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Biomedical Computer Laboratory

Washington University School of Medicine

St. Louis, Missouri

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 12

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TABLE OF CONTENTS

		Page
I.	INTRODUCTION	8
II.	SOURCES OF SUPPORT	10
III.	PERSONNEL	12
IV.	PHYSICAL RESOURCES	20
V.	RESEARCH PROJECTS	22
	Summary	22
	Individual Projects	28
	A. Ischemic Heart Disease and ECG Analysis	28
	A-1. Relationship of Ventricular Arrhythmias to Sudden Death: Clinical Data Gathering	28
	A-2. Processing of Argus/H Cycle Streams on the System/360	30
	A-3. Infarct Site and Size Versus PVC Rate	33
	A-4. A Study of the Relationship of CPK-Measured Infarct Size Versus Other Enzymes	34
	A-5. Study of the Relationship of Nontransmural Myocardial Infarction to PVC Rate	35
	A-6. Antiarrhythmic Drug Therapy Trials Using Argus/H	36
	A-7. Study of Antiarrhythmic Effect of LB-46 (Sandoz) Using Argus/H	36
	A-8. Mathematical Models for Estimation of Myocardial Infarct Size	37
	A-9. The Moving Window Discrete Fourier Transform (MWDFT) as It Applies to Arrhythmia Detection	38
	A-10. External Detection and Tomography of Ischemic Myocardium	39

		Page
A-11.	Modification of Infarct Size	41
A-12.	Ischemic Heart Disease SCOR Computer System	44
A-13.	Assessment of Diastolic Compliance of the Left Ventricle	45
A-14.	Holter Tape Processing	46
A-15.	Argus/H: Algorithm Development	47
A-16.	Progress Toward a Restructured Argus/H System	49
A-17.	Evaluation of Arrhythmia Detectors	50
A-18.	A Microcomputerized Argus	51
A-19.	MECCA, A Computerized System for Capturing Transient Electrocardiographic Data	52
A-20.	A Device for Synchronizing X-Ray Exposures to Any Point in the Cardiac Cycle	53
A-21.	Interactive Digital Acquisition of Electrocardiograms	53
A-22.	Real-Time Digital Echocardiography	54
A-23.	ECG Report Production	55
B.	Tracer Kinetics	57
B-1.	Noise Analysis of PETT-III	57
B-2.	PETT-IV: A Four-Slice Positron-Emission Transaxial Tomograph	57
B-3.	PETT-IV Electronics and Interfaces	59
B-4.	Mathematical Models for In-Vivo Measurement of Regional Cerebral Hemodynamics and Metabolism Using Postron-Emission Tomography	61
B-5.	Blood-Brain Barrier Permeability Studies Employing ^{15}O-labeled Water and ^{11}C-labeled Alcohols	64
B-6.	In-Vivo Measurement of Blood-Brain Transport of Glucose Employing ^{11}C-Glucose	66
B-7.	In-Vivo Measurement of DOPA Uptake Rate in Brain	67

		Page
C.	Monitoring the Critically Ill	69
C-1.	SICU: Overview and Evaluation	69
C-2.	West Pavilion Planning	72
C-3.	Clinical Physiologic Research Cart (CPRC)	73
C-4.	Measurement of Cardiac Output by Dye-Dilution Based on a Model Accounting for Tracer Recirculation	75
C-5.	ECG Telemetry with Arrhythmia Detection	78
C-6.	Evaluation of Pediatric Monitoring Instrumentation	78
C-7.	Cardiac Output by Thermodilution	79
C-8.	Ultrasonic Gas-Flow Instrument	82
C-9.	Pulsatile Perfusion System	83
C-10.	Infant Perfusion System	84
D.	Information and Communication Systems	85
D-1.	Information System Design Studies: Overview	85
D-2.	Resource Allocation in a Crosspoint Switch	87
D-3.	Simulation of an Information System Based on a Crosspoint Switch	88
D-4.	Database Extensions to Procedural Languages	90
D-5.	A PL/I Dialect Interpreter	92
D-6.	Multitasking Systems Evaluation	93
D-7.	A File System Prototype	95
D-8.	Characteristics of Clinical Database Files and Their Usage	96
D-9.	A Hardware Monitor for the Investigation of PDP-11 MUMPS Implementation Efficiency	97
D-10.	Medical Information System Applications: Overview and Support Activities	98

		Page
D-11.	Medical Care Group Information System	99
D-12.	MESCH	100
D-13.	Outpatient Appointment Systems Research	101
D-14.	COMAPS: COMputer-Aided Pharmacy System	102
D-15.	Glaucoma Center Registries	104
D-16.	Neonatal Database	106
D-17.	MUG/MDC: Activities of the MUMPS Users' Group (MUG) and the MUMPS Development Committee (MDC)	107
D-18.	MUG/MDC: Evaluation of Application Program Transfer	108
D-19.	MUG/MDC: Development of MUMPS Applications for Transfer	109
E.	Cardiac Catheterization Laboratory	111
E-1.	New Cardiac Catheterization Laboratory Computer System	111
E-2.	Automatic Pattern Recognition of Left Ventricular Pressure Waveforms	114
E-3.	A Computerized Ventricular-Contour Analysis System	115
E-4.	A Program for Calculating Relevant Parameters Derived from Catheterization Results	116
F.	Laboratory Biochemistry	117
F-1.	A Developmental Microcomputer System for Biochemical Instrumentation	117
F-2.	A Microprocessor Controller for Amino-Acid Analysis	119
F-3.	Cary Spectrophotometer Paper-Tape Punch Interface	120
F-4.	Parameter Estimation for Mass-Spectrometry Data	121
F-5.	Computer Simulation of the Kinetic Properties of Enzymes	122

		Page
G.	Speech and Hearing	123
G-1.	A Two-Dimensional Model of Cochlear Mechanics	123
G-2.	The PC Speech and Hearing System	124
G-3.	A Computer System for Auditory Research	125
G-4.	Voice Source Characteristics	126
G-5.	Speech Modeling (LP Analysis and Vocal Tract Model)	128
G-6.	Experiments in Tactile Loudness with a Single Channel Electrocutaneous Device	130
G-7.	MEGS: A System for Speech Reception Testing	131
G-8.	Analysis of Cochlear Nonlinearities Through Study of Microphonic "Signatures"	132
H.	Supporting Activities	134
H-1.	Microprocessor Development Support: Overview	134
H-2.	Microprocessor Development Support: Software	134
H-3.	Microprocessor Development Support: The Intelligent Console	136
H-4.	Microprocessor Development Support: Erasable ROM Programmer	137
H-5.	A Microprocessor Laboratory Unit for Signal Processing	138
H-6.	An Emergency Unload Fault Monitor for the Pertec Disc	138
H-7.	Optical Pen Reader for Diagnostic Radiology	139
H-8.	A Universal Storage Device	139
H-9.	AUGAT-Card Wiring-List Program	141
H-10.	OS/PC LIBRARY: Utility Programs for the PC/12	142
H-11.	PC-1200/System 7 Communications Routines	142
H-12.	Remez Filter-Design Program for PC-1200	143

		Page
H-13.	Ultrasound Explorations	143
H-14.	Analysis of Archaeological Dental Specimens	145
H-15.	Survival of Irradiated Tumor Cells	145
H-16.	Digital Storage and Analysis of Visual Field Data	146
H-17.	Library System - Medline Link	147
H-18.	RTOXY: A pH Data Acquisition System for the PC-12	147
H-19.	IDAS Processing Software	148
H-20.	Clinical Evaluation of CASNET	149
H-21.	Analog Input-Output System for Interdata Model 7/16	149
H-22.	PC-FORTRAN-Callable Versatec Plotter Subroutine	150
VI.	INDUSTRIAL COLLABORATION	151
VII.	TRAINING ACTIVITIES	153
VIII.	SEMINARS	155
IX.	PUBLICATIONS AND ORAL PRESENTATIONS	159
X.	MONOGRAPHS	170

I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1975 through June 30, 1976. 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 mini-computers 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 mini-computers to the IBM 360, Model 65 at the Washington University Computing Facilities, through development and support of a mini-computer based MUMPS system, to the establishment of an independent Medical Computing Facility to service 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 that 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 (WUCL) is a federation of computer research activities which includes the Biomedical Computer Laboratory and the Computer Systems Laboratory. This federation of laboratories functions through a coordinating committee composed of the laboratory directors and in addition, the Vice Chancellor for Medical Affairs, the Associate Vice Chancellor for Research, the Director of the University Computing Facilities and the Associate Directors of both laboratories.

The Computer Systems Laboratory, which is under the direction of Dr. Charles E. Molnar, is active in the design, development, evaluation and application of a compatible set of "macromodules" useful in the experimental design of arbitrarily large, complex, asynchronous, specialized computer systems. An important current project is aimed at producing and supporting a high-performance replicable graphics and modeling system that can be acquired by research groups elsewhere.

A National Advisory Panel assists in planning health-related activities of the Biomedical Computer Laboratory and Computer Systems Laboratory under the NIH Biotechnology Research Resources grant. Currently the Committee has the following membership:

W. A. Clark	Consultant and Past Director of Computer Systems Laboratory	Cambridge, Massachusetts
D. M. Kipnis	Busch Professor and Head of the Department of Medicine	Washington University School of Medicine
F. M. Richards	Professor in Molecular Biophysics and Chemistry	Yale University
R. S. Snider	Professor of Anatomy and Director of Center for Brain Research	University of Rochester

The Advisory Committee meets periodically with the WUCL Coordinating Committee to review developing projects and programs and to advise on desirable areas of applications.

II. SOURCES OF SUPPORT

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

RR 00396	A Resource for Biomedical Computing

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

HS 00074	Technology and Health Care

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

HL 18808	Prediction and Prevention of Sudden Cardiac Death

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

HS 01540	Pilot Project, MUMPS Users' Group

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

AM 13332	Metabolic Regulation and Interacting Enzyme Systems
CA 13053	Clinical Cancer Radiation Oncology Cancer Center
EY 00336	Glaucoma Clinical Research Center
GB 26483	Enzyme Structure and Function
GM 02016	Medical Scientist
GM 13925	Structural Studies on Dehydrogenases and Lipoproteins
HL 12820	Lipid Protein Interactions in Blood Clotting
HL 12839	Flow, Transport and Membrane Phenomena in Blood
HL 13803	Advanced Cardiac Valvular and Vascular Prostheses
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine
HL 14147	Specialized Center of Research in Thrombosis

HL 17646	Study of Ischemic Heart Disease
HL 18144	Preprocessor System for Cardiograms
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

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.*

Associate Director

Donald L. Snyder, Ph.D.*

Assistant Directors

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

Administrative Officer

Edward L. MacCordy, M.B.A.*

Business Manager

Virginia M. Bixon, B.S.

Senior Research Associate

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

Research Associates

Robert J. Arnzen, Ph.D.
R. Martin Arthur, Ph.D., and Associate Professor of Electrical Engineering
William R. Ball, D.Sc., and Professor of Computer Science
A. Maynard Engebretson, D.Sc.

*On August 1, 1975, J. R. Cox, Jr., founder of the Biomedical Computer Laboratory, became Chairman of the Department of Computer Science of the School of Engineering and Applied Science at Washington University. He was succeeded as Director by Lewis J. Thomas, Jr., who had been Associate Director of the Biomedical Computer Laboratory since 1971. On March 1, 1976, D. L. Snyder vacated the Associate Directorship of the Biomedical Computer Laboratory to become Chairman of the Department of Electrical Engineering. On February 28, 1976, E. L. MacCordy resigned as Administrative Officer for the Washington University Computer Laboratories and became Associate Vice Chancellor for Research at Washington University.

Philip M. Fishman, D.Sc., and Research Instructor in Computer Science in Psychiatry
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
Joan Zimmerman, D.Phil.

Research Assistants

H. Dieter Ambos
Philip S. Berger, M.S.
Andrew L. Bodicky, B.S.
Gary H. Brandenburger, M.S.
Kenneth W. Clark, M.S.
Stanley A. Garfield, B.S.
Robert H. Greenfield, M.S.
Ronald W. Hagen, M.S.
Richard E. Hitchens, B.S.
Frank Hummel, M.S.
Janet A. Johnson, B.S.
Margaret C. Jost, M.S.
Joanne Markham, M.S.
Charles N. Mead, M.D.
J. Philip Miller, B.A.
Patricia Moore, Ph.D.
Nizar Mullani, B.S.
Jeffrey C. Nathanson, B.S.
Michael C. Rigden, A.B.
Kenneth L. Ripley, M.S.
J. Alan Ritter, S.B.
Jeffrey H. Rixleben, B.S.
Bruce F. Spenner, M.S.
Robert K. Stimac, B.S.
David M. Ungar, B.S.
Nageswara R. Vemula, M.S.
Budimir Zvolanek, B.S.

Lecturer

Fred M. Domke

Technical Assistants

Donald R. Bassman, M.D.
Rita K. Bhola
Linda L. Brandenburger, B.S.
Gerald A. Burger, B.S.
Jeffrey D. Coe, B.S.
Gary R. Cook
Mary L. Dunne, B.S.
David C. Ficke, B.S.

Ross K. Hartz, B.S.
Robert L. Huck, A.B.
Margaret A. Hug
Gail S. Kuthe
Ronnie S. Malamud
Deborah K. McDermott, B.S.
Stanford M. Moran, B.S.
Donald A. Opila, B.S.
Stephen J. Potter
Wayne R. Roloff, B.S.
Thomas F. Schuessler, B.S.
John B. Schweitzer, B.S.
Robert W. Sheifler
David L. Shupe
Marc L. Smith, B.S.
Robert W. Sutherland, B.A.
Paul B. Webb

Electronics Technicians

Gary A. Appel, B.S.
Theron R. Baird
George L. Bickmore
Paul J. Hasser
Remo Moroni, III
James Murashige
Robert R. Peglar
Stanley R. Phillips
David T. Taylor

Machinists

Kenneth J. Spraul
Michael A. Ziegler

Librarian

Loretta M. Calcaterra, M.A.

Secretaries

Shirley A. Gonzalez-Rubio
Betty L. Hill
Clara E. Ingersoll
Sandra E. Katzen, B.S.
Faye L. Martin
Polly E. Raith
Rebecca Torrence

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

G. Charles Oliver, Jr., M.D., Associate in the Biomedical Computer Laboratory, Professor of Medicine and Chief of Cardiology, Jewish Hospital
Rexford L. Hill, 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:

Christopher R. Brigham, M.D.
Katherine M. Bruce, B.A.
Markku T. Hakkinen
Ada S. Jemison, B.S.
Basil Karpiak
Jung-Chang Lee, M.S.
Ross E. Morgan, B.S.
John J. Sueme, B.S.
Philip G. Winger, B.S.

RESEARCH COLLABORATORS

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

G. G. Ahumada, M.D., Medicine
J. R. Anderson, B.A., Neural Sciences
W. E. Ball, D.Sc., Computer Science
L. J. Banaszak, Ph.D., Biochemistry
J. Barman, B.S., Computer Science
G. R. Barbarash, B.S., Biochemistry
M. R. Bedford, B.S., Electrical Engineering and School of Medicine
R. J. Benson, J.D., Computing Facilities
B. J. Besserman, Medicine
P. E. Bock, Ph.D., Biochemistry
W. F. Boron, Ph.D., Physiology and Biophysics
S. D. Boxerman, D.Sc., Health Care Administration
D. A. Bridger, M.S. Computer Science
J. D. Byrne, CPT, Medicine
R. D. Camuto, B.S., Electrical Engineering
R. E. Clark, M.D., Cardiothoracic Surgery
G. M. Clarke, Medicine

W. G. Clark, Neurosurgery
C. M. Currie, B.S., Radiology
R. A. Dammkoehler, M.S., Computer Science
J. O. Eichling, Ph.D., Radiology
J. D. Elliott, B.S., Electrical Engineering
R. G. Evens, M.D., Radiology
H. Fotenos, Radiology
M. A. Franklin, Ph.D., Electrical Engineering and Computer Science
C. Frieden, Ph.D., Biochemistry
M. H. Gado, M.D., Radiology
J. H. Gammel, Medicine
D. G. Gantt, M.S., Anthropology
T. A. Gillespie, M.D., Medicine
R. J. Goggins, B.S., Electrical Engineering
S. A. Golden, B.S., Neurosurgery
S. Goldring, M.D., Neurosurgery
R. L. Grubb, Jr., M.D., Neurosurgery
E. P. Gruendler, B.S., Electrical Engineering
W. M. Hart, Jr., M.D., Ph.D., Opthalmology
B. K. Hartman, M.D., Psychiatry
A. Hernandez, M.D., Pediatrics
B. K. Herres, B.S., Electrical Engineering
H. Z. Hill, Ph.D., Radiology
J. Hirsch, B.S., Medicine
E. J. Hoffman, Ph.D., Radiology
S. R. Holmes, B.S., Biochemistry
J. T. Hood, B.S., Physics
S. Igielnik, Ph.D., Medical Computing Facilities
C. M. Jackson, Ph.D., Biochemistry
L. Jarett, M.D., Pathology
G. C. Johns, Computer Systems Laboratory
M. F. Johnson, Jr., M.L.S., Medical Library
D. R. Jones, M.S., Electrical Engineering
R. G. Jost, M.D., Radiology
R. P. Karlsberg, M.D., Medicine
J. L. Karpowicz, B.S., Electrical Engineering
M. A. Kass, M.D., Opthalmology
M. J. Kenner, B.S., Medical Care Group
J. R. Klepper, M.S., Physics
P. B. Kurnik, B.S., Medicine
R. G. Lagler, M.S., Biomedical Engineering
S. Lang, Ph.D., Physiology and Biophysics
C. L. Large, Medicine
J. L. Livingston, B.A., Opthalmology
P. A. Ludbrook, M.D., Medicine
R. E. Marshall, M.D., Pediatrics
M. M. Maurer, M.D., Pediatrics
J. R. Martin, Radiology
T. F. Martin, M.D., Medicine
J. G. Miller, Ph.D., Physics
C. E. Molnar, Sc.D., Computer Systems Laboratory

