be used by rearranging the fan-beam data into a parallel-beam format. However, in this format the data suffer from a nonuniformity in sampling due to the nonlinear relationship between the fan-beam and parallel-beam coordinate systems. Partly for this reason, as well as for the conservation of data storage and potential speed benefits, algorithms that make direct use of fan-beam data have been derived by a number of investigators.[1-5] We have initiated a study of the following two aspects of fan-beam algorithms that complement these published results.

1. Published fan-beam algorithms assume that the output of all detectors in the fan are sampled simultaneously at discrete source angles as the source rotates about the object. The samples so derived at each source angle are processed together in a filtering operation which is followed by an "inverse square-law" back projection to yield the tomographic section after all source angles have been completed. We have investigated the implications of processing each detector output independently as the source rotates and then combining these processed source outputs at the completion of all data collection to form the section. We have found that this can be accomplished without the back projection operation by using the emerging technology of adaptive charge-coupled devices. While a potential for very high-speed processing appears to exist, we have not yet obtained quantitative estimates of this. The algorithm is specified in terms of the following quantities:

α = source angle,

β = source-detector angle,

β_m = total fan angle,

R = origin-to-source distance,

(r,θ) = location of a point in the reconstruction image in polar coordinates,

$\alpha_0 = \theta-\beta$,

$D = R \sin\beta - r \cos(\alpha_0-\alpha)$,

$g(t)$ = filter response used in the parallel-beam algorithm,

$h_r(\alpha_0-\alpha,\beta) = g(D)\cos\beta$,

$m(\alpha,\beta)$ = data at source angle α and source-detector angle β,

$\mu(r,\theta)$ = attenuation density at (r,θ).

The algorithm is based on the relation that if

$$M_r(\alpha_0,\beta) \triangleq \int_0^{2\pi} m(\alpha,\beta)h_r(\alpha_0-\alpha,\beta)d\alpha,$$

then

$$\mu(r,\theta) = \tfrac{1}{2}\int_{-\beta_m/2}^{+\beta_m/2} M_r(\theta-\beta,\beta)d\beta.$$

2. We also have initiated a study of the noise performance of fan-beam algorithms. For this the measurements $m(\alpha,\beta)$ are modeled by Poisson process. Expressions for the mean and variance of $\mu(r,\theta)$, the reconstructed attenuation, have been derived, as have upper and lower bounds on the variance. These results are being compared to the noise performance for parallel-beam algorithms.

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B-4. Performance Characteristics of PETT IV

Personnel: N. A. Mullani, BCL
J. O. Eichling, Ph.D., Radiology
C. S. Higgins, A.B., Radiology
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851
NS 06833

The PETT IV system (PR 13, B-4, B-5) has been modified to collect seven simultaneous slices instead of four. The three additional slices are collected by summing the adjacent cross slices in the slice plane. The new system has the advantages of higher sensitivity and shorter slice to slice distance. Thus, two scans separated by 1 cm completely describe the field of view. The linespread functions for the seven-slice system for a point source in air are shown in Figure 1. Additional software has been developed on the Interdata 7/32 computer to automate and speed up the data processing. A new program has been written to utilize effectively the multiple slices collected by PETT IV into reconstructing in the sagittal and coronal planes. With this new technique the clinician is not limited to viewing the images in the transaxial mode alone, but can choose any planes in the other two dimensions. Figure 2 shows such sagittal and coronal reconstructions for the distribution of carbon monoxide in the human brain.

Several phantom studies have been completed. These have been aimed not only at characterizing the performance of the scanner, but also studying the requirements for quantification of the data collected by the scanner.

Positron emission tomography offers the major advantage of being able to quantitate the uptake and egress of radioactive tracers within the organ of interest. However, to be able to achieve this goal, a full understanding of the processes of scattered radiation and random coincidences and their effect on quantification of the radiotracers is required. Another issue that needs to be studied further is the effect of partial volume on the quantification of the data. We feel at this time that the information lost due to the partial volume scans can be retrieved in a multislice scanner like PETT IV by using a modification of the technique used for sagittal and coronal reconstructions. Work is continuing in an attempt to lead to a better understanding of these problems.

PETT IV has been moved to the Cardiac Care Unit (B-2), and software systems have been implemented on the Interdata 7/16 located in the unit so that data collection and processing can be accomplished. Several phantom studies have been carried out to check the system, and a few normal patients have been scanned.

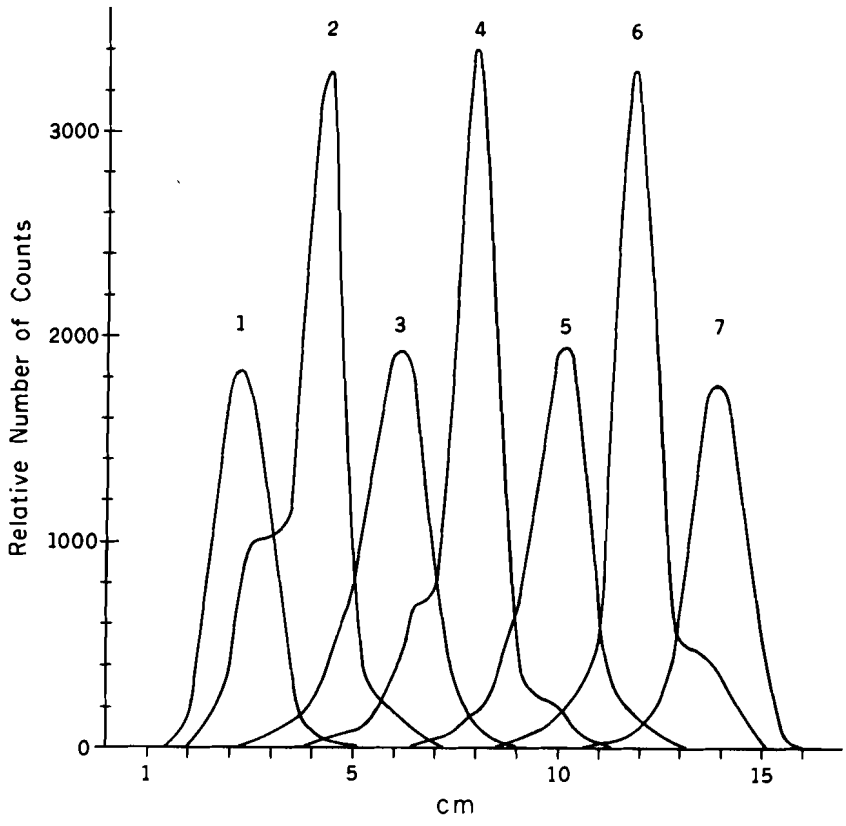


Figure 1. Linespread functions of the seven slices.

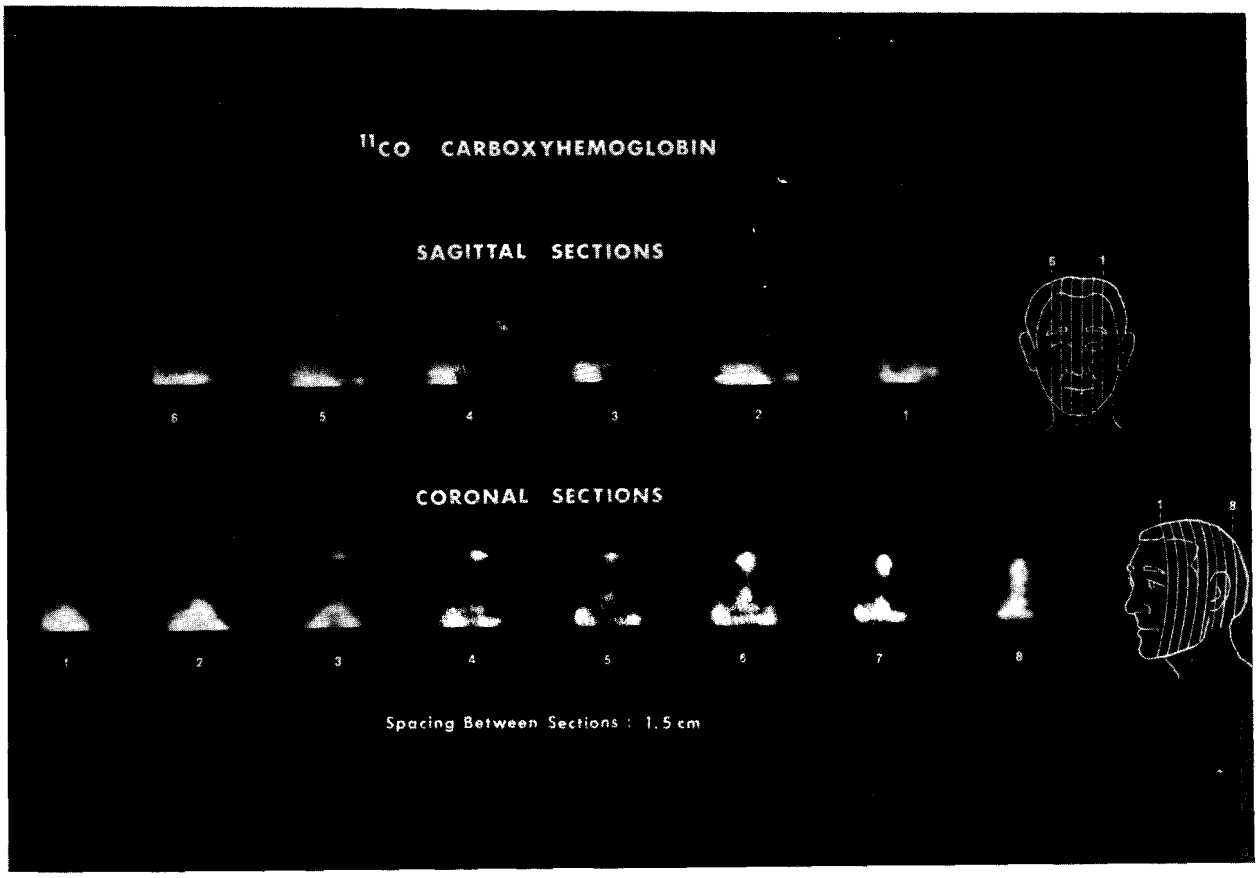


Figure 2. Sagittal and coronal reconstructions of the PETT IV data.

B-5. PETT V Design and Construction

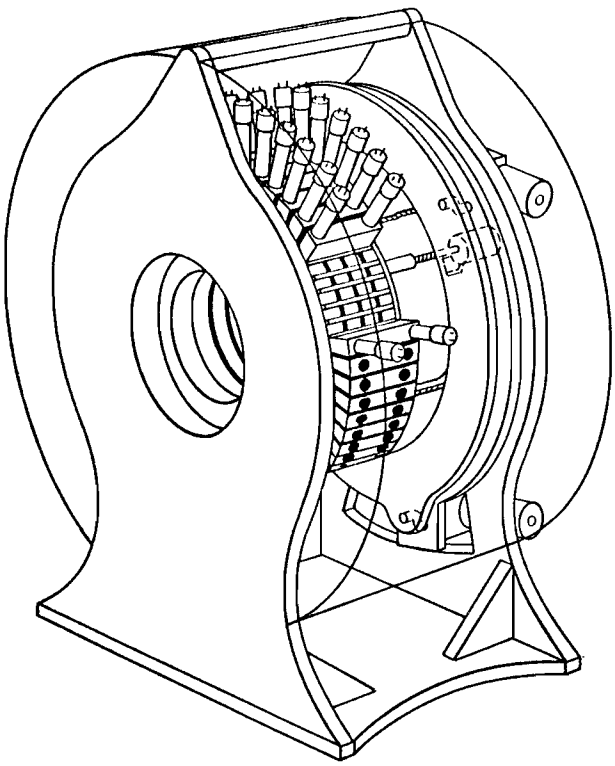
Personnel: N. A. Mullani, BCL
D. C. Ficke, B.S., Radiology
C. S. Higgins, A.B., Radiology
J. T. Hood, B.S., Physics
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851
HS 06833

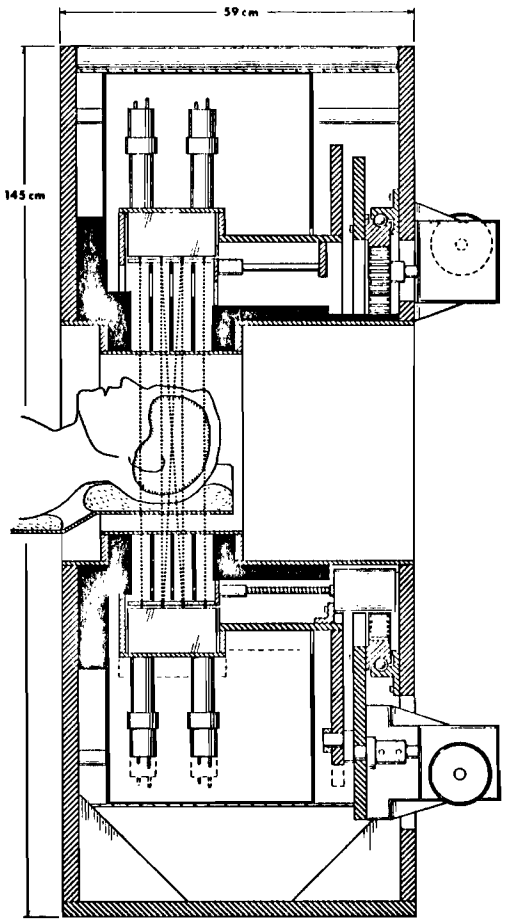
A new positron emission tomograph has been designed for use in human cerebral studies. The design of this new scanner, called PETT V, is tailored towards achieving very high sensitivity and short data collection time for the study of regional dynamic cerebral functions. To achieve this goal two major changes have been made in the design of the tomograph over the PETT IV design. They are: (1) the detector to detector separation is much smaller than in PETT IV and is set at 60 cm, and (2) the geometric placement of the detectors is circular rather than hexagonal as in PETT IV. The advantages of a circular geometry over a hexagonal one is that all the projections are collected at one time and that more coincidence lines are used for data collection for comparable size and number of detectors. In the past the circular geometry has suffered from a lack of sampling capability. This has been overcome in the PETT V design by wobbling the array of detectors in a small circle. The effect of the wobbling motion for each detector is to produce a scanning motion across the patient. Thus, samples can be acquired as finely as desired. A simplified drawing of PETT V is shown in Figure 1. The wobble and the rotation motions of the PETT V detector array are illustrated in Figure 2.

A total of 48 sodium iodide detectors are used in the PETT V. Each detector is 3 cm wide, 14 cm long, and 7 cm deep. Photomultiplier tubes attached to the back of the detector enable positioning of the gamma ray within the detector as in PETT IV. The detector is split into four regions and a total of seven simultaneous slices are collected in the PETT V system. The spatial resolution of PETT V is 15 mm FWHM in the low resolution mode and 7 mm in the high resolution mode. The slice thickness can be varied from 7 mm to 15 mm. Sensitivity is estimated to be 325,000 counts/sec/μCi/cc for a 20 cm phantom with the 15 mm × 15 mm resolution. The shortest data collection time is one second for the low resolution mode.

PETT V is being constructed at this time with an estimated completion date of September 15, 1978.



PETT V



Section thru PETT V

Figure 1. Simplified drawing of PETT V.

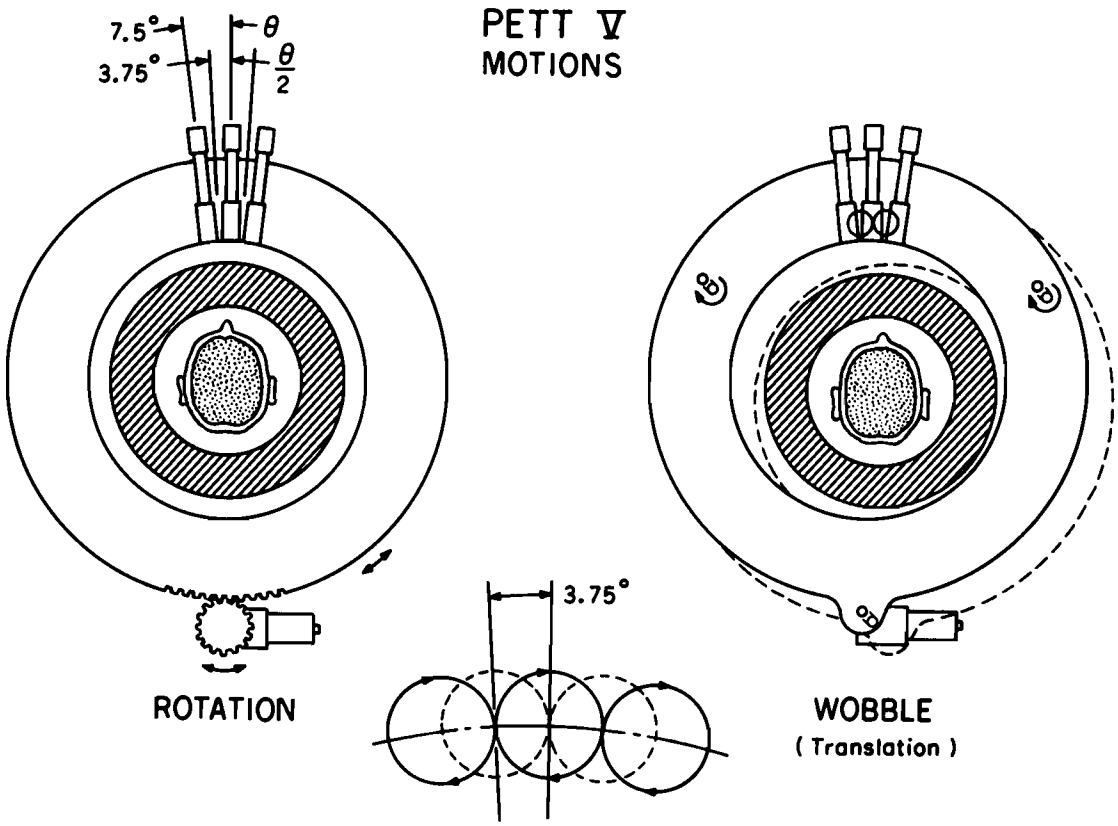


Figure 2. Wobbling and rotation motions of PETT V.

C. Clinical Pathophysiologic Research Activities

BCL activities specifically addressed to clinical pathophysiology began in 1970, the year after the Argus system for on-line cardiac arrhythmia analysis became operational in the Barnes Hospital Coronary Care Unit. In 1973 a minicomputer-based patient-monitoring system was installed in the Barnes Hospital Cardiothoracic Surgical Intensive Care Unit (SICU) to bring state-of-the-art continuous digital processing of physiologic signals to the bedside. After five years of continuous use the system is regarded highly, is well used for clinical purposes, and has set demanding standards in the local community for its planned replacement with a commercial system in new care units now under construction. The presence of the SICU system has heightened the awareness of clinical investigators to the value of on-line digital signal processing and external control in pathophysiologic research. To satisfy their demands a more flexible clinical physiologic research cart (CPRC) was implemented three years ago. For practical reasons the CPRC was coupled to the SICU system. Experience has taught us the importance of separating more clearly the clinical and research functions of such systems. Furthermore, escalating needs have stimulated us to develop more flexible and enduring solutions to digital-computing applications in pathophysiologic research. Current work addresses research needs in a Coronary Care Unit, but features a generalized approach to a Clinical Pathophysiologic Research System (CPRS) utilizing microprocessor-based programmable modules interconnected via a standard interface.

Recent work at BCL has built upon experience with an earlier prototype to develop an advanced cardiac catheterization system (COMCAT) which provides conventional functions but emphasizes flexibility and close integration with the clinical laboratory procedure in order to expedite data collection and analysis. Features which make the system more responsive to the user include simplicity of operation during the procedure, easy customization to other laboratories, provision for multiple patient conditions, availability of automated data-acquisition protocols, and convenient editing capabilities. Uncomplicated access to data for research applications adds to the usefulness of the system. COMVAS is a computerized ventricular-contour analysis system which, during its continuing development at Jewish Hospital, has been providing analysis and efficient archival storage for manually entered contours valuable both for research and for routine clinical diagnosis. Experiments are now in progress to establish optimum sampling strategies for real-time digitization of video images with sufficient resolution in the X, Y, and Z axes for automated ventricular-contour recognition. To this end state-of-the-art techniques are being applied to achieve a data-acquisition rate (to disk) of 9.6 Mbytes/sec. Work on the contour-recognition algorithm builds on published reports of others and seeks to capitalize on a larger image context by employing models of left-ventricular shape.

Studies of left ventricular compliance being conducted at the Washington University Catheterization Laboratory and the analysis of visual field in the Department of Ophthalmology have necessitated the development of specialized data-acquisition systems and data-processing software.

C-1. Cardiothoracic Surgical Intensive Care Unit System

Personnel: L. J. Thomas, Jr., BCL
M. W. Browder, BCL
R. E. Clark, M.D., Cardiothoracic Surgery
G. G. Garcia, Barnes Hospital
R. W. Hagen, BCL
W. R. Roloff, BCL

Support: RR 00396
Barnes Hospital
Washington University

During the past year operation of the Cardiothoracic Surgical Intensive Care Unit (SICU) computer system was successfully turned over to a monitoring technician employed by Barnes Hospital. Biomedical Computer Laboratory personnel continue to provide guidance and assume responsibility for maintenance and repair, but all routine operations, including patient interfacing, calibration, and minor troubleshooting, are now carried out by the new technician. This arrangement formally recognizes full integration of the system into routine clinical care. Also, Barnes Hospital now packages the BCL-designed patient-transducer fluid interface.

As noted last year (PR 13, C-1), plans are to retire the current system in 1980 when the SICU will be expanded and moved into a new wing (West Pavilion) now under construction (C-5). Functional specifications have been detailed for use in identifying a commercially available replacement for the existing system which was designed, built, and installed by the Laboratory some five years ago.

Because of BCL's reduced role in operating the system, less detailed information on system performance has been recorded. In general, reliability continues to be quite satisfactory, there being over the year only nine episodes of unintentional interruptions of patient monitoring, of which only four required attention by BCL personnel. The restructured software reported last year has proven its worth and the analysis of core dumps taken on the occasions of system failure continue to be valuable in identifying hardware problems.

C-2. Clinical Physiologic Research System

Personnel: R. W. Hagen, BCL
H. D. Ambos, BCL
G. J. Blaine, BCL
M. W. Browder, BCL
V. W. Gerth, BCL
W. R. Roloff, BCL
B. F. Spenner, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

The concepts which form the basis of the Clinical Physiologic Research System (CPRS) have developed out of our experience in applying digital techniques to clinical research activities. This experience has revealed a class of research applications with sufficient commonality in data acquisition, analysis, display, storage, and control needs that can be met by a system which is both portable and modular without sacrificing user convenience or economy. Furthermore, it is clear that within this application class even a small number of system elements can be readily adapted to serve multiple tasks. The existence of inexpensive microprocessor hardware, suitable standards for digital signal communication, a library of software routines, and convenient support for microprocessor development (G-1) suggested that identified common needs may be satisfied by a small set of programmable modules that communicate over a standard digital communication bus. With this in mind, several candidate bus structures were considered. Technical specifications, such as data rate, bus length, number of devices, and message length for the candidate bus structures, were compared with projected CPRS communication requirements. Non-technical considerations included the implementation costs, the ease of use, and the anticipated acceptance of the bus standard. The extent to which the bus standard will be accepted was an important consideration because the usefulness of the CPRS will be enhanced as more commercial manufacturers adopt the standard. The IEEE Standard 488-1975, Digital Interface for Programmable Instrumentation, was chosen because its characteristics best suited the CPRS objectives.

Programmable modules are packaged in TM 500 plug-in kits manufactured by Tektronix. Each module contains a microcomputer, a Standard 488 interface port, and a few function-specific components. A programmable module is connected to the standard bus by sliding it into any TM 500 power-module mainframe. These mainframes, available in one- through six-module versions, are modified by mounting a standard compatible connector on the back panel and appropriately wiring it to each module mating connector within the mainframe. The programmable modules then are able to communicate with each other and any commercially available device that possesses an IEEE Standard 488 interface.

The first application of the CPRS concept is in the Coronary Care Unit at Washington University Medical Center where researchers now use mobile carts to access, display, and record hemodynamic and electrocardiographic waveforms from patients subjected to aggressive therapeutic procedures. The physiologic signals are used to control the administration and evaluate the consequences of these procedures. At present the essential features of the measured waveforms are determined by manually examining calibrated recordings. This time-consuming method does not produce the desired continuous overview of the cardiovascular status, but provides instead only an intermittent sampling of physiologic variables. Therefore, it has been proposed that a set of programmable modules from the Clinical Physiologic Research System be configured to provide for the continuous determination and selective display of essential signal characteristics derived from the measured physiologic waveforms. In addition, the derived signal characteristics must be plotted as a function of time. This may be accomplished by using a commercially available x-y recorder which contains an IEEE Standard 488 interface. In this application the proposed approach to enhancing physiologic research data utilization does not require a physical or functional redesign of the existing research system, but rather an unobtrusive addition to the present system.

At the present time three experimental programmable modules have been implemented, each containing a kernel microcomputer system currently based on M6800 components. In addition to the kernel system, the Physiologic Signal Processing Module contains an A/D converter component, the Input/Output Module has an external alphanumeric display packaged with a special purpose keyboard, the Control Module contains no additional components. The QRS-detection algorithm which was developed for the Cardiothoracic Surgical Intensive Care Unit Monitoring System (C-1) has been translated and is being tested in the Physiologic Signal Processing Module. Intermodule communication tests have been conducted and programs for the Control and Input/Output Modules are being written.

To date our experience with the CPRS concept suggests that it will provide an improved approach to the application of digital computing to physiologic research activities by:

1) reducing the time required to implement a particular application,
2) reducing costs,
3) reducing system size,
4) reducing the number of ad hoc, application-specific devices,
5) allowing more time for the research effort because less time is spent interfacing peripherals,
6) reducing the number of redundant solutions and duplication of effort,
7) making the maintenance problem more manageable.

C-3. Pulsatile Perfusion System

Personnel: R. W. Hagen, BCL
R. E. Clark, M.D., Cardiothoracic Surgery

Support: RR 00396

BCL has collaborated with the Division of Cardiothoracic Surgery in the development of three different perfusion systems. The first system provides automatic control of the extra-corporeal perfusion circuit during cardiovascular surgical procedures. The second system was designed to provide prolonged pulmonary support for infants suffering from respiratory distress syndrome. The third system was developed to support planned pulsatile perfusion studies. The automatic control system has been successfully used in several difficult cases during the past year and system documentation and hardware have been shared with others. Animal experiments using the other two systems will resume during the next year.

C-4. Durability Testing of Prosthetic Heart Valves

Personnel: R. E. Clark, M.D., Cardiothoracic Surgery
R. J. Arnzen, BCL
R. W. Hagen, BCL

Support: RR 00396
HL 13803
Washington University

This is a continuing project for the accelerated fatigue testing of artificial heart valves. The valve tester operates at 31-35 cycles per second using water or glutaraldehyde as the fluid medium. Flows and pressures are measured and photographic recordings are made. Instrumentation efforts have included improving the high-frequency pressure-measuring system using semi-conductors and a time-lapse sequenced photography using a super 8 color movie camera which is triggered in steps of 1/24 of a valve cycle. The instrumentation has provided for accurate measurement and documentation of fatigue wear of commercial hard valves, experimental trileaflet prostheses, and commercial tissue valves. These studies have demonstrated that eccentric and central flow devices made of hard materials may last in excess of 20 years, whereas valves made with flexible polymeric materials, including the tissue valves, have a shorter durability. Of particular concern was the finding that tissue valves lasted in the range of only 40-100 million cycles. The studies have demonstrated that the components that fail in vitro are those which fail in patients at identical fatigue sites. Additionally, those valves that have performed longest with least wear in the machine appear to have the greatest longevity in patients.