J. A. Moore, M.S., Electrical Engineering
R. E. Olson, B.S., Computer Systems Laboratory
R. Parkes, Ph.D., Economics
T. A. Pavlovic, M.D., Medicine
C. A. Perez, M.D., Radiology
G. T. Perkoff, M.D., Medical Care Group
M. E. Phelps, Ph.D., Radiology
W. F. Pickard, Ph.D., Electrical Engineering
C. F. Pieper, M.S., Neurosurgery
S. M. Podos, M.D., Ophthalmology
S. V. Pollack, M.S., Computer Science
W. E. Powers, M.D., Radiology
D. P. Ragan, Ph.D., Radiology
M. E. Raichle, M.D., Radiology and Neurology
D. L. Rempel, M.S., Biochemistry
R. Roberts, M.D., Medicine
D. G. Robida, B.S., Electrical Engineering
M. H. Selikson, B.S., Radiology
W. R. Sherman, Ph.D., Psychiatry and Biochemistry
B. E. Sobel, M.D., Medicine
M. G. Straatmann, M.S., Radiology
M. J. Stucki, M.S., Computer Systems Laboratory
S. P. Sutera, Ph.D., Mechanical Engineering
D. Tao, M.S., Electrical Engineering
R. N. Tatum, B.S., Barnes Hospital
M. M. Ter-Pogossian, Ph.D., Radiology
A. W. Washington, M.B.A., Medical Care Group
A. N. Weiss, M.D., Medicine
E. S. Weiss, M.D., Medicine
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Surgery
R. Wette, D.Sc., Biostatistics
J. R. Williamson, Pathology
P. W. Winger, B.S., Mechanical Engineering

Central Institute for the Deaf, St. Louis, Missouri

D. H. Eldredge, M.D.
I. J. Hirsh, Ph.D.
J. D. Miller, Ph.D.
R. B. Monsen, Ph.D.
D. A. Ronken, Ph.D.
R. M. Sachs, Ph.D.
B. L. Scott, Ph.D.
J. W. Sharp

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

W. Perl, Ph.D.

Creighton University, Omaha, Nebraska

A. Zencka, M.D.

Georgia Institute of Technology, Atlanta, Georgia

F. Sias, Ph.D.

Jewish Hospital, St. Louis, Missouri

F. D. Biggs, M.D.
V. R. deMello, M.D.
R. E. Eggebrecht, M.D.
B. R. Hieb, M.D.
R. E. Kleiger, M.D.
R. J. Krone, M.D.
R. Ruffy, M.D.
A. Salimi, M.D.
B. A. Sandefur, B.A.
D. P. Wheeler

McMaster University, Hamilton, Ontario

G. Firnau, Ph.D.
E. S. Garnett, M.D.

Methodist Hospital, Houston, Texas

D. H. Glaeser, D.Sc.

Mt. Sinai School of Medicine, New York, New York

S. M. Weiss, Ph.D.

Northwestern University, Chicago, Illinois

F. M. Nolle, D.Sc.

Rutgers University, New Brunswick, New Jersey

C. A. Kulikowski, Ph.D.

St. Louis University, St. Louis, Missouri

S. Ayres, M.D.
G. C. Kaiser, M.D.
A. R. Lind, D.Phil. and Sc.D
H. Mueller, M.D.

Stanford University Medical Center, Stanford, California

E. L. Alderman, M.D.
W. J. Sanders, M.S.

University of California, Davis, California

R. F. Walters, Ph.D.

University of Washington, Seattle, Washington

A. Forrey, 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 MUMPS information 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 eleven 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 of 700 South Euclid; and by 3463 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 data transmission distribution system, a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules, and both analog and digital tape recorders. Direct communications with the IBM 360 Model 65 at the Washington University Information Processing Center is provided via phone lines, Programmed Consoles and LINCs.

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 is housed in 360 square feet of specially designed space within the unit. A computer-based Surgical Intensive Care Monitoring System designed and built by BCL was installed in Barnes Hospital in March, 1973. The computer and related hardware are located in a room within the intensive care facilities.

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 to function as a combined stored-program digital computer and remote display console for the IBM 360 Model 50 installed during May, 1966, at the Washington University Information Processing Center. (The Model 50 was converted to a Model 65 in April, 1973.) BCL's computational facilities now include three specialized Programmed Consoles built at the laboratory. In addition, thirteen Programmed Consoles have been built by SPEAR, Inc., from plans and specifications developed at BCL. Of these, six were evaluated under an NIH sponsored

program as an aid to radiation treatment planning at radiology centers in Stanford, California; Bethesda, Maryland; Houston Texas; Boston, Massachusetts; Philadelphia, Pennsylvania; St. Louis, Missouri; and Toronto, Canada. Two Programmed Consoles manufactured by SPEAR, Inc., are in use in other projects at BCL. In 1972, five new PC-1200 Programmed Consoles manufactured by Artronix, Inc. were installed at BCL in support of a variety of new and existing projects. All of the evaluation centers except that at Toronto, Canada have now replaced their SPEAR PCs with new Artronix PC-1200 systems. The SPEAR PC in the Cardiac Catheterization Laboratory was replaced in 1973 by a new Artronix PC-1200 System housed in newly renovated space for Catheterization Laboratory Instrumentation, and in 1974, an Artronix PC-12/7 MUMPS System was installed at BCL to be used in a variety of projects in Health Care Technology and information systems.

An IBM System/7 was installed at the laboratory in April, 1972 to become a major component of a system for 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.

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

Summary

The goal of the laboratory is the application of computer techniques to problems in medicine and biology. This often requires work in areas stretching from basic physiology through mathematical models and frequently to the design of specialized equipment. The laboratory's research program has traditionally been organized into several major project areas with many of the laboratory's staff grouped into teams whose interests focus in one of the project areas.

On June 1, 1975, our Mass Spectrometry program became established as a separate resource which retains strong BCL collaboration. The former title is now replaced by "Laboratory Biochemistry" to reflect a new collaboration with the Department of Biochemistry for the support of developmental work in analytical instrumentation.

In the area of Information and Communication Systems, our longstanding activities have expanded considerably in recent years and especially during the past year the information systems project has matured into a substantial cooperative effort between the Department of Computer Science, the Computer Systems Laboratory, and the Biomedical Computer Laboratory. Participation in this important work further strengthens our existing ties within the University.

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 entered a new phase during the past year. A re-designed clinical study is well under way, new algorithmic developments have improved the efficacy of Argus/H, and advanced hardware components are being applied to implementation of a high-performance cost-effective ECG processing system suitable for use by others. Production processing of Holter tapes is proceeding smoothly in that no backlog for the new study has been allowed to accumulate and yet substantial progress has been made in eliminating a large backlog from the previous four-year study which was terminated in June of 1975. During the past year, the equivalent of over 1250 twelve-hour tapes have been processed for a variety of studies. In the meantime, a PL/I program has been written to facilitate extensive analysis of the processing results (Argus/H Cycle stream) using the IBM System/360 Model 65. The power of this capability is clearly evident and early inquiries of the incomplete data have yielded some tantalizing results. A Myocardial Infarction Patient Information (MIPI) System has been developed to support the orderly management of clinical, demographic, and laboratory data for the new study. The MIPI system has been implemented in MUMPS on a computer system supported by the newly established Washington University Medical Computing Facilities (MCF) which is temporarily housed in BCL quarters. Completed during the year were other Argus/H-related studies including: examination of the relation between infarct site and size versus rate of ventricular arrhythmias (PVC rate), correlation of CPK-measured

infarct size with other enzymes, study of PVC rate in non-transmural infarctions, and antiarrhythmic drug therapy trials.

The development and evaluation of algorithm improvements has continued toward the ultimate objective of fully automated analysis. A context-based solution to previous Argus/H confusion of peaked T waves with PVCs has been added to the production processing system. Another strategy which also employs contextual information, uses coupling intervals as a PVC feature to substantially automate the editing process. It is now being subjected to thorough evaluation. Investigations continue on the application of computational linguistic techniques to ECG waveform feature detection. Early work applying a moving narrow-window discrete Fourier transform algorithm shows promise for ECG analysis in the frequency domain and will be explored further for two-channel processing.

Other Argus-related projects include persistent efforts in the formulation of plans for an Evaluation Group for Arrhythmia Detectors (EGAD), the implementation of an LSI-11 microprocessor-based Argus, and completion of a multi-patient system for retrospective retrieval of extended ECG recordings preceeding serious dysrhythmias. An interactive system for digital acquisition of pediatric ECGs, a burst analog sampling system for real-time digital echocardiography, and an automatic system for ECG report production are also reported in this section.

Over the past year, BCL collaboration in a SCOR (Specialized Center of Research) program (Division of Cardiology) has increased in six project areas: the development of mathematical models to describe the dynamics of enzyme (CPK) release after myocardial infarction; the evaluation of interventions addressed to infarct size modification; the implementation of a SCOR computer system; the assessment of diastolic compliance of the left ventricle; the construction of a device for synchronizing an X-ray unit to an ECG signal for non-invasive estimation of left-heart dimensions; and the application of positron-emission transaxial tomography for non-invasive visualization of ischemic myocardium (v.i.).

Tracer Kinetics. The tracer kinetics program has focused on implementation of a four-slice positron-emission transaxial tomograph (PETT-IV) interfaced to an Interdata 7/32 computer for both processing and control. High-speed logic accomplishes coincidence detection of positron-electron annihilation events at four cross sections simultaneously. The resulting parallel imaging capability is made possible by the use of a long cylindrical detector effectively subdivided into four sections by a combination of suitable collimation and fast positioning circuitry. The validity of the design criteria was confirmed through a simulation study which analyzed the performance characteristics of an earlier single-slice system (PETT-III). A new mathematical model has been developed to capitalize on the superior spatial resolution for in-vivo measurement of regional cerebral hemodynamics and metabolism. Exciting results have been obtained using PETT-III for the imaging of early myocardial infarcts so that the power of PETT-IV seems assured for both diagnostic and research studies in infarct-size estimation. Early installation of a PETT-IV system in the Barnes Hospital coronary care

unit (CCU) is planned. Gratification is found in the resulting convergence in the CCU of efforts in tracer kinetics, enzyme-release modeling, and ECG analysis.

The application of mathematical models to the interpretation of dynamic in-vivo studies continues to offer insights regarding the blood-brain barrier and cerebral blood flow. Studies employing techniques to modify barrier permeability and blood flow have delineated the predicted effects of hyperosmotic infusions whereas unanticipated results of direct stimulation of the cervical sympathetic chain suggest confirmation of the postulation that precapillary vessels may participate in the exchange of water and solutes between blood and brain. The modelling efforts have also yielded important results concerning the transport of glucose and DOPA across the blood-brain barrier. The finding that specific pharmacologic interventions may render the barrier highly permeable to DOPA may alter the interpretation of data obtained with labeled DOPA as a proposed brain-scanning agent.

Monitoring the Critically Ill. The digital computer system installed in the Cardiothoracic Surgical Intensive Care Unit (SICU) has now been in continuous clinical use for over three years. A rigorous engineering evaluation has been continued. A transient but major setback in reliability performance this year was traced to corrosion of integrated circuit leads and corrected. The majority of hardware failures causing unintentional interruption of patient monitoring have been properly diagnosed through careful analysis of documented memory contents ("core dumps"), the success of which can be largely attributed to the highly structured software system. Current utilization of the care facility is characterized by continued high occupancy (82%) with some increase in average length of stay this year from 2.3 to 2.7 days. The longer stays reflect the effect of a new intermediate-care annex on patient allocation patterns which are judged to result in more effective utilization of the computer-based patient-care system.

Recent attention has been directed toward extended application of the SICU computer-based patient monitoring experience. An opportunity to contribute to the design of a more advanced and enlarged system for use in a new hospital wing has been carefully considered in light of projected commercial trends, anticipated local needs, and broad BCL goals. With a view toward sharing our own experience with others, we have been deliberating with commercial vendors to explore bases for collaboration in the design and implementation of an advanced system for integrated pre-operative, and post-operative care.

A mobile clinical physiologic research cart (CPRC) interfaced to the SICU computer system has been completed and is seeing use in the development of a computer-controlled pulsatile perfusion system. Application software is being written for subsequent CPRC support of research in the coronary care unit and SICU. The more flexible CPRC system which brings a mini-computer to the bedside will support research needs without jeopardy to continuous patient care.

Substantial progress has been made in the past year in the development of devices suitable for physiologic research in the critical care environment. Work on an automated precision system for cardiac output by thermodilution has led to critical examination of both practical and theoretical problems. Alternative solutions are being examined in the animal laboratory in conjunction with study of a novel dye-dilution method based on a model of tracer transport that specifically incorporates the effects of recirculation. A prototype ultrasonic gas-flow instrument has undergone successful clinical trial and can be placed in routine use after reconfiguration.

Other activities have included the evaluation of pediatric monitoring instrumentation and the design of a self-regulating perfusion system which uses a membrane oxygenator to provide respiratory support of infants suffering respiratory distress syndrome.

Information and Communication Systems. During the past year, design studies toward an information system with improved performance have continued. A system organization based on a crosspoint switch has been selected and a modest experimental system is under construction. A working group from the Computer Systems Laboratory, the Biomedical Computer Laboratory and the Department of Computer Science has been assembled and has produced several technical reports on aspects of the system design. Related work has been reported on the characteristics and usage of clinical databases and on database system instrumentation.

The activities of the Biomedical Computer Laboratory begun five years ago in the development of medical information systems applications have continued. The number and diversity of our collaborators in these activities both at Washington University and nationally have grown substantially and reflect our perception of the importance of this aspect of biomedical computing.

Specific projects now active include new medical information system applications to ambulatory-care, outpatient appointments, pharmacies, glaucoma registries, clinical research and neonatal ICUs. Our work with the national users group for MUMPS has continued and currently emphasizes the development and evaluation of a methodology for effective transfer of application programs. Much of the service work in medical information systems at the medical center has been assumed by the fee-for-service resources of the Washington University Medical Computing Facility, now entering its second year of operation. This facility is an adjunct activity temporarily housed within the Biomedical Computer Laboratory.

Cardiac Catheterization Laboratory. During the past year, the first phase of a new cardiac catheterization laboratory computer system was completed, put into use at Jewish Hospital, and is now undergoing extensive evaluation. The new system addresses the needs of a catheterization team whose style of operation requests more automated data acquisition and analysis than was appropriate for the team which participated in development of the previous system. Thus the new system features specialized hardware and

redesigned software to provide automated but alterable sequencing through pre-programmed procedure protocols along with many other convenience features. For routine procedures, user interaction is required only to specify when valid data are available or to indicate any protocol modifications. Sequencing information is displayed on a clearly visible control panel which specifies throughout the procedure the currently appropriate anatomical site.

In conjunction with the new cath lab system, a new algorithm has been developed for automatic pattern recognition of left ventricular pressure waveform features. Novel digital processing techniques are used to identify end-diastolic and peak systolic pressures. For 410 determinations tested against eight cardiologists, a correlation coefficient greater than 0.99 was found. Additional work has focused on a computer-assisted system for rapid analysis of ventricular contours entered manually from projected angiographic images.

Laboratory Biochemistry. The main thrust of BCL's new and welcome collaboration with the Department of Biochemistry is in the application of digital techniques to instrumentation for analytical biochemistry. Such applications typically require on-line data acquisition and control with modest speed requirements. Although post-run calculations and data analyses may be demanding, most applications involve relatively simple on-line data reduction.

The general approach is to develop a repertoire of flexible computer modules and systems software suitable for general use with analytical instrumentation. Typical applications include automation of control, data acquisition and/or data processing for amino-acid analyzers, gas-chromatographs, spectrophotometers, and assay systems requiring variable-quantity reagent addition. Component selection has emphasized flexibility and modest cost. After consideration of various options, the Digital Equipment Corporation LSI-11 microcomputer has been selected as the basic CPU module along with compatible peripheral devices.

Applications to date include the adaptation of a small MCS-4 microprocessor system for programmed control of a new amino-acid analyzer designed to extend the chemical characterization of proteins to smaller samples; also, a punched-paper-tape interface has been designed for a Cary double-beam scanning spectrophotometer to generate machine-readable output. Other activities include application of a PDP-12 computer simulation system to analysis of full time stopped-flow data obtained with isoenzymes of malate dehydrogenase, coupled enzyme systems, and the pH, temperature and ligand-induced inactivation and reactivation of phosphofructokinase.

Activities will continue in support of the now separate Mass Spectrometry Resource. As gas-chromatograph mass spectrometer utilization has increased at the medical center, an opportunity has been identified for BCL contribution to solution of data-analysis problems requiring the application of signal processing techniques. Difficulties arising from partial separation of mixtures by gas-chromatography as well as chemical and electrical noise contaminations have been reviewed in the literature and with

local investigators. Mathematical models employing statistical techniques are being implemented to address the more pressing problems such as the precise measurement of the relative amounts of known compounds using selected masses which are unique to the compounds.

Speech and Hearing. The speech and hearing computer system continues to be heavily utilized for synthesis and analysis of speech signals in support of a wide range of activities in collaboration with the Central Institute for the Deaf (CID). These include speech-reception testing using the MEGS system for rapid, automatic convergency on sounds troublesome for the subject; identification of differences in glottal source characteristics between subjects with normal and those with impaired hearing; evaluation of discrimination thresholds for an electrocutaneous sensory aid; signal calibration and data analysis of frequency-dependent nonlinearities in the cochlear microphonic responses of the chinchilla; and evaluation of a linear prediction method of speech analysis as a training-aid display for the deaf. The computer system has been upgraded by the addition of a second dual-platter disc so that system and output data are on removable cartridges and the remaining two fixed discs provide temporary storage buffers. A two-channel analog system has been designed and built to accomodate binaural experiments at a 20 kHz sample rate.