C-5. West Pavilion Planning

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

Support: RR 00396
Barnes Hospital

A major expansion of the medical care facilities at Barnes Hospital is in progress. When completed in late 1979 this facility will contain operating rooms, intensive care units, and other patient-care areas. BCL has participated in the definition of patient-monitoring needs in this addition through staff appointment to a Barnes Hospital Monitoring Committee. This committee, together with staff representatives from each of the care areas involved, has engaged in deliberations regarding the unique needs of each area. BCL has prepared a request for proposal (RFP) which documents the results of these deliberations and selected vendors have been invited to respond.

Functional requirements and specifications for twelve different systems capable of monitoring a maximum of ninety-six patients are described in the RFP. Intensive monitoring systems are required for the transplant, respiratory, surgical, and cardiothoracic intensive care units, as well as for the cardiothoracic operating rooms, some general operating and recovery rooms. Telemetry-based ECG-monitoring systems are specified for use in the general surgical care area, the pre-surgical and post-intensive care areas associated with cardiothoracic surgery. The orthopedic and genito-urinary care areas will use hardwired ECG monitoring systems. Portable ECG/temperature monitoring units are to serve the operating and recovery rooms.

BCL's participation in the definition of these monitoring systems has enabled us to share our experiences in monitoring the critically ill with local clinical and administrative personnel. The monitoring system in the existing cardiothoracic surgical intensive care unit (C-1) has stimulated a local appreciation for the SICU style of continuous physiologic monitoring among clinical users.

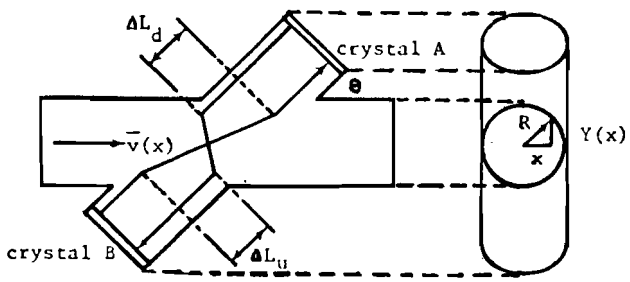
C-6. Ultrasonic Gas-Flow Instrumentation

Personnel: R. W. Hagen, BCL
R. J. Arnzen, BCL
M. L. McCartney, Sc.D., Electrical Engineering
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 22517

A ventilometer has been developed which measures volumetric gas flow by transmitting ultrasonic signals through a volume of the flowing gas. The prototype instrument has been used to acquire respiratory gas-flow data from cardiothoracic surgical patients in an operating room and intensive care unit. The patient monitoring system in the SICU (C-1) is designed to use respiratory gas-flow data for the determination of total thoracic compliance, tidal volume, and potential airway problems in mechanically ventilated patients.

In order to measure gas flow an acoustic signal passes through a specific volume of the gas medium and, in doing so, its propagation path may be changed. The change in the path of acoustic propagation is related to the magnitude and direction of the gas velocity vectors within that specific volume. Propagation path changes are determined by measuring the difference between "upstream" and "downstream" acoustic transmission times. The prototype transducer geometry, illustrated below, provides cylindrical flow and transmission paths.



For the hypothetical transmission paths diagrammed the difference between "upstream" and "downstream" transmission times can be represented by

$$\Delta\Gamma = \frac{4Y(x)\bar{v}(x)}{C^2 \tan\theta} \text{ [sec]}$$

where: $\bar{v}(x)$ is the mean flow velocity in a plane which is parallel to the plane containing the flow/transmission axis and located at position x. C is the free-space velocity of sound in the gas. x, Y(x), R and θ are the geometric variables shown in the figure.

If one assumes acoustic plane-wave propagation with negligible reflections and laminar gas flow then the preceding equation may be expanded to express transducer sensitivity. The transducer sensitivity which relates volumetric flow and the resultant time difference between "upstream" and "downstream" transmissions is given below.

$$\overline{\Delta\Gamma}/\dot{Q} = \frac{1.15\times10^{-3}}{RC^2 \tan\theta} \left[\frac{\text{sec}}{\text{liter/sec}}\right]$$

Experiments have been conducted in order to measure the transducer sensitivity ($\overline{\Delta\Gamma}/\dot{Q}$). A comparison between the measured and calculated sensitivities is tabulated below.

Gas Mixture	$\overline{\Delta\Gamma}/\dot{Q}$ Measured $\left[\frac{\text{microsec}}{\text{liter/sec}}\right]$	$\overline{\Delta\Gamma}/\dot{Q}$ Calculated $\left[\frac{\text{microsec}}{\text{liter/sec}}\right]$	$\frac{\text{Calculated}}{\text{Measured}}$
100% O_2	0.90	1.26	1.40
6.24% CO_2 in air	0.85	1.17	1.38
49.9% N_2 in O_2	0.84	1.18	1.40

The constant of proportionality relating calculated and measured transducer sensitivity is reassuring, but demonstrates the need to consider the composite acoustic signal resulting from an array of point sources with reflected components rather than assuming a simple plane-wave model. Collaboration with the Department of Electrical Engineering is directed toward an improved model of this transducer by using a corrected-ray theory for acoustic signal propagation through fluids[1] and the development of an ultrasonic ventilometer with measurement accuracy suitable for O_2 consumption studies and pulmonary function testing.

(1) M. L. McCartney, C. P. Mudd, and R. D. Livengood, "A Corrected Ray Theory for Acoustic Velocimetry," Journal of the American Acoustical Society, submitted.

C-7. Thermodilution Cardiac-Output Studies

Personnel: R. W. Hagen, BCL
R. J. Arnzen, BCL
R. E. Clark, M.D., Cardiothoracic Surgery
B. F. Spenner, BCL
L. J. Thomas, Jr., BCL

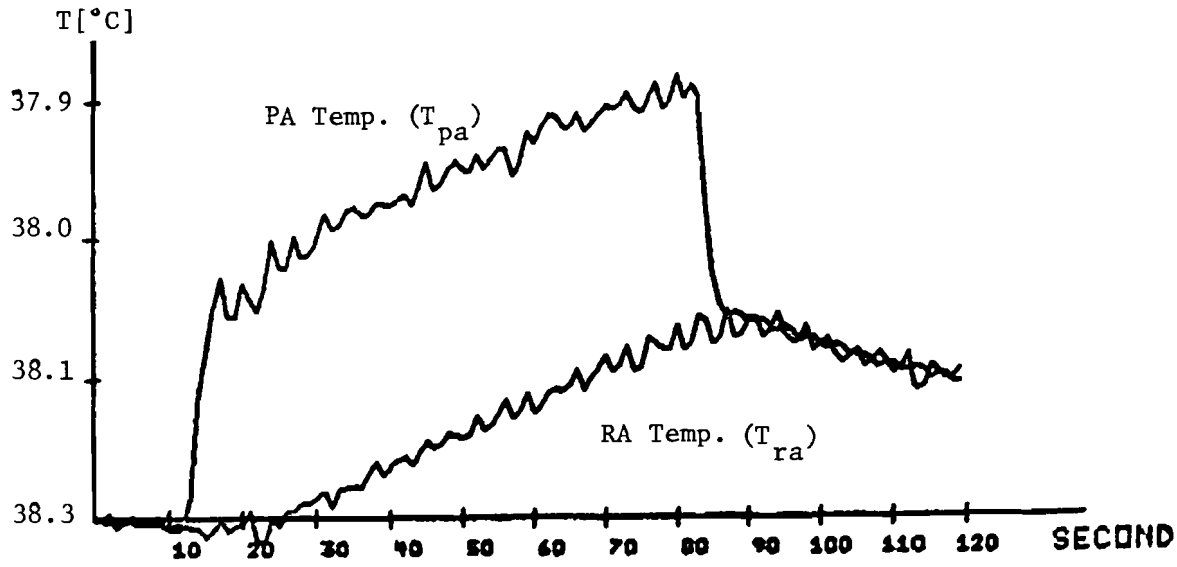
Support: RR 00396

The objective of our thermodilution cardiac output (CO) studies is to develop a convenient and accurate measurement system for clinical application. The popular CO measurement method which requires a bolus injection of thermal indicator has been automated by several commercial firms. However, our studies indicate that the inaccuracies inherent in that method may limit its application, especially in situations where patients are supported by positive pressure ventilation. Our experiments with this method frequently have shown large flow discrepancies between electromagnetic flowmeter and thermal bolus measurements in anesthetized dogs. An alternative expression for calculating cardiac output from the thermal bolus temperature data has been developed. The use of this expression improves the accuracy of the determination, particularly during low cardiac output states. Nevertheless, when cardiac blood flow is highly variable, as in patients who are subjected to positive pressure ventilation, then the conditions necessary to accurately determine flow by bolus indicator methods are not satisfied and significant errors can result.

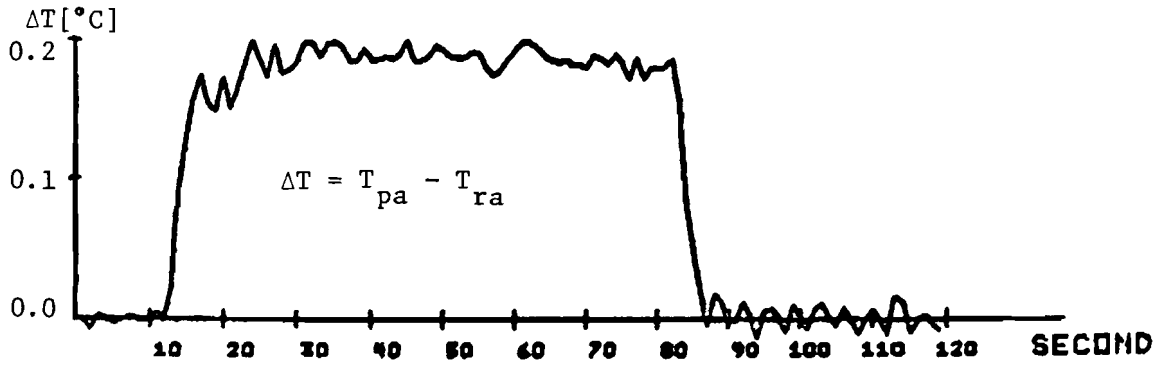
These observations prompted us to investigate a constant-infusion, thermal-indicator technique. The first approach was to measure the temperature in the pulmonary artery (PA) as a constant 0.50 cc/sec flow of room-temperature indicator solution was injected into the right atrium (RA) of anesthetized dogs. The temperature of the blood/indicator mixture in the PA did not approach the expected constant value but, instead, the initial temperature change was followed by a constant time rate of change in temperature. We tentatively assumed that the constant rate of change in temperature was due to recirculation of the thermal indicator. This hypothesis was tested in an experiment that recorded the RA fluid temperature as a constant flow of thermal indicator was infused into the PA. The results confirmed the hypothesis.

In a recent experiment a constant infusion of thermal indicator (room temperature dextrose solution) was injected into the right ventricle (RV) at 1.0 cc/sec as the fluid temperatures in both the PA and RA were

recorded on two channels of the Universal Storage Device (G-4). Aortic blood flow was measured by using an electromagnetic flowmeter and recorded on a third channel of the Universal Storage Device. The figure below shows a typical record of the two temperatures. Recirculation effects and respiratory artifact are apparent on the record.



The following figure displays the difference between the PA and RA temperatures shown above.



This record demonstrates that the temperature difference reaches a constant value if respiratory artifact is rejected. In order to determine cardiac output using this technique the following equation can be applied.

$$F_b(t) = F_i K \frac{(T_{pa}(t) - T_i)}{(T_{pa}(t) - T_{ra}(t))}$$

ρ = density	i = indicator
s = specific heat	b = blood
F = flow	pa = pulmonary artery
T = temperature	ra = right atrium
t = time	$K = \rho_i s_i / \rho_b s_b$

Currently we are examining various signal-processing strategies for evaluating this equation by using the time course of the PA temperature to deduce the steady-state value of the PA-RA temperature difference.

C-8. Cardiac Catheterization Laboratory Enhancement

Personnel: G. H. Brandenburger, BCL
S. A. Garfield, BCL
B. R. Hieb, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
R. G. Lagler, BCL
T. J. Marshall, BCL
H. A. Neuwirth-Hirsh, B.S., Biomedical Engineering
G. C. Oliver, M.D., Medicine
B. Zvolanek, BCL

Support: RR 00396
Jewish Hospital

The cardiac catheterization laboratory computer system (COMCAT) has enjoyed another year of continued routine daily use in acquiring and analyzing cardiovascular data. The extent to which certain of COMCAT's system design goals (PR 13, E-1) were realized was tested this year with the introduction of new catheterization laboratory (cath lab) personnel and new cardiology fellows in the cath lab. The cath lab personnel, with only minimal assistance from the COMCAT design personnel, were able to train the new technicians to operate the data-acquisition phase of COMCAT. New cardiology fellows mastered both data acquisition and data analysis phases of COMCAT in one or two learning sessions.

During this year the final two automated-analysis algorithms were developed, tested, incorporated in COMCAT, and accepted by the cath lab

physicians for routine clinical use. The algorithm for automatic atrial and pulmonary wedge pressure analysis relies upon simultaneously digitized ECG signals to provide additional temporal information. The algorithm identifies A and V waves and X and Y troughs for each individual beat of atrial and pulmonary wedge pressures under normal sinus rhythm conditions, while identifying and ignoring abnormal beats associated with premature ventricular contractions. A modified analysis is invoked for pressures associated with atrial fibrillation for which only X and Y troughs are identified. The algorithm automatically compensates for the time delay between the ECG and pulmonary wedge pressure measurements.

The final set of algorithms performs the waveform pattern recognition and computations for general mean and peak pressure gradient analysis. In addition to standard gradient analysis for each of the four cardiac valves, the algorithm works in conjunction with the unique linked-data-set and analysis features of COMCAT to provide several novel features:

1) Gradients can be computed for arbitrary, physician-defined pressure combinations, a notable example being the aortic root-femoral artery gradient,

2) No simultaneous ECG measurement is required,

3) Pressures to be used for gradient analysis can be conventionally digitized simultaneously, or digitized separately if conditions preclude simultaneous pressure sampling. The algorithm dynamically performs amplitude scaling and beat-by-beat temporal shift to ensure accurate gradient analysis, even for pressures with differing pulse rates and time delays, or measured with different amplifier gains.

Both sets of algorithms have been fully tested and their accuracy and error rates documented, as was done for previous algorithm development (PR 13, E-3).

COMCAT can now completely analyze an entire cardiac catheterization case without operator intervention. Physicians do retain the responsibility for reviewing all analyses. The COMCAT rapid graphic display, hardcopy report, and extensive interactive manual analysis features facilitate not only the review process, but also rapid analysis editing and alteration by the physician.

The complete automated-analysis capability has been in routine clinical use at Jewish Hospital for more than six months and physician acceptance has been excellent.

C-9. Automatic Ventricular Boundary Extraction from Video-Angiographic Data

Personnel: B. Zvolanek, BCL
R. M. Arthur, BCL
G. J. Blaine, BCL
B. R. Hieb, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
G. C. Oliver, M.D., Medicine
D. L. Snyder, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
Jewish Hospital

Steps toward a system for automated analysis of cardiac angiographic data have proceeded as previously outlined (PR 13, E-2). A complete closed-circuit TV (CCTV) video-image acquisition hardware/software subsystem has been developed for the purpose of digitizing serial angiograms from a video tape recorder in stop-frame mode. It is based on the CCTV video slow-scan digitizer interfaced to the PC-12 minicomputer and provides the capability for digitizing 512 horizontal by 244 vertical by 12 bits image arrays from static CCTV video signals. However, to retain uniform sampling in both vertical and horizontal directions, as well as to maintain the 3:4 aspect ratio for a maximum of 243 horizontal TV lines per TV field, the hardware/software subsystem has been configured to digitize 324 horizontal by 243 vertical image arrays from either even or odd TV fields. Other salient capabilities of the subsystem include digitization, display, and storage of variable-size TV rows and columns. Images now can be displayed on the PEP-400 scan-converted display system, as well as saved in system image files for further processing.

A second major effort has been devoted to upgrading the interactive image processing system, IMSYS (PR 13, E-2). It now fully supports the cine-angiographic image acquisition described above. The data-file structure has been carefully configured and implemented so that image, TV row, TV column, and left ventricular (LV) boundary files can be easily accessed for display, graphing, plotting, editing, processing, and storage. The IMSYS utilities now include extensive test programs for the CCTV video slow-scan digitizer, the PC-12 system hardware A/D converter, and the PEP-400 scan-converter display system.

The final major effort has been toward the implementation of the Latter-Day-Saints (LDS) LV boundary extraction algorithm (PR 13, E-2) on the PC-12. This algorithm has been flowcharted and is in the first stages of implementation. After its implementation has been completed its performance will be tested on two sets of data, LV images obtained by the image acquisition subsystem and LV images obtained through cooperative arrangement from the system at LDS Hospital in Salt Lake City. This is to verify the correctness of the algorithm implementation on the

PC-12, as well as to obtain empirical parameters necessary for optimum implementation of the real-time angiographic image-acquisition system.

The actual implementation of the ultimate real-time LV image data acquisition subsystem will depend largely on the results obtained from the performance of the LV boundary extraction algorithm and on the available high-speed A/D converter and disk-storage technologies. It is also closely tied to the implementation of the Digivision display system (G-17) which will have a TV "frame-grab" feature included.

The graphic tablet for manual LV boundary tracing has been acquired and interfaced to the PC-12, but awaits final debugging and incorporation into IMSYS.

C-10. Left-Ventricular Compliance Studies

Personnel: P. A. Ludbrook, M.D., Medicine
J. D. Byrne, CPT, Medicine
B. R. Hieb, M.D., Jewish Hospital
J. Hirsch, B.S., Medicine
P. B. Kurnik, M.D., Medicine
S. R. Phillips, BCL
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646
Washington University

This project is designed to characterize and quantify left ventricular (LV) diastolic compliance in normal subjects, patients with ischemic heart disease or with other cardiac disorders, and to examine the relationship between compliance and extent of ischemic injury, duration of ischemia, and degree of hemodynamic dysfunction. Improved interpretation of changes in conventionally measured hemodynamics and, hence, more effectively directed therapy may result from improved characterization of changes in compliance accompanying myocardial impairment. Changes in diastolic behavior produce alterations in ventricular filling and altered pulmonary capillary pressures, just as do alterations in ventricular systolic contractile performance. However, changes in diastolic function frequently precede alterations of systolic performance, particularly in the setting of acute myocardial ischemia. Furthermore, evaluation of cardiac performance based on conventional isovolumic and ejection-phase indices of systolic function may fail to demonstrate subtle changes in cardiac function which may be reflected by altered parameters of diastolic function. Techniques for quantification of compliance are being developed in the Hemodynamic Laboratory and will be extended to the Clinical Investigation Unit by utilizing noninvasive techniques for left ventricular dimensional analysis.

Quantification of compliance requires simultaneous measurement of left ventricular pressure and myocardial geometry. Earlier work (PR 13, E-4) has focused on developing and refining protocols for safe and accurate measurement of both parameters during diagnostic cardiac catheterization. After measurement of resting right and left heart hemodynamics and cardiac output patients are positioned precisely in the 45° RAO projection. Left ventricular pressures measured via micromanometer and fluid-filled catheter systems are equilibrated initially and before and after each ventriculogram to exclude drift within the micromanometer system. To observe the effects of radiographic contrast injection upon resting hemodynamics, ventricular pressures are recorded initially during submaximal inspiration for an interval similar to that required for ventriculography ("mock run"). Left ventriculography and simultaneous pressure recording then are performed under controlled respiratory conditions, with injection of 30 to 40 ml of sodium and meglumine diatrizoate (Hypague 76) into the ventricle over a 3 sec interval by means of an ECG-triggered injector via an additional angiographic catheter. After the first ventriculogram a pause of 20 min is permitted for dissipation of the hemodynamic and myocardial effects of the contrast agent. When baseline systolic and end-diastolic left ventricular pressures and heart rate are restored a specific drug is administered, or maneuver performed, and the intervention ventriculogram performed. Both the patient and the x-ray equipment are maintained in precisely the same position and projection for both ventriculograms. In patients with known or suspected left ventricular asynergy, RAO-LAO or PA-lateral biplane left ventriculography is substituted for single plane ventriculography.

Left-ventricular pressures, systemic-arterial pressures, right-ventricular pressures, ECG, contrast-injector timing pulses, and cine-frame pulses are recorded on magnetic tape. Left ventriculograms are recorded at 60 frames/sec on 35 mm film via a cesium-iodide image intensifier. The integrated system of electronic equipment and computer programs provides precise synchronization of pressure and volume data, accurate instantaneous measurements of pressure and volume, and their expression in selected formats with the use of an Artronix PC-1200 computer.

The computer system digitizes the analog left ventricular pressure recordings at a rate of 1,000 times per second. Ventricular volumes and wall thicknesses are calculated automatically after the operator has traced the ventriculographic outline directly from the viewing screen of a Vanguard XR-35 projector with a Graf/pen sonic x-y coordinate digitizer. The computer program then matches the frame-by-frame serial ventricular volume data with the simultaneous left ventricular pressure. In addition to display of the pressure-volume loop for the entire cardiac cycle, the program currently provides for analysis of observed pressure-volume data in terms of linear, first and second order exponential and polynomial functions, fit by the least squares technique, together with an analysis of variance to identify the best fit function. It also provides for computation of left ventricular wall thickness and mass from the dimensions of a representative segment of left ventricular wall traced directly from the screen of the cine-projector using a Sonic digitizer. Normalization of parameters of wall stiffness then can be performed for wall thickness, chamber mass,

or more appropriately, the volume-mass ratio (V/Vm), considered to be an important determinant of wall stiffness.

Descriptions of the computer software required for automated computation of diastolic pressure-volume relations in man during cardiac catheterization have been published and the need for accurate digitization of left ventricular pressure at a sampling rate of 1,000/sec documented.[1] In studies performed to evaluate the influence of selected loading factors, nitroglycerin displaced left ventricular diastolic pressure-volume curves downward and leftward without inducing a significant change in slope, suggesting the existence of a family of pressure-volume curves for each ventricle with similar slope but variable position dependent upon immediate loading conditions. Absence of any significant change in the rate constant of the exponential fit to the pressure-volume curve (reflecting an index of left ventricular chamber stiffness) or in the rate of relaxation suggested that the displacement may have been mediated indirectly by relaxation of extracardiac constraints to ventricular distensibility.[2] To investigate this mechanism further the effects of amyl nitrite upon LV pressure-volume relationships were compared to those of nitroglycerin, with simultaneous assessment of right ventricular hemodynamics. Nitroglycerin decreased both coronary perfusion and right ventricular pressures, with downward displacement of the pressure-volume curve. In contrast, amyl nitrite did not change right heart pressures, although it reduced coronary perfusion pressure and, importantly, did not shift the compliance curve. Thus, change in right ventricular hemodynamics related to altered venous return contributed to the downward displacement of the pressure-volume curve after nitroglycerin, possibly mediated by changes in the bulging of the septum into the right ventricle.[3] These results imply that in the left ventricle with compromised function, elevated wall tension and increased myocardial oxygen demands may be influenced more favorably by reduction of both preload and afterload together, than by systemic vascular impedance alone.

Although studies in our own and other laboratories have utilized a simple monoexponential model for fitting observed pressure-volume data with generally satisfactory coefficients of determination (average $r = 0.93$), use of exponential analysis in the intact human heart has not been fully validated. Therefore, we plan to analyze the data using bi- or multi-exponential functions, and polynomial expansion or power series functions, with analysis of variance to identify the most appropriate function. These procedures will be added to the existing software. Also, emphasis will be placed upon determination of the most appropriate form of normalization for individual ventricular dimensions, wall thickness, and geometry, in order to permit valid interpatient comparisons.

Peak negative dP/dt has been used as an index of the activity of the myocardial relaxing system in the intact heart. Aware of the dependency of peak negative dP/dt on hemodynamic variables, however, we and others have utilized a function derived from the rate constant of the exponential pressure decline during the isovolumic portion of diastole as an index of the rate of ventricular relaxation. This parameter has been shown to be more sensitive than peak negative dP/dt for the detection of myocardial

ischemia. Since it is independent of concurrent hemodynamic alterations it appears to be a suitable index of relaxation in the intact heart. This function is included in the existing computer software to assess its correlation with peak negative dP/dt and its sensitivity for detection of changes in ventricular relaxation rate elicited by selected interventions (including pacing and calcium blockade with Nifedipine). We also plan to determine whether normalization of this parameter for heart volume, mass, or geometry will improve its sensitivity for detection of changes in relaxation in individual patients.

Demonstration that newly developed algorithms describe diastolic behavior more precisely than their precursors is difficult in the absence of an accepted "gold standard" index of diastolic function for comparison. Thus, we plan to assess the ability of each to (a) distinguish differences in diastolic behaviour in hearts from normal patients and those with ischemic (or other) myocardial disease, and (b) differentiate changes in diastolic function in response to interventions known to influence isolated muscle.

(1) J. D. Byrne, P. B. Kurnik, J. A. Hirsch, and P. A. Ludbrook, "Computer Assisted Analysis of Left Ventricular (LV) Compliance," Analyzer, vol. 7, no. 2, p. 7, 1977.

(2) P. A. Ludbrook, J. D. Byrne, P. B. Kurnik, and R. C. McKnight, "Influence of Reduction of Preload and Afterload by Nitroglycerin on Left Ventricular Diastolic Pressure-Volume Relations and Relaxation in Man," Circulation, vol. 56, p. 937, 1977.

(3) P. A. Ludbrook, J. D. Byrne, and R. C. McKnight, "The Influence of Right Ventricular Hemodynamics on Left Ventricular Diastolic Pressure-Volume Relations in Man," Circulation, submitted.

C-11. Visual Fields and Ocular Hypertension

Personnel: W. M. Hart, Jr., M.D., Ph.D., Ophthalmology
G. J. Blaine, BCL
D. L. Snyder, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
EY 00336
EY 02044

Glaucoma is a chronic ocular disease characterized by elevated intraocular pressure (ocular hypertension) and progressive visual-field loss. The primary clinical test used in the diagnosis and management of glaucoma is the visual field examination. Although modern instrument design permits accurate quantification of the results of visual-field examination, present techniques of data analysis are qualitative. We are developing a computer-based system for the storage, analysis, and display of visual-field data that will take full advantage of the quantitative information inherent in the test results.

A retrospective study was done[1] involving digitization of visual-field charts taken from the records of patients followed in the Glaucoma Center of the Department of Ophthalmology. Statistical characterization of the visual fields of ocularly normotensive and hypertensive sub-populations has established the presence of quantitative, pressure-related visual-field changes that appear prior to the development of classical, permanent, glaucomatous defects. It is suspected that these more subtle changes are reversible and, more importantly, that they may portend the future development of the permanent defects.

Thus far this project has been carried out using the PC-1200 minicomputer. Recent approval of grant support from the National Eye Institute will fund the purchase of a PDP-11 system to be installed onsite in the Glaucoma Center. Existing programs will be largely transferrable to the new system with minor modifications. The intent is to add prospective data acquisition to the system. In this environment further development will be directed toward (a) improved formats of graphic data display, (b) automation of graphic data record keeping, (c) data analysis (signal processing) of individual and cross population records, and (d) predictive models to estimate the risk of visual-field loss in individuals with ocular hypertension.

[1] W. M. Hart, Jr., M. Yablonski, M. Kass, and B. Becker, "Quantitative Visual Field and Optic Disc Correlates Early in Glaucoma," Archives of Ophthalmology, in press.

C-12. A Microprocessor-Based Data Acquisition System for the Goldmann Perimeter

Personnel: R. K. Hartz, BCL
G. J. Blaine, BCL
W. M. Hart, Jr., M.D., Ph.D., Ophthalmology

Support: RR 00396
EY 00336
EY 02044

In an effort to obtain computer readable visual field data at the time of patient examination a prototype microprocessor-based acquisition system has been designed to interface with a Goldmann perimeter (PR 13, I-2). This system does not attempt to replace the perimetrist, but provides the ability to obtain digitized field information at a reasonable cost.

The M6800-based device contains five major peripherals: 1) a keyboard with an alpha-numeric display for entry of patient related demographic data and test protocol, 2) point-location and stimulus-setting transducers for defining a threshold point, 3) an oscilloscope for field display and editing, 4) a floppy-disk drive for the storage of both demographic and field information, and 5) a serial communication link for transfer of the data to a host minicomputer. The position of the perceived stimulus is transduced by performing the sonic triangulation of a cursor attached to the pantographic linkage of the perimeter. The stimulus level is transduced by noting the pattern of energized magnetic reed switches mounted at each discrete stimulus setting. The accuracy of the computed Cartesian coordinates has been measured to be within $\pm$ 1 mm over the area of interest.

User evaluations have influenced refinements in the system's procedural logic. All functions are accessed from a menu by depressing the appropriate key on the keyboard. This menu includes:

A. Obtain the index of all sessions on the diskette,
B. Retrieve a session from the diskette,
C. Enter a new session (demographic and field data),
D. Edit the demographic data,
E. Edit the current field,
F. Display the current field as a set of closed contours,
G. Save the data on the diskette,
H. Enable serial communication with the host computer.

As referenced in the menu, a session may consist of demographic and field data for either or both eyes. Storage of data on the floppy disk is accomplished on a one-patient-per-diskette basis. Once a patient's name and birthdate have been recorded they may be recalled for identification and computation of age. This reduces the possibility of multiple spelling representations for an individual patient.

A fast algorithm has been developed to draw a straight line between two points. Therefore, isopters can be presented as closed contours during field display or editing. In editing an isopter it is helpful to know its relationship to all previously acquired contours. In addition, the ability to view the field as a set of straight-line contours helps in deciding when enough information has been acquired.

Serial communication has been established with a PC-1200 minicomputer in order to take advantage of existing FORTRAN field-analysis programs. An effort is under way to improve the mechanical attachments to the perimeter. In addition, the system is being packaged as a portable desk unit.

D. Databases for Disease Management and Research

The need for database facilities in several BCL projects became compelling in the early 1970s. The quantity and diversity of data for these projects had grown unmanageable by manual methods. Prior experience underscored the desirability of interactive data entry in order to assure adequate quality and to provide easy access to up-to-date information. Primarily through external funding a minicomputer-based system (MUMPS) capable of supporting database activities was imported, rewritten for the PC-1200, and applied in radiation oncology. Over the intervening years this application has developed into a flourishing installation located within the Mallinckrodt Institute of Radiology (MIR). A fee-for-service installation, the Medical Computing Facilities (MCF), was organized within the Medical School to provide MUMPS service to those who do not desire to operate their own installations. BCL, itself, operated a MUMPS facility for training purposes and investigation into database characteristics until the end of the current period. By that time the applications still operating on the system were deemed mature enough to migrate to either the MCF or MIR installations.

Current activity of the lab includes the development and operation of several information systems for the support of ongoing research projects and routine clinical practice. Almost all of these databases concentrate on chronic diseases because of the importance of a long-term database to clinical investigators studying long-standing illnesses. Our enthusiasm for MUMPS has continued and efforts over the past few years have been in support of the MUMPS Users' Group's (MUG) objective to become self-sufficient. Concurrent with the termination of the major governmental funding, the office of the national MUMPS Users' Group (MUG) executive secretary was moved from BCL to The MITRE Corporation. The standardization of MUMPS and the subsequent commitment of major vendors to the support of that standard has provided promising opportunities for application program transfer and has given added impetus to research in new methods for the development of medical applications packages.

Following a long-standing tradition of the laboratory, an increasing emphasis has been placed on allocating the appropriate computer resource to each information processing task. As the databases which are described in this section mature their analyses become of increasing importance. Because of the richness of the software development and because of the overall suitability of a general-purpose large-scale computer for analysis tasks, they have been performed largely on the University's IBM System/360. SAS, a popular statistical-analysis/data-management package, has provided the primary vehicle for the analyses of databases managed on other computing systems.

Experiences with disparate applications and with the instrumentation of conventional information systems continue to benefit design activities. Development activities directed toward a high-performance information system capable of smooth growth have been federated within the Information Systems Group, a sister Resource group based in the Computer Science Department.

D-1. Glaucoma Center Registries

Personnel: R. H. Greenfield, BCL
W. L. Becker, Ophthalmology
L. A. Bernstein, B.A., Radiology
M. A. Kass, M.D., Ophthalmology
S. J. Knaster, Ophthalmology
J. P. Livingston, A.B., Ophthalmology
L. D. Peterson, D.M.D., Ophthalmology
R. T. Rassieur, Ophthalmology

Support: RR 00396
EY 00336

In 1974 investigators in the Glaucoma Center initiated automation of their records to facilitate clinical research. From BCL's interest in characterizing clinical databases and their usage[1] a collaborative effort emerged. Rather than design a new information system, MISAR[2] was imported (PR 12, D-15). Since then the registries have grown and their supporting programs have been improved. The registries have facilitated both clinical and database research. Utilization of the registries has increased with over 1600 of the Glaucoma Center's estimated two to three thousand charts included three quarters of those entered representing a complete summary of encounters. An indication of growth is given by the following summary of the Glaucoma Registry:

	June 1976	July 1977	May 1978
Records	640	1,272	1,634
Characters	360,000	1,510,000	2,120,000
Avg. No. of characters per record	560	1,190	1,300

In the last year the emphasis of this project has been toward database growth, quality control of Glaucoma Center data, and clinical utilization of the computer stored information. Only modest changes, improvements, and additions to the MUMPS programs themselves have been made.

To assist in quality control of Glaucoma Center data several (10 to 12) subject records from this registry are selected each week for reading and comparison to the medical chart. Omissions and corrections, such as needed examinations and items of history, are noted and reminders to obtain the required data are entered both into the computer and are clipped to the paper chart. These data then are obtained by the examining physician when the subject is next seen.

Clinical utilization of the computer system has been increased. Researchers frequently request searches to select subjects for new studies and to analyze their records. Recent activities include the analysis of

the relationship between HLA type, diabetes mellitus, and glaucoma[3] (D-14), evaluating the results of unilateral irridectomy for narrow-angle glaucoma, monitoring subjects who develop field loss, selecting cases for pilocarpine therapy, and collecting data on epinephrine effectiveness. A new analysis seeks to examine the diurnal variations of intraocular pressure.

Modest changes in the MUMPS-based programs include support for a distribution (frequency) plot, a time-oriented printout, maximum-mean-minimum statistics, and mailing label capabilities. A Davidson phonetic name match permits the user to find record numbers, knowing only the subjects' names. A new "relative" data type has also been introduced. These advances have been described in the literature.[4-8]

In March, 1978, the Oncology Data Center (ODC), Mallinckrodt Institute of Radiology, was selected to provide the computer support for these registries. The ODC under contract transferred and translated the routines and databases from the BCL Artronix PC-1200, running Extended MUMPS-PC, to the ODC Artronix MODULEX, running Extended MUMPS, an implementation of Standard MUMPS. This was done from April through June 1978. It is still too early to evaluate the effect of the new environment (ODC) on our project.

A new printing terminal, a DEC LS-120, four times faster than the previous printer, has been acquired. This terminal greatly speeds searches and printouts from the registries. It is also capable of printing mailing labels and various other forms that the previous thermal printer could not.

[1] R. H. Greenfield, "Clinical Data Base Usage," Proceedings of Third Illinois Conference on Medical Information Systems, pp. 47-56, 1977.

[2] R. H. S. Karpinski and H. L. Bleich, "MISAR: A Miniature Information Storage and Retrieval System," Computers and Biomedical Research, vol. 4, no. 6, pp. 655-660, December 1971.

[3] M. A. Kass, P. F. Palmberg, B. Becker, J. P. Miller, "Histocompatibility Antigens and Primary Open-Angle Glaucoma - A Reassessment," Archives of Ophthalmology, in press.

[4] R. H. Greenfield, M. A. Kass, and J. P. Livingston, "A Computerized Glaucoma Data Base," Archives of Ophthalmology, vol. 95, no. 8, pp. 1365-1367, August 1977.

[5] R. H. Greenfield and M. A. Kass, "A Computerized Glaucoma Data Base Research Resource," Proceedings of the Sixth Annual New England Bioengineering Conference, pp. 93-96, March 1978.

(6) R. H. Greenfield, "A Database System for Ophthalmology," presented at the MUMPS Workshop, Fourth Illinois Conference on Medical Information Systems, Champaign, Illinois, May 1978.

(7) R. H. Greenfield, "Evolution of an Ophthalmologic Data Base," presented at the Seventh Annual Conference of the MUMPS Users' Group, June 1978.

(8) R. H. Greenfield, "OISAR: An Ophthalmic Version of MISAR," presented on the Comparison of Clinical Data Base Systems Panel, Seventh Annual Conference of the MUMPS Users' Group, June 1978.

D-2. MIPI (Myocardial Infarction Patient Information) Database

Personnel:
P. Moore, BCL
L. L. Brandenburger, R.N., Jewish Hospital
A. A. Camuto, BCL
K. W. Clark, BCL
V. R. deMello, M.D., Jewish Hospital
J. R. Humphrey, R.N., Jewish Hospital
S. E. Katzen, BCL
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
B. R. Kurnik, BCL
T. F. Martin, BCL
J. R. Meuleman, BCL
J. P. Miller, BCL
M. T. Mitchell, Jewish Hospital
G. C. Oliver, M.D., Medicine
C. J. O'Rourke, BCL
S. J. Potter, BCL
M. A. Province, BCL
R. Roberts, M.D., Medicine
J. B. Schweitzer, BCL
E. Thornton, BCL

Support:
RR 00396
HL 18808
Barnes Hospital
Jewish Hospital
Washington University

During the past year the MUMPS-based MIPI system (PR 12, A-1; PR 13, D-2) has supported the activities of the Sudden Death Study in three different

areas, 1) the gathering of data and the passage of coded data to a SAS database for statistical analysis, 2) the notification of patients and physicians concerning the termination of the study, and 3) the definition and performance of certain "cleanup" tasks which are needed to complete the database and convert all responses to coded format to facilitate final analyses. Since the registration and enrollment of patients was terminated as of April 1, 1978, effort is now being devoted to these cleanup projects.

The gathering and management of data is still proceeding in all three phases of the project, 1) the recording of CCU admissions for Barnes and Jewish Hospital patients (10/27/75 - 03/31/78) and the gathering of relevant clinical data for all MI cases, 2) the scheduling of Holter recordings and the acquisition of related data elements, and 3) the follow-up done on all surviving MI patients. Software changes in this area have been mainly for the follow-up phase and the development of both MUMPS and SAS programs to transfer data to the SAS database via tape (D-12).

All patients admitted to the Barnes CCU or Jewish MICU were recorded in the system via a Registry Enrollment form, and then depending upon the admitting and final diagnoses, the system controlled the entry of all data relevant to the in-hospital phase of the study. The major emphasis of the data collection process was on patients diagnosed as definite MIs. The CCU stays of these patients were documented and an attempt was made to recruit these patients into the Holter monitoring program if they survived their CCU stay.

For patients recruited into the Holter monitoring program two recordings are made, the first 10-14 days post-MI and another 2-3 months post-MI, and then, for qualifying patients the recordings are continued at three month intervals for a minimum of one year. The MIPI system notes patients to be scheduled and generates all applicable correspondences. A tracking record controls all of the diverse sources of data for each recording, 1) forms completed at the time of recording, 2) the digitization and Argus/H edit of the tape (A-4), 3) the cardiologic review of the Argus/H edit results, 4) serial reading of the 12-lead ECG taken at the time of the Holter recording, 5) successful passage of Cycle-save data to the IBM System/360 and subsequent recycling of digital tapes, and 6) data collected for a special lipid research project. As with the in-hospital phase of the system, tracking records control the entry of data, relate the status of any file, and allow the generation of work lists and management reports.

All surviving MI patients are followed at six-month intervals to determine their post-MI status. A periodic computer listing of patients to be contacted is made. Since the previous source of contact is included the nurse conducting the follow-up can decide upon one of several methods of contact, 1) a computer generated letter to the private physician which contains previous follow-up information and last known address and phone number, 2) a computer generated letter to the patient or some other contact, or 3) a telephone conversation with the patient or some other contact. A computer generated log containing appropriate names, phone numbers, and addresses is used to keep track of attempts to contact by phone. The

MIPI files for Study I patients (A-7) have been updated to include address and phone information and the files for both studies have been updated to contain information on another source of contact. For patients who have expired a blinded summary of the circumstances surrounding death is prepared and coded.

Data from all three phases of the project are transferred to the project's SAS database via tape in a multi-step process. Data are transferred according to the form on which they appear. All qualifying forms are first checked, using the same edits performed at the time of entry and then data from the error-free forms are reformatted according to parameters stored on disk into records suitable for SAS. Any errors found are stored and can be printed in an error report or data conversions can be done automatically. These reformatted records then are stored on tape and read into the SAS database. When the data have been recorded in the SAS database forms which contain no free-text items and/or items needed to make future decisions about a patient are removed from the MIPI database and a paper record of this removal is made.

Presently the data for Study II stored in the MIPI system can be summarized as follows:

	BARNES	JEWISH
Patients Admitted	2737	2730
Diagnosis of Definite MI	603	469
Holtered Patients	235	206
Holter Recordings Made	562	543
In-Hospital Data Forms Entered	17650	16773
In-Hospital Data Forms Passed to SAS	11890	10850

Although data concerning the in-hospital stays of patients are still being gathered because of the delay in the receipt of hospital charts, the "cleanup" of the MIPI database is now proceeding. The system has generated lists of patients who are missing required items such as blood gases, the documentation of concurrent problems, or risk factor and onset of symptom data. These data are being obtained and added to the database through special entry procedures. Recordings of drugs taken either at hospital discharge or at the time of an out-patient recording, which are entered in free-text format, are being converted to codings which indicate the reason for prescription. Because the dosages and schedules of all drugs are entered in a free-text fashion a scheme to standardize these codings and then edit the records of them in the database is being devised. Other data collected in free-text, such as diagnoses, locations of pain, and exercise programs, have been displayed by the system and coding schemes

have been developed. Most of these conversions are being done through special update procedures. For these and all other data cleanup tasks the various tables and table-driven routines have been used to produce lists documenting the problem, make changes automatically where possible, and to provide the basis for the easy generation of new entry or update routines.

The MIPI system has aided project personnel both in the collection of data and the conversion of it to codes. Because the system guides the user through the entry procedure and flags errors immediately the number of errors occuring because of omissions has been few.

D-3. PIM (Protection of Ischemic Myocardium) Database

Personnel: P. Moore, BCL
L. Cusanelli, St. Louis University
A. E. Deyer, R.N., St. Louis University
R. G. Evans, B.A., St. Louis University
S. A. Kaiser, R.N., St. Louis University
J. P. Miller, BCL and Biostatistics
H. S. Mueller, M.D., St. Louis University
J. M. Paine, B.A., Biostatistics

Support: HZ 62960
St. Louis University

The MUMPS-based PIM system (PR 13, D-3) continues to coordinate the double blind propranolol intervention study for the reduction of infarct size, run by St. Louis University and two collaborating institutions, St. John's Mercy Medical Center and Veteran's Administration Hospital. For this study the original Myocardial Infarction Patient Information (MIPI) system (D-2) was generalized and upgraded to produce a more elaborate system. Data are collected concerning the hospital and especially the CCU stay of any patient admitted to any of the three participating CCUs to rule out an MI and then follow-up data are gathered for all recruited patients. As in the MIPI system, the PIM system manages and controls the entry of all data forms once the patient is entered into the system, via tracking records and the immediate flagging of errors. One enhancement to the information system for the PIM study has been the ability to run a batch program which performs those special tracking and editing tasks which are more time consuming and do not require operator intervention. Any files needing special attention are saved until time is available for inspection by the data entry clerk. This feature allows data to be edited by comparing responses made on different forms.

The forms completed documenting the patient's stay are determined by classifying the patient's case into one of four categories, 1) recruited for study, 2) eligible but not recruited, 3) not eligible but MI was diagnosed, and 4) not eligible and no diagnosis of MI. The patient is noted in the PIM system via entry of the CCU Admission Form and the classification of the patient is determined from two other forms completed and entered for all patients, Study Admission and CCU Discharge.

The major thrust of the system revolves around recruited patients for whom 38 different forms are employed. Besides data similar to that obtained by the MIPI system (D-2) hemodynamic measurements are made for 72 hours, metabolic measurements for 4 days, propranolol blood levels for 10 days, and CK measurements for a maximum of 126 hours. Thallium, pyrophosphate, and HSA scans are made at various scheduled intervals during the hospital stay and 6 Holter recordings are also taken. All medications administered during the first 14 days of the hospital stay are recorded with a computer code number and dosage, and any significant event during this time also is noted by time of occurrence via an elaborate coding system. Presently all in-hospital data, except scan data, are entered into the system upon receipt. Since the data which will be collected relating to the thallium, pyrophosphate, and HSA scans have not been fully defined, only the occurrence of the scan has been noted.

Software support for the follow-up phase of the study has been developed over the past year. Recruited patients are scheduled for follow-up visits at 3, 6, and 12 months post-MI, at which time five procedures are done, stress test, HSA scan, ECG, Holter recording, and chest X ray, and a follow-up form is completed. All data except data relating to HSA scans are entered and, as with the in-hospital data, when a file is completed the results are printed for review by the study's investigators. Also, for the follow-up phase, a report of patients to be scheduled can be produced for each hospital.

Another enhancement to the system has been the ability to transfer data from the MUMPS database to a SAS database for statistical analyses. Using the same tables which drive the entry and edit of data, data can be pulled off by form and formatted suitably for entry into a SAS database (D-12). These data then can be put on tape and read into the SAS database using SAS programs also written this past year. The removal of most forms from the MUMPS database after their transfer to the SAS database will require the conversion of free-text data. Therefore no data have been removed from the MUMPS system yet. This problem will be solved by either converting these data or combining all of them into a special form.

In addition to the software developed for the follow-up phase of the study and the transfer of data to the SAS database, special routines were written to make certain calculations and display of the data. These were done so the progress of the study could be reported. The decision was made to perform these tasks in the MUMPS database rather than transfer the data to SAS and have SAS perform the operations because of time constraints and ease of production.

At this time there are 1466 patients registered in the PIM system. Of these, 399 are documented MI's and 89 met the entrance criteria for the propranolol intervention study. So far 68 patients have been recruited into the study. In addition, follow-up data have been collected concerning 86 visits made on 42 patients.

D-4. SCOR Patient Information Database

Personnel: J. Markham, BCL
H. D. Ambos, BCL
M. K. Campbell, R.N., Medicine
A. A. Ehsani, M.D., Preventive Medicine
E. M. Geltman, M.D., Medicine
F. Hummel, BCL
R. Roberts, M.D., Medicine
B. E. Sobel, M.D., Medicine
H. D. Strauss, M.D., Medicine

Support: RR 00396
HL 17646

A system of general purpose programs was written for the SCOR Interdata computer (PR 13, A-12; A-14) to facilitate the entry of discrete SCOR patient data into a computer database. Data records are entered into the Interdata, then written on magnetic tape which is transported to the IBM System/360 where the permanent SAS database (D-12) is maintained. Approximately 450 patients have been entered into the SCOR patient database. In addition to selected items pertaining to the patients' cardiovascular history and physical condition during the hospital stay, follow-up information has been obtained for most of the patients. This database has been utilized in studies of the relationship between indices of ventricular impairment obtained during hospitalization and long term prognosis.

A subset of 63 patients who were less than 60 years old at the time of their initial myocardial infarction and who had survived for at least five days so that their infarct size was estimated enzymatically were followed for up to 21 months. Infarct size index, ISI, in survivors was significantly smaller, 22 ± 2(mean $\pm$ SE) CK-g-eq/(m^2 of BSA), than that in the 5 patients who died, 71 ± 7 ($p<.001$). In addition, the frequency of premature ventricular complexes (PVCs) in 28 patients, as measured by automated analysis of 24-hour Holter tapes obtained between 2 to 21 months after infarction, averaged 241 ± 117 per 24 hours in patients with small infarcts (ISI<15) as compared to 1292 ± 840 in patients with large infarcts (ISI<15) ($p<.05$).[1] Thus, ISI is correlated with the severity of ventricular dysrhythmias as long as one year after MI as well as during the acute episode.

The effect of the site and size of transmural myocardial infarction on long term prognosis was investigated by following 238 patients with transmural myocardial infarction for up to 21 months. In this study inferior MI was found to be associated with a lower mortality rate (17%) than that observed in patients with anterior infarction (37%) one year after MI ($p<.002$).[2,3] Presumably this reflects the fact that in anterior infarction damage is confined to the left ventricle while both ventricles are frequently damaged in inferior infarction.

[1] A. A. Ehsani, M. K. Campbell, E. M. Geltman, R. Roberts, and B. E. Sobel, "Correlations Between Late Ventricular Dysrhythmias and Infarct Size," American Journal of Cardiology, vol. 41, p. 424, 1978 (abstract).

[2] H. D. Strauss, H. D. Ambos, B. E. Sobel, and R. Roberts, "Relationships Between the Site of Infarction, Infarct Size and Mortality," American Journal of Cardiology, vol. 41, p. 427, 1978 (abstract).

[3] H. D. Strauss, B. E. Sobel, and R. Roberts, "The Effect of Site of Infarction on Infarct Size and Mortality," Annals of the Royal College of Physicians and Surgeons of Canada, vol. 11, p. 28, 1978 (abstract).

D-5. Neonatal Database

Personnel: P. Moore, BCL
N. J. Colarelli, BCL
G. R. Cook, BCL
J. A. Johnson, BCL
R. E. Marshall, M.D., Pediatrics
M. M. Maurer, M.D., Pediatrics
C. N. Mead, BCL
E. Thornton, BCL
G. Willer, BCL

Support: RR 00396
Missouri Division of Health, Special Project Grant

From June, 1975 to June, 1977 a MUMPS-based system was developed which allowed for the rapid entry and searching of data documenting admissions (identification information, maternal history, perinatal history, immediate post-delivery data, and initial ICU admission evaluation) of babies to the Neonatal Intensive Care Unit (NICU) at St. Louis Children's Hospital. This database, which was developed on the Artronix PC-1200 system at the Oncology Data Center (ODC), Mallinckrodt Institute of Radiology, was designed around three basic criteria:

1) Patient files could be quickly searched for user-specified criteria,
2) physicians would perform the searches rather than programmers,
3) the system would be for research and not for patient management.

Over an 18 month period admission data were collected on over 800 patients and the coding structure for admission data was improved and stabilized. At the same time methods were developed which allowed for the coding of free-text in-hospital data in a consistent fashion so different neonatologists could review charts and record data similarly.

The system for collection of admission data was then transferred to the ODC Artronix MODULEX system and software was developed to support the collection and manipulation of in-hospital data. The same design criteria were followed for the in-hospital phase of the system. Admission and in-hospital data now are recorded in this new system for all patients admitted to the NICU after July 31, 1977. Patient data stored on the PC-1200 was not transferred.

The entry of a patient's entire file into the system is a multi-step process. The hospital's daily census sheet is checked for any NICU admissions by the data-entry clerk and all new NICU patients are registered into the system by him. Thereafter, the system ensures the computer entry of all required data. Admission data are collected and coded by an LPN, reviewed by the neonatologist, which serves as a quality control, and then entered. When the census sheet is checked for admissions hospital discharges also are noted in the system by the data-entry clerk so the system can assign the chart to one of the neonatologists for coding of in-hospital data. Monthly a list of patient names and hospital identification numbers, sorted by the neonatologist, is generated and sent to medical records so charts can be pulled. Final disposition and in-hospital data are coded by the appropriate neonatologist with a problem/concurrent event/complication approach (each date of onset is recorded also), reviewed by the neonatologist, and then entered. The in-hospital data are recorded according to 17 major classifications, 1) pulmonary, 2) infectious disease, 3) cardiovascular, 4) G.I. disorders, 5) endocrine, 6) hematology, 7) tumors, 8) metabolic, 9) neurology, 10) fluids and electrolytes, 11) immune disorders, 12) renal -- G.U., 13) skin, 14) orthopedics, 15) ophthalmology, 16) diagnostic procedures, and 17) events of interest. All data which are entered into the system are reviewed by the data-entry clerk and then printed out and checked by other personnel for typing errors. A copy of the in-hospital data is printed after this review and placed in each patient's chart. Certain charts are flagged by the system for a second review by the neonatologist, which serves as a quality control (for both admission and in-hospital data) so the validity of the system can be continually monitored.

All patient data collected for this system are stored in both a master file and an inverted file. For the inverted file each patient is assigned a bit position and then bits are set on to indicate the presence of responses. Data are stored in this manner so the database can be rapidly

searched by physicians using criteria they have specified. This is the major goal of the system. Physicians manipulate the data in order to look for interesting subsets of patients. In addition to searches of the database, the inverted bit files can be used to produce histograms and cross-reference tables. Data are stored in the master file so that printouts of patients' files or subsets of patients' files can be produced easily.

Since conversion to the MODULEX system and start-up of the in-hospital phase of the system ran smoothly, many enhancements were made to the system during the past year. Routines have been written to perform various analyses of the inverted bit file and comparisons of the master file and inverted bit file so the database can be checked for any file errors. Update routines have been written so data can be changed even after they have been filed in the inverted bit files. A monthly management report has been implemented, which documents the month's patient activity in comparison with previous months, assigns charts for review of in-hospital data, summarizes the progress of data acquisition, and publishes other counts of interest. The generation of various printouts has been improved and the ability to specify a group of patients as a search subset has been developed. In addition, a display of search results via cross-reference tables or histograms has been implemented.

Currently there are 500 patients registered in the system. Although there have been some problems in obtaining in-hospital data, this should be rectified shortly. Future plans for the system include the ability to search the in-hospital data for complications which occurred according to certain rules of precedence and/or time constraints. This enhancement is being made at the suggestion of the neonatologists.