As an outgrowth of the longstanding CID-BCL collaboration, the Research Department of CID is installing a central computer system (Eclipse) to be shared by several laboratories. In addition, a number of simpler but compatible minicomputer (Nova) systems will be deployed in the department, primarily for use in on-line data collection and stimulus control. These CID-supported systems will help relieve heavy current demands on the BCL speech and hearing system.

A two-dimensional spatially-discrete model of cochlear mechanics has been formulated and solved in both the time and frequency domains. Simplifying assumptions consider two rectangular chambers to be symmetrical about the cochlear partition and the viscosity and compressibility of the cochlear fluid are ignored. Since the model solution is independent of partition characteristics, it allows the incorporation of any hypothesized nonlinearity and thereby becomes a powerful tool for advancing our understanding of the peripheral auditory system.

Supporting Activities. As in previous years, mathematical, equipment or program development supporting two or more of the major programs of the laboratory or computer applications for users not related to any of the major programs are grouped together in this section. As predicted last year, microprocessors have become more visibile in this section of the report as well as elsewhere. This new tool has assumed a role of increasing importance in systems development.

Individual Projects

A. Ischemic Heart Disease and ECG Analysis

A-1. Relationship of Ventricular Arrhythmias to Sudden Death: Clinical Data Gathering

Personnel: J. P. Miller, BCL
D. R. Bassman, BCL
L. L. Brandenburger, BCL
K. W. Clark, BCL
V. R. deMello, M.D., Jewish Hospital
R. L. Huck, BCL
A. S. Jemison, BCL
S. E. Katzen, BCL
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
T. F. Martin, M.D., Medicine
P. Moore, BCL
S. M. Moran, BCL
R. E. Morgan, BCL
G. C. Oliver, M.D., Medicine
T. A. Pavlovic, M.D., Medicine
R. Roberts, M.D., Medicine
B. A. Sandefur, B.A., Jewish Hospital
J. B. Schweitzer, BCL
L. J. Thomas, Jr., BCL
D. P. Wheeler, Jewish Hospital

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

Following closure of the clinical data gathering activities of our previous study (PR 11, A-1) our attention was turned to assessing the adequacy of our previous approach. Each clinical datum collected and coded was verified with the help of the microfilmed charts; ambiguities were then resolved. The prognostic and clinical utility of each item was reviewed in light of our own accumulated experience with some 1150 patients and in accordance with current medical practices. Based on this extensive experience a new protocol has been developed for the enrollment of myocardial infarction (MI) patients into a natural-history study. The major objective of this study is to determine the importance of ventricular premature complexes (PVCs) as prognostic indicators of sudden death in patients recovering from a documented MI. The basic thesis is that ventricular irritability, as manifested by ventricular ectopic activity found on 24-hour Holter recordings, will allow stratification of patients into groups at high and low risk of sudden death and permit the assessment of the independence of this predictor

from other clinical information obtained at the time of the acute infarct. Goals for this first year of support under a new NHLI grant have included the initiation of an enrollment procedure for patients recovering from myocardial infarctions, recording the clinical and demographic features of their infarcts, estimation of their infarct sizes using CPK analysis of serial blood samples (A-11), and the establishment of a MUMPS-based management information system.

An essential element which allows the orderly management of the ongoing clinical study has been the implementation of the Myocardial Infarction Patient Information (MIPI) system. This system has been implemented in MUMPS on a new computer system operated by the Washington University Medical Computing Facilities (MCF). Data collection activities are centered around the completion of a variety of different forms. Each form for a particular patient may be completed at a particular time in the patient's course and the resulting information promptly entered into the MIPI system at one of three terminals which are located at Jewish Hospital, BCL, and Barnes Hospital. Data entry is done by project personnel, permitting the rapid correction of computer-detected errors. An appropriate subset of forms is completed for each patient entering the Barnes CCU or the Jewish Hospital MICU. Depending on the diagnosis of each patient and events occurring during the patient's stay in the hospital, an additional sequence of forms might be completed on the patient. All patients with an admitting diagnosis of "rule-out MI" who later did not meet the criteria of a definite MI would have only the enrollment, risk-factors, onset-of-chest-discomfort, and CCU-diagnosis forms completed; patients with a proven diagnosis of an MI would have additional forms completed to document physical, hemodynamic, and electrocardiographic findings observed during the CCU stay. If serial blood samples were obtained, results of the CPK infarct size analyses are supplied from the enzyme laboratory and merged with the clinical information.

All patients with documented infarcts are approached for participation in the ambulatory recording phase of the study and, if agreeable, receive a 24-hour Holter recording following their discharge from the CCU but prior to hospital discharge. A second recording is obtained 2 to 3 months following discharge with subsequent tri-monthly recordings obtained on consenting patients exhibiting significant ventricular ectopic activity during either of the first two recordings. A blood sample from consenting patients is obtained at the time of the second recording for detailed lipoprotein quantification as part of a collaborative study with the Washington University Lipid Research Clinic.

During the first seven months of operation of the MIPI system, 6369 forms on 1219 patients had been entered into the system. Sixty-five percent of these patients were diagnosed as rule-out MI, probable MI or definite MI. Of the 297 patients with a definite MI, 37 expired in the hospital and 142 were successfully recruited into the ambulatory recording portion of the study and subsequently monitored.

During the entire procedure the MIPI system coordinates the information about patients and assists in the generation of appropriate correspondence. Letters to the patient's physician are generated by the system to confirm the patient's enrollment into the study and to communicate the results of the Argus/H processing of the Holter recording (A-14) and the results of the Lipid studies. MIPI allows periodic examination of forms which are expected but not yet received by the system, provides hard-copy compilations of all data on particular patients to assist in the medical auditing of the data previously entered, and coordinates the microfilming of the charts. Barnes Hospital's census information is obtained daily via industry compatible tape in order to assist in the tracking of the patient during his hospital stay.

MIPI has been implemented in a table driven fashion allowing: 1) the rapid alteration of forms as the necessity for revision emerges; 2) validity checking for allowable responses and ranges at the time of data entry; 3) ease of linking of the MUMPS-based system to the IBM System/360 for subsequent large scale data processing and statistical analyses; 4) certain responses entered in free-text format with a coding structure added at a later date; and 5) modification of the system to other similar research projects.

In the past, the decentralization of this project's facilities has led to an information flow which was somewhat inefficient, logistically awkward and in constant danger of scrambling important information. The implementation and continued successful operation of MIPI has allowed the centralization of all information in machine readable form with appropriate cross links available under the system.

A-2. Processing of Argus/H Cycle Streams on the System/360

Personnel: J. P. Miller, BCL
K. W. Clark, BCL
M. A. Hug, BCL
P. Moore, BCL
G. C. Oliver, M.D., Medicine
J. A. Ritter, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808

Previous analyses of the relationship of ventricular ectopic activity (VEA) to subsequent coronary events, particularly sudden death, have encouraged us to believe that a real and important relationship exists (PR 11, A-5). Under previously supported systems of analysis, only the most elementary information concerning the PVCs identified by Argus/H on a Holter tape was utilized. This kernel included the frequency of PVCs on the Holter tape,

average heart rate and cardiologist's judgments concerning both Lown class and whether or not the earliest PVC observed on a given tape was in or abutting the T-wave of the previous beat. Despite the crudeness of this latter measure, it was observed to be one of the most powerful predictors of subsequent sudden death. It was recognized that further progress on the elucidation of the relationship between VEA and subsequent coronary events required examination of the more subtle quantification of the VEA available within Argus/H but not utilized for analysis.

This information is encoded in the Argus/H Cycle stream; but until Spring, 1975, the Argus/H editing system did not allow for easy correction of Argus/H errors, particularly false-negative PVCs and coupling intervals. At that time changes were made in the editing capabilities and protocol so that the coupling intervals could be manually adjusted by the editors, erroneous beat labels deleted, and labels changed (PR 11, A-4). The sheer magnitude of the computer processing required to extract this information from a large number of Holter tapes precluded systematic analysis of these characterizations of the VEA and subsequent sudden death. At present the editor-corrected Cycle streams from approximately 40 ten-hour Holter tapes can be accumulated on one 2400 foot reel of industry compatible tape. The latter is then transported to the IBM System/360 Model 65 for bulk processing of these Cycle streams and the extraction of information describing the VEA in a form appropriate to subsequent statistical analysis.

A computer program (Summary) was written for the Model 65 which reduces the beat-by-beat annotation of the Holter tape to 154 variables chosen for their relevance to current clinical research interests. Summary was written in a higher level language (PL/I) to facilitate its maintenance and to allow rapid modification as additional insights are gained into the prognostic utility of particular features of VEA. Processing on the large, general purpose machine allows the utilization of fast, computationally oriented hardware, assures the availability of significant blocks of computer time necessary to process large volumes of Cycle streams, and allows the utilization of more traditional data processing resources such as archival tape storage, computer output microfiche, and large volume printed outputs. The average time for processing a ten-hour Cycle stream is 7 seconds of Model 65 CPU time or about 30 seconds of elapsed time.

A MUMPS database is maintained as part of the MIPI system (A-1) to assist in the management of this library of Cycle streams and abstracted information. Cycle streams which are used as input to Summary are logged into the system along with notations regarding any problem Cycle streams. By merging this information with other information in the MIPI system, lists requiring action may be produced. One list, for example, might indicate which digital tapes could be re-used since their Cycle streams had been processed by Summary and their folders had completed the cardiological review process.

The output from Summary is in turn passed as input to a System/360 statistical data management package (SAS) which is utilized for analysis of the resulting data and its merging with relevant clinical information

obtained through the MIPI system (A-1). Summaries of new Cycle streams are added to the database as additional Holter tapes are processed with Argus/H; the entire database of Cycle streams may be reprocessed as new clinically relevant variables are identified. This augmentation with additional variables may be accomplished at costs approximately the same as the original processing of the Cycle streams (50¢ per 10-hour Cycle stream).

The resulting database contains information about the coupling intervals of the PVCs on the tape, analysis of coupling intervals of various categories of PVCs (e.g. isolated PVCs, PVCs initiating salvos, PVCs within salvos), time-of-day-dependent PVC rates, heart rate information and average morphological features of the PVCs. These data are then conveniently merged by use of SAS with other recordings of that patient, with information resulting from the cardiological review of the tapes, and with information abstracting the patient's clinical features.

One problem which has interested investigators has been the coupling interval of the initiating beat of a salvo of PVCs. We, as others, have unexpectedly observed, on the basis of manual scanning, that couplets and runs are usually initiated by a late PVC. Despite this, early PVCs were often seen elsewhere on the tape. Analysis of 151 tapes with couplets and 48 tapes with runs has provided quantitative data demonstrating the longer average coupling interval of PVCs initiating salvos. The coupling intervals of isolated PVCs averaged 488 ms on tapes with couplets and 493 ms on those with runs. The initial PVC of couplets averaged 528 ms and those of runs 561 ms.

Many investigators have observed that tapes demonstrating high PVC frequencies were also apt to contain early PVCs. Two alternative hypotheses may be entertained for these findings: 1) an attribute of the injured myocardium promotes frequent PVCs as well as PVCs with shorter coupling intervals or 2) a statistical explanation which simply stated is "the more PVCS you have, the greater the chance that one of them will be less than some particular threshold." The quantification now possible with Argus/H has allowed us to regard the second as the more probable explanation. Of 577 tapes with PVCs, the correlation between the PVC rate and the earliest non-PVC to PVC interval was .39, but the correlation between the PVC rate and the <u>average</u> PVC coupling interval was only .08.

One of the problems plaguing investigators of anti-arrhythmic drugs has been the variability of responses exhibited by individual patients in terms of the frequency or severity of VEA observed. The increased quantification afforded by the new Argus/H system has allowed examination of more subtle parameters as response variables for drug studies. For example, in a recent cross-over double-blind study utilizing placebo, phenytoin sodium, procaine amide and quinidine, a coupling-interval-dependent effect was observed. While 4.2% of the PVCs observed while the patients were on placebo were less than 400 ms, 9.9% of the PVCs were less than 400 ms when the patients were on phenytoin sodium, but only 1.9% while on quinidine. This is consistent with the known physiological actions of quinidine and phenytoin sodium on the refractory period of myocardial tissue.

A-3. Infarct Site and Size Versus PVC Rate

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

Support: RR 00396
HL 18808
Jewish Hospital
Washington University

As part of the continuing study of arrhythmias occurring in outpatients who are recovering from myocardial infarction (MI), we have analyzed the PVC rates occurring at up to three months following MI to determine if the site or the size of the MI would in any fashion influence the PVC rates observed.[1] Holter tape recordings were obtained on 222 patients, and the average hourly PVC rates were determined by Argus/H analysis of those tapes. A number of variables obtained during the CCU admission were analyzed to see which were related to subsequent outpatient PVC rates. Five important subgroups of patients have been identified: (I) patients with a non-inferior MI and cardiomegaly (CM) with peak serum glutamic-oxaloacetic transaminase (SGOT) values greater than 240 units; (II) non-inferior infarctions, CM, and SGOT less than 240 units; (III) inferior infarction; (IV) non-inferior infarction, no CM and peak SGOT > 120; (V) non-inferior infarction, no CM and SGOT < 120. The following results were found:

Hourly PVC Rate by Subgroup

	I	II	III	IV	V
2 wk	1.0	1.7	1.4	0.4	0.3
1 mo	2.5	1.7	3.6	1.2	0.4
2 mo	8.9	4.9	1.6	1.1	0.5
3 mo	32.4	5.0	2.8	1.7	0.2

The differences are most marked at three months with group I showing roughly 160 times the PVC rate of group V. By analysis of variance, differences between groups for all periods are significant ($P<0.01$). From this it seems clear that subgroups of patients who have markedly different PVC rates during their recovery from an MI can be readily identified using easily available clinical measurements. We have yet to determine whether these differences in PVC rates which we have observed for these subgroups also correlate with differences in mortality.

(1) J. P. Miller, R. E. Kleiger, R. J. Krone, and G. C. Oliver, "The Influence of Site and Extent of Myocardial Infarction on PVC Rates During Recovery from Myocardial Infarction," Circulation, vol. 52, supplement II, p. 217, October 1975 (abstract).

A-4. A Study of the Relationship of CPK-Measured Infarct Size Versus Other Enzymes

Personnel: G. C. Oliver, M.D., Medicine
G. G. Ahumada, M.D., Medicine
R. E. Kleiger, M.D., Jewish Hospital
J. P. Miller, BCL
R. Roberts, M.D., Medicine

Support: RR 00396
HL 17646
HL 18808
Jewish Hospital
Washington University

Analysis of serum creatine phosphokinase (CPK) activity has been used at a number of institutions as a measure of extent of myocardial infarction (MI). It seemed of interest to determine whether or not there was a close correlation between this measure of extent of myocardial damage and other measures which have been more traditionally used such as electrocardiographic indicators of location (anterior, etc.), type (transmural or nontransmural, etc.), the presence or absence of clinical complications (congestive failure, etc.), and the measurement of daily serum enzymes. A prospective study was performed on 67 patients recovering from an acute MI unaccompanied by cardiogenic shock. For all patients, information was obtained on conventional risk factors including admission heart rate and blood pressure, daily electrocardiograms for three days, and serum enzymes. A positive correlation was noted between serial-CPK-based infarct size index (ISI) and both the peak daily serum CPK activity ($r=0.83$), and peak alphahydroxybutyrate dehydrogenase (HBD) activity ($r=0.82$). A multiple regression analysis was conducted using both CPK and alpha HBD. The analysis revealed a slightly higher correlation coefficient ($r=0.86$), but inclusion of the peak lactate dehydrogenase (LDH) and serum glutamic-oxaloacetic transaminase (SGOT) activities appeared not to enhance the predictive powers. It was of interest to note a highly significant correlation between the number of ECG sites coded electrocardiographically and the ISI ($P<0.001$). For example, patients who had electrocardiographic changes of both an anterolateral and inferior MI had higher ISIs than patients who had only an inferior MI. Patients with cardiomegaly ($P<0.05$), congestive heart failure ($P<0.01$), pulmonary edema ($P<0.05$), heart block ($P<0.05$), and early mortality ($P<0.05$) had higher ISIs than patients without these findings. Interestingly, these differences were less prominent in patients older than age 60. From this we conclude that

the high association between enzymatically estimated ISI and other independent clinical criteria indicative of severe MI reflects the extent of damage to myocardial tissue.

A-5. Study of the Relationship of Nontransmural Myocardial Infarction to PVC Rate

Personnel: G. C. Oliver, M.D., Medicine
V. R. deMello, M.D., Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
J. P. Miller, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808
Jewish Hospital
Washington University

It has recently been shown that cardiomegaly (CM) can influence ventricular ectopic activity (VEA) in patients recovering from a transmural myocardial infarction (MI). A preliminary analysis of our data suggested that patients with "noncodeable" MI had significantly higher PVC rates in the presence of CM than patients without CM. Because of the lack of data on the natural history of VEA in patients with noncodeable MI, a prospective study examined VEA in 16 patients during recovery. All patients had a history compatible with an MI and diagnostic changes in serum enzymes. Electrocardiograms in general showed transient S-T and T-wave abnormalities but did not contain new Q-waves diagnostic of an acute MI. A few patients had conduction defects which made the diagnosis of MI not possible by ECG analysis alone. The patients had Holter tape recordings at two weeks, one, two and three months. The tapes were analyzed and PVC rates determined by Argus/H. CM was determined by chest X-ray taken during the Coronary Care Unit stay. The following results were obtained:

Average PVCs/Hour

	2 wk-3 mo	2 wk	1 mo	2 mo	3 mo
No CM (n=8)	0.7	0.2	1.1	0.9	0.4
CM (n=8)	15.9*	14.2*	12.2*	17.5*	23.9*

*$p < 0.05$

These results seem to indicate that in these patients the presence of CM is associated with significantly higher VEA during the period two weeks to three months following MI. The differences between the ectopic rates is particularly striking at two weeks and at three months. These findings may help identify subgroups of patients prone to sudden death; their prognoses are being followed intensively.