D-6. Computerization of Cardiology Tests/Reports at Jewish Hospital

Personnel: R. J. Krone, M.D., Jewish Hospital
M. Broderson, Jewish Hospital
J. P. Miller, BCL and Biostatistics
P. Moore, BCL
M. Wade, Jewish Hospital

Support: HL 18808
Jewish Hospital

The feasibility of computerization of cardiology reports was demonstrated as a pilot project (PR 13, D-6) and currently is in the process of being implemented on a production basis at the Washington University Medical Computing Facility. The system was designed to meet the following goals: 1) provide accurate data regarding all interactions of individual

patients with the cardiology division, 2) reduce the professional and secretarial time required to generate clinical reports, 3) establish a database in a computer readable form to facilitate data management and clinical research, and 4) be economically viable as a clinical tool, paying for itself from savings in secretarial and professional time as well as reduced copying costs for the multiple reports. It is operated by the divisional secretaries rather than a specialized computer technician.

The pilot project involves the automation of the stress lab reports. The stress test is divided into two parts. Part I requires no physician over-read and includes information such as indication for test, medications taken, details regarding the actual test such as tread-mill speed and grade, as well as any symptoms which developed. These data are entered by the secretary prior to physician review. The actual stress test is read by a cardiac fellow on a daily basis and twice a week the fellow, a cardiologist, and a secretary gather at the video terminal for a reading session. Comments regarding all aspects of the test are entered in code and then expanded into full sentences for the report. The report is entered by the secretary while the staff cardiologist and fellow are checking the next report. The completed report is displayed on the video terminal and over-read quickly by the physicians before being approved. The actual printing of the report takes place after the reading session with as many copies as required being produced. With this system reports are over-read, entered into the computer, and proofread at an average of about three minutes per report. In most cases the report can be sent out the next day. The system has met with enthusiastic acceptance by the secretaries and staff and is also acceptable to the fellows. It has been the sole method of stress test report generation since June, 1977.

The final system will have some modifications in its further implementation. Several changes in text have been made to correct deficiencies which were noted in the previously coded responses. The patient index will be stored on-line in the MUMPS system, but all the detailed data from individual tests are to be transferred to tape in a form which would be readable by SAS (D-12). Simple searches for diagnoses will utilize MUMPS search packages. Searches for full details of the individual's test will be implemented on the S/360 using SAS. Preliminary design work on cardiac catheterization reports and coronary angiogram reports has been completed and is expected to be implemented within the next year.

D-7. Information Systems Group: Experimental System

Personnel: J. R. Cox, Jr., Computer Science, BCL, and Computer Systems Laboratory
G. L. Bickmore, BCL and Computer Systems Laboratory
G. J. Blaine, BCL
R. E. Hitchens, BCL
R. E. Olson, B.S., Computer Science and Computer Systems Laboratory
S. R. Phillips, BCL
S. L. Rankin, B.S., Computer Science

Support: RR 00396
Washington University

A modest experiment was defined to study the feasibility of a proposed high-performance information system configuration.(1) The experimental implementation(2) consists of two user modules, two data modules, and a 2 x 2 crosspoint communication switch.

The PDP-11 family of processors (LSI-11, PDP-11/34) was selected for the user module processor and data module processor because of software compatibility, ready availability of peripheral devices, and an expanding "local" user community. Storage within the data module is provided by 80 Mbyte disk storage modules.(3)

The 2 x 2 crosspoint switch has been implemented using restructured macromodules (RMMs). RMM compatible controllers have been developed which provide full-duplex channels supported by direct memory access for both the PDP-11/34 and LSI-11 computers.

One data module is equipped with a removable RK05-compatible cartridge drive disk to facilitate program transfer between the experimental system and other PDP-11 resources used for software development. A bootstrap loading facility was developed, which permits program loading of both user modules and the second data module through the crosspoint switch.

The experimental system provides a facility for time/space cost evaluations of the multitasking system software developments(4) and system instrumentation.

(1) J. R. Cox, Jr., "Development of a Technology for High-Performance Information Systems," Information Systems Group, Working Paper No. 1, 1976.

(2) G. J. Blaine, J. R. Cox, Jr., R. E. Olson, "An Experimental Information System," Information Systems Group, Working Paper No. 17, 1978.

(3)G. J. Blaine, J. P. Rankin, "File Module: Storage Unit Description," Information Systems Group, Working Paper No. 11, 1977.

(4)R. A. Dammkoehler, "Multitasking Systems Evaluation," Information Systems Group, Working Paper No. 3, 1976.

D-8. A Research Bibliography System

Personnel: R. H. Greenfield, BCL

Support: RR 00396

An automated bibliography system[1] was created in 1975 to support the study of clinical data files and their usage (PR 12, D-8; PR 13, D-15). Only modest improvements have been made to the programs in the last year. The major emphasis has been the utilization of the programs to support a comprehensive personal bibliography on computerized information systems in medicine, ophthalmologic uses of computers, bibliographic uses of computers in medicine, databases and information retrieval, and other related areas of interest. During the past year the number of citations increased from 700 to approximately 900.

In May, 1978, this system was transferred to the Artronix MODULEX computer at the Oncology Data Center, Mallinckrodt Institute of Radiology. The programs now are being modified to operate in the Standard MUMPS environment. The previously published documentation[2] will be revised.

(1)R. H. Greenfield, "A Unique On-Line/Off-Line Bibliographic System," Proceedings of the 1977 MUMPS Users' Group Meeting, pp. 41-46, 1977.

(2)R. H. Greenfield, "A Bibliography System," BCL Monograph No. 311, February 1977.

D-9. MUG Publications and Plans Towards Self-Sufficiency

Personnel: J. Zimmerman, BCL
J. Rothmeier, Ph.D., University of Massachusetts Medical Center
R. F. Walters, Ph.D., University of California, Davis
R. E. Zapolin, M.S., The MITRE Corporation

Support: HS 01540
The MITRE Corporation

In September, 1977, the Executive Directorship of the international MUMPS Users' Group passed from Dr. Joan Zimmerman at the Biomedical Computer Laboratory to Mr. Richard E. Zapolin at The MITRE Corporation, Bedford, Massachusetts. The machine-readable mailing list of almost 5000 people, relevant MUMPS code, and copies of the dozen publications available from MUG were forwarded to MITRE. The MITRE Corporation offered $20,000 to continue and expand the activities of the MUMPS Users' Group, following the demonstrated success of the Group (PR 13, D-9). The new projects begun this year with the support of The MITRE Corporation include a tutorial "Introduction to Standard MUMPS" (at the Biomedical Computer Laboratory), translation into Standard MUMPS of a risk-factor program and the CONVERSE questionnaire driver (at the University of Massachusetts Medical Center), development of a self-contained personal MUMPS computer based on the Z-80 microcomputer (at The MITRE Corporation), and the revision of the MUMPS Development Committee's Primer (at the University of California, Davis).

D-10. MUMPS Application Transfer

Personnel: J. Zimmerman, BCL
R. K. Stimac, BCL

Support: RR 00396
HS 01540
HS 02760

The "QUEST" questionnaire driver, interactive Standard MUMPS teaching program, and the "DOC" documentation package (PR 13, D-10) were expanded and documented. All three were submitted to the DECUS (Digital Equipment Computer Users Society) and the BCTIC (Biomedical Computing Technology Information Center) libraries and are available nationwide from those sources. Copies of the revised material were sent to:

1. Digital Equipment Corporation (Paul Stylos),
2. Frankfurt University (Dr. Wolfgang Giere),
3. George Washington University (Dr. Bruce Waxman),

4. Hospital Data Center of Virginia (Richard O. Dozier),
5. Ohio State University (Brian Pflug),
6. Prime Computer (John Bowles),
7. University College Hospital (David Hall),
8. University of Kentucky (Patty Cole),
9. University of Michigan (Cecil Murray),
10. Veteran's Administration, Seattle (Dr. Arden Forrey),

and were sent also to representatives of MUG-Europe and MUG-Japan for distribution outside of North America.

DOC was used on itself, on QUEST, and on the 923-routine COSTAR package. Its major values were, first, in detecting syntax errors in code, second, in providing cross reference listings of local and global variables by the routines in which they appeared, and third, in listing the routines invoking and invoked by each routine. Several other capabilities (PR 13, D-10) were helpful.

The Standard MUMPS teaching program was used locally by nine novice students, none of whom had significant previous experience in MUMPS. Among the areas in which students called for expansion of the program were in explaining the use of the terminal and in the distinction between hardware and software. They also asked for more explanations on when to use various punctuation symbols, particularly commas, quotation marks, and spaces. The use of the "free-text" question type[1] was particularly useful in finding out what errors students would make in writing MUMPS code. Many of their errors were due to carelessness, giving the teaching program the opportunity to emphasize the care and precision required in specifying computer instructions. Other difficulties detected from inappropriate free-text responses were mostly in the areas of specifying a series of arguments for the KILL command, use of the DO command for temporary (rather than permanent) branching, the $DATA and $NEXT functions, the pattern-match operator, and the concatenation operator. Student responses were, on the whole, positive toward the program, encouraging us to revise it and use it more widely.

[1] C. R. Brigham, J. D. Halverson, and J. Zimmerman, "QUEST: A Teaching Program Driver," Journal of Computer-Based Instruction, vol. 3, no. 2, pp. 42-50, November 1976.

D-11. MESCH and Computers for the Physician's Office

Personnel: J. Zimmerman, BCL
S. B. Boxerman, D.Sc., Health Administration and Planning Program
R. S. Gordon, B.A., Baptist Memorial Hospital, Memphis
A. L. Rector, M.D., University of Nottingham, England
R. K. Stimac, BCL
D. K. Tao, BCL

Support: RR 00396
HS 01540
HS 02760
Washington University

Results of last year's survey of computer applications in 72 St. Louis group practices (PR 13, D-13) were compiled.(1) The major conclusions were:

1. 40 (56%) of the practices in St. Louis City and County used automation,

2. 97% of the computer-using practices had financial (especially billing and accounting) applications, 64% had administrative applications, only 2.5% (1 of the 40) had medical applications,

3. For half the practices, at least 2 months elapsed from the time that automation was put into operation to the time it was considered integrated into the office routine,

4. Reliance on vendors was strong, with 61% citing vendors as a source of information (two-thirds of which cited only vendors),

5. Advantages experienced by at least a third of the practices that used automation were that work was done faster, information was more readily available, and costs were reduced,

6. The most commonly cited disadvantage was inflexibility,

7. Most (89%) believed that automation was preferable to their previous manual system.

A ground work of systems design and analysis before implementing a computer system was recommended in a second paper.(2) Practices were advised how they could proceed to analyze their needs, beginning with a specification of missions, objectives, constraints, and strategies. The process was illustrated by three case studies.

Information on automation for ambulatory care was compiled into a book, "Computers for the Physician's Office."[3] The text begins with a review of services that can be facilitated by computer and an introduction to technical terms and concepts. Operational record systems and ancillary systems are illustrated. Other major topics include the structure of the medical record (with emphasis on the problem-oriented record), data-entry methods, security and privacy, evaluation, and a "do it yourself" approach to implementation of the automated record.

The Multi-Environment Scheme (MESCH) questionnaire driver (PR 13, D-12) has been translated into Standard MUMPS and expanded to allow more capabilities, including complex branching. Frame types added include the ability to handle branching logic by using answers to frames asked earlier, and to enter numeric answers within prespecified ranges. Multiple-line free-text replies are now allowed, up to 18 lines may be entered instead of only 1. Editing capabilities have been expanded, particularly by allowing any frame to change its question type or even by changing the entire frame completely.

The material described above is forming the basis of a MESCH questionnaire that can lead the representatives of a group practice through a specification of their needs and help them design a suitable system.

[1] J. Zimmerman, R. S. Gordon, D. K. Tao, and S. B. Boxerman, "The Acceptability of Computer Applications to Group Practice," The Journal of Medical Systems, in press.

[2] S. B. Boxerman, D. K. Tao, and J. Zimmerman, "The Decision to Automate: How to Make it," Group Practice, vol. 27, no. 2, pp. 20-25, March/April 1978.

[3] J. Zimmerman and A. L. Rector, Computers for the Physician's Office, Research Studies Press, in press.

D-12. SAS As an IBM System/360 Data Management Tool

Personnel: J. P. Miller, BCL and Biostatistics
J. Achtenberg, A.B., Medicine
F. Hummel, BCL
M. M. McCrate, B.S., Biostatistics
P. Moore, BCL
J. M. Paine, B.A., Biostatistics
S. J. Potter, BCL
M. A. Province, BCL

Support: RR 00396
AM 17904
EY 00336
HL 17646
HL 18808
HZ 62960
Washington University

The utilization of minicomputers under MUMPS as an environment for the interactive data acquisition and the management of the information-gathering process has been quite successful for a number of projects involving the study of chronic diseases (D-1, D-2, D-3, D-4). However, for analytic tasks requiring the processing of large sets of patient data, the application of more computationally burdensome statistical procedures, or the production of large reports, the general-purpose IBM System/360 has provided a more appropriate environment.[1,2]

Because of its strong data management components, SAS 76[3] has continued to be the chief tool for the analyses of databases gathered with these other computer systems (PR 13, D-17).

By providing the necessary tools for the listing, creation, and deletion of data sets within a SAS library, SAS removes from the user much of the administrative burden associated with database management on a large IBM System/360. Industry-compatible tape has been the primary mode for interfacing the IBM System/360 to the data collection computers, including the MCF machine (D-2, D-3), the SCOR computer system (A-14, D-4), and the MUMPS PC System (D-1, D-14). The interface between DATA3, a table-driven interactive data-entry and management system,[4] and SAS has been made through a three-stage semi-automatic process which utilizes the tables used to drive the data-entry/retrieval operations.[5]

SAS facilities for rearranging records within a data set or merging information across data sets are clearly superior to other statistical/data management systems. Easy merging of information from separate data sets facilitates studies in which there are multiple pathways by which the data become available to the SAS system, as well as providing a friendly environment for a multiple-form data collection strategy, as used in the MIPI and PIM studies (D-2, D-3). A common problem in the analysis of

longitudinal data results from the fact that for some analyses one may wish to treat each encounter with the patient as a separate observation, while for others, the patient and all of his encounters become the unit of analysis. Other analyses are to be performed on a subset of data, or analyses repeated for each of a collection of subsets. Often it is necessary to compute derived measures as functions of the original data. All of these operations are facilitated by the programming statements available in SAS.

In support of the analysis and data cleaning operations it is often desirable to produce selected lists of the database or subsets thereof for further examination. These lists, either in a quick and dirty or in a more stylized report form, are exemplary of the traditional data processing operations performed on the database with the resulting printed and/or microfiche reports produced for subsequent review. Easily accessible archival data storage, file updating operations (in either old master/new master or isolated data value forms), are also often desired. A new SAS procedure, DISPLAY, was written to produce a well annotated display of the data suitable for inclusion in patient charts or for manual review. DISPLAY produces one or more pages of output for each observation with each variable listed along with its label and the formatted value.

In addition to the data management facilities described above, SAS provides a full complement of standard statistical analysis routines commonly utilized for the subsequent analysis of clinical data. The general linear model procedure (analysis of variance, analysis of covariance, multiple regression) represents state of the art techniques for the analysis of the unbalanced data sets normally encountered in clinical research.

In order to facilitate the use of SAS a number of ROSPROCs have been developed to allow the user to easily utilize ROSCOE, a S/360 based text editor which includes facilities for the submitting and retrieving of batch S/360 jobs. In several instances terminals normally attached to MUMPS based systems have been utilized to connect to the S/360. A preliminary design has been completed to enable the MUMPS based systems operating on the MCF system to be directly connected to the S/360 for the submission of SAS jobs.

(1)K. W. Clark, P. Moore, J. P. Miller, and L. J. Thomas, Jr., "A Total Systems Approach to the Quantitative Analysis of Holter Recorded ECGs," Proceedings of the Second International Symposium on Ambulatory Monitoring, Harrow, United Kingdom, September 1977, in press.

(2)J. P. Miller, P. Moore, J. Achtenberg, and L. J. Thomas, Jr., "Computer Resource Allocation for Long-Term Clinical Studies," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 77CH1254-2C, pp. 151-159, 1977.

(3) A. J. Barr, J. H. Goodnight, J. P. Sall, and J. T. Helwig, A User's Guide to SAS 76, SAS Institute, Raleigh, North Carolina, 1976.

(4) J. A. Achtenberg, J. P. Miller, P. Cryer, and J. Santiago, "Data 3 -- A Form Management System," in Proceedings of the 1976 MUMPS Users' Group Meeting, MUMPS Users' Group, St. Louis, Missouri, pp. 1-8, 1976.

(5) J. Achtenberg and J. P. Miller, "Interfacing a MUMPS-Based Data Entry System to SAS," in Proceedings of the Third Annual Conference of the SAS Users Group International, SAS Institute, Inc., Raleigh, North Carolina, pp. 161-167, 1978.

D-13. Methodological and Technical Developments for Risk Function Analysis

Personnel: J. P. Miller, BCL and Biostatistics
G. C. Oliver, M.D., Medicine
M. A. Province, BCL
L. J. Thomas, Jr., BCL
R. Wette, D.Sc., Biostatistics

Support: RR 00396
HL 18808
HZ 62960
Washington University

A frequent problem in the analysis of data obtained on chronic diseases is to select a mathematical function which will allow the estimation of the probability of some future event, such as death, given a set of data for a patient. Alternative formulations of the problem deal with the estimation of the expected survival distribution for a group. Generally, data are available on a vector of observations and the subsequent presence (and its time of occurrence) or absence of the predicted event for a group of patients.

Risk function analysis may be performed for several distinct, but overlapping, purposes. First is the empirical identification of individuals with increased risk of morbidity or mortality. Treatments or observations with significant monetary cost or potential for adverse reactions may be justified only for high-risk patients. High-risk patient participation may provide for more efficient evaluations of interventions. Secondly, by identifying which variables contribute to the ability to predict a future event it may be possible to more clearly elucidate the potential mechanisms of the subsequent event, thus providing clues for potential intervention strategies. Finally, risk function analysis should allow

the evaluation of the independence of a risk marker or of an observed intervention in predicting subsequent morbidity or mortality.

As previously described (PR 13, D-18), there are four statistical models which are commonly utilized for risk function analysis when the object is to predict the probability of occurrence of an event within a specified period of time. Linear discriminant analysis (LDA) and quadratic discriminant analysis are both based on least square techniques and are supported by many different statistical packages. The third model involves the identification of subgroups of patients who are homogenous with respect to the risk of the subsequent event. The use of this model as explicated by Feinstein[1] is dependent upon enlightened inquiry of a database and relies upon relatively straightforward statistical computations. The fourth model, that of the multivariate logistic, has been unsupported by all of the widely available statistical packages. A new statistical procedure (PROC PREDICT)[2] was implemented as part of the SAS[3] system. PREDICT utilizes the solution from an LDA as initial values and rapidly converges to the maximum likelihood estimates of the parameters. By utilizing the matrix of second partial derivatives of the estimates of the parameters as estimates of the asymptotic variance-covariance matrix, confidence intervals and statistical tests may be made.

For many years the examination of survival times has been examined by utilizing the actuarial life-table method.[4] Statisticians have long been wary of the approach but the lack of accessible software has inhibited the widespread application of more suitable techniques. During the past year the Health Sciences Computing Facility at UCLA implemented a new improved survival analysis program[5] which supports the Kaplan-Meier estimates of the survival distribution from censored samples (not all individuals being observed until death). This program also supports tests for the equality of two or more survival curves. This allows for the examination of the value of a single risk factor's influence on the survival curves. While this is of some utility in risk function analysis, its lack of dealing with risk factors in a multivariate fashion is severely limiting. A model due to Cox[6] attempts to deal with such situations under the assumption of proportional hazards. Statistical software for the solution of this model is not widely available and its interpretation remains an item of statistical research. We have obtained copies of programs from several sources and anticipate the implementation of a SAS procedure drawing on these programs.

If all of the risk factors are categorical, then the multivariate logistic may be solved by the use of the loglinear model techniques developed for the analysis of multidimensional contingency tables. We have utilized this technique in the evaluation of HLA antigens as risk factors for glaucoma (D-14).[7] Categorizing continuous variables both loses power and protects against a wide class of non-linear relationships between a risk factor and outcome. Alternative strategies include transformations of the variables to a form thought to be linear in risk. A new methodology involving a regression on the original scale to the expected values of the normal order statistics has been developed.[8]

While recent advances have been made in the estimation of error rates by jack-knife techniques, the best method of estimating the adequacy and accuracy of a particular statistical model is the validation of the estimation procedure in a separate replication sample. For the study of sudden death (A-7) we have two separate studies, disjoint in time, and two institutions at each time, so that estimates may be made from one study and replicated in the other, or from one institution and replicated in the other. The PIM study (D-3) which utilizes many of the same data collection protocols offers still another replication sample with a totally different set of institutions and investigators.

(1) A. R. Feinstein, Clinical Biostatistics, C. V. Mosby, St. Louis, 1977.

(2) J. P. Miller, M. M. McCrate, M. A. Province, and R. Wette, "Maximum Likelihood Estimation of the Multivariate Logistic," Proceedings of the Third Annual Conference of the SAS Users Group, International, SAS, Inc., Raleigh, North Carolina, pp. 303-305, 1978.

(3) A. J. Barr, J. H. Goodnight, J. P. Sall, and J. T. Helwig, A User's Guide to SAS 76, SAS Institute, Raleigh, North Carolina, 1976.

(4) S. J. Cutler and F. Ederer, "Maximum Utilization of the Life Table Method in Analyzing Survival," Journal of Chronic Diseases, vol. 8, pp. 699-713, 1958.

(5) J. Benedetti and K. Yuen, "Life Tables and Survival Functions," in BMDP-77: Biomedical Computer Programs, P-Series, W. J. Dixon and M. B. Brown, eds., University of California Press, Berkeley, pp. 743-770, 1977.

(6) D. R. Cox, "Regression Models and Life-Tables," Journal of the Royal Statistical Society, Series B, vol. 35, pp. 187-220, 1972.

(7) J. P. Miller, E. L. Spitznagel, Jr., and M. A. Kass, "The Use of Log-linear and Multivariate Logistic Models to Assess the Associations Between HLA Antigen Responses and Disease," accepted for presentation at the 1978 Joint Statistical Meetings, San Diego, California, August 1978; to be published in the Proceedings of the Statistical Computing Section of ASA.

(8) J. P. Miller, "A Parsimonious Approach to Data Transformation," 1977 Proceedings of the Statistical Computing Section, American Statistical Association, Washington, D.C., pp. 327-331, 1977.

D-14. Statistical Analysis of the Relationship of HLA and Diabetes to Glaucoma

Personnel: J. P. Miller, A.B., Biostatistics
B. Becker, M.D., Ophthalmology
R. H. Greenfield, BCL
M. A. Kass, M.D., Ophthalmology
J. P. Livingston, A.B., Ophthalmology
L. D. Peterson, D.M.D., Ophthalmology
R. T. Rassieur, Ophthalmology
E. L. Spitznagel, Jr., Ph.D., Biostatistics
R. Wette, D.Sc., Biostatistics

Support: RR 00396
EY 00336
Washington University

Previous statistical utilization of the Glaucoma Center data has been in terms of small subsets of patients with particular characteristics, who were evaluated according to more detailed protocols (D-1). A continuing interest within the Department of Ophthalmology is the association between specific HLA haplotypes and the presence of glaucoma. Since diabetics appear to be at increased risk of glaucoma and diabetes also has been associated with specific HLA haplotypes, a study of the relationship between the two diseases and HLA has been conducted.

As previously described (PR 13, D-19), the relevant information from the Glaucoma Center Registry (D-1) was transferred from the MUMPS database system to the S/360 for analysis with SAS (D-12). Since this reanalysis failed to replicate the previously reported associations between HLA and glaucoma, considerable effort was expended to insure an analysis which was appropriately reflective of our experience. All diagnoses of glaucoma were reviewed by two ophthalmologists who were blind to the HLA typing results. Only patients with primary open angle glaucoma (POAG) were labeled as having glaucoma, and all patients with atypical case histories were excluded. The utility of having the patient records in a computer readable format greatly facilitated the exploration of a number of alternative hypotheses which were entertained as providing possible reasons for the failure to replicate.

While weak associations with POAG and decreased prevalence of the A1 antigen and increased prevalence of Aw31 and B7 were noted in the white subpopulation, these results were not confirmed when compared to an analysis of patients not in the Glaucoma Center, but who were referred to the full time staff of the Department of Ophthalmology.[1] In an effort to simultaneously control for the effects of race, diabetic diagnostic status, and age, loglinear and multivariate logistic models (D-13) were utilized.[2] These analyses also failed to confirm the earlier reported strong associations between HLA antigens and POAG.

(1) M. A. Kass, P. Palmberg, B. Becker, and J. P. Miller, "Histocompatibility Antigens and Primary Open-Angle Glaucoma - A Reassessment," Archives of Ophthalmology, in press.

(2) J. P. Miller, E. Spitznagel, Jr., and M. A. Kass, "The Use of Loglinear and Multivariate Logistic Models to Assess the Associations Between HLA Antigens and Disease," accepted for presentation at the 1978 Joint Statistical Meetings, San Diego, California, August 1978; to be published in the Proceedings of the Stastical Computing Section of ASA.

E. Speech and Hearing

The main thrust of the early collaboration with Central Institute for the Deaf was to develop digital instrumentation suited to speech-and-hearing research. The first systems that were developed, a Random-Access, Programmable (RAP-I) digital recorder and a computer system for processing sampled speech, continue to be used in a variety of research applications, including the analysis of sampled speech sounds and glottal source waveforms and the synthesis and tailoring of speech sounds for psychoacoustic experiments with human and animal subjects.

The RAP-I system has been invaluable in the study of speech perception with infants, adults, hearing-impaired subjects, and animals. Because of its convenience and simplicity of operation, the RAP-I system also is being used by a number of persons in unexpected ways. Examples are the study of speech waveforms, the evaluation of hearing aids, and the measurement of spectral characteristics of complex sounds in conjunction with a wave analyzer.

The proven usefulness of these first two systems has led to the development of newer RAP systems that can be programmed to accommodate a variety of psychoacoustic experiments and a central computer system with increased sampled data capability. This work is nearly finished and laboratories at Central Institute for the Deaf presently are undergoing renovation to accommodate these new systems.

More recently a major emphasis has been directed towards certain basic questions related to hearing and deafness, that require the digital instrumentation available through the collaboration. These areas of study include the following:

1) Measurements of psychophysical characteristics of electrocutaneous stimulation to determine if this sensory modality can serve as a substitute input for speech for profoundly deaf patients.

2) The measurement of glottal source characteristics of normal and deaf talkers. This study has involved developing glottal tube instrumentation and supporting computer programs.

3) Psychoacoustic studies related to questions of speech perception. Simplified speech-like sounds and exemplary speech sounds have been generated and used for testing human adults and infants and chinchillas.

These speech discrimination studies provide additional impetus for continued development of the Spenner-Cox model of the cochlea. Since the model is physically based it can serve as a guide in choosing appropriate scaling relations based on anatomical measurements.

4) More recent work has begun on developing methods for generating rapidly changing visual displays that can be used in lipreading studies. This work was started in an attempt to delineate the facial cues that are important in lipreading.

E-1. Hydromechanics of the Cochlea

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

Support: RR 00396

Our desire to model the hydro-mechanical operation of the cochlea stems from our belief that studying the response of such a model operating in the time-domain may be helpful in suggesting some operational characteristics of the cochlea which have not been suggested by the limited number of available cochlear response measurements. These characteristics may be used to explain previous experimental results and to suggest further experiments. The Spenner-Cox cochlear model[1] which we are using represents the cochlea as a pair of rectangular-shaped fluid-filled chambers, joined along their long axis and separated only by a membrane whose mechanical characteristics are model parameters. The model is structured to be stimulated by a pressure source defined as a boundary condition for one end of each of the rectangular chambers. The model response is measured as the membrane motion that results from applying a particular pressure stimulus.

An issue we have addressed concerns how the response of the Spenner-Cox model is affected by changes in membrane characteristics with all other model parameters held constant and sinusoidal excitation of constant frequency and amplitude. Results have been obtained for two cases, one where the partition mass was varied while partition damping and compliance were held constant and the other where the partition damping was varied while partition mass and compliance were held constant. In the first case, where the partition damping was varied, the predominant effect observed was a change in the slope of the response curve on the basal side of the point of maximum response. In the second case, where partition mass was varied, the most noticeable effect was the change in both the sharpness of the response and the apical shift of the point of the maximum response for decreasing values of mass. Characterizing the model as we have allows us more readily to adjust it's response to conform to experimentally measured responses obtained from various animal species.

Verification of the Spenner-Cox model with other published models is one of our continuing objectives. To this end we have recently compared our model with the one described by Allen,[2,3] using partition impedance values defined earlier by Lesser and Berkley.[4] The results of the comparisons for both 100 and 500 point implementations showed the two model responses agreed well in both amplitude ($\pm$ 3 db) and phase until the responses were attenuated 60 db from the peak. The differences that were noticed can be explained plausibly as being caused by the slightly different boundary conditions used to define the two models. Results from both the parameter variation and the model comparison studies were presented at the Acoustical Society Meeting in December of 1977.[5]

One of the principal motivations for developing this model was and still is, to apply it as a tool in the investigation of speech where the goal is to identify those characteristics of speech that are important to its interpretation. To accomplish this goal it is necessary that the model be made to operate in an interactive manner. This requires the model algorithm to be implemented where speed increases of the order of 100 are achieved over the present implementation. Potential means for accomplishing this improved performance, which are under investigation, include modification of the microcode in the present system, the addition of restructured macromodules allowing the processing tasks to be distributed outside the present system, or the use of an array processor or distributed microprocessors to permit distribution of the processing tasks. Any one or all of these possible techniques may be employed to bring about the desired interactive operation.

(1) B. F. Spenner, "A Two-Dimensional Model of Cochlear Mechanics," D.Sc. Dissertation, Washington University, St. Louis, Missouri, August 1976.

(2) J. B. Allen, "Two-Dimensional Cochlear Fluid Model: New Results," Journal of the Acoustical Society of America, vol. 61, no. 1, 1977.

(3) M. M. Sondhi, "Method for Computing Motion in a Two-Dimensional Cochlear Model," Journal of the Acoustical Society of America, vol. 63, no. 5, 1978.

(4) M. B. Lesser and D. A. Berkley, "Fluid Mechanics of the Cochlea. Part 1," Journal of Fluid Mechanics, vol. 51, part 3, 1972.

(5) B. F. Spenner and J. R. Cox, Jr., "A Computational Model for Cochlear Mechanics," Journal of the Acoustical Society of America, vol. 62, supplement 1, Fall 1977.

E-2. Analysis of Speech Sounds Using a Digital Model of the Ear

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
A. P. Allen, B.S., Central Institute for the Deaf
J. R. Cox, Jr., BCL
J. D. Miller, Ph.D., Central Institute for the Deaf
B. F. Spenner, BCL

Support: RR 00396
NS 03856

Speech sounds recorded in the free-field are processed on the Central Institute for the Deaf Eclipse system to arrive at stapes velocities. This transformation is simulated with the digital filter consisting of two complex-conjugate pole pairs with center frequencies of 2.4 and 4.0 kHz and bandwidths of 0.7 and 2.0 kHz, respectively. These values are consistent with descriptions of the outer ear by Shaw and of the middle ear by Zwislocki.

The cochlear model of Spenner and Cox has been adapted in a preliminary way for the study of speech. This model is two dimensional and physically based. It has been implemented on a computer system (MMS-X) originally developed at Washington University for display of complicated molecules. The coordinate transformer of the MMS-X is used to perform the matrix multiplications required for the time-domain solution of the model. The model parameters were set to values appropriate for the human, that is, length 3.5 cm, depth .07 cm, mass .05 cm, stiffness $10^9e^{-3.0x}$ dyne/cm^2, and damping $1000e^{-1.5x}$ dyne sec/cm^2. With these parameters the model was implemented with 50 sections. Analyses of a few syllables spoken by a male and a female talker indicate that the envelopes of the traveling wave patterns show dimensional characteristics similar to those suggested by Fant, i.e., grave-acute and compact-diffuse.

These preliminary studies of speech with the cochlear model have been difficult. For example, since the MMS-X system does not include an A/D converter, sampled data were taken originally from RAP disks and transmitted to the MMS-X disk via a 4800 baud serial communication link. This is no longer necessary since we have modified the RAP-disk controller of the Eclipse system and written appropriate subroutines so that the speech data can be written on disk in a format appropriate to the MMS-X. The BCL MMS-X system is being enlarged by the addition of peripherals to enhance program development. Also under consideration is alteration of the microcode to increase computational speed (E-1).

E-3. Computer System for Auditory Research

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
S. A. Garfield, BCL
D. E. Hanpeter, Central Institute for the Deaf
A. P. Rueter, B.S., Central Institute for the Deaf

Support: RR 00396
NS 03856

A plan for economic deployment of small computer systems in the research laboratories at Central Institute for the Deaf has been described in PR 13. This plan includes a central computer system and compatible but simpler satellite systems, where one such satellite system will serve an individual laboratory. Currently the central system, which includes major portions of a satellite system, has been checked out thoroughly and is being used primarily for the development of application programs.

Two free-standing satellite systems have been completed and are in use at Central Institute for the Deaf. The first one is installed in the Comparative Psychoacoustics Laboratory and is being used currently to automatically measure thresholds in chinchillas with noise-induced hearing loss. The second satellite system is used in the Digital Methods Laboratory for hardware checkout. One additional satellite system is under construction and is scheduled for completion in the fall.

Several major application programs have been completed. One such program is the implementation of a Clark-threshold paradigm which automatically selects and plays stimulus sounds, monitors the animal's response, and dispenses food-pellets for reinforcement of correct responses. The stimulus intensity is changed in variable steps until certain criteria are met to indicate that a stable threshold measure has been achieved. Summary data are displayed during the experiment to aid in monitoring the performance of the test animal. Another program, hearing-aid design program (E-8), enables an experimenter to establish optimum values for parameters of the Limiting Master Hearing Aid in conjunction with specific patient hearing deficiencies. A third program is RAPISIM, a general utility program for recording, editing, filing, and playback of speech sounds. A variety of smaller programs and subroutines have been developed also, that include: 1) graphics plotting subroutines for the Tektronix terminal, 2) disk file subroutines that utilize the PC and RAP disk formats, 3) programs for display of sampled data waveforms, and 4) various specialized programs for generating one and two-channel audio tapes with randomized sequences of speech sounds.

Major programs that are under development include: 1) an automated implementation of the Burdick-Miller paradigm for testing animals in the Comparative Psychoacoustics Laboratory, and 2) an implementation of a test facility for the Psychoascoustics Laboratory that will be capable of testing four human subjects at a time using binaural stimuli.

In addition to the development of application programs, work is continuing on modifying RDOS, the real-time-operating system, to accommodate the special peripherals that have been added through the satellite system. This work includes adding I/O drivers that are compatible with system calls and FORTRAN.

E-4. Voice Source Characteristics

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

Support: RR 00396
NS 03856

In continuance of this project (PR 12, G-4; PR 13, G-4), the glottal measurement apparatus has been newly designed and with the new equipment data have been collected for several related research projects.

The results of previously collected data on glottal vibration in normally-hearing male and female adults[1,2] may be summarized briefly in the following broad outline:

(1) Speakers control changes of fundamental frequency (F_0) and intensity by altering subglottal air pressure and vocal-fold tension. In different linguistic contexts one or the other of these control mechanisms may predominate.

(2) The glottal wave changes over time in one of two different ways, depending upon whether the change is produced by subglottal air pressure or vocal-fold tension.

(3) Differences exist between male and female phonation, which are similar to differences in male phonation associated with changes in vocal-fold tension.

(4) The glottal wave may be different depending upon the vocal mode in which it is produced. The primary vocal modes are normal or chest voice, falsetto voice, and creaky voice. However, loud and soft voice (in the "chest register") are also qualitatively different apart from mere differences of fundamental frequency or intensity.

A detailed description of the method used here to measure glottal vibration is to be found in Sondhi,[3] and Monsen and Engebretson.[1] Briefly, glottal data in the form of volume velocity waveforms are collected by means of a pseudo-infinite termination of the vocal tract. Previously,

a steel tube six feet long with an inside diameter of 2.2 cm was used to collect data from both male and female adults. The tube was divided into two parts and a wedge of polyeurethane foam was used as a termination inside the last half of the tube. This device has been improved in the following ways:

(1) Four new tubes of different inside cross-sectional areas have been constructed. Ideally, the tube should have the same inside cross-sectional area as the average cross-sectional area of the subject's vocal tract, in that way acting merely as an extension of the vocal tract. In our previous studies the same tube was used for both male and female adults. This involved some inaccuracy, since males have larger vocal tracts than females, who in turn have larger vocal tracts than adolescents or children. The four newly-constructed tubes were designed to more closely match the subjects' vocal-tract sizes, with inside cross-sectional areas of approximately 3, 4, 5, and 6 cm^2. These four tubes should make it possible to collect data accurately from female adults, adolescents of both sexes, and children. Individual subjects are matched with a tube as follows: male adults, tubes 5-6 cm^2; female adults, tubes 4-5 cm^2; non-adults, tubes 3-4 cm^2. The second formant frequency of the vowel /i/ is used to estimate the size of the speaker's vocal tract. Before recording with a tube each subject is asked to phonate the vowel /i/ in elongated fashion. One period from this vowel is isolated and subjected to Fourier analysis. Based upon the second formant frequency of this vowel, the following match is made between subjects and tubes: if the second formant lies above 3000 Hz, then the 3 cm^2-tube is used; if the second formant is less than 3000 Hz but greater than 2600 Hz, the 4 cm^2-tube is used; less than 2600 Hz but greater than 2200 Hz, the 5 cm^2-tube is used; less than 2000 Hz, the 6 cm^2-tube is used. For comparison, Peterson and Barney cite average second formant values of 3200 Hz for children, 2790 Hz for female adults, and 2290 Hz for male adults.

(2) The new tubes have been constructed out of stainless steel. This makes cleaning somewhat simpler and, although some moisture normally collects inside the tube during phonation, there is no problem of rust.

(3) As previously, the new tubes are constructed in two parts, connected by an outer metal sleeve. In the new tubes, however, the wedge-end of the tube is proportionately larger (approx. 4½ feet) and the mouthpiece-end shorter (approx. 1½ feet). The wedge is thus longer and this improves the acoustic termination. The microphone is now located somewhat nearer the subject's mouthpiece.

(4) New mouthpieces were constructed out of nylon. Previously, the mouthpiece was entirely circular at both ends, forcing the subject to open the mouth wider than is desirable. The new mouthpieces are nearly elliptical at the mouth-end and circular at the tube-end so as to fit perfectly onto the tube and comfortably into the subject's mouth. The inside cross-sectional area of the ellipse-shape is identical to that of the circle (i.e., of the tube), so that there is no mismatch

between subject/mouthpiece/tube. The elliptical shape allows the subject to phonate in a more natural, speech-like manner.

With the new equipment, data are being collected in the following areas:

(1) The effect of deafness on phonation: data from 20 hearing-impaired adolescents have been collected and are being analyzed. The hearing impairments of these subjects vary from severe to profound deafness. The subjects were asked to phonate neutral vowels into the tube and to produce a distinction between normal and soft voice. Subjects also were asked to produce three-syllable vocalic "words" which differed in the placement of the linguistic stress, such as /a-á-a/ and /a-a-á/. To get the children to produce these word patterns, a comparison was made between phrases such as "John came in" or "I saw John."

The phonation characteristics of these deaf subjects will be compared with those of normally-hearing subjects and with glottal data generated synthetically by the Ishizaka-Flanagan two-mass model of vocal-fold vibration. It is of interest to determine the following: is there anything qualitatively different about individual glottal pulses generated by the hearing-impaired speaker, or are differences between hearing-impaired and normal speakers due primarily to the way in which the glottal wave changes over time; how does the hearing-impaired speaker control the changes of fundamental frequency and intensity in speaking; do severe hearing impairment and profound deafness have different effects upon phonation.

(2) Differences of phonation depending upon the language spoken, a comparison of English and Japanese: in previously collected data it was seen that (English) speakers control the change of fundamental frequency, intensity, and duration of the glottal wave in such a way that stressed syllables are typically of higher fundamental frequency and of greater intensity than the unstressed syllables. By a comparison of these (human) glottal data with synthetic data from the Ishizaka-Flanagan two-mass model of vocal-fold vibration, it was determined that the subjects use increased subglottal air pressure and increased vocal-fold tension to produce the heightened frequency and intensity of the stressed syllables. In Japanese, syllables differ from each other, not by being stressed or unstressed, but by being either "high" or "low" in "tone". It is possible, therefore, that Japanese speakers use characteristically different patterns of subglottal air pressure and vocal-fold tension to control fundamental frequency. Japanese subjects were asked to phonate into the glottal tubes in the same manner as the English-speaking subjects, except that instead of being asked to imitate syllables which differ in stress, they were asked to imitate Japanese words which differ in tonal pattern. Data are being collected and analyzed currently.

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(2)R. B. Monsen, A. M. Engebretson, and N. R. Vemula, "Indirect Assessment of the Contribution of Subglottal Air Pressure and Vocal-Fold Tension to Changes of Fundamental Frequency in English," Journal of the Acoustical Society of America, in press.

(3)M. M. Sondhi, "Measurement of the Glottal Waveform," Journal of the Acoustical Society of America, vol. 57, pp. 228-232, January 1975.

E-5. Experiments in Tactile Loudness with Single Channel Electrocutaneous Stimulation

Personnel: R. M. Sachs, Ph.D., Central Institute for the Deaf
J. D. Miller, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

We have continued to study the perceived magnitude of single electrode stimulation, (PR 12, G-6; PR 13, G-5, G-6), using a scheme of pulse number modulation of current developed by F. A. Saunders at the Smith Kettlewell Institute in San Francisco. The current stimulus is a periodic burst of pulses, with a burst rate R, number of pulses per burst N, and individual pulse width τ. During the last progress period we studied loudness growth in a cross-modality-matching (CMM) paradigm. Since then we have studied two more aspects of perceived magnitude.

In one study we wanted to understand the relations of the three variables R, N, and τ necessary to produce a constant perceived magnitude. Under the assumption that this magnitude is only a function of rms electrode current, and since current is proportional to $\sqrt{\tau NR}$, we predicted a 1:1:1 trade among the three variables. First, we had two subjects vary the pulse duration τ at tactile threshold with either N or R as the independent variable. Stimuli were presented every 5 sec with a 0.5 sec duration. It was clear that threshold was determined primarily by τ and was a weak function of N and R. On log-log coordinates the slope relating τ to N or τ to R exceeded 8:1. Next we measured the tradeability of N and R at fixed τ for suprathreshold levels in a tactile loudness balance task, alternating a standard tactile stimulus (R=30 Hz, N=16 and 64) with one in which the subject could adjust N for various R values. In general we observed 1:1 trade of N and R over a 20-fold increase in R.

This trade begins to break down for lower burst rates (below 30 Hz), suggesting that loudness is based on individual bursts of pulses if the bursts occur far enough apart in time. From this study we concluded that it is not feasible to code information simultaneously in the frequency and intensive dimensions by varying R and N respectively, both parameters affecting loudness similarly. A better choice would be to use the τ and R variables.

In a second study we were interested in the number of intensive levels (using the N variable) that could be absolutely identified in an informational sense. We chose 3, 5, or 7 values of N in approximately equal logarithmic steps in the range N=2 to 150. All values were easily discriminable. R and τ were fixed at 30 Hz and 9 μsec. For our two subjects results showed that an upper limit of about 1.8 bits of information could be transmitted. This corresponds to 3.5 values of N that could be absolutely identified. Thus, when only three values of N were presented no errors were made, but more confusions occurred when more alternatives were introduced. It should be realized that each experiment took place under laboratory conditions on a given day. Our experience last year with cross-modality matching tells us that the perceived magnitude of a given stimulus can be quite variable from day to day. A more conservative estimate of transmitted information would be 2 to 3 alternatives if this coding scheme were used in a practical sensory aid.

A manuscript covering these studies, including CMM, is in progress. No further work on tactile loudness is planned at this time.

E-6. Development of Computer-Controlled Synthetic Mouth Outlines for Lip-Reading Research

Personnel: R. M. Sachs, Ph.D., Central Institute for the Deaf
N. P. Erber, Ph.D., Central Institute for the Deaf
S. A. Garfield, BCL

Support: RR 00396
NS 03856

Several perceptual experiments have been performed this year to examine identification of simple elliptical lip outlines to simulate vowel articulation. These lip shapes have been generated by wired analog circuits, in which slowly varying control voltages change the amplitudes of sinusoidal waveforms. We also have been investigating ways of generating mouth shapes with a digital computer. This digital approach seems to be more efficient over the long term - for synthesis of all visible articulators (inner and outer lip borders, teeth, tongue, jaw) - than does the development of more complex hardware. The parameters necessary to

change these articulator outlines dynamically during speech could be stored on a magnetic disk for random access during the presentation of on-line experiments.

Different approaches to computer control have been examined using the speech and hearing computer system. A five-parameter model for mouth synthesis has been defined. Lip shape was specified by two half-ellipses with a common horizontal axis (lip width) and two vertical axes (upper and lower lip displacement measured from midline). Upper and lower teeth were depicted by two straight horizontal lines inside the ellipse with vertical distance measured from the midline. The goal was to update these five parameters in 100 time frames during a given brief speech utterance. Two 12-bit D-to-A converters were used with the computer programs to generate x and y inputs to an external oscilloscope.

Two related strategies were considered in the development of the program. The first was whether to calculate ahead of time all x and y locations required to create the dynamic mouth shape, and then output these from a temporary file in real time. An alternative approach was to calculate successive x and y positions (in real-time) during the time between display of successive points. A related decision was whether to present the moving mouth shape as a dot or a vector display. After evaluating a variety of software and hardware approaches we chose to use real-time calculations and a vector display. The vector display required far fewer calculations per time frame to produce smooth mouth outlines. However, the speech and hearing computer system is not a vector-display machine. Our approach, then, was to calculate successive x/y locations, to output the <u>difference</u> between successive points, and to pass these time-varying step-change signals through a pair of wired integrators to produce ramp-like changes that appeared as straight-line segments on the oscilloscope screen. We found that a 20-segment approximation to an ellipse was acceptable. To generate both "teeth" and "lips" (requiring about 25 calculations per frame), it was necessary to provide a x input or "blanking" signal to the oscilloscope. This was required to remove, for example, the line that joined the last lip segment to the tooth border. Unfortunately, the three D-to-A outputs (x, y, and z) cannot be changed simultaneously on this machine. There is a minimum of 10 μsec delay between a change in the x/y signals and the z signal. While this may seem fast enough it should be realized that we chose a duration for each segment of 400 μsec (25 segments were able to produce a lip/teeth frame in 10 msec). This meant that 1/40 of the blanked line segment would remain visible and that 1/40 of the visible line segment would be blanked whenever the z output changed. Even greater proportions of the lines would be involved if more vectors were needed per 10 msec time frame. This was considered objectionable. Therefore, we decided to abandon further development of this strategy with the speech and hearing system pending possible use of a RAP-III system (E-3) or the MMS-X system. The hardware for these systems enables one to produce simultaneous x, y, and z output changes.

In the meantime, we have reverted to displaying a more basic lips-only model with the speech and hearing system. In this scheme the three control parameters for lip shape are outputted from the D-to-A converter, and these signals are fed to wired multipliers to control the amplitudes of the sinusoidal waveforms delivered to the oscilloscope. With this method the control signals can be changed within 1 msec, which is more than adequate for lipreading studies.

Support programs have been written to create mouth parameter files, which can control the shape of lips and location of teeth on an oscilloscope display. Two alternative methods may be used to input data. One is graphical, in which a stylus and tablet are used to specify 100-frame values for each parameter. The second approach is a simplification. One merely specifies the duration and amplitude of the steady-state portions of each articulatory parameter during an utterance (e.g., upper or lower displacement). The computer stores these amplitude values for each frame number and then interpolates the amplitudes for intermediate durations with a raised-cosine function. The first method, graphic approach, is useful for mimicking articulator-movement data obtained from frame-by-frame motion picture measurements. The second, analytical approach, is useful in certain perceptual experiments in which a precise set of "equally-spaced" synthetic mouth shape stimuli are desired.

A program to run visual-articulation identification experiments in real-time also has been written for the speech and hearing system. This program presents a randomly chosen file (from a set of 16) as a changing lip outline on the oscilloscope during each trial of the experiment. The subject then uses the keyboard to label the stimulus with one of up to 16 possible alternatives. At the end of a test sequence the trial-by-trial response history is stored in a disk file and a stimulus-response confusion matrix is printed.

E-7. Determination of the Vocal Tract Area Function During Phonation Using Input-Output Measurements

Personnel: N. R. Vemula, BCL
D. L. Elliott, Ph.D., Systems Science and Mathematics
A. M. Engebretson, BCL and Central Institute for the Deaf

Support: RR 00396
NS 03856
ENG 76-16812

The linear prediction model has been widely studied as a method of speech analysis. In these studies the glottal source function and lip radiation are generally modelled in such a way that their effect

can be removed by compensating the sampled data with a +6 dB/octave filter characteristic. Our work with the linear prediction model indicates that the results are sensitive to the exact form of this compensating function. Also, our measurements of glottal waveforms indicate that the glottal source function is variable and cannot be characterized simply. These considerations have led to a study of an alternate method of analysis of the vocal tract, using as an input a signal derived from an accelerometer attached to the throat wall.

At present a phenomenological model for the throat-wall vibration is used. The throat-wall vibration signal has two components, one is acoustic, arising from the sound pressure in the supraglottal region, and the other is mechanical, arising from the dynamic forces generated by the vibrating vocal folds during phonation. The acoustic transfer function of the wall (the ratio of the supraglottal sound pressure to the acoustic component of the vibration) has been studied. This transfer function is obtained by driving the outside surface of the neck with a vibrator and measuring the resulting supraglottal pressure within a glottal tube. The acoustic transfer function has a resonance at 150 Hz and an antiresonance at about 50 Hz. The magnitude squared transfer function falls off at about -12 dB/octave between 150 Hz and 1800 Hz.

A parametric model of the throat-wall has been derived through simultaneous measurements of the throat-wall vibration and the supraglottal sound pressure during phonation of a neutral vowel into the glottal tube. Measurement of the supraglottal sound pressure and the vibration at various pitches and intensities suggest that the throat-wall can be considered to be a linear system with the supraglottal sound pressure as input and the sum of acoustical and mechanical components of throat-wall vibration as the output when the subject phonates with normal pitch and intensity.

Vocal tract area functions have been derived, using the measured speech signal as output and the supraglottal sound pressure as input. The supraglottal sound pressure is obtained by filtering the throat vibration signal with the inverse of the parametric throat-wall model. Preliminary results indicate that this procedure yields reasonable vocal tract area functions for vowel phonation. A study is under way to compare these results with the results obtained from linear prediction models.

E-8. Hearing-Aid Design Aid

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
A. F. Heidbreder, B.S., Central Institute for the Deaf
A. F. Niemoeller, Sc.D., Central Institute for the Deaf
A. P. Rueter, B.S., Central Institute for the Deaf

Support: RR 00396
NS 03856

A 13-channel Master Hearing Aid has been developed at Central Institute for the Deaf for testing patients who are difficult to fit with standard aids. This device allows independent control of maximum output and relative gain in each channel. Each channel begins with a half-octave, 3-pole, Butterworth filter, followed by a variable-gain amplifier which controls the relative linear gain in the channel. Next is the "limiter" section which can be adjusted to prevent loud sounds from exceeding the patient's discomfort level. It consists of a variable gain amplifier followed by a non-linear element (a diode limiter), which in turn is followed by a second variable-gain amplifier. The controls to the two amplifiers are interconnected to keep the gain through the "limiter" equal to zero dB. The last block in a channel is a second filter, identical to the first, which serves to remove distortion products introduced by the nonlinear element. Additional features of the master aid include a preamplifier so that output of the microphone can be varied, a mixer amplifier to sum the output of the 13 channels, and a final power amplifier to shift the overall gain of the system. An additional useful feature is a light-emitting diode mounted over the controls for each channel, which indicates whether a channel is, in fact, limiting its signal.

The Limiting Master Aid has been recently redesigned and modified to improve it with respect to noise, gain, and bandwidth. Each of seven subsystems for each of twelve frequency channels has been measured precisely with regard to (i) input noise, (ii) output noise, (iii) maximum undistorted output, (iv) maximum allowable input, and (v) gain. These measures were made for one-third octave bands centered on the center frequencies of each of the channels. These data were collected for each setting of each of the available controls resulting in 5200 numbers. Audiometric measures with patients of threshold, most-comfortable loudness level, and the threshold of discomfort are made with a similar set of one-third octave bands.

Study of the device reveals that theoretically desirable configurations can be achieved for a variety of hearing impairments. However, because of the large number of adjustments associated with the master aid, it is difficult to optimize the internal limiting and gain characteristics with respect to the audiological workup for a specific patient. For many patients the dynamic range between threshold and discomfort

is limited and superposition of this range with the acoustic input in each frequency band is crucial if relevant speech information is to be both audible and comfortable.

As an aid in establishing parameter settings of the master hearing aid a program has been developed that simulates conditions in each channel. The program utilizes a method that was developed to systematically represent gain, limiting level, noise floor, discomfort level, and threshold in a common coordinate system so that crucial parameters can be referred either to the sound field or the eardrum.

The electroacoustic description of the hearing aid is stored in a computer, as are the audiometric results for individual patients. The program allows the audiologist to select various settings of the master hearing aid and then displays for each channel all of the relevant parameters so that the noise floor can be evaluated relative to the patient's threshold, the limiting level can be evaluated relative to the discomfort level, and the average level of speech in each band can be evaluated in relation to threshold and the limiting level.

The results of the parameter settings are displayed graphically either as input - output functions for a specified channel or as a frequency response function of all channels. Along with the overall gain function are displayed the patient's hearing threshold and discomfort level, the noise floor of the overall system, and the average spectral level of speech. The program is written so that the audiologist can quickly change hearing aid parameters and select appropriate graphical displays. The optimum parameter settings and graphs can be written on the printer/plotter for permanent record. Other program options can be chosen to create files that specify the characteristics of the microphone, output amplifier, and receiver.

E-9. Speech-Synthesis Library

Personnel: S. A. Garfield, BCL

Support: RR 00396

A library of subroutines, functions, and programs was created to allow easy development of speech synthesis programs. The library is based on FORTRAN for the PC-12. To synthesize any arbitrary waveform a user adds appropriate data initialization and subroutine calls to an existing FORTRAN program shell. When compiled and loaded the program will perform the synthesis and store the output on a RAP disk while producing a log on the line printer.