A-6. Antiarrhythmic Drug Therapy Trials Using Argus/H

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

Support: RR 00396
HL 18808
Jewish Hospital
Washington University

The ability of Argus/H to quantitate ectopic ventricular beats has permitted its use to evaluate the effectiveness of antiarrhythmic drug therapy. A protocol has been described (PR 11, A-8) for the evaluation of diphenylhydantoin, quinidine sulfate, procaine amide, and placebo. The additional capability of Argus/H to evaluate the coupling intervals from normal beats to PVCs as well as PVCs to PVCs holds promise of opening a new dimension in the analysis of the effectiveness of antiarrhythmic medication. An evaluation of these new data is currently underway.

A-7. Study of Antiarrhythmic Effect of LB-46 (Sandoz) Using Argus/H

Personnel: R. J. Krone, M.D., Jewish Hospital
F. D. Biggs, M.D., Jewish Hospital
J. P. Miller, BCL
G. C. Oliver, M.D., Medicine

Support: Sandoz-Wander, Inc.

The ability of Argus/H to scan Holter tapes rapidly is being utilized to evaluate the antiarrhythmic efficacy of LB-46, a cardioselective beta-blocking agent developed by Sandoz-Wander, Inc. A double blind protocol comparing LB-46 to placebo was devised with a projected involvement of 20 patients. To date 5 patients have been enrolled and data collected; however,

the detailed analysis of these data has been deferred pending collection of the entire data set.

A-8. Mathematical Models for Estimation of Myocardial Infarct Size

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

Support: RR 00396
HL 17646

During the past year, our efforts in the use of mathematical models to describe the dynamics of the enzyme CPK released after myocardial infarction have concentrated on attempts to explain the disappearance of CPK from plasma (PR 11, A-23).

Estimation of infarct size from plasma CPK activity depends on CPK disappearance rate (k_d) as a parameter. We have previously estimated k_d in dogs from single exponential fits to serum CPK values obtained by frequent sampling after i.v. injections of purified myocardial CPK. However, early CPK values conform poorly to a single exponential, and in the present study, we found that the apparent disappearance of plasma CPK activity after myocardial infarction is only 21% as rapid in conscious dogs (n=18) as after i.v. injection of purified enzyme (n=20). Thus, like some other proteins, CPK may distribute in extravascular pools. Accordingly, we developed a two-compartment model to characterize k_d, based on the following assumptions: 1) CPK distributes in an extravascular compartment with continuing exchange with blood, 2) CPK activity is eliminated from blood only, 3) transfer rates between compartments and elimination from blood are first order. Model parameters were then estimated by two-exponential fits to seven CPK injection curves. CPK data conformed to these fits much more closely than to a one-compartment model with an overall average standard deviation of the observed values from the fitted curve only 50% as large. Average k_d obtained with this model was 0.0086 ± 0.0009 (SE), approximately double that obtained with the mono-exponential model. Although relative estimates of infarct size are not affected, this model of CPK behavior would account for the recovery of twice as much of the CPK activity released after myocardial infarction as recognized previously.

The double exponential behavior of serum CPK could be caused by a heterogenous composition of CPK in which different molecules have different

kinetics as do the isoenzymes of CPK. The isoenzymes of purified CPK have been measured and less than 2% of the total is MB while the remainder is MM. This small an amount of MB could not alone account for the two-exponential nature of the CPK data curves.

We are examining three factors which could explain the difference in the kinetics of the purified enzyme and the serum CPK activity following myocardial infarction: 1) continuing release of CPK after infarction blunting true disappearance of the enzyme, 2) presence of a third compartment which exchanges so slowly with blood that it is not significant in the limited time course of bolus injection experiments, 3) differences in the biochemistry of purified and endogenous CPK activity.

To explore the possibility of a third compartment, we simulated conditions of infarction by injecting a conscious dog with purified CPK every hour for nine hours. The disappearance curve of the serum activity after nine hours was not different from results obtained from single bolus injections, suggesting that a third compartment is unlikely. We are presently investigating the possibility of differences in the kinetic behavior of purified and endogenous CPK.

A-9. The Moving Window Discrete Fourier Transform (MWDFT) as It Applies to Arrhythmia Detection

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

Support: RR 00396

Preliminary investigation has begun to determine the feasibility of using the MWDFT[1] to enhance the operation of the present Argus/H arrhythmia detection algorithm. The MWDFT algorithm provides a computationally simple procedure for calculating the discrete frequency-component coefficients of a time varying signal as it passes through an analysis window. Preliminary analysis of ECG frequency-component coefficients, calculated with the MWDFT, has shown that some coefficients exhibit a distinct increase in amplitude correlated to the entry of the QRS into the analysis window, and a distinct decrease in amplitude correlated to the exit of the QRS from the analysis window. The sharpness of the increase and decrease of the frequency-component coefficients amplitudes suggests that they may possibly provide a means for identifying QRS onset and termination more accurately than the present technique.

The above observations not only strongly suggest the usefulness of the MWDFT as a technique for enhancing the operation of Argus/H but also suggest an unexplored potential for basing ECG arrhythmia analysis on

narrow-window time-varying frequency-component coefficients.

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A-10. External Detection and Tomography of Ischemic Myocardium

Personnel: E. S. Weiss, M.D., Medicine
C. S. Higgins, A.B., Radiology
E. J. Hoffman, Ph.D., Radiology
N. A. Mullani, BCL
M. E. Phelps, Ph.D., Radiology
B. E. Sobel, M.D., Medicine
M. M. Ter-Pogossian, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology
J. R. Williamson, Pathology

Support: RR 00396
HL 13851
HL 17646

During the past year a series of studies was undertaken to visualize ischemic myocardium quantitatively.(1-5) The principle of this work is that accumulation of free fatty acid (FFA), the major substrate of aerobic myocardium, is attenuated in ischemic tissue and ceases in zones of infarction.

In the first study we perfused isovolumically beating rabbit hearts under conditions of selected flows with cyclotron-produced, short-lived ($t_{\frac{1}{2}}$ = 20.4 minutes), ^{11}C-labeled isotopes of glucose and FFA. Tension-time index decreased 83% and lactate production increased from 0.5±1.9(SE) to 5.3±2.1 μmol/min per g of dry weight reflecting myocardial ischemia after flow was reduced from 20 to 5 ml/min. After 30 minutes of low flow the myocardial accumulation of ^{11}C-octanoate, expressed as the extraction fraction, declined from 56±15% to 30±3%, reflecting metabolic suppression of FFA extraction during low flow. Effects attributable exclusively to prolonged residence time were excluded. Similar results were obtained with ^{11}C-palmitate. The myocardial avidity for ^{11}C-palmitate was demonstrable by rectilinear whole body scanning in dogs given 5 mCi of the agent intravenously. Diminished ^{11}C-palmitate uptake in zones of myocardium rendered ischemic for 20 minutes prior to reflow in intact dogs was delineated by electrocardiographically gated positron-emission transaxial computer reconstruction tomography.(1,6,7)

Subsequently, we extended these observations to intact canine hearts in-vivo. Myocardial infarction was quantified externally with the use of cross-sectional computer-reconstructed images obtained within 10 minutes by positron-emission transaxial tomography (PETT) in 20 closed chest dogs 48 hours after coronary ligation. Infarct delineated in each PETT cross section was measured by planimetry of the digital printout of the myocardial image to define the area with counts not exceeding values in the ventricular chambers, and was compared to infarction estimated histologically and biochemically in corresponding sections of the ventricle. A series of PETT images from the apex to the A-V valve, each with a 1.5 cm thick field of view, was obtained after i.v. injection of 5 mCi ^{11}C-palmitate ($t_{\frac{1}{2}}$ = 20.4 minutes) in each dog. Ten minutes before sacrifice each animal was given 250 μCi ^{14}C-palmitate i.v. The left ventricle was subsequently sectioned at levels corresponding to each tomogram, subdivided, and assayed for CPK (IU/g myocardium), ^{14}C-palmitate (dpm/g), and gross infarction estimated by planimetry of 1 cm thick sections and corroborated histologically. The percentage of infarct in each PETT reconstruction (0-68%) correlated with depletion of myocardial CPK activity (r=.93), diminished accumulation of ^{14}C-palmitate (r=.90), and morphometric estimates in corresponding sections (r=.91). These results indicate that myocardial infarcts in 1.5 cm cross sections of the heart can be rapidly quantified externally by computer-reconstructed images obtained by PETT after i.v. injection of a positron-emitting tracer of a physiological substrate of myocardium.(5,8-10)

In preliminary studies the tomographic technique has been applied to normal human subjects with successful delineation of left ventricular free wall, interventricular septum, right ventricular free wall, and distinguishing anatomic features of each. Based on the results in animal studies, it appears likely that quantitative estimation of infarction in man will be possible.

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(2)M. M. Ter-Pogossian, E. J. Hoffman, E. S. Weiss, R. E. Coleman, M. E. Phelps, M. J. Welch, and B. E. Sobel, "Positron Emission Reconstruction Tomography for the Assessment of Regional Myocardial Metabolism by the Administration of Substrates Labeled with Cyclotron Produced Radionuclides," in Proceedings from the Conference on Cardiovascular Imaging and Image Processing Theory and Practice, vol. 72, D. C. Harrison, H. Sandler, and H. A. Miller, eds., Society of Photo-Optical Instrumentation Engineers, Palos Verdes Estates, pp. 277-282, 1975.

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(4)M. M. Ter-Pogossian, E. S. Weiss, R. E. Coleman, and B. E. Sobel, "Computerized Axial Tomography of the Heart," American Journal of Roentgenology, in press.

(5)E. S. Weiss, S. A. Ahmed, M. J. Welch, J. R. Williamson, M. M. Ter-Pogossian, and B. E. Sobel, "Quantification of Infarction in Cross Sections of Canine Myocardium in Vivo with Positron Emission Transaxial Tomography and ^{11}C-palmitate," Circulation, in press.

(6)E. S. Weiss, E. J. Hoffman, M. E. Phelps, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel, "External Detection of Altered Metabolism of ^{11}C-labeled Substrates in Ischemic Myocardium," Clinical Research, vol. 23, p. 383A, 1975 (abstract).

(7)E. S. Weiss, E. J. Hoffman, S. A. Ahmed, M. E. Phelps, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel, "Positron Emission Transaxial Tomography of Ischemic Myocardium in Vivo with Physiological ^{11}C-fatty Acid Substrate," Circulation, vol. 52, Supplement II, p. II-52, 1975 (abstract).

(8)E. S. Weiss, S. A. Ahmed, J. R. Williamson, A. K. Robison, M. M. Ter-Pogossian, and B. E. Sobel, "Tomographic Images of Myocardial Infarcts: Biochemical and Morphological Validation," American Journal of Cardiology, vol. 37, p. 181, 1976 (abstract).

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(10)E. S. Weiss, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel., "External Quantification of Myocardial Infarction in Vivo," Clinical Research, vol. 24, p. 422A, 1976 (abstract).

A-11. Modification of Infarct Size

Personnel: R. Roberts, M.D., Medicine
H. D. Ambos, BCL
B. J. Besserman, Medicine
G. M. Clarke, Medicine
J. R. Cox, Jr., BCL
J. H. Gammel, Medicine
C. L. Large, Medicine
B. E. Sobel, 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 observed (ISO) was estimated from serial plasma creatine phosphokinase (CPK) changes during a 72 hour interval. Infarct size was predicted (ISP) from CPK values projected by least squares approximation to the log-normal curve best fitting data obtained hourly for seven hours after the initial plasma CPK elevation. The difference between ISP and ISO was compared to that observed in controls matched for predicted infarct size. All Holter tapes were digitized and processed by the Argus/H computer system. Hemodynamics including cardiac output were determined by the Swan-Ganz thermodilution technique and the effect of each drug assessed by comparing hemodynamics before and after its administration.

Studies initiated in 1974 to evaluate the effect of methylprednisolone in patients with myocardial infarction were completed in 44 patients with acute myocardial infarction. Methylprednisolone, 30 mg/kg, was administered intravenously in 22 patients, 12 of whom received multiple doses of the drug at six hour intervals for 48 hours and 10 patients received only a single dose. Concomitant controls included 22 patients who did not receive the drug. Patients who received a single dose of the drug exhibited no effect on PVCs, hemodynamics or infarct size (ISP 64±17 vs ISO 63±14). However, patients receiving multiple doses showed a marked increase in infarct size (ISO 103±22 vs ISP 56±13) of 84%. This was significantly different from controls matched for ISP in which ISP and ISO were virtually identical (ISP 53±16 vs ISO 55±19). The deleterious effects of methylprednisolone as evidenced by increased infarct size were also associated with increased PVCs. Post-mortem findings in 5 of the 12 patients given multiple doses of the drug exhibited massive myocardial infarction and in 3 cases rupture of the ventricular septum or free wall.[1-3]

Studies were performed in 39 patients to assess the effect of dobutamine, a beta-antagonist that increases myocardial contractility without significantly increasing heart rate or blood pressure. It may also increase coronary flow by direct coronary vasodilation. Dobutamine was administered i.v. (1-40 mcg/kg/min) to 12 patients with moderate to severe hemodynamic impairment reflected by a wedge pressure of $\geq$15 mm Hg and cardiac index of <2.5 liters/m^2/BSA and results were compared to those in 12 control patients matched for ISP. The drug increased cardiac output, decreased wedge pressure and did not change heart rate, blood pressure, or PVC frequency. These favorable results were obtained without any apparent increase in infarct size, a finding in marked contrast to that observed with isoproteronol or norepinephrine in which hemodynamic improvement occurs at the expense of a marked increase in infarct size, mortality, and morbidity.[4]

Studies have been initiated to assess the effect of Nifedipine, a calcium antagonist and potent dilator of smooth muscle known to increase coronary flow and decrease systemic resistance. Nine patients have been entered in the study thus far. Preliminary results fail to delineate either favorable or deleterious effects on infarct size, PVCs, or hemodynamics.[5]

Fourteen patients have been studied after receiving acebutolol, a cardio-selective beta-blocker. Patients have tolerated the drug well with

no increase in arrhythmias or cardiac failure. Definitive results of the effect of this drug on infarct size are not yet available.

Studies evaluating verapamil (0.2 - 0.7 mg/kg/min), a calcium antagonist, in 20 dogs with myocardial infarction have now been completed. Verapamil increased coronary flow to normal myocardium (measured by radioactive microspheres) but did not affect flow in ischemic areas. This lack of increased coronary flow to ischemic areas may explain why no favorable effect on infarct size was seen based on comparison of ISO and ISP.[6]

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[2]V. R. deMello, R. Roberts, and B. E. Sobel, "Deleterious Effects of Multiple Dose Methylprednisolone on Evolving Myocardial Infarction," Circulation, vol. 51, supplement II, p. II-106, 1975 (abstract).

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A-12. Ischemic Heart Disease SCOR Computer System

Personnel: J. Markham, BCL
D. C. Ficke, BCL
F. Hummel, BCL
J. C. Lee, BCL
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646

A computer system for the Ischemic Heart Disease project was installed in the CCU computer room in August. This system consists of an Interdata Model 7/16 processor with 64K bytes of memory, a 10 megabyte disc, a Mini Bee video terminal, an industry compatible magnetic tape unit, and a Versatec matrix printer/plotter. The system runs under DOS (Disc Operating System), and a FORTRAN compiler is available as well as other support software.

Extensive software for various applications has been developed for this system. The infarct size estimation programs, formerly run on the IBM System/360 Model 65, have been implemented on the Interdata computer, and all routine infarct size studies now make use of this system (A-11). In addition, several statistical programs have been developed for the Interdata; these provide basic statistics such as means, standard deviations, correlation coefficients, t-test values, and linear regression curve fits. General-purpose plotting capabilities are provided through a Versatec software package which was modified to run on the Interdata.

Current software work is focusing on the establishment of a patient information database for this project. Approximately 200 patient files have been collected to date. A set of programs which allows data to be entered on the video terminal, stored on disc, and eventually written on magnetic tape has been developed. Statistical analysis of the data on tape will then be performed on the Model 65 making use of the statistical packages available there.

A-13. Assessment of Diastolic Compliance of the Left Ventricle

Personnel: P. A. Ludbrook, M.D., Medicine
G. H. Brandenburger, BCL
J. D. Byrne, CPT, Medicine
B. R. Hieb, M.D., Jewish Hospital
J. Hirsch, B.S., Medicine
P. B. Kurnik, B.S., Medicine

Support: RR 00396
HL 17646
Jewish Hospital
Washington University

This project is designed to study diastolic compliance in the intact left ventricle in patients with ischemic heart disease. Techniques for quantification of compliance are currently being developed in the Hemodynamic Laboratory and will be extended to the Clinical Investigation Unit by employing noninvasive techniques for analysis of ventricular dimensions.

Characterization of left ventricular compliance requires simultaneous measurement of ventricular dimensions and high-fidelity pressure recording using transducer tip micromanometer catheters during radiographic contrast ventriculography in the single-plane mode. Techniques for the following have already been accomplished:

1. Data acquisition during ECG-timed slow administration of ventriculographic contrast media in order to minimize stimulation of ventricular premature beats and avoid artifactual ventricular distension due to contrast medium.

2. Data acquisition with angiographic transducer-tip catheters especially designed to avoid arrhythmogenic jets when contrast medium is injected, and to minimize catheter motion.

3. Continuous high-fidelity recording of pressures on magnetic tape systems with appropriate frequency response during cineangiography. The frequency response of the recording system has been examined using an analog method for determining frequency spectra of nonrepetative signals with components in the physiological range between 0.05 Hz and 1.0 kHz. This method utilizes an analog record/play-back tape, memory oscilloscope, and a spectrum analyzer. Even with high-fidelity Millar transducer recordings in patients no frequency components were present outside the frequency band of the analog tape.