Use of the library requires some understanding of the OS/PC operating system, editor, and FORTRAN compiler. Minimal knowledge of FORTRAN is required. Following is a list of library components:

1) Triangular glottal wave function,
2) Polynomial glottal wave function,
3) Constant-duration polynomial glottal wave function,
4) Pulse generator function,
5) Pulses and noise Haskins synthesis subroutine,
6) Male bandwidth as function of frequency,
7) Female bandwidth as function of frequency,
8) Coefficient subroutine for filters,
9) Resonator filter function,
10) Anti-resonator filter function,
11) Radiance effect function,
12) Linear transition function,
13) Cosine pedestal function,
14) Parabolic transition function,
15) FORTRAN program shell,
16) Sample FORTRAN program.

In addition, routines available from the speech subroutine library and the BCL library are used for file handling, RAP disk output, speech playback, and numerical conversions.

To date ten programs have been written using the Speech-Synthesis Library. Program development time has been significantly reduced for experienced programmers due to the many general subroutines. Inexperienced users who previously relied upon experienced programmers can develop their own programs.

F. Central Nervous System Diseases and Electroencephalogram Analysis

The Biomedical Computer Laboratory's involvement in clinical neurology, neurosurgery, and in neurophysiological research reaches back to the Laboratory's beginnings. In 1965 and 1966 a LINC computer at BCL was applied in processing radioisotope brain-scan data transmitted over telephone lines from the hospital radiology unit, and in 1966 a LINC-controlled evoked-response display system was installed, providing neurosurgeons in the operating room with continuous EEG monitoring capability via closed-circuit television. In 1969 and 1970 a LINC computer was interfaced to a six-probe system designed by the radiology department for in-vivo cerebral blood-flow and oxygen-metabolism studies employing cyclotron-produced radioisotopes. The next two years saw further development of this approach with the construction of a twenty-six-probe brain blood-flow and metabolism unit capable of increased spatial resolution.

At this juncture it was recognized at BCL that new initiatives in central nervous system and other radiotracer studies must stem, in part, from an improved understanding of the manner in which the underlying physiological phenomena reveal themselves through gamma rays and annihilation photons to the external data-gathering instruments. Thus, in collaboration with scientists at Washington University and at other institutions, the Laboratory undertook a substantial augmentation of its program in tracer kinetics by expanding its activities in physiological modeling and parameter estimation. These collaborative efforts led to successful quantitative methods of studying in vivo such diverse processes as brain-glucose transport and metabolism, blood-brain-barrier permeation of water, alcohols, ammonia, and carbon dioxide, and the autoregulation of cerebral blood volume and blood flow.

Research efforts at BCL in application of computers and mathematical models to CNS disease management and EEG analysis, reported last year in PR 13, have continued to be productive and this year's results are summarized here. Progress has been made in all of the projects previously described: in regional in-vivo brain metabolism studies, in experiments using a high-speed graphics system for creating three-dimensional images of brain structures from CT scans, and in development of computerized systems for automatic processing and monitoring of signals generated in the neurophysiology laboratory and during neurosurgical procedures. This year two novel projects were initiated at BCL in collaboration with the Departments of Anatomy and Neurology. These are (a) the development of a computerized system for acquisition of visual evoked-response data and extraction from this data of clinically significant indices, and (b) design studies for an automated system to process brain-autoradiography images. Progress in these two new undertakings is reported in the following.

F-1. Visual Evoked Response

Personnel: G. J. Blaine, BCL
M. W. Browder, BCL
L. A. Coben, M.D., Neurology
J. K. Montrose, BCL
S. R. Phillips, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
MH 31054

The visual evoked response (VER) is used as an indicator of cerebral physiology. Electrophysiological responses evoked by repeated visual stimuli are separated from other ongoing electrical activity by a signal-averaging process. Features extracted from the averaged responses to stationary white flash and to reversing black and white checkerboard patterns are to be included with behavioral measures and cerebral structure metrics in a temporal study of patients with senile dementia.

Current activities include a pilot study to develop experimental protocol, development of a microprocessor-based two-channel VER acquisition system, and algorithm development for computer-assisted feature extraction.

The pilot study, currently in progress, tests feasibility of recording VERs from patients who have a moderate or severe degree of dementia, and provides an initial database for development of feature-extraction algorithms. The pilot study utilizes a single-channel VER acquisition system based on the Hewlett-Packard 5480 signal analyzer, augmented with a multichannel FM tape recorder and a two-channel Grass EEG recorder. The on-site FM tape recorder is used to collect the evoked occipital EEG signal and the visual-stimulus event trigger.

The two-channel Grass unit provides a paper record of the occipital-central EEG and also eye movement as determined by an EOG between left outer canthus and left ear. The record is used to assess patient drowsiness. The tape-recorded evoked signal (occipital-central EEG) is later digitized, averaged, and stored using a PC-1200 minicomputer system.

The two-channel VER acquisition system will utilize Grass Model P511 EEG amplifiers to provide high-level signals which will be sampled and digitized. The digitized evoked responses are to be averaged, displayed, and then stored on floppy diskettes. The digital data characterizing the VER will be transported to a PC-1200 minicomputer system for analysis and long-term storage.

A VER clinician or technician will be assisted by the minicomputer in the extraction of features. Preliminary development of an algorithm for extraction of relevant features in the VER was initiated. The

extracted features are to be recorded on industry-compatible nine-track magnetic tape for transport to the main campus computing facility. This will facilitate incorporation of the VER results in the long-term temporal study of the senile dementia syndrome.

F-2. Development of an Automated System for the Monitoring of Epileptic Patients with Indwelling Electrodes

Personnel: C. F. Pieper, M.S., Neurological Surgery
S. A. Golden, B.S., Neurological Surgery
S. Goldring, M.D., Neurological Surgery
K. L. Ripley, BCL

Support: RR 00396
NS 06947
Washington University

The development of this system has proceeded according to previously described specifications (PR 13, H-5) with the construction of a 128 by 64 solid-state crosspoint switching matrix controlled by a Motorola M6800 microprocessor system. While this unit has been under construction we have used a 24 by 16 version that incorporates patient-protective current-limiting devices. The smaller switching unit has been operated on line during surgery in order to speed selection of electrode input to our present recording system. Still being implemented are circuits for system calibration and auto-testing so that integrity of the matrix can be confirmed after each event of interest (e.g., seizure). A scheme to reduce EEG amplifier saturation during direct cortical stimulation through the recording electrodes has been proposed and design is in progress.

Nearly complete is a device for real-time encoding of synchronization information and audio onto the voice track of a video tape recorder. Work is progressing also on the digital communication link between the patient's bedside and the computer.

F-3. Three-Dimensional Display of Cerebral Ventricles

Personnel: V. W. Gerth, Jr., BCL
C. D. Barry, Ph.D., Computer Systems Laboratory
S. Goldring, M.D., Neurological Surgery

Support: RR 00396

Experiments using the MMS-X high-performance graphics system to allow visualization of the cerebral ventricles and intracranial lesions have continued. A reduction in the number of sections from fifty in the original experiments (PR 13, H-6) to twenty resulted in an expected loss of realism, but was still felt to be clinically useful. This reduction in the number of sections is motivated by economics and by X-ray exposure to the patient. The latter consideration is becoming somewhat less of an issue due to the rapid progress in CT scanner technology.

In order to consider a moderate amount of actual CT data instead of the single case used in the early experiments, a procedure has been developed in conjunction with the Radiation Treatment Planning project (G-6) which reads CT image data from industry-compatible tape and generates images which are plotted on a Versatec printer-plotter interfaced to a PC-1200. This system will be used to evaluate other methods of display within the clinical limitations of the number of sections available. In addition, interactive graphic techniques for user definition of structures will be developed in conjunction with a means of data transfer from the PC-1200 to the MMS-X system. This will allow a limited number of cases to be processed with existing hardware and minimal software development in order to get the additional feedback from clinicians needed to further define the goals of the project.

F-4. In-Vivo Measurements of Regional Brain Metabolism

Personnel: M. E. Raichle, M.D., Radiology and Neurology
N. J. Caston, M.S., Radiology
J. O. Eichling, Ph.D., Radiology
R. L. Grubb, Jr., M.D., Neurological Surgery
C. S. Higgins, A.B., Radiology
A. B. Kliefoth, M.D., Radiology
K. B. Larson, BCL
B. E. Laux, B.S., Radiology
J. Markham, BCL
N. A. Mullani, BCL
M. M. Ter-Pogossian, Ph.D., Radiology
T. J. Tewson, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

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

We have continued to apply our method[1] (PR 13, H-1) of using positron-emission tomography (B-4, B-5) to measure, in vivo and regionally, the utilization in brain of metabolic substrates labeled with positron-emitting radioisotopes produced by a cyclotron. We expect that when it is completed the positron-emission tomograph designed and being built at Washington University specifically for neurological investigations (B-5) will enable us to realize improved spatial resolution in our regional studies of metabolism in the brain.

The successful outcome of our brain-metabolism work[1] and the generality of the underlying mathematical model[2] have led us to believe that our method could be used advantageously for in-vivo studies of regional metabolism in other organs as well. We have, therefore, planned a program for possible validation of the method to measure metabolic utilization rates in the heart (A-20).

The unique behavior of ammonia labeled with the positron emitter, nitrogen-13, as a tracer in the brain and in the heart, has been noted by us[3] and by other groups of investigators.[4,5] During passage of the tracer through a region of interest a relatively large fraction of the amount injected is deposited in tissue and remains fixed for prolonged times. The fraction of the injected bolus of tracer that is deposited in tissue has been shown to be flow-dependent.[3] However, our experiments have shown further that blood pH and vascular permeability also produce effects. On theoretical grounds it appears that additional variables, such as tissue pH and cellular-membrane permeabilities, also can influence the extraction of ammonia. The exact role played by these factors is poorly understood. There exists, therefore, the concern that unexamined use of ^{13}N-ammonia to measure perfusion without due attention to the

effects of other parameters could lead to possibly erroneous conclusions. Beyond the more utilitarian application of labeled ammonia as a means of measuring local perfusion, we hope with our experiments to gain a more fundamental understanding of the metabolic behavior of ammonia in the brain, where it has been implicated as a cause of hepatic coma.

In order to provide a framework for examining these issues we have developed a mathematical model that has the potential of allowing critical analysis of the available data and of aiding in the design and interpretation of further experiments. The model describes the time-dependent uptake, washout, and ultimate retention of ^{13}N-labeled ammonia in the brain. It assumes two barriers, arranged in series, to the passive-diffusion transport of ammonia between cerebral blood and the metabolic sites. These barriers are identified with the capillary epithelial membranes [blood-brain barrier (BBB)] and the brain-tissue cellular membranes. Only non-ionized ammonia in aqueous solution is assumed to be capable of passage through these membranes, so that concentrations in blood and in interstitial fluid, which constitute the driving forces for diffusion, are dependent upon pH on both sides of the BBB. Tracer in interstitial fluid can back-diffuse to blood, but tracer that has passed into brain-tissue cells is incorporated immediately into metabolic products which remain sequestered within intracellular space.

The model assumes that tracer transport along the axial direction in capillaries occurs solely by convection, while transport in the radial direction is wholly diffusive. Additionally, radial diffusivities in blood and in interstitial fluid are assumed to be large relative to membrane diffusivities. Thus, while longitudinal gradients are nonzero, radial gradients within fluids are vanishingly small.

Preliminary simulations of the time-course of radioactivity as registered by an external probe, based on plausible values of physiological parameters in the equations derived from the model, have produced computed curves whose shapes correspond closely to those obtained experimentally in rhesus monkeys. This has encouraged us to use the model for estimating these parameters from experimental data obtained under widely varying conditions of blood flow, blood pH, and with altered BBB permeabilities, such as are encountered in disease states.

We hope, ultimately, to be able to apply our model to ammonia-tracer data from patients, particularly those with liver disease, in order to better characterize the data in relation to the clinical condition. We anticipate achieving this goal by applying our approach through use of the neurological positron-emission tomograph presently nearing completion (B-5).

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(5)T. F. Budinger, Y. Yano, and B. Hoop, Jr., "Comparison of $^{82}Rb^+$ and $^{13}NH_3$ for Myocardial Positron Scintigraphy," Journal of Nuclear Medicine, vol. 16, pp. 429-431, 1975.

F-5. A Mathematical Model for Measurement of Glucose Transport in Isolated Brain Preparations Using ^3H-Glucose

Personnel: D. D. Gilboe, Ph.D., University of Wisconsin
M. R. Bedford, B.S., Electrical Engineering
K. B. Larson, BCL
J. Markham, BCL
M. E. Raichle, M.D., Radiology and Neurology

Support: RR 00396
NS 06833

Researchers at the University of Wisconsin have used a model developed and tested at Washington University for the estimation of parameters describing the transport of glucose in the brain (PR 13, H-2).(1) In this approach, the parameters of the model are calculated from concentration histories of radioactivity in venous blood following rapid injection of ^3H-glucose, together with ^{22}Na as an intravascular tracer, into the carotid artery of an isolated dog-brain preparation.

Data from about thirty experiments have been analyzed by the investigators at the University of Wisconsin, using software developed at Washington University and modified by them for a Univac 100 computer. Values for glucose extraction computed by this method agree with values computed by the method of Yudilevich, et al.(2) However, the values computed by this method for glucose metabolism frequently are not consistent with those computed by other methods. This discrepancy may be due to

numerical difficulties in the optimization routines used, since the effect of the metabolism rate on the radioactive concentration curves is small. Future investigations will seek to determine whether the incorrect values for metabolism are due to numerical problems in the computer algorithms or to limitations of the model.

(1) M. E. Raichle, K. B. Larson, M. E. Phelps, R. L. Grubb, Jr., M. J. Welch, and M. M. Ter-Pogossian, "In-Vivo Measurement of Brain-Glucose Transport and Metabolism Employing Glucose-^{11}C," American Journal of Physiology, vol. 228, pp. 1936-1948, 1975.

(2) D. L. Yudilevich and N. De Rose, "Blood-Brain Transfer of Glucose and Other Molecules Measured by Rapid Indicator Dilution," American Journal of Physiology, vol. 220, pp. 841-846, 1971.

F-6. Studies of an Image-Processing System for Neuroanatomy

Personnel: V. W. Gerth, Jr., BCL
G. J. Blaine, BCL
J. Hanaway, M.D., Anatomy and Neurology
E. G. Jones, M.D., Ph.D., Anatomy
L. J. Thomas, Jr., BCL

Support: RR 00396

Autoradiography is a useful technique frequently employed in the study of the anatomy of the nervous system. Since manual analysis of autoradiographic specimens is tedious and error-prone, some means of automation is highly desirable. Such a system has been designed to support experiments proposed in a program project grant application submitted by the Department of Anatomy to study regenerative and functional recovery in the cerebral cortex. This system processes autoradiographic specimens using three interconnected microprocessor systems implementing the functions of automatic stage control, video processing, and overall supervision. Much of the system philosophy is based on previous experience gained in the development of a system for automatic silver-grain counting.(1) The Automatic Stage Control Processor and certain features of the Video Processor are based on systems currently under development in the Biomedical Computer Laboratory in support of other projects.

The partitioning of the three functions into three separate processors allows a modular approach that eases modification complexities when adapting to different microscope, stage, and television systems. This partitioning also enhances the speed capability of the system since many

functions can be overlapped. As an example, once a given frame has been acquired by the Video Processor, the Stage Control Processor can move toward the next field while the previous field is being processed.

The Supervisory Processor generates high-level commands which are transmitted to the other processors via the IEEE-488 Bus. This interconnection standard is rapidly becoming a preferred means of configuring an instrumentation system since there is a wide variety of instruments available and there now exists a number of sophisticated integrated circuits for interface design. In addition, the Supervisory Processor receives status information and processed data over the same communication link. In this manner the Supervisory Processor controls the logical flow of an experiment and stores the results according to a pre-defined protocol which can be invoked simply at the Operator Control Panel.

The Stage Control Processor accepts position commands and drives the motorized stage until the requested position is reached. At that time it signals completion and awaits its next command. Position commands can originate either from the Operator Control Panel in manual mode or from the Supervisory Processor in automatic mode.

The Video Processor digitizes the television image and captures the resulting data in its internal memory. The rest of the system is then free to do other things as appropriate while the Video Processor executes algorithms according to the pre-defined protocol. The user can select either individual silver-grain counting or an area-ratio "density" method. Because the Video Processor is implemented with a microprocessor, there is an inherent flexibility that allows other algorithms to be conveniently developed and tested.

F-7. Processing and Display of Neurophysiological Data

Personnel: C. F. Pieper, M.S., Neurological Surgery
D. Y. Chi, M.S., Neurology
S. A. Golden, B.S., Neurological Surgery
S. Goldring, M.D., Neurological Surgery
C. P. Hughes, M.D., Neurology

Support: NS 06947
Washington University

The PC-1200 data-display and manipulation software for the processing of IDAS-generated LINC magnetic tapes (PR 12, H-19; PR 13, H-3) has been modified slightly to ease its use. We continue to use this system routinely for ongoing studies of the motor potential in man and the macaque, and of single-cell responses to visual stimuli within the lateral geniculate nucleus in the cat.

G. Supporting Activities

Activities at BCL which contribute to the goals of more than one of the major programs of the laboratory or to the needs of individual users who can benefit from the special expertise of the staff and the inventory of computer and test equipment are called supporting activities. Service to users does not follow the usual computation-center pattern. No fee schedule has been established, nor is there a centralized facility. Instead, senior laboratory staff members consider requests from investigators for assistance in biomedical computing. Some investigators may be directed to commercial vendors or existing fee-for-service facilities. Others may be advised of the unavailability of appropriate technology. The remaining investigators may have problems that match the special capabilities within BCL. Usually, such a project is assigned to a staff member with similar previous experience. If the project can be completed quickly, the investigator has his results and a short note describing the work will appear in the annual report and in the open literature if appropriate. Other projects occasionally prove impractical and the best alternative is recommended. A few of the user projects may develop into major initiatives within the laboratory. Most of the present successful projects began in this fashion and we value the opportunities that such projects provide.

Although the projects reported in this section span a variety of topics, they can be grouped conveniently as biomedical applications, system development aids, or digital hardware designs. The biomedical applications represent new initiatives in which basic exploration is being conducted, which may or may not ultimately result in a major, long term program. The collaborative effort with the Department of Anatomy relating to a microprocessor-controlled cinemicrography system, and the investigation of new techniques for radiation dose calculation with the Division of Radiation Oncology are examples. Even in cases where an extended effort does not materialize, the relationships which are cultivated frequently prove beneficial to future work.

System development aids mostly benefit the BCL staff, but also are utilized by other groups where appropriate. An excellent example here is the microprocessor development support system which, although still evolving, is an almost routine tool used in data acquisition, signal processing, and control applications. System software development for the PC-1200 and the AUGAT wirelist program reported here are also widely used in supporting a variety of projects.

The digital hardware designs reported in this section are frequently one-time, special purpose designs. The RS-232 translator and CDC Disk Exerciser fit this description. In contrast, other designs may have wide appeal and construction of multiple copies can easily be envisioned. The USD (Universal Storage Device) is such a design and is eagerly anticipated by users with a need for off-line data acquisition and local mass storage.

G-1. Microprocessor Development Support

Personnel: G. J. Blaine, BCL
R. M. Arthur, BCL
M. W. Browder, BCL
R. K. Hartz, BCL
B. F. Spenner, BCL

Support: RR 00396

Our microprocessor development support includes a FORTRAN-based cross-assembler, FOCRAS, intelligent console, InC, and a small library of "standard" M6800 system modules.

FOCRAS is currently operational on Texas Instruments Model 980B, Artronix Modulex, and Digital Equipment Corporation Model PDP-11 minicomputers. The implementation of the FOCRAS Version 5 cross-assembler, which consists of a relocatable assembler and a linking loader, has increased our ability to handle large programs by allowing modules to be assembled separately and then combined using the linking loader. The collection of generally useful subroutines into a shared microprocessor library which is accessed by the FOCRAS linking loader is under way.

The Intelligent Console is itself a microprocessor-based instrument with the present design centered on the M6800 processor. The console electronics include an M6800 processor, three 1K × 8 read-only memories, seven peripheral interface adapters, one serial interface adapter, and a mixture of 50 small and medium scale integrated circuits. Figure 1 illustrates the console, the target plug, and a target system. When fully assembled the console weighs approximately 15 pounds, allowing it to be easily moved from one project area to another. At present target dependent interfaces have been designed to interface the console with M6800, M6802, and I8080 processors. A zero-insertion force socket incorporated on the rear panel of the console is interfaced to the console processor to provide the facility to program the Intel type 2758 EPROMs from the host minicomputer.

Three InC units have been assembled, tested, and are currently used to support a variety of laboratory projects. A fourth InC unit has been assembled and tested by the Electrical Engineering Department to provide both teaching and research support.

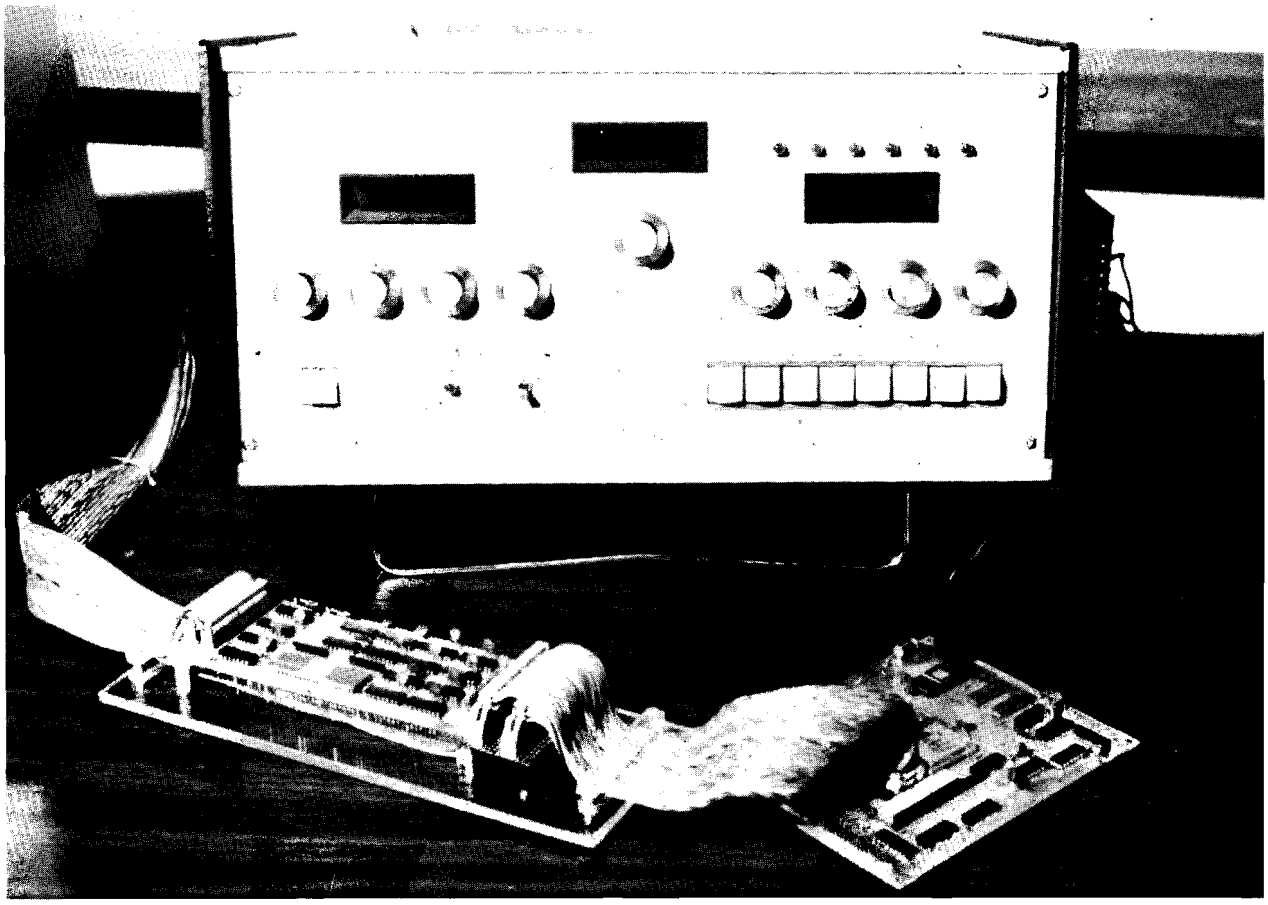


Figure 1. Intelligent Console, Target Plug, and System

G-2. System Software Development for the PC-1200

Personnel: S. A. Garfield, BCL
G. H. Brandenburger, BCL
D. C. Sawyer, A.B., Radiology

Support: RR 00396
Washington University

The source files for OS/PC, the single-user operating system for the PC-1200, were obtained from Artronix to allow errors to be corrected and improvements to be made. The first major change was to develop a version of the FORTRAN compiler which would utilize in-line floating point instructions. Previous investigations (PR 13, I-9) showed that the execution times of FORTRAN programs could be improved by as much as a factor of eleven. This limit was later revised to a factor of thirteen in the extreme case of a program which consisted only of statements of the form Y=-X.

After modifying the compiler, the speed improvement of existing programs using floating point computation was observed to vary from a factor of two to a factor of seven. This improvement has been of significant benefit to a variety of applications.

Among the more significant enhancements were the removal of restrictions on the size of common and on the size of arrays in common, the ability to use arbitrary expressions in a computed GO TO, and the increase in the length of valid names from five to six characters. The DATA, EQUIVALENCE, and named COMMON statements were made available and were quite useful in reducing the size of programs and in managing variable storage for overlays.

All known problems with the compiler were corrected and error checking was greatly improved. Cosmetic changes in listings and error messages were made.

The FORTRAN runtime library, consisting of 86 modules, was modified to correct errors, improve execution time, add new features, and improve accuracy. The most significant changes were in the I/O package, where the accuracy of formatted input and output conversions was dramatically improved. The input conversion method is now identical to the one used by the FORTRAN compiler, so floating point numbers which appear as constants in programs will not differ from those read in from the keyboard during execution.

The other fourteen commands of OS/PC were all modified to remove errors, improve user interaction, and add desirable features. The editor was extensively modified to remove all absolute references and render it in a state where it could be modified and maintained. The new version of the editor displays a header line at the top of the page, containing editor parameters, system date, and file name. The sole error message

of the old version, "NO", was replaced by a complete set of specific error messages. The characters "&" and "#" can now be entered. Anachronisms dating back to LAP6 on the LINC were encountered and removed.

The linking loader was significantly changed to allow unlimited COMMON for FORTRAN, to store the entire binary image in a work area, to keep a copy of each library unit's index in memory, and to process library files. Library files are collections of relocatable modules filed under one name in the index to conserve index entries. The composite external symbol dictionary can now utilize all available memory.

OS/PC LIBRARY (PR 12, H-10; PR 13, I-9) is now called BCL/LIB and has been updated to be compatible with the revised OS/PC. Many new commands and routines were added in response to user requests. The library has gained wide acceptance and is routinely used in most PC-1200 programming applications. The library is now organized as follows:

I. COMMANDS (30)

- A. Those which require Pertec disk (4)
- B. Those which use but do not require Pertec disk (12)
- C. Those which do not use Pertec disk (10)
- D. Those which require Pertec tape drive (4)

II. SOURCE FILES (3)

- A. Faster versions of arithmetic package (2)
- B. Generalized interrupt handler (1)

III. SUBROUTINES (88)

- A. Resident Monitor (3)
- B. Index Manipulation (7)
- C. Overlay (5)
- D. Disk/Tape I/O (3)
- E. Hardware (10)
- F. Character Display (9)
- G. Character String Processing (4)
- H. Scope Display (10)
- I. Plotting (4)
- J. Mathematical (15)
- K. Data Conversion (6)
- L. Data Storage (9)
- M. Keyboard Handlers (3)

IV. FUNCTIONS (24)

A separate tape is now maintained, which contains documentation for OS/PC and BCL/LIB. The tape, called DOCUMENT, contains twenty-eight documentation files, including a software directory, OS/PC update notices and addenda, complete BCL/LIB documentation, sample programs, and hardware

documentation. OS/PC is now distributed on a single tape and BCL/LIB is distributed on two tapes. These three tapes, together with DOCUMENT, form the OS/PC system software, library programs, and documentation as supported by BCL. They have been given to other institutions and are in heavy use at BCL and in Radiology.

G-3. A Wirelist Program for Augat Hardware

Personnel: J. A. Ritter, BCL

Support: RR 00396

In anticipation of the decommissioning of the Artronix MUMPS system, the wirelist software was recoded in Standard MUMPS and transferred to the Medical Computing Facilities Standard MUMPS system. The transfer to a faster computer system, along with substantial modifications to the global variable structure, resulted in marked improvements in system response time.

A buffered line printer controller based on the RS-232 translator (G-16) was built and the line printer from the Artronix MUMPS system was moved to the BCL shop for hardcopy generation. The revised system has been operational since early June and documentation is currently undergoing complete revision to reflect the changes that were made.

G-4. A Universal Storage Device

Personnel: B. F. Spenner, BCL
M. L. Smith, BCL

Support: RR 00396

The Universal Storage Device (USD) was conceived as a research tool that would be useful in experimental situations where analog or digital data needs to be collected at a site that is remote from the computer system which will be used to analyze the data. An M6800 microprocessor, a floppy disk drive and controller, and a small portion of random logic have been combined into a single package that operates as a portable recorder. This device is designed to be operated in as simple a manner as a classical tape recorder, but provides the advantages associated with digital recording. The USD is configured to sample up to four analog

channels and one digital channel with sampling rates selectable over the range of 1 sample/second to 2000 samples/second with sampling controlled either internally or externally. Retrieval of information from the USD is accomplished by linking a host computer system to the USD through either an RS-232 serial interconnect or an IEEE-488 parallel interconnect.

The past year has seen an extensive redesign of the USD disk controller with special emphasis placed on improving the performance of the disk data encode and decode circuits. This effort was essential to ensure the usefulness of the USD in a research environment where the reliability of instrumentation must be exceptionally good as the loss of experimental data is unacceptable. Reliability tests performed on the redesigned disk controller have shown the recoverable error rate to be less than one bit in every 8×10^9 bits read from the disk. This value is consistent with the specifications given by disk drive and diskette manufacturers. The non-recoverable error rate has not been determined because of the extensive amount of test time required to establish the bound.

The prototype version of the USD is operational and being used to collect data generated during cardiac output experiments, as described in C-7. Current plans are to construct four additional units to satisfy various data recording needs which occur throughout the medical center. BCL Monograph No. 325 provides an in-depth description of both the design and operation of the USD.

G-5. Quantization Errors in Floating-Point Arithmetic

Personnel: D. L. Snyder, BCL
A. B. Sripad, D.Sc., Systems Science and Mathematics

Support: RR 00396
Washington University

A non-zero real number, x, is represented in radix-2, normalized, floating-point arithmetic as $x = \pm m2^{\nu}$, where the mantissa, m, is a positive fraction satisfying $\frac{1}{2} \leq m < 1$, and where the exponent, ν, is an integer. When x is zero, both m and ν are taken to be zero. A floating-point representation has the advantage of large dynamic range compared to a fixed-point representation because ν can have many values depending on the number of bits in the register used to store it. However, there is still unavoidable quantization error when using floating-point arithmetic in practice because m must also be stored in a register having a finite number of bits. Statistical models for this quantization error have been postulated on the basis of experiments or on the basis of intuition developed from fixed-point models. In these empirical models, m is presumed to have a reciprocal probability-density, and the error in the quantized representa-

tion of m is presumed to have a uniform probability-density. We have[1] (1) established a necessary and sufficient condition on a real-valued number for the mantissa in its normalized floating-point representation to have a reciprocal probability density, and (2) determined a statistical model for the quantization-error in a floating-point quantizer if these conditions hold. These results are useful for predicting finite register effects when numerical operations and filtering are implemented digitally in floating-point arithmetic.

[1] A. B. Sripad and D. L. Snyder, "Quantization Errors in Floating Point Arithmetic," BCL Monograph No. 323, September 1977.

G-6. Radiation Treatment Planning

Personnel: K. B. Larson, BCL
W. C. Chen, BCL
S. A. Garfield, BCL
V. W. Gerth, Jr., BCL
R. L. Hill, III, M.S., Radiology
R. G. Jost, M.D., Radiology
C. A. Perez, M.D., Radiology
S. C. Prasad, Ph.D., Radiology
J. A. Purdy, Ph.D., Radiology
D. C. Sawyer, A.B., Radiology

Support: RR 00396
Washington University

We have continued our validation of the mathematical model that is the basis of our method of calculating absorbed dose in the presence of inhomogeneities (PR 13, I-3). For this purpose we compared our computed values of absorbed dose with the published experimental results of Young and Gaylord,[1] who used 5-cm absorbing blocks of widely varying electon densities in a water phantom to simulate the effects of inhomogeneities. The measurements of Young and Gaylord[1] used in our previously reported validation work (PR 13, I-3) were those taken along the central axis of a 10- by 10-cm ^{60}Co gamma-ray field at varying depths below inhomogeneity blocks spanning the entire field. Our subsequent validation calculations correspond to their measurements in which blocks spanned only one-half the radiation field and with dosimetry points off the central axis. Since our intent is to verify the physical validity of our dose-calculation model, we have employed exact analytical expressions rather than numerical approximations for evaluating attenuations of primary and scattered radiation along ray paths in the absorbing media and in water. Although our validation work is not yet complete, we expect to find as good agreement between experiment and theory as in our previous results (PR 13, I-3).

In addition to our work with data from the above-described geometrically simple phantoms, we have initiated a validation effort using the more realistic Alderson Average-Man RANDO phantom. To this end, we have generated computed tomographic scans of this phantom using an EMI CT-5000 "Emerald Unit" whole-body scanner. The resulting X-ray absorption data (in the form of "EMI numbers") for each 1- by 1- by 13-mm pixel were converted through use of an empirical correlation to electron densities needed for our calculation of Compton attenuation and scatter. To carry out this conversion and to aid in examining the scan data, we have programmed a PC-12 computer to read the data from magnetic tapes generated by the scanner unit and to produce printed output as well as a two-dimensional visual display of individual scan slices. Our objective in our validation work with the RANDO phantom is to develop practical algorithms based on our model and to compare calculated values of absorbed dose with experimental dosimetric data.

(1) M. E. J. Young and J. D. Gaylord, "Experimental Tests of Corrections for Tissue Inhomogeneities in Radiotherapy," British Journal of Radiology, vol. 43, pp. 349-355, 1970.

G-7. Physiologic Signal Processing

Personnel: B. F. Spenner, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

Our interest in evolving improved techniques for processing physiologic signals makes it necessary for us to carefully analyze the signals we intend to process as we search for a set of characteristics which optimally differentiate the different signal morphologies of interest. Our efforts have been enhanced by work with alternative signal processing algorithms and by the availability of inexpensive processing elements. Now that it is feasible to incorporate a digital processor into an inexpensive monitoring module (C-2) the performance of processing algorithms can be enhanced, thereby improving the quality of the information derived from the physiologic signal.

During the past year we have been investigating the characteristics of electrocardiograms (ECG) in the frequency domain. The signals we have been analyzing are excerpts from 24-hour ECG recordings that were processed by the Argus system and each beat has been labeled as either normal, positive premature ventricular contraction, or one of several other labels (A-4). An example of results from our ECG analysis is presented in Figure 1.

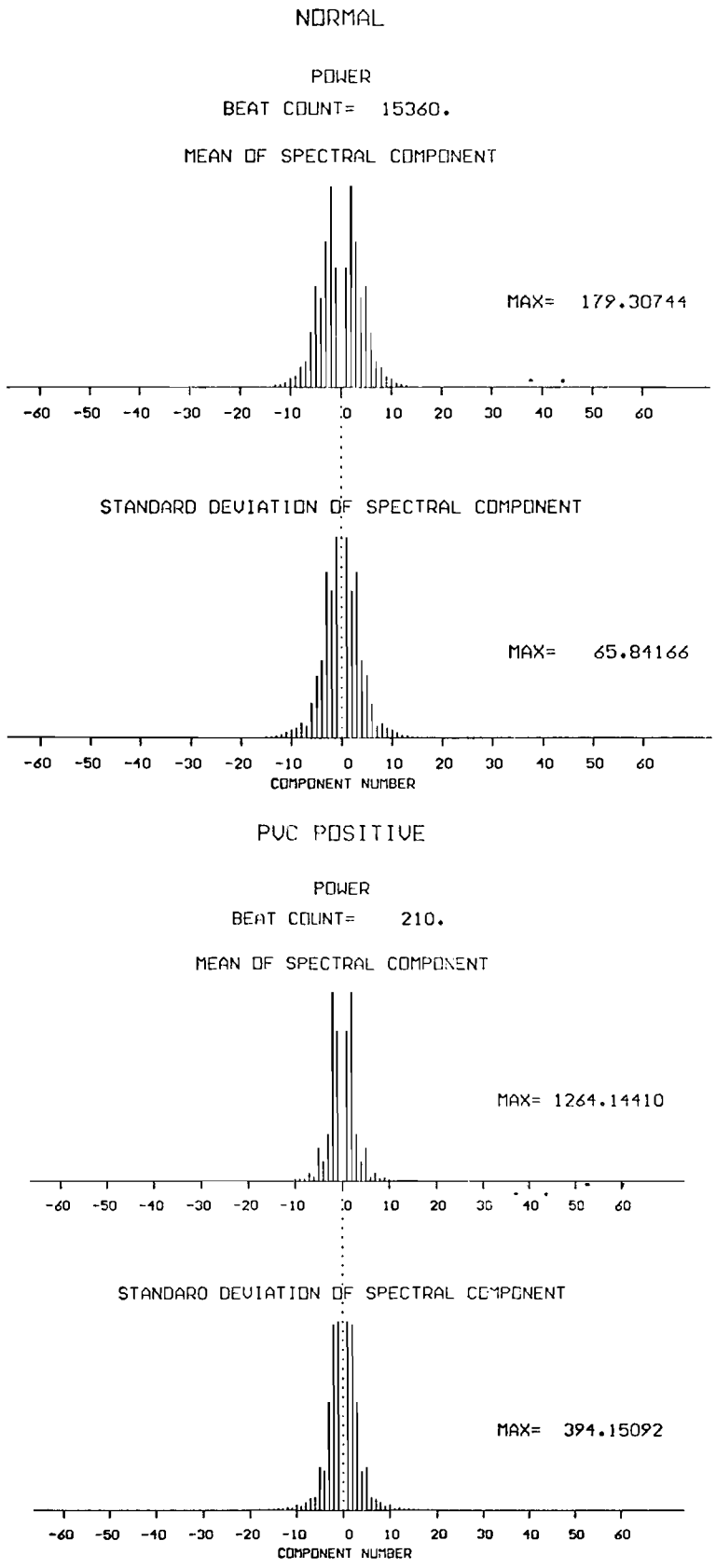


Figure 1. Mean and standard deviation of the amplitude coefficients of a Fourier series representation of an ensemble of normal and PVC complexes.

In this figure the length of any vertical bar represents the amplitude of the mean or standard deviation of the energy contained in a particular frequency component of an ensemble of QRS events. The analysis window was chosen to have 128 points which is equivalent to 512 ms. The signal is automatically centered in the analysis window, using the Argus-generated time-of-occurrence. The upper half of the figure presents the statistics collected from an ensemble of 15,360 Argus-labeled normal beats, while the lower half shows the statistics from an ensemble of 210 Argus-labeled positive premature ventricular contractions. All the beats represented by the statistics in Figure 1 are taken from the same channel for a single patient.

As suggested by the statistics in Figure 1, the shape of the energy spectra for the normal beats is generally different from the shape of the spectra for the premature beats. However, these statistical measures describe the characteristics of a particular frequency component across the ensemble of QRS events. Therefore, they may not accurately represent the shape of the energy spectra for each QRS event in the ensemble. To better characterize the shape of energy spectra, we defined the "first spectral moment" as the first moment of the spectral distribution. This parameter has proven to be a reasonable measure of signal morphology and is currently being applied to enhance the operation of the Argus system (A-1).

We intend to continue to improve our characterization of the ECG signal in the frequency domain by gathering statistics across different patients, and across different recording sessions for the same patient. We are searching for an appropriate set of parameters that will allow us to define an algorithm that reliably differentiates QRS complexes of different morphologies.

G-8. Random Point Processes

Personnel: D. L. Snyder, BCL

Support: RR 00396
ENG 76-11565

A random point process is a mathematical model for data characterized by highly localized events in time, space, or a combination of time and space. The Poisson process is an important example and is the basic building block for more complicated models. Our goal in studying random point processes is to develop algorithms and information processing structures for making inferences about underlying phenomena that influence observed data that are modeled as a random point process. As further goals, we want to develop performance measures on how well such inferences can be

made, and we want to characterize how information is conveyed by a random point process. Over the past year, studies have been made of position sensing and tracking,[1,2] martingale models,[3] information transmission,[4] and noise effects in fan-beam algorithms for reconstructive tomography (B-3). The results of these studies are summarized briefly as follows:

a. Position Sensing and Tracking. Available data are modeled by a point process in which each point has a temporal coordinate and a spatial coordinate. A point might model a light flash in a spatially distributed scintillation detector or a photoelectron conversion in a spatially distributed photodetector. Points occur at a rate that fluctuates randomly in time and as a two-dimensional Gaussian function in space, where the center of the Gaussian function wanders about the plane in a random-walk motion. For certain models,[1,2] we have identified how to estimate the location of the center of the Gaussian function from measurements of the location of individual points, and we have derived upper and lower bounds on the errors involved in doing this.

b. Martingale Models. The objective of this study is to develop an approach for making inferences about nonobservable processes that influence data modeled as a mixture of continuous and discontinuous components. The topics studied[3] include the characterization of filtering, smoothing, and prediction estimates, hypothesis testing, and estimation-performance bounds.

c. Information Transmission. One advantage of optical communication systems is the potential they provide for high signaling rates. An implication of this whenever the information to be transmitted is produced at a lower rate than the available channel rate is that coding for error detection and correction can be used to reduce the effects of photoconversion noise and channel disturbances. This potentiality for optical communication systems to accommodate the expanded bandwidths associated with coding has motivated our study of (1) receiver structures for optical communication systems employing trellis and convolutional coding,[2] and (2) the coordinated design of the optical modulator and demodulator to maximize the channel cutoff rate.[4]

[1] I. B. Rhodes and D. L. Snyder, "Estimation and Control for Space-Time Point-Process Observation," IEEE Transactions on Automatic Control, vol. AC-22, no. 3, pp. 338-346, 1977.

[2] D. L. Snyder, "Applications for Stochastic Calculus for Point-Process Models Arising in Optical Communication," BCL Monograph No. 318, August 1977.

[3] M. V. Vaca and D. L. Snyder, "Estimation and Decision for Observation Derived from Martingales: Part II," IEEE Transactions on Information Theory, vol. IT-24, no. 1, pp. 32-45, January 1978.

(4) D. L. Snyder and I. B. Rhodes, "Some Implications of the R_0 Criterion for Coded, Direct-Detection, Optical Communication Systems," BCL Monograph No. 347, April 1978.

G-9. Measurement of Corneal Pressure Using Video Techniques

Personnel: R. J. Arnzen, BCL
R. A. Moses, M.D., Ophthalmology

Support: RR 00396
EY 00256

A technique has been investigated for the continuous measurement of corneal pressure by means of video techniques. An important aspect of this technique is to provide the ability to continuously and automatically monitor and record pressure over a period of several minutes. This data will subsequently be used for the study of those physiological mechanisms that govern the generation and relief of fluid pressures behind the cornea and mechanisms associated with glaucoma.

The apparatus consists of a clear plexiglass cylinder whose one end contacts the subject's cornea with a constant, known force, flattening a portion of the cornea into a disk shaped contact surface. The flattened area is viewed through the opposite end of the cylinder with a low power microscope whose optical path is made available to a vidicon television camera. The microscope image is then available on a video monitor. The display may be used by the investigator to assure that the flattened area of the cornea is centered on the cylinder.

Prior to the application of the plastic cylinder to the cornea, a small amount of contrast medium is applied to the eye. When the cornea is flattened, the monitor image appears as a black disk in a white field. This high contrast image may be processed for the automatic determination of the disk diameter and, ultimately, the cornea pressure since the contact force is known.

Feasibility of this idea has been explored by a search for suitable contrast medium and video taping of these experiments. The analog video signal has been studied with the use of equipment previously developed for cath lab use and the results have been very encouraging. It appears that very good contrast can be achieved so that the process of locating edges of the image will be quite simple. The next step will be the development of hardware to automate this process and design of a high speed counter which can be triggered by the edge detector and provide a measure of the disk diameter. Feedback to the video monitor will also be used to indicate where the disk diameter is being taken so that the operator can change

that position if desired. Alternatively, automatic search for the maximum width dimension of the disk could be implemented but, at the current state of development, tradeoffs between complexity and usefulness of features are being evaluated.

G-10. A System for Multiplexed Time-Lapse Cinemicrography of Cultured Cells

Personnel: V. W. Gerth, Jr., BCL
R. J. Arnzen, BCL
R. R. Heye, Radiology
E. W. Kiebler, Radiology
L. J. Tolmach, Ph.D., Anatomy and Radiology

Support: RR 00396
CA 04483

Time-lapse cinemicrography is a powerful tool for the study of cell growth and proliferation, and of the response of cultured cells to radiation and/or chemotherapeutic agents. A time-lapse system that has been used for some time in the Anatomy Department employs a light microscope, 16 mm motor-driven camera, and a solid state timer to expose single, sequential frames every few minutes over a period of several days. The resulting time-lapse film is analyzed, using a film viewer whose frame counter is interfaced to a PDP-11 computer. The operator enters data related to cell activity via PDP-11 interactive software.

Since the camera-microscope system is configured for single field operation, all experiments must proceed in serial fashion. In order to remove this single-field limitation and allow multiple experiments to proceed in parallel, a new system has been designed and is currently under development.

The new system allows multiple field operation through the use of a motor-driven x-y stage controlled by an M6800 microprocessor. The microscope fine-focus is also controlled by the microprocessor to allow for irregularities in the dish surface from field to field. The original camera could have been used, but some type of post experiment sorting of frames would have been required in order to generate n separate time-lapse films for n separate fields of interest. As an alternative, a new camera has been designed which is capable of fast, random access to any frame under microprocessor control. This allows the frames to be sorted at the time of exposure so that analysis can begin immediately following film development. Since the microprocessor also controls the camera shutter, exposure time can be varied conveniently with software parameters.

The operator interacts with the system during experiment setup through a control console which contains a joystick for x, y, and fine-focus control and buttons for mode selection and parameter entry. As each field is selected and focused, its coordinates are stored for later retrieval. The film length, and exposure interval and duration, are selected with rotary hex-encoded switches. After the setup is complete and verified by the operator, selection of the automatic mode turns control over to the microprocessor which moves the stage to each field in sequence, focuses, positions the film to the correct frame position, and exposes the film.

The adaptation of the microscope to accept the x-y stage and fine-focus drive is complete. Installation of limit switches and culture-dish holder is in progress. The M6800 microprocessor system has been designed and partially fabricated, and all software has been flow charted. Critical subroutines have been coded to gain confidence in the accuracy of timing estimates, and the manual control of the stage and fine-focus via the microprocessor has been breadboarded to allow human factors consideration of stage motion relative to joystick motion. Design of the camera and control console are nearly complete.

G-11. A Device for Studying Patient Medication Compliance

Personnel: V. W. Gerth, Jr., BCL
G. J. Blaine, BCL
M. A. Kass, M.D., Ophthalmology
L. J. Thomas, Jr., BCL

Support: RR 00396

The difficulties encountered in monitoring the compliance of patients with prescribed medication can limit the confidence in results observed in clinical trials and routine treatment. This is especially true in situations where the disease produces no immediate discomfort to the patient and where the drug may produce annoying side effects. A prototype pharmaceutical dispenser with circuitry for sensing and recording the use by a patient had previously been developed and subjected to limited testing, but was judged to be too large and heavy for widespread replication and use. This device was based on CMOS, SSI, and MSI technology and used the concurrence of removing the cap and tilting the bottle as the event which was recorded in memory.

Although the prototype device has serious limitations due to size and weight, the need for a practical solution still exists and represents an important problem. In an effort to identify such a solution, a study has been begun to determine the feasibility of implementing the dispenser with the hybrid bonding of integrated circuit dice as opposed to standard

dual inline packages. Some of the required functional circuits have been selected and are available from integrated circuit manufacturers as standard parts. A search is currently underway for the remaining parts. CMOS technology is preferred because of the need for low power to enable self-contained battery operation for a one month period.

G-12. An LSI-11-Based Microcomputer System for Laboratory Automation

Personnel: M. C. Jost, BCL
D. L. Rempel, BCL
W. F. Holmes, BCL

Support: RR 00396

In this project we are involved in the development of a flexible set of hardware and software modules for use in automation of control, data collection, and data processing for certain analytical instruments used routinely in biochemical research. Such instruments include amino acid analyzers, gas chromatographs, spectrophotometers, and assay systems requiring variable quantities of reagent addition. These applications typically require on-line data acquisition and control with modest speed requirements. Most applications require relatively simple on-line data reduction, with certain applications calling for more sophisticated post-run calculations and data analyses. Costs must generally be kept to a few thousand dollars, even less for simpler instruments.

A usable general-purpose minimum system should include a central processor, RAM memory at the 1, 4, or 8K word level, ROM memory for permanent program storage, a small alphanumeric printer (15-20 characters wide), an alphanumeric keyboard having a number of special function keys, an analog input module with a wide range (1 mv to 10 v full scale) variable-gain amplifier and multiplexed analog-to-digital converter, a digital I/O module for control of relays, valves, DC motors and stepping motors, and a programmable clock. The hardware required for an application will be housed in a box with a control and monitoring panel in front and connectors in the rear for the analog and digital I/O, the printer, and the keyboard. This dedicated system will be located at the instrument site.

To permit development and testing of hardware and software modules, and to permit quick and easy maintenance or system improvement should problems develop or should modifications and improvements to the system be necessary, it is convenient to have a mobile, dual floppy disk-based development system. This development system should contain the minimum laboratory automation system components specified above, as well as a CRT terminal, a hard copy device, additional RAM memory, and a sophisticated operating system supporting programming in a higher-level language such as FORTRAN, BASIC, or FOCAL.

A DEC LSI-11 microprocessor was the initial choice for the laboratory automation system central processor. The basic LSI-11 cpu module, which contains a 16-bit central processing unit with fixed and floating-point capability and 4K of 16-bit RAM memory, has been combined with two serial interface modules, three 16-bit dual input-output modules, 4K of 16-bit core memory, 8K of 16-bit RAM memory, and a dual floppy disk controller. This LSI-11-based microcomputer, together with a Charles River Data Systems FD11 Dual Floppy Disk unit, a DEC VT-55 CRT terminal, and a Teletype has been used under the DEC RT-11 operating system and RT-11 FORTRAN to develop the following hardware and software modules: an analog input unit containing a Burr-Brown ADC80 12-bit analog-to-digital converter preceded by a unity gain operational amplifier-based low pass filter and a low level (0-50 mv) Burr-Brown 3662 instrumentation amplifier, a Keytronic C-1400 alphanumeric keyboard having 18 special function keys, and a Bowmar TP-3100 Thermal Printer capable of printing up to 18 alphanumeric characters per line. This same LSI-11 microcomputer system has also been used to develop the hardware and software modules for an Axiom EX-810 plotter, as described in another report (G-19).

While setting up this laboratory microcomputer system, the requirements of a number of potential applications have been considered. This ensures that the design will be readily adaptable to new uses. Enough capacity has been included in the initial microcomputer system so that further applications will not require a redesign of system components.

One of our basic goals in setting up the laboratory microcomputer system has been to plan the system components so that they are essentially independent of the microprocessor chosen. This has been done by using a simple scheme of parallel data transmission between each component. As other more suitable microprocessors become available, or for those applications where all the capabilities of an LSI-11 processor are not required, suitable, or economically feasible, another processor may be selected and included in the laboratory automation system without a complete redesign. The microprocessor portion can differ, depending on the device chosen, but can be so designed as to present the same interface to each of the other system components (G-18).

The first application selected for the LSI-11-based laboratory microcomputer system involves a new amino acid analyzer built in Dr. Leonard Banaszak's laboratory in the Department of Biochemistry. This analyzer employs a new fluorescent reagent[1] for detecting amino acids down to the 100 picomole level, a dramatic increase in sensitivity compared with conventional analyzers. This permits the sequencing of many proteins hitherto available only in quantities too small for analysis. Fluorescence data from the fluorimeter detector will be collected and stored in the computer memory. Peak detection, peak separation, and calculation of component concentrations will be done either during or after completion of the run, depending on the complexity of the analysis. Work to date with the hardware of the LSI-11-based microcomputer system is sufficiently complete to permit development of data collection and data processing routines. Software for this application has previously been specified to the detailed flowchart level (PR 12, F-1).

(1) J. R. Benson and P. E. Hare, "o-Phthalaldehyde: Fluoregenic Detection of Primary Amines in the Picomole Range. Comparison of Fluorescamine and Ninhydrin," Proceedings of the National Academy of Sciences, vol. 72, no. 2, pp. 619-622, 1975.

G-13. A Gated Radionuclide Cardiac Imaging System

Personnel: H. D. Ambos, BCL
R. E. Hitchens, BCL
S. A. Jones, M.D., Radiology
B. A. Siegel, M.D., Radiology
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646

A portable, cost-effective system has been developed for performing noninvasive ECG-gated radionuclide multiple gated blood-pool imaging studies. A prime requirement for the system was its potential for use in conjunction with portable gamma cameras at any bed in a fifteen bed coronary care unit. Data are recorded on nine-track tape using a portable collection unit and framed off-line with a Univac V76 computer system. The portable digital data collection system was designed as a lower cost alternative to available but expensive video-tape recording equipment, with additional flexibility beyond that provided by a permanently wired data communication network from individual beds to a remote computer system.

The data collection system converts the gamma camera analog signals to digital form and stores pixel values in list mode on tape along with time-mark and ECG-gate information. It can accommodate 40,000 bytes/second (20,000 counts per second from the X and Y signals). Pixel resolution is 128 by 128 and the differential linearity of the analog-to-digital converter is 3 percent.

The off-line analysis of the quantitative data provides characterization of ejection fraction and rate, ventricular volumes, and regional wall motion abnormalities, by averaging frames of cardiac cycles obtained from segmenting the average R-R interval into 22 equal portions. Presently, images are displayed in static format, but plans are underway to display the gated images in endless loop movie format.

This cost-effective system facilitates the performance of ventricular function studies among critically ill patients, such as those with acute myocardial infarction, who can not be moved conveniently to a central processing facility.