4. An integrated package of computer programs and electronic equipment has been assembled to quantify compliance from the pressure-volume data collected during ventriculography. The program is divided into two sections - data acquisition and data investigation. Data acquisition entails five sets of data: first, a calibration-pressure signal is obtained from each patient

in the form of a 0 to 100 mm Hg deflection. Second, four simultaneous channels of information are collected from the cine run within the period of dye injection and angiographic framing. In addition to samples of pressure recording, ECG and timing pulses from the dye injector and cine camera are acquired and stored. The third data set utilizes up to ten seconds of three channels of information containing pressure, ECG, and injector timing-pulse data. The system developed digitizes the analog recording of LV pressure 1,000 times per second and stores it on a magnetic disc. Ventricular volumes are calculated by the computer from the input of a rho-theta transducer which is manually placed around the ventriculographic outline. We are in the process of developing an automated technique for rapid and accurate computation of serial ventricular volumes. Ventriculographic planimetry will be performed directly on the viewing screen of the Vanguard XR-35 projector using a Graph/pen 3 sonic X-Y coordinate digitizer. The calculated volume will then be entered automatically into the computer program, which will synchronize it with the appropriate left ventricular pressures. Thus digitization of pressures and precise chronologic alignment of volume and pressure measurements are facilitated by this system. The computer output can display the raw data in a variety of standard formats, it can display selected and computed functions of the raw data, it can fit the data to formulae for estimation of compliance and thereby test hypotheses underlying the estimates, and it can aid in finding useful functions which are compatible with the raw laboratory data.

A-14. Holter Tape Processing

Personnel: K. W. Clark, BCL
H. D. Ambos, BCL
R. K. Bhola, BCL
K. M. Bruce, BCL
G. R. Cook, BCL
M. L. Dunne, BCL
S. E. Katzen, BCL
P. Moore, BCL
S. J. Potter, BCL
R. W. Sutherland, BCL
P. B. Webb, BCL

Support: RR 00396
HL 18808

During the past year, the System/7 has been used for software development and Holter tape processing. The major thrust of software effort has been towards algorithms to reduce the time required to human-edit the Argus-flagged PVCs (A-15). Considerable effort has also been invested in operational program improvement; the changes are many but not major and are not described here.

Numerous tapes have been digitized, scanned, and edited during the year. The tapes have come from a variety of sources: the study of ventricular arrhythmias and sudden death or "core project study" (PR 11, A-1), 750 ten-hour tapes; infarct size study (A-9), 60 tapes; Sandoz drug study (A-6), 15 twelve-hour tapes; the new natural history study (A-1), 220 twenty-four-hour tapes.

We have given processing priority to the twenty-four-hour tapes from the new study (A-1). In so doing, we are able to provide 12 to 48 hour turnaround time and prevent a backlog of tapes from accumulating. Processing of these tapes includes the generation of a report describing the ventricular ectopic activity on the tape. The report is mailed to the patient's physician and includes a cover letter generated on the MIPI system (A-1); a plot of PVC frequency over time; a summary of the numbers of PVCs, couplets, and runs; and several representative ECG strips.

Non-PVC to PVC coupling intervals have been the focus of attention since so-called "early" PVCs seem to correlate with sudden death (A-1). In addition to the flagging of Argus/H labeled PVCs as true or false, the editor also adjusts onsets of PVCs and prior beats to ensure accurate coupling intervals. No doubt this has increased the time required to edit a tape; however, some program improvements have decreased the edit time. Of the 10-hour core study tapes, 88% took one hour or less to edit; the average edit time for all of the 10-hour tapes was about 40 minutes. For the 24-hour tapes, the average edit time was about 75 minutes.

Patient records of Holter recordings, analog tape manual-scanning records, and editing records continue to be maintained in MUMPS/7 databases for 10-hour tapes of the "core study" (PR 11, A-14). For the 24-hour tapes, the corresponding information and more extensive data are maintained in the MIPI system (A-1).

A-15. Argus/H: Algorithm Development

Personnel: C. N. Mead, BCL
K. W. Clark, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808

During the past year, Argus/H algorithm development has centered around efforts to further reduce the amount of time a trained technician ("editor") must spend reviewing and validating PVCs detected during Argus/H processing. The initial strategy[1] combined the four Argus/H morphological

measurements ("features") of a beat with a candidate beat's coupling interval, defined via human interaction, to "teach" the machine the "five features" of a true-PVC focus. Having established this characterization, the machine would then search the entire digital data stream (Cycle stream) and label as true-PVC, without human interaction, all beats falling sufficiently "close" in a 5-dimensional sense to the editor-defined true-PVC. This iterative process would continue until the editor had viewed and the machine had edited all true-PVC clusters, each cluster representing a distinct morphological focus. All false-positive PVCs were still reviewed by a technician on an individual beat basis.

Initial results were based on ECG segments of approximately 1 hour in length. When longer tapes (6-12 hours) were processed, several unexpected problems surfaced. First, significant variation in heart rate generated substantial numbers of false-positive PVCs when the average R-R interval on one section of tape approached or became less than the coupling interval of a true-PVC seen on another section of the same tape. When initial correction for changing R-R intervals was inserted in the algorithm, the machine editing portions of the existing algorithm failed to edit more than 10-15% of the true PVCs on a given tape compared to 60-75% on the 1 hour tapes. Second, because of variations in beat morphology over time and sensitive Argus/H measurements, editor-defined true PVC clusters no longer represented a single morphological focus. This required the editor to view a considerable number of beats of similar morphology which were nevertheless in different clusters. As a result, the percentage reduction in editing time was less than that for the one-hour tapes.

Algorithms developed since last year have successfully eliminated the necessity of human interaction in the characterization of a true-PVC and allow much of the editing of true-PVCs to be done as a 4th stage of Argus/H processing. These algorithms concentrate on the definition of a true-PVC using the beat's four morphological features, its Argus/H assigned label (e.g. PVC), an analysis of the coupling intervals of all beats of similar morphology, and the relationships of the forward and backward coupling intervals to an updated R-R interval average. False-positive PVCs are flagged in a similar manner.

To date, this new strategy has been tested on 20 randomly selected tapes of 5-7 hours in length with promising results. On all tapes, more than 75% (average 84%) of the Argus/H-flagged PVCs were correctly labeled as true or false by the machine without any human interaction. Happily, the false-negative rate decreased 50% while the false-positive rate stayed below 0.5%. A final evaluation of broader scope is currently in progress.

(1)C. N. Mead, T. Ferriero, K. W. Clark, L. J. Thomas, Jr., J. R. Cox, Jr., and G. C. Oliver, "An Improved ARGUS/H System for High-Speed ECG Analysis," Proceedings of the Conference on Computers in Cardiology, Rotterdam, The Netherlands, pp. 7-13, October 1975.

A-16. Progress Toward a Restructured Argus/H System

Personnel: R. E. Hitchens, BCL
H. D. Ambos, BCL
T. R. Baird, BCL
K. W. Clark, BCL
J. D. Coe, BCL
M. A. Hug, BCL
K. L. Ripley, BCL
J. A. Ritter, BCL
R. W. Sutherland, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808

Efforts are now underway to produce a version of Argus/H which would process 24-hour dual-channel Holter tapes. The primary goal of this new version is a system which would be exportable to current and potential Holter tape scanning centers. Toward that end, hardware with more on-line mass storage and less costly than the System/7 configuration has been selected and installed.

The processing system will be implemented on two Cal Data 135's, one with 48K and the other with 16K words of memory and both with PDP-11-compatible extended and floating point instruction sets. These processors are user-microprogrammable, and both are equipped to use writeable control-store memory. One processor also includes a microprogramming console with 32 words of control-store memory, which is adequate to check out short microprogrammed routines. Standard peripherals include two CRT terminals, a shared line printer, and a cartridge disc system which is software and media compatible with the DEC RK11/RK05 disc. The two processors would be used to perform parallel processing tasks and thus speed up analysis.

Following is a summary of special peripherals for the new system:

High Speed Display Oscilloscope. The Hewlett Packard CRT display is currently implemented with a programmed I/O interface. Preliminary work has been done toward the design of a direct memory access interface with special features for displaying annotated ECG data.

High Speed Strip Chart Recorder. The Siemens ink-jet recorder is driven from a four-channel interface and contains two signal channels. Future plans are to add two channels to the recorder, so that 2-channel annotated strips can be generated.

Dual Density Tape Drive. A Pertec 800/1600 PBI 75-inch-per-second tape-drive interface has been designed. The tape system will be used for archival storage of 24-hour tapes at 1600 BPI and for access to the larger System/7 database at 800 BPI. The tape drive will also be used to back up system programs stored on disc.

Storage Module Disc Drives. A System Industries 9500 dual computer-disc system with two Control Data 9760 disc drives will be used for on-line

random access storage of ECG data. The total formatted capacity of the system is 33.6 mega-words, which is adequate to store 24 hours of 2-channel ECG data (real time sample rate of 250 sps).

General Purpose DMA Board. A general purpose direct-memory-access interface has been designed and built for use with the tape drive, A/D converter, and high-speed oscilloscope.

Dual Channel A/D Converter. A 2-channel analog-to-digital converter has been built and tested. The sample rate is variable between real time (250 sps) and 120 times real time. A 60 Hertz rejection filter is included. An interface between the A/D converter and the general purpose DMA has been designed.

The initial software task will be to duplicate the scan and edit programs from the System/7. Toward that end, the Argus/H scanning algorithms of Primitive and Cycle have been translated to Cal Data code. These algorithms are currently being debugged using a well established database of 15 minute Aztec data segments from 39 patients. This same database was used to evaluate the System/7 Argus/H and Argus/Sentinel (PR 11, A-17). Concurrently, an edit program is well underway as are numerous utility programs. Source data for these routines are obtained via a 9600-baud serial link between the System/7 and the Cal Data.

A-17. Evaluation of Arrhythmia Detectors

Personnel: K. L. Ripley, BCL
K. W. Clark, BCL
J. R. Cox, Jr., BCL
C. L. Feldman, Ph.D., Worcester Polytechnic Institute
F. M. Nolle, D.Sc., Northwestern University
G. C. Oliver, M.D., Medicine
L. J. Thomas, Jr., BCL
A. Zencka, M.D., Creighton University

Support: RR 00396
HL 18808
Jewish Hospital
Washington University

As part of a continuing interest in the availability of valid performance data for the comparison of computerized arrhythmia detectors, three independent efforts are currently in progress. The primary effort is directed toward the actualization of goals developed by the Evaluation Group for Arrhythmia Detectors (PR 11, A-19) which seeks to provide a large set of well-documented and cardiologist-annotated ECG data. These data will serve as a standardized database which can be used by developers of arrhythmia detectors for test and evaluation purposes. Since all developers will hopefully draw on this same database, the comparison of

performance data from different systems will be a valid exercise. Communication has been established with the American Heart Association in this regard, and they have expressed a willingness to sponsor a funding request to the National Heart and Lung Institute. Preparation of this request is currently underway.

As an interim measure, since the implementation of the above database is at least a year away, nineteen (19) one-hour tapes of ECG data have been selected (PR 11, A-18) for cardiologist-annotation and distribution to interested parties. This effort to provide a moderate-sized and well-documented database which might be used for evaluation purposes resulted from several requests by manufacturers and researchers currently developing computerized arrhythmia detectors. Realizing the need for an interim standard, we have committed resources to the preparation of the needed database. The final cardiologist-annotations are currently being incorporated into the database and distribution is scheduled to begin later this summer in the form of three (3) 2400 foot, 800 bpi magnetic tapes. A manual will accompany these tapes describing formats and use of the tapes. At the time the tapes are available, a formal announcement of the existence of this database will be made in a prominent journal.

Finally, at the request of Hewlett-Packard (HP), a small-scale comparison is being made between the HP78220 computerized arrhythmia detector and Argus/H. Although the two systems have many differences, the Argus algorithms served as the basic model for the HP programs. Hence, there is much interest in how the two systems compare. HP has previously conducted an evaluation of their system using a set of data collected at Stanford University. These data have now also been processed by Argus/H and a beat-by-beat comparison is being made between the HP78220, Argus/H, and the cardiologist.

A-18. A Microcomputerized Argus

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

Support: RR 00396

In response to the need for a low-cost ECG rhythm monitor, the feasibility of a microprocessor or microcomputer-based system was considered. The system of choice was a Digital Equipment Corporation LSI-11. The LSI-11 offers the computational power of the PDP-11 in a smaller, less expensive package. In addition, there exists proven ECG monitor software for the PDP-11, which can be readily modified to run in the smaller machine. Also, the ongoing development of a PDP-11-compatible high-speed ECG analysis system (A-16) provided the ability to develop the programs on a larger, more fully equipped system, circumventing the hazards of program development on a minimal system.

At present, several versions of the Argus software are being explored as candidates for use in the LSI-11. Preliminary plans for application of the LSI-11 system include the processing of data gathered by the SICU telemetry system (C-5) or to implement an arrhythmia detection system as part of the portable SICU research cart (C-3).

A-19. MECCA, A Computerized System for Capturing Transient Electrocardiographic Data

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

Support: RR 00396

A multi-patient data-acquisition system has been developed to provide the facility to retrospectively capture two-hour segments of ECG data on up to eight channels in a coronary care unit. The system is composed of a CPU, an A/D converter, a graphics display and an 80 megabit disc storage device. Data storage efficiency is increased through the use of Huffman encoding, a data compression technique which allows exact recovery of the original signal. Using this technique, the effective storage capacity of the disc has been increased by a factor of three. The digitized and encoded data from each channel are stored in one of eight circular buffers on disc. A current two-hour history is always available for each channel. At any time, a given buffer(s) may be captured for subsequent study and analysis. For example, should an episode of ventricular fibrillation occur, those circular buffers assigned to that patient may be "frozen" at will, providing the investigator with a permanent digital record of the event itself and the preceding two hours. These data buffers are automatically transferred to separate permanent files on disc and monitoring is quickly reestablished. This occurs without any interruption in the monitoring of other channels.

The MECCA system has been in operation in the Barnes Hospital Coronary Care Unit since April, 1976. There, the computer system senses the bedside "code" buttons for those patients being monitored by the system and uses these code alarms as commands to save a given data buffer. We have collected various episodes which include examples of ventricular tachycardia, ventricular fibrillation, asystole, and marked bradycardia.

Data episodes collected by MECCA are immediately applicable to two specific areas: a) research on warning arrhythmias and b) collection of a standardized ECG database for arrhythmia detector evaluation. Much conjecture has occurred recently concerning the presence and/or utility of warning arrhythmias for episodes of ventricular tachycardia and

ventricular fibrillation. MECCA provides a virtually automatic method for capturing events which precede these life-threatening arrhythmias. MECCA also provides a vehicle for satisfying the goals of the Evaluation Group for Arrhythmia Detectors (EGAD) (A-17). EGAD has proposed the establishment of a high quality cardiologist-annotated database for evaluation of arrhythmia detectors. This database must consist of a variety of events and waveforms obtained under routine monitoring conditions. Through the use of MECCA, those events which are rare and difficult to obtain may be captured with a minimum of effort.

A-20. A Device for Synchronizing X-Ray Exposures to Any Point in the Cardiac Cycle

Personnel: H. D. Ambos, BCL
B. F. Spenner, BCL

Support: RR 00396
HL 17646

The measurement of left-heart dimensions with a non-invasive technique required the construction of a device capable of synchronizing an X-ray unit to an ECG signal. The device consists of a QRS detector with a variable-delay circuit and an oscilloscope to display the ECG signal and trigger pulse. The user-variable-delay feature of the device allows the X-ray unit to be triggered at any point in the cardiac cycle. Portability of the X-ray unit and synchronizing device permit left-heart dimensions to be measured at the bedside.

A-21. Interactive Digital Acquisition of Electrocardiograms

Personnel: R. J. Goggins, B.S., Electrical Engineering
R. M. Arthur, BCL
A. Hernandez, M.D., Pediatrics
A. N. Weiss, M.D., Medicine

Support: RR 00396
HL 18144
HS 00074
Washington University

A digital cart was developed which tests the signal quality of 6-second segments of three simultaneous leads of ECG acquired at 500 samples/second (PR 11, H-2). The tests were designed to eliminate

records which might not meet the demands of automatic ECG analysis systems. The original cart utilized an Intel 8008 central processing unit to perform tests for signal out of range, noise and transient content, baseline shift, and absence of QRS complexes. The cart was evaluated in the acquisition of pediatric vectorcardiograms taken both from analog tape recordings and directly from patients.

Cart capability has been improved by upgrading the processor to a compatible Intel 8080 unit and by adding a serial output port for transfers to a permanent storage device. A five-fold increase in execution time permits the acquisition of 8 leads at one time so that the standard lead set can be collected simultaneously. Programs have been streamlined to make use of the expanded order code. The pediatric vectorcardiogram database consisting of about 400 analog tape records is being studied to characterize clinical-environment signal quality with emphasis on noise and baseline shift.

A-22. Real-Time Digital Echocardiography

Personnel: D. R. Jones, M.S., Electrical Engineering
R. M. Arthur, BCL
A. Hernandez, M.D., Pediatrics
A. N. Weiss, M.D., Medicine

Support: RR 00396
HL 18144
HS 00074
Washington University

An acquisition system for ultrasonic echoes based on a burst analog sampling approach has been implemented (PR 11, H-3).[1,2] Analog samples, acquired at a high rate, are stored in a series of sample-and-hold circuits. During the period between ultrasonic pulses, samples are accessed slowly for analog-to-digital conversion. Conventional input/output ports available with most minicomputers or microprocessors can handle the resultant data rates.