G-14. A Disk Exerciser for CDC 9700 Drives

Personnel: S. R. Phillips, BCL
R. E. Hitchens, BCL

Support: RR 00396

Construction of the disk exerciser (PR 13, I-14) is now complete. Final evaluation of the exerciser is in progress and it is felt that this unit will be quite useful in routine maintenance and trouble-shooting of the CDC drives.

G-15. An 80 Megabyte Disk Interface for the IBM System/7

Personnel: R. E. Hitchens, BCL

Support: RR 00396
HL 18808

The design of an interface between the System/7 channel interface (PR 10, A-7) and a System Industries Model 9500 disk system is underway. The system includes one Control Data 9762 80 Mbyte drive which will accommodate 24 hours of ARGUS/H sample and cycle data and eliminate the need for Huffman encoding of the sample data. Eventual plans are to upgrade the system by adding a second 80 Mbyte drive, allowing a second ECG channel to be stored.

G-16. An RS-232 Translator for Parallel-Input Line Printers

Personnel: M. W. Browder, BCL

Support: RR 00396

In order to fulfill the desire to connect parallel input line printers to various systems through standard RS-232 serial computer interfaces, a general purpose, programmable RS-232 translator was developed, based on the Motorola M6800 microprocessor. Use of the M6800 introduces a high degree of flexibility which has allowed the connection of various parallel input line printers to several different computer systems. In addition, use of a microcomputer provides the ability to increase line printer usage by connecting several computer systems to the same line printer through additional RS-232 serial data ports on the translator.

G-17. Raster Scan Video Technology

Personnel: V. W. Gerth, Jr., BCL
G. H. Brandenburger, BCL
J. R. Cox, Jr., BCL
B. R. Hieb, M.D., Jewish Hospital
T. J. Marshall, BCL

Support: RR 00396

The requirement for information display continues to be a major consideration in many systems under development or in the planning stages at BCL. In the past these needs have been met by CRT terminals, x-y refresh displays, both storage tube and silicon target scan converters, direct-view x-y storage tubes, and special-purpose raster scan systems for display of physiological waveforms. All these systems have strengths and weaknesses which make them more or less suitable for specific applications.

Raster scan video technology is attractive for a number of reasons. The cost of a raster scan monitor is considerably less than a comparably sized x-y monitor of similar video bandwidth. Another economic factor is a result of the mass production of CCTV transmission hardware and related accessories. Also, as a result of the widespread use of the CRT terminal as a computer peripheral, integrated circuit manufacturers now provide LSI chips which greatly simplify the design and lower the cost of new systems. The added dimension of color display, made practical by the home entertainment industry, is another motivation for considering raster scan video technology for new display systems. Color display in x-y systems is limited almost exclusively to beam penetration tubes which are both expensive and critical in adjustment while providing only a limited range of color. The continuing reduction in price of digital memory devices also affects the cost of a raster scan display system in a favorable way. Because of the refresh requirement on a rigid schedule, virtually all raster scan systems employ integral memory in order not to burden the computer main memory with significant overhead.

There are currently three areas of activity relating to raster scan display technology at BCL. The first goes back to the display system developed for the SICU monitoring project (PR 8, D-2) and a color display system used in operating room monitoring (PR 10, C-14). This activity is aimed at the moving, non-fade display of physiologic waveforms. A special purpose system addressed to this class of needs is justified because of economics and human factors in the monitoring environment. Another more recent development activity is addressed to a wider variety of needs and promises to eliminate many of the instability and alignment problems inherent in storage tube and silicon target scan converters by using semi-conductor digital storage. Finally, techniques for overcoming or reducing some of the artifact inherent in raster scan displays are being investigated by theoretical analysis and experiment.

The completion of the RS-232 interface for video display (PR 13, I-11) has been suspended in order to incorporate projected display needs of the Clinical Physiologic Research System (C-2). This will allow the inclusion of an IEEE-488 bus port to achieve compatibility with the CPRS modules and use of newly available CRT control chips which will significantly reduce the parts count. Another facet of activity relating to physiologic waveform display is the expansion of the existing color video display O.R. monitoring system to service an additional operating room. Barnes Hospital has purchased an additional color monitor and digital display package which will be combined with a standby video and color processor in the current system to yield a new stand-alone system. The excellent reliability experienced in the past three years suggests that non-redundant systems will be satisfactory.

A recent study of the computer-display needs in the Washington University medical community revealed widespread need for a general purpose raster scan video display system. The most common set of attributes for such a system formed the basis for a design which is near full implementation. Those attributes are:

1) Low cost (under $5000),

2) High resolution character, graphic, and grey-scale display generation, realizable with a 512 × 512 display grid and four bit (expandable) grey-scale resolution,

3) Standard 525-line video compatability,

4) Digital I/O port capable of reading or writing at full video rates (512 × 512 words in 1/30 second) for video "frame snatch" capability,

5) Medium speed (625 kilo-words/sec read/write ports for general computer display generation),

6) Intelligent, microprocessor-based, lower speed read/write port capable of automatic character, vector, variable-size grey-scale pixel, and random point display generation,

7) Dynamic (real-time) grey-scale windowing.

Some applications envisioned for this system include:

1) Ultrasonic tomographic reconstruction (grey-scale and character/graphics) display generation, using medium speed and "intelligent" ports (B-1),

2) Ultrasonic pulse echo (grey-scale and character/graphics) display generation using "frame snatch" and "intelligent" ports (A-17),

3) Electron microscopy (grey-scale) display using "frame snatch" port,

4) Gamma-camera image generation (grey-scale and character/graphics) using the medium speed and "intelligent" ports,

5) X-ray angiographic image processing (grey-scale and character/graphics) using all three I/O ports (C-9).

The system is based on a bit-map architecture and constructed around 16k bit dynamic random access memory chip arrays such as the Matrox MSBC512. The memory is continuously read into a fast, deglitched, multiplying digital-to-analog converter, the output of which is added to composite sync to produce composite video. Up to 24 bits of grey-scale can be supported by the system. The medium speed I/O port is implemented with FIFO registers to reduce the communication complexity with the host computer. The "intelligent" port is implemented with a Motorola 6800 microprocessor and will support parallel or serial (RS-232) communication with the host.

The system will be installed initially on the PC-12 for use in X-ray angiographic and ultrasonic tomographic research and will be accessed through FORTRAN-callable subroutines and through a modification of the PC-12 FORTRAN I/O handler software. Manual (potentiometer), as well as programmable real-time dynamic grey-scale windowing, will be provided to permit viewing images with wider dynamic ranges than are realizable with video monitors. The prototype system has already generated bi-level images and is expected to be fully operational in August.

As suggested earlier, the discrete nature of raster scan displays is responsible for potentially annoying artifact. Even if wideband monitors are used to allow good response along a scan line, the finite number of scan lines imposes a type of "sampling" process on an arbitrary image. The nature of some of these artifacts and potential means of reducing them are being investigated. One approach under consideration utilizes beam shaping by Z-axis modulation derived from an algorithmic procedure accomplished dynamically and, if successful, would trade high speed hardware for the large memory requirements of a high resolution bit map architecture.

G-18. The Compatibility of Parallel Interfaces for Three Microprocessor Systems

Personnel: W. F. Holmes, BCL
D. L. Rempel, BCL

Support: RR 00396

The laboratory automation microcomputer system described in G-12 is based on the Digital Equipment Corporation (DEC) LSI-11 microcomputer, interfaced to I/O modules for analog and keyboard input, printing, and plotting. A standard DEC parallel I/O card, with 16 bits of input and output on separate data lines, is used for interfacing these modules. The LSI-11 microcomputer simplifies program development, since PDP-11 software may be used. However, system cost may be too great for some applications. Therefore, a study was made of the Motorola MC6800 and Intel 8080 microprocessor families to see if they could substitute for the LSI-11 without changing the design of the I/O modules. In practice, the Motorola MC6820 and Intel 8255 peripheral interface chips were examined to see if they could serve as a substitute for the DEC LSI-11 (and PDP-11) parallel interface cards when used with the corresponding microprocessor.

Either of these chips can handle 16 data lines as input or output; separate lines would require two chips. The MC6820 is compatible with the DEC parallel interface protocol with two exceptions; the RESET and COMMAND lines will each require a data line to implement, reducing the total to 14 lines. If more data lines are required, a second MC6820 can be used. The 8255 interface chip is also compatible if the REQUEST line in the DEC protocol is inverted to serve as the 8255 STROBE.

G-19. Low Cost Graphic Printer/Plotter

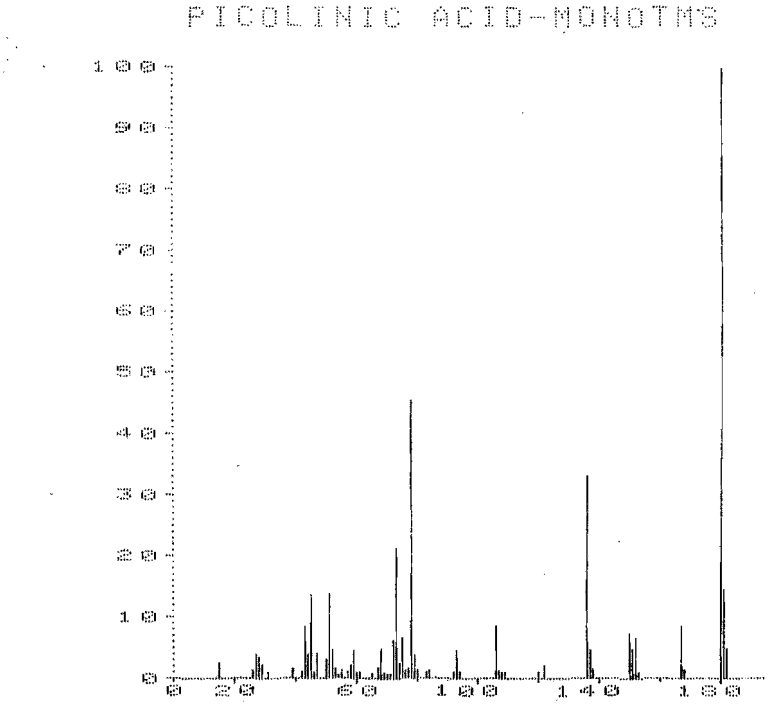
Personnel: M. C. Jost, BCL

Support: RR 00396

Certain of the candidate applications of the LSI-11-based microcomputer system for laboratory automation (G-12) could also make use of an inexpensive printer/plotter for output of alphanumeric and graphic data. The Axiom EX-810 electrosensitive graphic plotter, priced at $795, seems well suited for such applications. We have obtained one of these plotters and developed the hardware and software required for it to function in our system.

The EX-810 plotter has an 8-wire printhead. A simple TTL-compatible controller contained in the plotter permits direct control of printhead motion, with margin and position markers for accurate synchronization with the input raster. Plotting is achieved by providing a parallel 8-bit pattern, allowing eight rows of dots to be plotted at a single pass across the paper. The printer is capable of plotting approximately 128 dots per inch over 4.25 inches of the 5-inch wide paper, at a rate of two, eight row lines per second. Using a 5 × 8 dot matrix, up to 80 characters can be printed on a line. Hence, when the controlling computer is programmed appropriately, 160 alphanumeric characters can be printed per second.

Using the LSI-11-based development system (G-12), hardware and software modules have been designed to drive the plotter. A set of FORTRAN and FORTRAN-callable assembly language routines provide for plotting horizontal or vertical lines and dots at any position or level on a page. Dot densities of either 256 or 512 dots across the page may be selected. Alphanumeric characters can be placed at any point along a print line, in any of four orientations. Graphic and alphanumeric fields may be combined in the same line. An example of the output which can be obtained is shown in Figure 1.



VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Industrial collaboration provides an additional outlet for laboratory developments and benefits the staff by keeping it abreast of the practical considerations of reliability, maintainability, and cost. Progress being made in this important phase of the laboratory's activities is summarized here.

A. Arrhythmia Monitoring. Following evaluation of the Mennen-Greatbatch ARGUS/SENTINEL computerized arrhythmia detection system, it was installed in the Barnes Hospital Coronary Care Unit. Subsequent to the successful completion of a battery of acceptance tests administered by BCL, it was released to CCU personnel for clinical use. The system has been in routine clinical use for over two years. This collaboration has continued through sharing algorithm improvements of mutual interest, an activity that has been increasing during the past year. (BCL personnel: K. W. Clark, C. N. Mead, J. A. Ritter, L. J. Thomas, Jr.)

B. Reconstructive X-Ray Tomography. The work in collaboration with Picker Corporation, first reported in PR 10, VI-D, has led to the issuance of three patents:

Brunnett, C. J., Cox, Jr., J. R., Snyder, D. L., and Mattson, R. A., "Tomography System Having Nonconcurrent, Compound Axial Scanning," U.S. Patent 3,976,885, August, 1976.

Cox, Jr., J. R., and Snyder, D. L., "Transverse Tomography System Having Multibeam Orbital Scanning with All Beams Offset from the Center of Orbit," U.S. Patent 3,983,399, September, 1976.

Cox, Jr., J. R., and Gerth, Jr., V. W., "Tomography System Having an Ultra High Speed Processing Unit," U.S. Patent 4,044,240, August, 1977.

C. Collaborative Drug Study. A research project has been in progress during the past two years with Sandoz-Wander, Inc., for a pilot study to evaluate the safety and efficacy of a new beta-adrenergic antagonist, LB-46, on ventricular irritability. Following FDA approval of the experimental design the study was initiated in May, 1976. This Phase II study consists of a double-blind crossover against placebo, of four weeks duration for each of twenty ambulatory patients with twenty or more premature ventricular contractions per hour. In addition to the appropriate clinical observations and laboratory tests, seven 24-hour Holter tapes are being collected and analyzed via Argus/H for each patient. Beyond a substantial participation in the study design, the primary role of the laboratory is analysis of the Holter tapes. Provision has been made for optional analyses to include time-of-day-independent PVC rates, as well as frequencies of couplets, runs, and early PVCs. Initial analyses of variance then would consider dependent variables as being either the number of couplets, runs, or early PVCs per 24-hour period, and the sources of variation as treatment, order of treatment, and patients.

The results of processing tapes of the first fifteen patients have been incorporated into a preliminary report which has been submitted to the FDA through Sandoz. The opportunity to examine the power of Argus/H for such studies is welcome. It is particularly appropriate that this pilot design-feasibility study is small enough not to compromise our on-going Argus/H-based research efforts (section V., A.) and yet allows us to examine system performance in the context of a carefully drawn drug study. The "machine-edit" algorithms previously reported (PR 12, A-15) have proven to be invaluable for this work. It is this type of study upon which systems such as Argus/H are likely to have a major impact. (BCL personnel: K. W. Clark, J. P. Miller, G. C. Oliver, L. J. Thomas, Jr.)

VII. TRAINING ACTIVITIES

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

Survey of Biomedical Computer Techniques, Fall, 1977

This series of presentations was directed toward biological scientists to provide an appreciation of the capabilities and limitations of digital computers as applied to biomedical problems. Topics included elements of sampling theory relevant to computer processing of biological signals, computer fundamentals, implementation of a computer using macromodules, software techniques, including machine, assembler, and higher level languages, and input/output devices. Microprocessor support, signal processing, and presentation of application techniques, as exemplified by existing systems (e.g., clinical and laboratory research systems), were included also.

Presentations were given by BCL staff members, G. J. Blaine, S. A. Garfield, V. W. Gerth, Jr., B. F. Spenner, and L. J. Thomas, Jr. Attending the course were:

John R. Baird	WUMS IV Medical Student
Nancy Caston, M.Ed.	Radiology
David Chi, M.S.	Neurology
Lawrence A. Coben, M.D.	Neurology
Louis F. Combrevis	Biomedical Computer Laboratory
David E. Crowley, Ph.D.	Computer Systems Laboratory
Mokhtar Gago, M.D.	Radiology
Ross K. Hartz, M.S.	Biomedical Computer Laboratory
John E. Helzer, M.D.	Psychiatry
Kenneth B. Larson, Ph.D.	Biomedical Computer Laboratory
Michael Lincoln	WUMS IV Medical Student
Stanley R. Phillips	Biomedical Computer Laboratory
Luis Reuss, M.D.	Physiology
Wayne R. Roloff, B.S.	Biomedical Computer Laboratory
Rao Vemula, M.S.	Biomedical Computer Laboratory

Introductory MUMPS Computer Programming Course, Spring, 1978

A high-level programming language (Massachusetts General Hospital Utility Multi-Programming System - MUMPS), especially well suited for medical information systems and other textual and database applications, was presented by Dr. Robert H. Greenfield. Guest speakers (Mary M. McCormick, Charles N. Mead, Donald P. Ragan, Joel F. Achtenberg, John W. Lewis, III, and Joan Zimmerman) introduced their MUMPS applications to the class. Laboratory exercises were conducted, using the MUMPS computer resources of the Oncology Data Center, Mallinckrodt Institute of Radiology, Washington University School of Medicine. Attending the course were:

Steven R. Bergmann, M.D., Ph.D.	Cardiology
Virginia Bixon, B.S.	Biomedical Computer Laboratory
Robert L. Chan, M.S.	Blood Bank, Barnes Hospital
Sheryl Flieder	Computer Science
Juanita H. Gammel, M.S.	Cardiology
Stuart A. Golden, BSME	Neurosurgery
George G. Granich, M.T.	Microbiology Laboratory, Barnes Hospital
Mary Hicklin	Computer Science
Albert Jacobson, Ph.D.	Pathology
Kenneth K. Kaiser, B.S.	Neurology
Robert M. Kolodner, M.D.	Psychiatry
Nancy Beth Leon	Radiation Oncology, Mallinckrodt Institute of Radiology
Ray Levine, M.D., Ph.D.	Cardiology, Jewish Hospital
Shigeki Nonoyama, D.Sc.	Systems Science and Mathematics
Barbara Norton, BSPT	Irene Walter Johnson Institute of Rehabilitation
Patricia Pickett, B.S.N.	Irene Walter Johnson Institute of Rehabilitation
Randall D. Rhodes	Physical Plant, School of Medicine
David Sandel	Radiation Oncology, Mallinckrodt Institute of Radiology

VIII. SEMINARS

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

"A Microprocessor-Based System for the Acquisition of Visual Field Data from a Goldmann Perimeter" November 4, 1977	Mr. Ross K. Hartz Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Pattern Recognition in the Differential Diagnosis of Hypercalcemia" April 4, 1978	Dr. James C. Boyd Department of Pathology and Medicine Washington University Medical School St. Louis, Missouri
"Argus/RT: A Microcomputer-Based System for Clinical Arrhythmia Monitoring" April 7, 1978	Mr. J. Alan Ritter Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Computer-Based Medical Records" May 2, 1978	Dr. Bruce D. Waxman National Center for Health Services Research (DHEW) and George Washington University Washington, D.C.
"Computationally Efficient Evaluation of Dynamic Left Ventricular Function from Serial Angiocardiograms" (jointly sponsored by the Department of Electrical Engineering) May 26, 1978	Dr. J. W. Modestino Department of Electrical and Systems Engineering Rensselaer Polytechnic Institute Troy, New York
"An Algorithm for QRS Shape Classification in Computerized Electrocardiogram Analysis" June 8, 1978	Dr. K. P. Birman Department of Medicine College of Physicians and Surgeons Columbia University New York, New York

IX. PUBLICATIONS AND ORAL PRESENTATIONS

Achtenberg, J., and Miller, J. P., "Interfacing a MUMPS-Based Data Entry System to SAS," in Proceedings of the Third Annual Conference of the SAS Users Group International, R. H. Strand, ed., SAS Institute, Inc., Raleigh, North Carolina, pp. 161-167, 1978.

Achtenberg, J. A., Miller, J. P., Cryer, P., and Santiago, J., "Data 3 -- A Forms Management System," Proceedings of the 1976 MUMPS Users' Group Meeting, Madison, Wisconsin, pp. 1-8, September, 1976.

Ahmad, S., Kleiger, R. E., Connors, J., and Krone, R., "The Echocardiographic Diagnosis of Rupture of a Papillary Muscle," Chest, vol. 73, pp. 232-234, 1978.

Ahumada, G. G., Karlsberg, R. P., Jaffee, A. S., Ambos, H. D., Sobel, B. E., and Roberts, R., "Salutary Effects of a Cardioselective β-Blocker (Acebutolol) in Patients with Myocardial Infarction," Circulation, vol. 56, supplement III, p. III-147, 1977 (abstract).

Ambos, H. D., Jones, S. A., and Hitchens, R. E., "A Gated Radionuclide Cardiac Imaging System," accepted for presentation at the IEEE Conference on Computers in Cardiology, San Francisco, California, September 12-14, 1978.

Ambos, H. D., Moore, P., and Roberts, R., "A Database for Analysis of Patient Diagnosis Data," accepted for presentation at the IEEE Conference on Computers in Cardiology, San Francisco, California, September 12-14, 1978.

Biggs, F. D., Lefrak, S. S., Kleiger, R. E., Senior, R. M., and Oliver, G. C., "Disturbances of Rhythm in Chronic Lung Disease," Heart and Lung, vol. 6, pp. 256-261, 1977.

Boxerman, S. B., Tao, D. K., and Zimmerman, J., "The Decision to Automate: How to Make It," Group Practice, vol. 2, no. 2, pp. 20-25, 1978.

Brandenburger, G. H., "Medical Computers and Electronics - Part II," seminar presented to the Jewish Hospital Cardiology Department, St. Louis, Missouri, April 10, 1978.

Byrne, J. D., Kurnik, P. B., Hirsch, J. A., and Ludbrook, P. A., "Computer Assisted Analysis of Left Ventricular (LV) Compliance," Analyzer, vol. 2, p. 7, 1977 (abstract).

Clark, G. L., Robison, A. K., Gnepp, D. R., Roberts, R., and Sobel, B. E., "Effects of Lymphatic Transport of Enzyme on Plasma CK Time-Activity Curves after Myocardial Infarction in Dogs," Circulation Research, vol. 43, p. 162, 1978.

Clark, G. L., Siegel, B. A., and Sobel, B. E., "Qualitative External Evaluation of Regional Cardiac Lymph Flow in Intact Dogs," Physiologist, vol. 20, no. 4, p. 17, 1977 (abstract).

Clark, K. W., Ambos, H. D., Mead, C. N., Hitchens, R. E., Oliver, G. C., and Thomas, Jr., L. J., "Argus/H: A Computer System for Rapid Analysis of Long-Term ECG Recordings," Proceedings of the First Annual Symposium on Computer Application in Medical Care, Washington, D. C., pp. 347-353, October 3-5, 1977.

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X. MONOGRAPHS

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.

Monograph Number	Author(s)	Title	Date
318	Snyder, D.L.	Applications of Stochastic Calculus for Point Process Models Arising in Optical Communication	8/77
319	Spenner, B.F.	9-Track Tape for the Programmed Console	8/77
320	Clark, K.W. Ambos, H.D. Mead, C.N. Hitchens, R.E. Oliver, G.C. Thomas, Jr., L.J.	ARGUS/H: A Computer System for Rapid Analysis of Long-Term ECG Recordings	8/77
321	Zimmerman, J. Stimac, R.K.	Survey of Registration and Encounter Forms	Incomplete
322	Ritter, J.A.	An Automated Wiring List Generation System	9/77
323	Snyder, D.L. Sripad, A.B.	Quantization Errors in Floating-Point Arithmetic	9/77
324	Brunnett, C.J. Cox, Jr., J.R. Snyder, D.L. Mattson, R.A.	U.S. Patent 4,008,400 - Transverse Tomography System Having Multibeam Orbital Scanning with all Beams Offset from the Center of Orbit	8/77
325	Smith, M.L.	A Microprocessor Based Universal Storage Device	9/77

Monograph Number	Author(s)	Title	Date
326	Mead, C.N. Johnson, J.A.	A MUMPS-Based Information System for Clinical Research in Neonatology	10/77
327	Mead, C.N. Clark, K.W. Oliver, G.C. Thomas, Jr., L.J.	Progress Toward Fully Automated Processing of Ambulatory ECGs	10/77
328	Tao, D.K.	Survey of Medical Computing Application Vendors	2/78
329	Zimmerman, J. Tao, D.K.	Survey of Software Libraries	Incomplete
330	Clark, K.W. Moore, P. Miller, J.P. Thomas, Jr., L.J.	A Total Systems Approach to a Quantitative Analyses of Holter-Recorded ECGs	10/77
331	Brunnett, C.J. Cox, Jr., J.R. Snyder, D.L. Mattson, R.A.	U.S. Patent 3,976,885 - Tomography System Having Nonconcurrent, Compound Axial Scanning	10/77
332		Incomplete	
333	Ritter, J.A. Thomas, Jr., L.J. Ripley, K.L.	ARGUS/RT: A Microcomputer System for Clinical Arrhythmia Monitoring	12/77
334	Zimmerman, J.	Final Report on Grant HS 01540 "Pilot Project - MUMPS Users' Group" 1 June 1974 to 30 September 1977	1/78
335	Zimmerman, J.	MUMPS Application Design Manual for a Standard MUMPS Teaching and Testing Program	1/78

Monograph Number	Author(s)	Title	Date
336	Spenner, B.F. Cox, Jr., J.R.	A Computational Model for Cochlear Mechanics	1/78
337	Greenfield, R.H.	An Experiment to Measure the Performance of Phonetic Key Compression Retrieval Schemes	1/78
338	Sobel, B.E. Markham, J. Karlsberg, R.P. Roberts, R.	The Nature of Disappearance of Creatine Kinase from the Circulation and its Influence on Enzymatic Estimation of Infarct Size	1/78
339	Markham, J. Karlsberg, R.P. Roberts, R. Sobel, B.E.	Mathematical Characterization of Kinetics of Native and Purified Creatine Kinase in Plasma	1/78
340	Miller, J.P. Ritter, J.A. Clark, K.W. Thomas, Jr., L.J. Oliver, G.C.	Extended Analysis of Argus/H Quantified Ventricular Ectopic Activity	1/78
341	Arthur, R.M. Wantzelius, D.G. Hernandez, A. Weiss, A.N.	Interactive Acquisition of Diagnostic Electrocardiograms	1/78
342	Brandenburger, G.H. Hieb, B.R. Garfield, S.A. Krone, R.J. Ludbrook, P.A. Cox, Jr., J.R. Oliver, G.C.	A New Cardiac Catheterization Laboratory Computer System	2/78

Monograph Number	Author(s)	Title	Date
343	Clark, K.W. Hitchens, R.E. Ritter, J.A. Rankin, S.L. Mead, C.N. Moore, S.M. Potter, S.J. Oliver, G.C. Thomas, Jr., L.J.	A Computer System for the Processing of Dual-channel Holter-recorded Electrocardiograms	2/78
344	Cox, Jr., J.R. Bridger, D.A. Ripley, K.L. Zacher, R.	Computers in Medicine	2/78
345	Ripley, K.L. Oliver, G.C.	Development of an ECG Database for Arrhythmia Detector Evaluation	2/78
346	Miller, J.P. Moore, P. Achtenberg, J. Thomas, Jr., L.J.	Computerized Information Handling for Long-term Clinical Studies	2/78
347	Snyder, D.L. Rhodes, I.B.	Some Implications of the R_0 Criterion for Coded, Direct-Detection, Optical-Communication Systems	4/78
348	Ritter, J.A.	ARGUS/RT: A Microcomputer-Based System for Clinical Arrhythmia	5/78
349	Zimmerman, J. Tao, D.K.	Incomplete	
350	Ambos, H.D. Roberts, R. Sobel, B.E. Thomas, Jr., L.J.	Detection of Primary Ventricular Dysrhythmia by CCU Nurses	6/78