A digital echocardiographic system was designed and built which combined burst-analog-sampling circuitry with a central processor consisting of two Motorola M6800 microprocessors operating in parallel.[3] One microprocessor controlled the acquisition circuitry, real-time displays, and a 512-byte shared memory which linked the two microprocessors. The second microprocessor performed real-time data reduction on the echo signals, stored the reduced data in a 12K buffer, and controlled displays of the stored information. A 10-cm tissue window was described by acquiring 256 samples from each echo period at a 2 mHz rate. The system can process each set of 256 samples in 5 msec, so that it can determine the position and acoustic properties of internal structures 200 times a

second. A-mode (echo amplitude vs time) and M-mode (position of reflection producing structure vs time) displays were generated both in real-time and from the stored characteristics of about 4000 reflections from tissue interfaces. The stored information typically depicted the position of cardiac structures for 4 seconds. The stored reflections make possible on-line processing to enhance images or to derive parameters such as chamber dimensions, wall thickness and valve leaflet velocities.

(1) R. M. Arthur and R. J. Myrick, "A Real-Time Digital Echocardiograph," presented at the 48th Scientific Session of the American Heart Association, Anaheim, California, October 1975. Circulation, vol. 52, no. 4., supplement II, p. II-33, October 1975 (abstract).

(2) R. J. Myrick and R. M. Arthur, "Real-Time Digital Echocardiography Using Burst Analog Sampling," IEEE Transactions on Sonics and Ultrasonics, in press.

(3) D. R. Jones, "A Microprocessor-Based Digital Echocardiography System," Master of Science thesis, Department of Electrical Engineering, Washington University, St. Louis, Missouri, 1976.

A-23. ECG Report Production

Personnel: J. L. Karpowicz, B.S., Electrical Engineering
R. M. Arthur, BCL
R. N. Tatum, M.S., Barnes Hospital

Support: HS 00074
Barnes Hospital
Washington University

Tracings of electrocardiograms to be analyzed by the Bonner program[1] on the IBM System/370 computer at Barnes Hospital are generated at the Heart Station from remote units throughout the hospital. The analysis of the ECG is also printed at the Heart Station. A line printer attached via direct lines to the System/370 writes the unconfirmed diagnostic report on a label which is then attached to the ECG tracing.

The objective of this project was to develop a technique for automatically combining tracing and unconfirmed report on a single sheet. Not only would such a technique save time and eliminate errors in matching reports with tracings, but it would also substantially reduce printer and paper costs. A savings of about $2,000/year is projected for the combined-report technique compared to present procedures.

A printer connected to the System/370 via a modem has been added to the system to write the report directly on the ECG tracing. Logic is being

developed to control paper flow between the ECG writer and the report printer. The logic senses both a fiducial mark associated with each ECG lead set and the drive-on time of both units to position the tracing properly in the report printer. The combined tracing and report system will operate in parallel with the existing system during its evaluation phase. If the technique is successful, the existing line printer could be removed.

(1) R. E. Bonner, IBM Health Care Support/Electrocardiogram Analysis Program, program number 5736-H15 (DOS), White Plains, New York, 1974.

B. Tracer Kinetics

B-1. Noise Analysis of PETT-III

Personnel: P. M. Fishman, BCL
C. S. Higgins, A.B., Radiology
N. A. Mullani, BCL
M. E. Phelps, Ph.D., Radiology
D. L. Snyder, BCL

Support: RR 00396
HL 13851

A collaborative study with the Mallinckrodt Institute of Radiology (MIR) was undertaken to determine the performance characteristics of transaxial emission tomography. The goals of this study were to obtain optimal design criteria for such a device and to aid in the understanding of the observed performance of the positron-emission transaxial tomograph (PETT-III) presently in operation at MIR. A FORTRAN program was written to simulate an ideal emission tomographic reconstruction of a disk of spatially uniform radioactivity. The radioactivity level and noise variance along a diameter through the disk were reconstructed and plotted for measurements both corrected and uncorrected for attenuation. The resulting signal and noise reconstructions were in close agreement with experimentally obtained reconstructions using the PETT-III device, thus lending support to the validity of the design criteria used in its construction.

B-2. PETT-IV: A Four-Slice Positron-Emission Transaxial Tomograph

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

Support: RR 00396
HL 13851
Washington University

The experience gained with the PETT-III system (PR 11, B-8, B-9) in animal experimentation and with human subjects has made it apparent that a serious disadvantage of its design is that it is capable of imaging only one slice at a time. This is a serious disadvantage for two reasons: (1) the time for complete examination of a structure is prolonged and (2) different sections of an organ are imaged at different times. Earlier

work was carried out at MIR to develop a strategy for addressing these limitations by increasing the detection efficiency of the PETT-III system through the use of a detector capable of imaging four slices simultaneously. Such parallel imaging capability would be made possible by the use of a long cylindrical detector effectively subdivided into four sections by a combination of suitable collimation and fast electronic positioning circuitry.

Current efforts are directed toward system implementation. The positioning circuits and the electronics of the new PETT-IV system are briefly described in B-3. A pictorial drawing is shown in Figure 1. Pilot studies and prototype evaluation of the four-section detection system have shown that this approach is comparable in performance to that attainable with separate detectors for each section. The PETT-IV system is presently under construction, and is expected to be operational by November 1976. It will eventually be placed in the Barnes Hospital Cardiac Intensive Care Unit for visualization and study of myocardial infarcts.

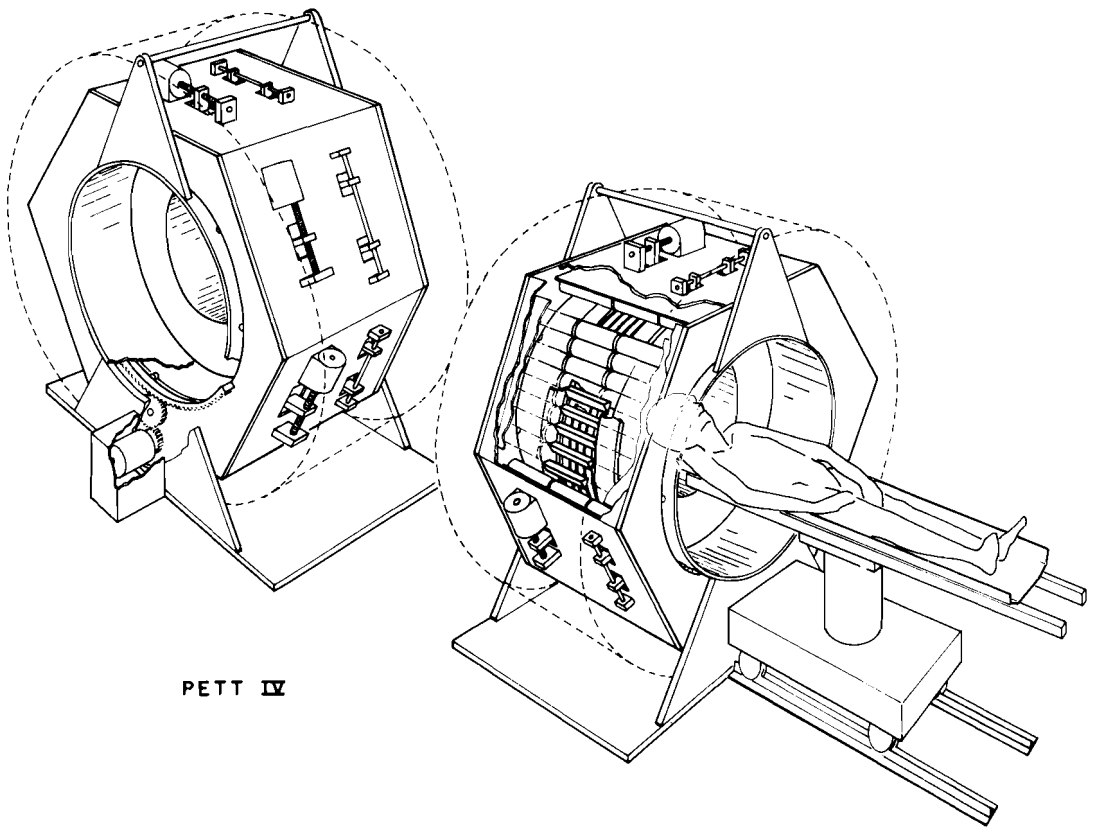

Figure 1. Pictorial representation of the PETT-IV system.

B-3. PETT-IV Electronics and Interface

Personnel: N. A. Mullani, BCL
C. M. Currie, B.S., Radiology
J. R. Martin, Radiology
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851
Washington University

The photon detectors in the PETT-IV system use a one-dimensional electronic gamma-ray positioning circuit similar in concept to that used in the Anger scintillation camera. A positron-electron annihilation photon impinging on the NaI(Tl) detector crystal transfers some of its energy to the crystal, which in turn releases this energy in the form of visible-light photons. This light is detected by two photomultiplier tubes, one at each end of the detector, and is converted to an electrical pulse whose size is related to the position of the impinging annihilation photon and to the energy it deposits in the crystal. The pulses generated by the two photomultiplier tubes are first amplified and then summed to give the energy deposited. A fast positioning circuit takes the ratio of the two signals and digitizes it to a two-bit binary number.

If a coincidence event is detected between two sets of opposing detector banks, and if in addition the digitized positions correspond, the event is accepted as a positron-electron annihilation, and the data are stored in buffer latches until interrogated by the counting circuit. The counting circuit consists of a 16-bit up counter used as an adder, and a 256-word bipolar memory for each set of opposing banks. Data are transferred from this memory to the computer (PR 11, B-6) at the end of a preset time interval controlled by a real-time clock. A block diagram of the circuitry appears in Figure 1. The PETT-IV system will be interfaced to an Interdata, Inc. 7/32 computer running under OS 32/MT software.

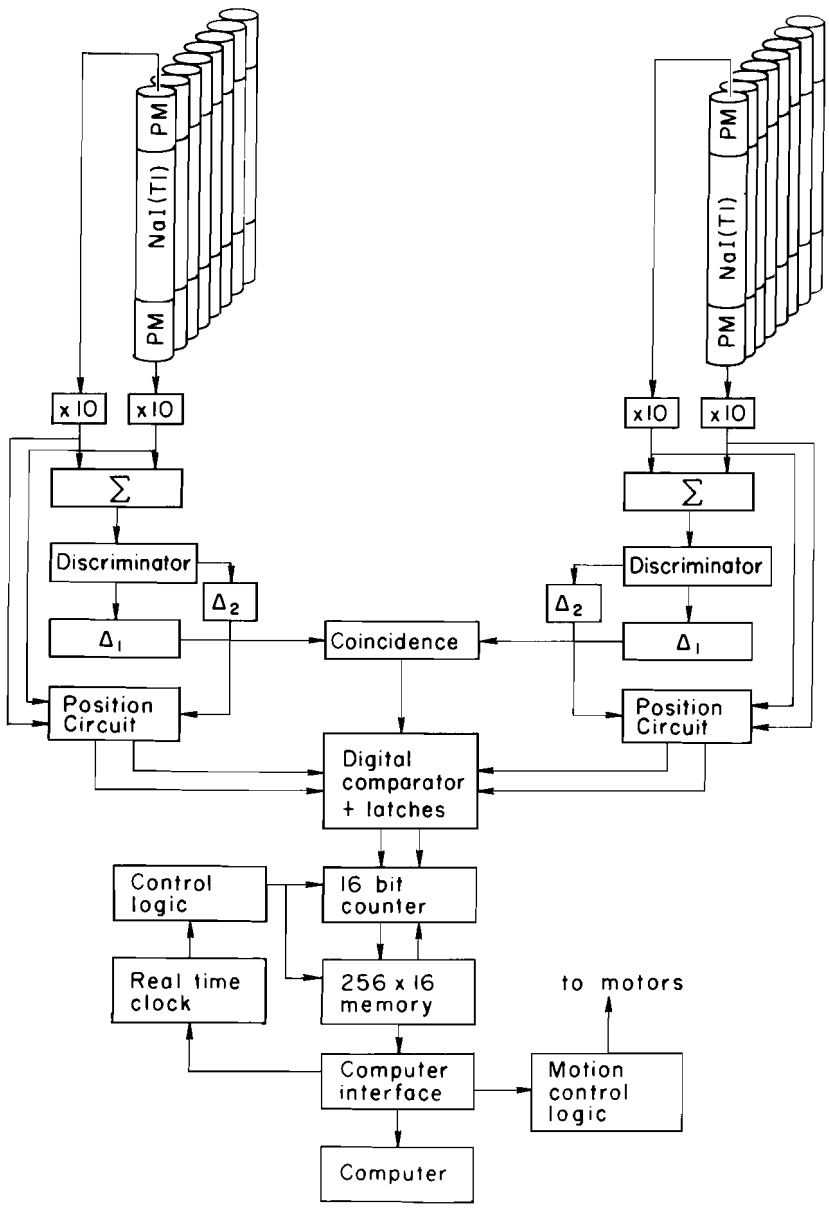

Figure 1. Block diagram of PETT-IV system electronics and interface.

B-4. Mathematical Models for In-Vivo Measurement of Regional Cerebral Hemodynamics and Metabolism Using Positron-Emission Tomography

Personnel: K. B. Larson, BCL
M. R. Bedford, B.S., Electrical Engineering and School of Medicine
J. O. Eichling, Ph.D., Radiology
M. E. Raichle, M.D., Radiology and Neurology

Support: RR 00396
GM 02016
HL 13851
NS 06833
NS 11059

Positron-emission tomography (PR 10, B-13; PR 11, B-7; PR 11, B-8; B-1, B-2, B-3) is a novel imaging technique with possible applications for in-vivo studies of dynamic processes on a regional basis. The spatial resolution the new technique can achieve is superior to any attained to date with conventional multiprobe and nuclear-medicine photon-imaging methods, and its ability to portray three-dimensional distributions of biologically appropriate radiopharmaceuticals sets it apart from X-ray-transmission tomography as a potential tool for the study of regional hemodynamics and metabolism. However, in order to obtain images having sufficient detail, positron-emission tomography in its present state of development requires data-collection periods whose durations are longer than the times characteristic of certain biological events of interest. This aspect of the new technique precludes interpretation of the data on the basis of mathematical models[1-4] developed for conventional external-detection methods whose temporal resolution is generally adequate for following such relatively rapid events.

The imminent completion of a new positron-emission tomographic scanner (B-2, B-3), capable of obtaining simultaneous multiple images in the brain, has motivated examination of the possibility of devising new mathematical models that could circumvent the difficulties posed by presently attainable imaging rates. These models would be used to extract dynamic information from the static-image data in conjunction, if necessary, with fast sampling of blood radioactivity.

Two mathematical models have been devised for this objective. Each leads to prescription of a distinct experimental protocol for the new scanner. For each procedure, equations deduced from the premises on which the models are based show how the tomographic data, together with arterial-blood specific activities, can be interpreted in order to obtain regional estimates of desired hemodynamic and metabolic parameters.

The first of these procedures is based on establishing dynamic steady-state distributions of labeled compounds in the tissues. The labeled compounds are infused intravenously at exponentially increasing rates so chosen as to compensate exactly for physical decay of the radiotracer. By this means, a true dynamic steady state is achieved. The

positron-emission tomograph then records the resulting stationary distribution of radiotracer in brain tissues. From these data, together with the specific activity in arterial blood at steady state, the model equations permit values to be derived for regional cerebral blood flow (rCBF) and regional cerebral metabolic rate of oxygen ($rCMRO_2$). For measurement of rCBF, the radiopharmaceutical infused is ^{15}O-labeled water, while for $rCMRO_2$, it is ^{15}O-labeled oxyhemoglobin carried in the subject's own red blood cells.

The second procedure proposed for the new scanner has the potentiality of allowing in-vivo measurements of regional cerebral metabolic rate of glucose (rCMRGlu) to be made. This method is a natural outgrowth of previous efforts (PR 7, C-24; PR 8, C-4; PR 9, C-1, C-3, C-6; PR 10, B-12) that culminated in a successful model[4] for the interpretation of data from experiments employing intravenous injections of ^{11}C-labeled glucose to study glucose metabolism in brain on a global basis.[5]

For measurement of rCMRGlu in brain, the proposed modifications to the global method are two: (1) substitution of the new scanner for the single scintillation probe used previously to monitor radioactivity in the head, and (2) substitution of a glucose analog, 2- or 3-deoxyglucose, labeled with the positron emitter, fluorine-18, employed as the tracer. As before, administration of tracer is by intravenous injection. The positron-emission tomograms will allow total tracer uptake to be measured regionally, while the new radiotracer will allow more complete adherence to a key assumption of the global model. This assumption is that there be no egress of labeled intracellular metabolites of glucose during the course of the experiment. That the metabolites of the glucose analog have the desired property of remaining within the cells of brain tissue has been well established.[6]

The logical structure of the new regional mathematical model is identical with that of the global model described previously.[4,5] Thus, the new model is based on the assumption that all glucose pools are compartments, i.e., that concentration gradients of glucose are negligible within a spatial-resolution volume element. Use of the model is based on the following equation derived from the basic assumptions:

$$\tilde{\Phi} = \lim_{t \to \infty} \frac{q(t)/\Delta V}{\int_0^t a(\tau)d\tau}$$

Since this expression is free of undetermined parameters, it can be used simply and directly to compute the regional metabolic rates. Here, ΔV is the geometrical volume of the spatial resolution cell containing an amount $q(\infty)$ of radiotracer. This amount is the molar mass of regionally sequestered ^{18}F, corrected for radioactive decay, imaged by the scanner after sufficient time to allow washout of tracer in extracellular fluid and clearance from blood. The quantity $\tilde{\Phi}$ represents the desired parameter, rCMRGlu, provided

all kinetic constants in the model are the same for tracer and tracee. The function a(t) is the time course of the decay-corrected specific activity of labeled glucose analog in arterial blood, monitored continuously at a peripheral site.

We plan to validate our proposed methods of measuring rCBF, $rCMRO_2$, and rCMRGlu in a series of animal experiments. Volume-averaged values of the parameters obtained with the new mathematical models will be compared against values obtained in the same subjects by standard global techniques. Parameter-estimation algorithms based on the new models can readily be implemented on the Radiation Sciences Division computer system (PR 9, C-15; PR 10, B-9; PR 11, B-6).

(1) K. L. Zierler, "Equations for Measuring Blood Flow by External Monitoring of Radioisotopes," Circulation Research, vol. 16, pp. 309-321, 1965.

(2) K. B. Larson and D. L. Snyder, "Measurement of Relative Blood Flow, Transit-Time Distributions, and Transport-Model Parameters by Residue Detection when Radiotracer Recirculates," Journal of Theoretical Biology, vol. 37, pp. 503-529, 1972.

(3) G. W. Roberts, K. B. Larson, and E. E. Spaeth, "The Interpretation of Mean Transit-Time Measurements for Multiphase Tissue Systems," Journal of Theoretical Biology, vol. 39, pp. 447-475, 1973.

(4) K. B. Larson, M. E. Raichle, M. E. Phelps, R. L. Grubb, Jr., M. J. Welch, and M. M. Ter-Pogossian, "A Mathematical Model for-In Vivo Measurement of Metabolic Rates Using Externally-Monitored Radiotracers," in Information Processing in Scintigraphy, C. E. Metz, S. M. Pizer, and G. L. Brownell, eds., U. S. Energy Research and Development Administration Publication No. CONF-780687, National Technical Information Service, Springfield, Virginia, 1975, pp. 28-61.

(5) 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.

(6) M. Reivich, N. Sano, and L. Sokoloff, "Development of an Autoradiographic Method for the Determination of Regional Glucose Consumption," in Proceedings of the International Cerebral Blood-Flow Symposium, London, 1970, pp. 397-400.

B-5. Blood-Brain Barrier Permeability Studies Employing ^{15}O-labeled Water and ^{11}C-labeled Alcohols

Personnel: M. E. Raichle, M.D., Radiology and Neurology
M. R. Bedford, B.S., Electrical Engineering and School of Medicine
C. M. Currie, B.S., Radiology
J. O. Eichling, Ph.D., Radiology
R. L. Grubb, Jr., M.D., Neurosurgery
B. K. Hartman, M.D., Psychiatry
C. S. Higgins, A.B., Radiology
K. B. Larson, BCL
N. A. Mullani, BCL
M. H. Selikson, B.S., Radiology
M. G. Straatmann, M.S., Radiology
M. M. Ter-Pogossian, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

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

Our previously reported studies (PR 10, B-7; PR 11, B-15) of the factors influencing the permeability of the rhesus-monkey blood-brain barrier to water and non-electrolytes have continued. Experimentally, these studies are based on external monitoring of the passage of a bolus of radioactively labeled test substance through the brain after injection into the internal carotid artery. From the resulting data, both blood flow and permeability-surface-area product are computed on the basis of appropriate mathematical models of tracer transport.[1-5]

One of the objectives of our studies is to test whether blood-brain barrier permeability to water is preferentially modified by procedures thought to affect the "tight junctions" between capillary endothelial cells of brain. To this end, we measured the fractional extractions of ^{15}O-labeled water before and after infusions of hyperosmotic solutions into the carotid artery. Since intracarotid perfusion of 3 to 5 osmolar urea for 25 to 30 seconds has been shown reversibly to open the blood-brain barrier for periods of less than 30 minutes,[6] we thought to test our method by making measurements before and after a similar treatment. Additionally, because of the complex action of urea on vascular smooth muscle, producing both inhibition and excitation[7], we wished to compare its effect on permeability with those of another agent also known to produce transient permeability changes, viz., sucrose[6], whose effect on vascular smooth muscle is only one of relaxation.[7] The effects of sucrose, as well as of mannitol, which was also administered, were the expected ones of increasing both permeability and blood flow over control levels. In the case of urea, permeability was also seen to increase; predictably, however, blood flow was depressed.

Another objective of our studies is the elucidation of the role of the peripheral sympathetic nervous system in the modulation of flow and of permeability. The collective experience of other workers, recently summarized by Edvinsson[8], would suggest that a slight reduction in flow would be observed on direct electrical stimulation of the cervical sympathetic chain in the neck. We would not, however, expect an increase in brain-water permeability because these nerves are associated only with resistance vessels. Surprisingly, however, our results showed an increase in permeability-surface-area product, as well as the expected modest reduction in blood flow. We interpret these results to indicate, as suggested by others[9,10], a greater involvement than heretofore thought of vessels other than capillaries in the mechanisms of blood-brain water and solute exchange.

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B-6. In-Vivo Measurement of Blood-Brain Transport of Glucose Employing ^{11}C-Glucose

Personnel: M. R. Bedford, B.S., Electrical Engineering and School of Medicine
K. B. Larson, BCL
M. E. Raichle, M.D., Radiology and Neurology

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

The experimental study of glucose transport across the blood-brain barrier (BBB) of the rhesus monkey, made possible by the mathematical modeling efforts described previously (PR 11, B-2), has been completed. The tracer method developed for the estimation of the fraction, E, of ^{11}C-glucose extracted by the brain during a single capillary transit employs two injections: an arterial injection into the internal carotid artery and a second venous injection into the superior vena cava. The method also makes use of a vascular reference tracer, C^{15}O-hemoglobin, to estimate parameters of the vascular transit-time distribution using the model developed by Huang.(1) Analysis of the data was based on a transport model consisting of a Krogh capillary-tissue cylinder to represent the brain microcirculation.

The unidirectional rate of glucose transport, ϕ_+, was calculated from the relation, $\phi_+ = EC_aF$. Here C_a is the arterial blood-glucose concentration and F is the relative cerebral blood flow. The latter was measured from the clearance rate of ^{15}O-labeled water following an intracarotid injection. The observed variation of ϕ_+ over an arterial blood-glucose concentration range of 62 to 582 mg/100 ml exhibited the saturation characteristic of facilitated diffusion. Fitting the results from 14 trials to the Michaelis-Menten equation yields an apparent K_m of 8.20 ± 0.74 mm and a V_{max} of 1.34 ± 0.06 μg min^{-1}g^{-1}, which is consistent with values reported previously in the literature.(2) The model also predicted a ratio of the forward-to-reverse glucose flux across the BBB of 1.52, a brain-to-blood glucose-concentration ratio across the BBB of 0.733, and a relative free-glucose space of 19.8%. All the previous values are in agreement with values estimated by Raichle et al(3) (PR 9, C-3).

In addition, the analysis of the ^{11}C-glucose data on the basis of the model permitted evaluation of the accuracy of a graphical method for estimating the extraction fraction. The graphical method involves a simple subtraction of the normalized venous response curve from the arterial response curve to account for recirculating tracer activity in the arterial response. The extraction fraction is then obtained by exponential extrapolation from 30 sec back to the perfusion peak, in a method analogous to that currently used for ^{15}O-water and ^{11}C-alcohols(4) (PR 11, B-15; B-2). A significant correlation was found between the extraction fraction computed using this graphical technique and that using the numerical analysis based

on the model. The resulting regression equation is E(graph) = 0.946 E(model) + 0.0138; ρ = 0.992. The graphical method for computing the extraction fraction thus offers a quick and accurate technique that is particularly attractive for use in the laboratory environment. It seems likely that the graphical technique can be used (after initial verification in each case through use of the model) for the study of other low-extraction compounds that can be labeled with positron-emitting radionuclides.

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B-7. In-Vivo Measurement of DOPA Uptake Rate in Brain

Personnel: E. S. Garnett, M.D., McMaster University
G. Firnau, Ph.D., McMaster University
K. B. Larson, BCL

Support: RR 00396
McMaster University
Washington University

The amino acid 3,4-dihydroxy-phenylalanine (DOPA), suitably labeled for external detection, has been suggested as a specific brain-scanning agent.(1) DOPA is known to enter the endothelial cells and pericytes of healthy, mature capillaries in brain. Once it has entered the endothelial cells it is decarboxylated to dopamine. The resulting local concentration of dopamine can be increased through administration of an amine-oxidase inhibitor. Since damaged or immature capillaries do not exhibit this behavior(2), it should be possible to delineate areas of brain with normal

capillaries from areas of brain replaced by neoplastic tissue, as well as infarcted tissue, by the use of suitably labeled DOPA.

To examine the suitability of DOPA as a brain-scanning agent, DOPA labeled[1] with the positron-emitter ^{18}F has been injected into the circulation of live baboons and the uptake of radioactivity in brain followed with a scintillation detector. Data obtained after specific pharmacological interventions suggest that appreciable fractions of DOPA may pass from blood directly through the blood-brain barrier to undergo decarboxylation within the synaptic neurons. This phenomenon may alter the interpretation of data obtained with labeled DOPA as a proposed brain scanning agent. As an aid in understanding the various uptake mechanisms of DOPA in brain, application of a mathematical model to interpret the data suggests itself. Modifications of the previously described[3,4] (PR 7, C-24; PR 8, C-4; PR 9, C-1, C-3, C-6; PR 10, B-12) model used in the study of brain-glucose transport and metabolism are being examined for their possible utility in this objective. Our initial efforts in this direction have been in the construction of simulated data on the basis of the equations implied by the modified models. As further data are accumulated, judgments can be made concerning the fidelity of the simulations, and hence, the plausibility of the underlying models.

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C. Monitoring the Critically Ill

C-1. SICU: Overview and Evaluation

Personnel: L. J. Thomas, Jr., BCL
A. L. Bodicky, BCL
R. E. Clark, M.D., Cardiothoracic Surgery
R. W. Hagen, BCL
J. A. Johnson, BCL
W. R. Roloff, BCL
T. B. Schuessler, BCL

Support: RR 00396
Barnes Hospital
Washington University

The cardiothoracic surgical intensive care unit (SICU) system (PR 11, C-1 through C-5) has been in continuous operation for 39 months (3.25 years) as of June 1976. During the past year, activities concerning the existing system have been limited largely to maintenance and evaluation. When the patient-care facility was expanded late last year, plans were made to increase the computer-system capacity to eight beds by replacing the PC-1200 with a Texas Instruments TI 980B minicomputer. It was announced shortly thereafter, however, that the care unit would be expanded further and moved to a new hospital wing to be completed in 1979-80. Since the revised system would then be relatively short-lived, it was judged improvident to invest in it the necessary effort to translate the software and redesign computer interfaces. A more extensive redesign effort to meet the needs of the new facility was rejected for two reasons. First, eventual maintenance of a large custom-designed system would be an inappropriate and burdensome BCL activity; second, commercial systems are rapidly becoming more sophisticated and flexible so that they are likely to satisfy the projected clinical-care and research needs of the new unit by the target date. The current strategy is to utilize the current four-bed unit as an acute-care area and the contiguous three-bed annex for graduate care with more conventional monitoring devices but augmented with a mobile cart (C-3). With a view toward bringing to others our own experience and lessons learned, deliberations with commercial firms have been initiated to explore bases for collaboration in the design and implementation of an advanced computer-based patient-monitoring system which would integrate pre-operative, intra-operative, and post-operative care (C-2).

Since the current system will continue to be used without major modification, increased attention has been given to more thorough and up-to-date documentation. All logic drawings and wiring lists have been thoroughly compared and corrected to existing hardware and a detailed System-Hardware Description Manual is in preparation. A Technician's Manual has been completed and the User's Manual has been revised. A line-by-line check of current software against existing documentation has been initiated in preparation for a more formal and complete description as a BCL monograph. The

SICU-system software has been essentially stable for the past 18 months except for minor retouching and those changes necessary to accomodate the satellite cart system (C-3).

Training activities have continued (PR 11, C-5) as necessary to meet the rapid turnover of nursing personnel and the medical and biomedical engineering students who serve as part-time monitoring technicians. In addition, a replacement biomedical technician has been trained to take over responsibility for total system maintenance and trouble shooting as well as the further training of users and other support personnel.

Work has continued over the past year to improve the performance characteristics of the fluid patient-transducer interface. Attention has been focused on mechanical reliability and frequency response of the stopcocks, connectors and tubing. A system which minimizes accidental disconnect, decreases the trapping of air bubbles, and provides a suitably high resonant frequency (21 Hz; +3 db at 10 Hz) has been developed, thoroughly tested and described in detail as an internal document. Packaging and sterilization are done locally since no comparably suitable commercially available system could be found.

We continue to gather utilization data for the four-bed SICU. Figures for the past four years are summarized below:

5 months beginning:	Occupancy as % of capacity (24-hr. day; 7-day week)	Average length of stay (days)
Jan. 1973	76	3.2
Jan. 1974	77	2.6
Jan. 1975	83	2.3
Jan. 1976	82	2.7

Note that occupancy has leveled off and the average length of stay has risen this year after successive declines previously. The reason for the increased length of stay probably follows from use of the three-bed annex which is new this year. Patients returned to the care unit from the ward usually require short supplemental care and go to the annex. Also, patients with uncomplicated courses and/or less major surgical procedures will be placed in the annex if the main unit is fully occupied with more critically ill patients. There is thus a bias toward longer stays in the main unit even though many patients are subsequently moved to the annex for graduate care. The result is that care is probably better since fewer patients are moved from the SICU prematurely; and utilization of the computer-based system is better dedicated to care of the most critically ill.

Careful documentation of every failure of the computer-based system continues to be made for the purpose of an on-going engineering evaluation. As reported previously,[1] the mean time between unintentional interruptions of patient monitoring showed a progressive increase during the first 18 months

and exceeded 2100 hours in the third six month period. This very favorable record was sustained for another six months but then showed rapid deterioration in the first half of the second year. It became promptly apparent that the use in sockets of integrated circuit (IC) packages with untinned silver-plated leads had been a mistake. As had been predicted by one of our more astute engineers, after about two years the pins develop sufficient corrosion to increase contact impedance. This was established by confirming the malfunction of the ICs in situ, cleaning the pins and then retesting to establish the integrity of the IC itself. Now that most of the ICs in question have been replaced by those of another manufacturer, failure statistics have recently returned toward the more favorable level.

The highly structured programming done for this system has paid substantial dividends. Multiple changes have been made with minimal effort and in over three years of continuous use there has been only one failure due to a software error. Even more important, however, is the relative ease with which even transient hardware failures have been pinpointed by analysis of core dumps taken at the time of monitoring failures. Careful records and subsequent review of previous core dumps have been important since the precise causes of intermittent defects have often required several failure episodes before the "tracks" left in memory became sufficiently incriminating. The key here is that because the programs are highly structured, the tracks are often very clear and definitive. In 39 months, a total of 54 monitoring interruptions were observed to result from 25 different causes of which four were undocumented, unresolved and presumed to be different from known causes for sake of discussion. Eight failure causes were obvious hardware (e.g. power supply) failures not requiring software analysis, twelve were identifiable only by software analysis (all were intermittent hardware failures except the programming error), and one has not yet been resolved even though full documentation was taken. The core-dump analysis can be tedious at times but its importance to keeping the system reliable and highly regarded by the users cannot be overemphasized.

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C-2. West Pavilion Planning

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

Support: RR 00396
Barnes Hospital
Washington University

BCL is collaborating with the Department of Surgery in planning a new Cardiothoracic Surgical Facility to be located in the West Pavilion of Barnes Hospital. The anticipated completion date for this facility is late 1979. BCL's efforts to date have focused on three topics:

1. Physical configuration of the facility.

2. Information collection and distribution needs for the facility.

3. Commercially available patient monitoring systems in 1979.

Patient utilization data suggest that the facility should contain a surgical suite (with three open-heart rooms, a pacemaker room and a bronchoscopy room), a nursing division with twenty Pre-Op beds, twelve Intensive Care Unit (ICU) beds, and twenty Post-Intensive-Care beds. The ICU floor plan features distributed information stations with centrally located medicine preparation and clean utility areas. Experience and reviews of applicable literature have been important factors in planning and will continue to be so as the final physical configuration evolves.

The collection and distribution of physiologic data are significant parts of the patient information used in a Cardiothoracic Surgical Facility. BCL has gained considerable experience in handling this information via the existing Surgical Intensive Care Unit (SICU) monitoring system (C-1). A feature of the existing SICU system that has been a very useful tool is the capability for a nurse to provide routine care to one patient while observing the real-time physiologic data from any other patient in the unit. In the new facility, this capability will be extended to include the Surgical Suite. Thus, real-time and trended physiologic data for any patient in the ICU can be reviewed in the Surgical Suite. When a patient enters the Cardiothoracic Surgical Facility he will be introduced into the system and all patient information will remain accessible until that patient is discharged from the facility.

In order to anticipate the characteristics of systems that will be in production in 1979, BCL solicited information from six leading suppliers of patient monitoring systems. The series of meetings that followed leads

to the conclusion that commercial patient monitoring systems in production in 1979 will meet the needs of the Cardiothoracic Surgical Facility. Certain manufacturers have indicated an interest in collaboration with BCL in the design of such a system. BCL is currently in the process of developing a set of system specifications to be submitted to the manufacturers for their responses.

C-3. Clinical Physiologic Research Cart (CPRC)

Personnel: J. A. Johnson, BCL
R. W. Hagen, BCL
R. Moroni, III, BCL
L. J. Thomas, Jr., BCL
B. Zvolanek, BCL

Support: RR 00396

During the past year, the Clinical Physiological Research Cart (CPRC) has found use in the development of a pulsatile perfusion system (C-9) while work has continued to render it suitable for use in the clinical environment. A critical review of the CPRC capabilities as of last fall revealed several hardware deficiencies and software needs which would need attention in order to guarantee enthusiastic clinical acceptance.

Hardware refinements included redesign of the chart-recorder driving circuit, the addition of a switch and LED indicator for manual hardcopy-unit operation, and the installation of an additional power supply and voltage regulator. Also, the TI 980 I/O bus and CPRC cabling were rearranged to render the unit more fit for the clinical environment.

Work on software for the CPRC has progressed in three areas: 1) sampling, analysis, and display routines for the TI 980, 2) programs for the storage, retrieval, and transfer of these programs from the PC-1200 disc, and 3) additions to the SICU Monitoring System software to handle the video display and disc storage needs of the cart system.

The cart continues to sample ECG and arterial pressure data through the analog channels, processes them using QRS detection and arterial pressure algorithms translated from the SICU system and with the help of the PC, displays four parameter values and the ECG and arterial pressure waveforms. It now also has the capability to preserve and display the ECG and arterial pressure information. Two hour trends of heart rate, systolic, diastolic, and mean arterial pressure may be obtained on the video screen starting 2, 3, or 4 hours previous to the request. A two-channel strip-chart recorder gives hard copy of the two analog waveforms. In addition, a question and answer routine using the video screen has been written to provide user

interaction with system functions. The clinical personnel may enter patient information to be displayed on the video screen; they may alter the criteria for QRS detection, change the conditions which cause warning signals to be displayed, and control the speed of the strip chart recorder. Finally, a group of programs has been completed to allow the various I/O interfaces to be tested and calibrated while the other functions continue. Work has begun on a scheme to store data generated by the cart system on the PC disc.

All of the programs for the TI 980 were written with the help of TIPCI, the PC FORTRAN program which allows programs for the TI to be written and edited using the facilities of the PC (PR 11, C-2). However, because TIPCI is a FORTRAN program, the required execution time makes it unsuitable for communications between the TI and PC in a real-time interrupt-controlled environment. Furthermore, the loader provided with the TI operating system is quite large and requires that the programs it is loading be preceded and followed by a number of control words. Therefore, efforts were made to simplify and speed up the loading of programs into the cart. Programs were written to properly format the cart system for incorporation into the SICU Monitoring System. These include a TI program to format the application programs (previously loaded by TIPCI) into the proper format for storage on the PC disc, a PC program to read these formatted words and store them on disc, and a loader capable of being loaded by the TI bootstrap loader.

Changes in the SICU Monitoring System have been made to allow these newly formatted cart programs to be loaded into and executed from the TI 980. An option has been added to the SICU question and answer routine to call in a program which will send to the TI the loader followed by the cart system. A bootstrap loader read from the TI read-only memory, reads the loader and transfers control to it. The loader then reads the cart system and when all the programs have been loaded, control is passed to a driver program and the cart system begins its sampling, evaluation and display activities. However, the TI and the PC remain in communication with newly added programs in the SICU system reading 240 words per second sent from the TI. These words are coded so that the program in the SICU system knows to display a graphic waveform or an alphanumeric character or to save the word in a buffer for later storage on disc. Thus, all cart activities can be handled during execution of the SICU Monitoring System.

Programming in support of CPRC application to the pulsatile perfusion system is summarized in C-9.

C-4. Measurement of Cardiac Output by Dye-Dilution Based on a Model Accounting for Tracer Recirculation

Personnel: J. C. Nathanson, BCL
G. H. Brandenburger, BCL
R. E. Clark, M.D., Cardiothoracic Surgery
R. W. Hagen, BCL
B. R. Hieb, M.D., Jewish Hospital
S. Lang, Ph.D., Physiology and Biophysics
K. B. Larson, BCL
D. L. Snyder, BCL

Support: RR 00396
HL 13803
Washington University

The interpretation of indicator-dilution data obtained in the measurement of cardiac output is generally based on mathematical models [1,2] that ignore the physiological fact of tracer recirculation. Consequently, an important limitation of the methods depending on these models is that they can be used successfully only when the major portion of the indicator curve is obtainable prior to the first reappearance of indicator following its injection into the blood. We have developed a mathematical model of tracer transport in the blood that specifically incorporates the effects of recirculation, and by accounting rigorously for these effects, can form the basis of a method for measuring cardiac output accurately in clinical and laboratory situations that invalidate current indicator-dilution technique.

The expedient commonly employed to circumvent the effects of tracer recirculation in current methods of measuring cardiac output entails fitting some portion of the indicator curve to an arbitrary mathematical function which is then extrapolated forward in time. In this way, it is hoped that the primary curve that would have been observed in the absence of recirculation or its equivalent, can be recovered for use with the conventional Henriques-Stewart [1,2] no-circulation model. However, long experience has shown that when recirculating tracer appears relatively early after injection, the primary response curve cannot be satisfactorily recovered in so simple a fashion.[3]

We have employed a more fundamental analysis that consists in applying elementary ideas from the theory of linear systems to the observed stimulus-response behavior of tracer in the circulation.[4-9] In this approach, the information sought is the density, h(t), of tracer transit times through a vasculature of interest, or more commonly, the mean-transit time, $\bar{t}$, i.e., the first moment of this density. In turn, the mean-transit time allows relative blood flow to be evaluated as $F/V = 1/\bar{t}$ by appeal to the central-volume principal.[4,5,10] Here, V is the vascular volume through which blood flow is F. When tracer recirculates, the stimulus-response theory allows the density to be obtained provided multiple tracer injections or multiple sampling sites are employed.[6,9] We have derived equations that

allow relative blood flow to be obtained directly by simple numerical integrations of tracer concentration data when tracer recirculation invalidates the conventional methods (PR 11, B-3). As applied to the measurement of cardiac output, our method uses two injections of tracer and records three indicator-dilution curves. Our equations show how to employ these curves to compute mean-transit times for the pulmonary and systemic circulations. The sum of the two transit times yields V/F, where F is the cardiac output and V is the total blood volume. The latter is obtainable from the dose-normalized steady-state tracer concentration, thus allowing evaluation of the cardiac output, F.

Our equations do not depend for their validity on any model of the microvasculature. The calculations they imply need not rely on curve-fitting of the data, nor do they call for troublesome numerical solution of integral equations. Instead, they require only simple numerical integrations of the observed concentration histories. In addition to cardiac output, our method can yield absolute lung and systemic blood volumes separately if these are desired.

To validate our method and to ascertain the practical requirements for reliable results, as well as to assess the associated experimental variability, we have planned a series of measurements in dogs. These measurements will be performed concurrently in the same preparations used for evaluation of the technique under development for measuring cardiac output by thermal dilution (PR 11, C-7; C-7). In addition to intercomparison of results obtained by the two methods, an additional control will be provided through use of a calibrated electromagnetic flowmeter during each procedure.

The simultaneous dye curves will be recorded using an Ampex FR 1300 frequency-modulation tape recorder. Off-line, the analog data will be played back and digitized using a PC/12 computer. The multichannel dye-curve acquisition section of the cardiac catheterization laboratory computer system (E-1) will be used for the digitization. PC/12 FORTRAN software is being written to implement the data-processing algorithms based on the model equations and to output the computed values of cardiac output.

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C-5. ECG Telemetry with Arrhythmia Detection

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

Support: RR 00396
Barnes Hospital
Washington University

An ECG Telemetry System which includes arrhythmia detection has been recommended for installation in the Cardiothoracic Surgical Service of Barnes Hospital. This recommendation was submitted by BCL to the Department of Surgery in response to their request concerning the monitoring of post-surgical intensive care and pacemaker patients. The application of a telemetry system in contrast to a hardwired system offers obvious advantages for this existing twenty-seven bed service where a limited number of possibly ambulatory patients require centralized ECG monitoring. In addition, coupling this telemetry system to an arrhythmia detection system can enhance patient care in this situation where arrhythmia problems are frequent and patient-to-nurse ratios are high.

A commercially available telemetry system has been ordered by Barnes Hospital and the installation of this system is scheduled for July 1976. A locally designed LSI-11 Argus arrhythmia detection system (A-18). is scheduled to be interfaced to the telemetry system in September 1976.

C-6. Evaluation of Pediatric Monitoring Instrumentation

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

Support: RR 00396
HS 00074

The design and execution of a comprehensive evaluation protocol for pediatric monitors were previously described (PR 11, C-12). Identical procedures utilizing the same laboratory test signals and the same patient waveforms were applied to all three monitors in the study: the Abbott CA-8 with heart-rate and apnea alarms, the KDC IM-300 AR, and the Mennen-Greatbatch 402/A. Details of the protocol were also reported previously. More recently results of both the laboratory and the clinical tests have been analyzed.

Ability to detect QRS complexes in the ECG and the inspiration waveform in the respiration signal, along with the accuracy of the rate

meters, were carefully studied. To complement the laboratory test signals a database consisting of ECGs and respiration signals from 10 pediatric patients was established. Each record was 8.75 minutes long. A total of 12,425 QRS complexes and 3375 breaths were contained in the database.

Both detection and false-positive rates were expressed as a percentage of the number of QRS complexes or inspiration waveforms for the ECG and respiration signals, respectively. The results are summarized below:

	ECG		Respiration	
	% det.	% false pos.	% det.	% false pos.
Abbott	99.5	0.6	-	-
KDC	99.6	0.0	87.1	0.9
M-G	87.2	0.4	85.4	61.1

Accuracy of the rate meters was determined at 30, 60, 90, 120, 150, 180 and 210 beats/minute for heart rate and 15, 30 and 60 breaths/minute for respiration rate. Accuracy was also studied using the clinical waveforms with results consistent with the laboratory tests. Clearly, difficulty in the detection of QRS complexes and breaths was the factor which limited monitor performance and thereby the clinical value of measurements or alarms dependent upon the detection process.

C-7. Cardiac Output by Thermodilution

Personnel: R. W. Hagen, BCL
R. J. Arnzen, BCL
G. A. Burger, BCL
R. E. Clark, M.D., Cardiothoracic Surgery
K. B. Larson, BCL
L. J. Thomas, Jr., BCL
B. Zvolanek, BCL

Support: RR 00396
HL 13803
Washington University

Theoretical and experimental aspects of measuring cardiac output by thermodilution have been addressed during the past year. These investigations were motivated by the need to provide an accurate, reliable and convenient system for measuring cardiac output. Experimental procedures were improved through the use of a pneumatically operated syringe for bolus delivery of tracer material. The previously developed instrumentation has

been functioning reliably (PR 11, C-7). The digital recording system (PR 11, H-6) has been a useful aid in the collection of digitized temperature and flow data.

Experimental results show substantial differences between computed cardiac output and the electromagnetic flowmeter output. Thus an independent development of the equation relating computed average flow and measured temperature difference was formulated. The considerations on which our approach is based suggest that the physiological response to the addition of a volume of tracer must be better understood before a meaningful computation of average flow can be made. One view is that the addition of tracer can add to the overall flow through the vessel. In the other view, the addition of tracer material would have no effect on the net flow. Therefore, before processing the temperature data, it is essential to know whether the flow to be calculated is blood plus tracer flow or blood flow alone. In order to resolve this question, additional animal experiments will be performed. During each experimental measurement the respirator will be stopped so that the respiratory artifact can be eliminated from the data. The cardiac outputs will be calculated using the following equations we have derived on the basis of thermodynamic considerations.

A) for blood alone:

$$\dot{Q} = \frac{K\,V_i}{\int_{t=o}^{\infty} \frac{T_b - T_m(t)}{T_m(t) - T_i}\,dt}$$

B) for blood plus tracer:

$$\dot{Q} = \frac{V_i}{\int_{t=o}^{\infty} \frac{T_b - T_m(t)}{T_b + (K-1)T_m(t) - KT_i}\,dt}$$

Where: $K = \frac{\rho_i\, S_i}{\rho_b\, S_b}$,

ρ = density,
s = specific heat,
$\dot{Q}$ = flow,
V = volume,
T = temperature,
t = time,
i = indicator,
b = blood, and
m = mixture of i and b.

The results of the calculations implied by these equations will be compared with the cardiac output measured by the electromagnetic flow system to determine which assumption most accurately reflects the actual situation.

The equation that has been universally employed to compute cardiac output from thermodilution data is

$$\text{C)} \qquad \dot{Q} = \frac{V_i K(T_b - T_i)}{\int_{t=o}^{\infty} \left[T_b - T_m(t)\right] dt} .$$

This equation is derived by using conservation of thermal energy in the familiar dynamic flow model of indicator dilution theory, which, in the case of a material tracer, leads to the Stewart-Hamilton equation. Equation C is based on the assumptions that the thermal properties of blood and of blood-injectate mixture are the same and that $\dot{Q}$ represents total flow of blood and injectate. Note that equation B reduces to equation C when K = 1. If K were unity, then the assumption on which equation C is based would be justified. However, the assumption that the thermal properties of blood are unaltered by admixture of injectate may not be justified in careful thermodilution measurements. It is felt that the error introduced by tacit acceptance of this assumption through use of equation C has eluded past investigators because its magnitude relative to other errors may be small under certain commonly encountered conditions. On the other hand, there may exist situations in which use of equation C in lieu of equations A or B may introduce relatively large errors. Our proposed animal experiments are intended to resolve this issue.

The simplifying assumption that the thermal properties of blood and of blood-injectate mixtures are identical has been alluded to in the literature [1] but without consideration of its quantitative consequences. Using the expression, $T_b - T_m(t) = (te^{1-t})^3$, which approximates the time (t) course of a typical thermodilution curve recorded from the pulmonary artery after right-atrial injection, we have examined by numerical techniques the simplification error. Comparing equation B to equation C, the absolute error in cardiac output is approximately proportional to the deviation from 1.0 of the ratio, K, of the thermal properties of injectate and blood; directly proportional to injectate volume, V_i; and independent of both cardiac output and injectate temperature. The result is that the simplification may lead to overestimation by 1 to 3 percent at low cardiac outputs depending on precise conditions. Even though such errors are small compared to other vagaries of the method, it seems desirable to avoid them, especially since this can be readily accomplished through use of a digital computer for data processing.

The same numerical techniques show that the difference between equations A and B may exceed 30 to 40 percent at low cardiac outputs. Both equations

are correct; they simply describe different models of the events leading to generation of thermodilution curves after indicator injection. Resolution of which expression is most appropriate to the Swan-Ganz-catheter technique will require the animal experiments outlined above.

(1) K. F. Hosie, "Thermal-Dilution Technics," Circulation Research, vol. 10, pp. 491-504, 1962.

C-8. Ultrasonic Gas-Flow Instrument

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

Support: RR 00396

The performance of the ultrasonic gas-flow instrument has been evaluated in the Surgical Intensive Care Unit and the Cardiothoracic Operating Room. The instrument performed satisfactorily during these clinical trials and demonstrated excellent zero-flow stability. Heaters were added to prevent the condensation of water vapor in the transducer. The prototype transducer is larger than desirable and additional work is required to reduce its size. An effort has begun to reproduce the prototype of the instrument, incorporating circuitry for the determination of the velocity of sound in the gas. This determination will make it possible to automatically compensate for the theoretically predictable sensitivity changes.

C-9. Pulsatile Perfusion System

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

Support: RR 00396
Washington University

The benefit of pulsatile flow during coronary bypass surgery has been reported.(1) In the study referenced above, an intra-aortic balloon pump was used to deliver pulsatile flow whereas the system developed here uses a standard roller-pump head driven by a stepper motor. The stepper motor is interfaced to the clinical physiologic research cart (CPRC) (C-3). The CPRC provides precise control of the pump head and therefore the flow of blood in the extracorporeal circuit. In this application the CPRC functions as a flexible controller, a pump operator console, a real-time monitor and a long-term data-collection system. The appropriate physiologic variables are sensed by the signal amplifiers in the CPRC and are then available to the CPRC computer.

The initial software to drive the pump is based on the CPRC monitoring system written for the SICU and contains programs to control the speed and duration of the pump's operation. The question and answer routine which uses the cart keyboard and video screen allows the user to control the rate of the pump, in cc/100 steps, based on the size of the tubing used, the volume of blood to be pumped, in cc/sec, and the duration of the pumping and the onset of pumping both as percentages of the interval between heart beats. During operation of the pump system the ECG and arterial pressure are sampled and displayed as video waveforms and the ECG is scanned for the appearance of QRS complexes. When a QRS is detected a new beat-to-beat interval is calculated and the onset time is determined using this new interval. At onset time, pumping begins and continues for the duration specified by the user. The speed, in steps/sec, at which the pump is driven is dependent on the volume, duration, and pump rate (speed= volume/(duration $\times$ rate)). In cases where the volume is high and the duration of pumping is short, the speed at which the pump needs to operate cannot be reached instantaneously. Therefore, work is being done to gradually increase the speed during a pumping cycle while continuing to pump the volume requested.

(1) G. Maddoux, G. Pappas, M. Jenkins, D. Battock, R. Trow, S. G. Smith, and P. Steele, "Effect of Pulsatile and Nonpulsatile Flow During Cardiopulmonary Bypass on Left Ventricular Ejection Fraction Early After Aortocoronary Bypass Surgery," The American Journal of Cardiology, vol. 37, pp. 1000-1006, 1976.

C-10. Infant Perfusion System

Personnel: P. G. Winger, Mechanical Engineering
R. E. Clark, M.D., Cardiothoracic Surgery
R. W. Hagen, BCL
S. P. Sutera, Ph.D., Mechanical Engineering

Support: RR 00396
HL 12839
HS 00074
Washington University

A self-regulating perfusion system which uses a membrane oxygenator has been designed to provide respiratory support for infants suffering respiratory distress syndrome.[1] The principal objective of this design was to produce a unit capable of unattended operation while maintaining adequate blood flow through the extracorporeal oxygenation circuit. A prototype of the system was assembled and tested. TThe arterial pump was controlled as described in PR 11, C-14 while the venous pump was a non-occlusive roller pump. The prototype system has been used successfully in a partial bypass experiment on a small dog.

[1] P. W. Winger, "Control of a Neonatal Membrane Oxygenator," M.S. thesis, Sever Institute of Technology, Washington University, 1976.

D. Information and Communication Systems

D-1. Information System Design Studies: Overview

Personnel: J. R. Cox, Jr., BCL and Computer Science
W. E. Ball, D.Sc., Computer Science
G. J. Blaine, BCL
R. A. Dammkoehler, M.S., Computer Science
M. A. Franklin, Ph.D., Electrical Engineering and Computer Science
W. F. Pickard, Ph.D., Electrical Engineering
S. V. Pollack, M.S., Computer Science
J. Zimmerman, BCL

Support: RR 00396
HS 00074
Washington University

During the past year, design studies toward an information system with improved performance have continued. Several system organizations have been reviewed and discarded primarily because of our inability to find ways for these organizations to respond smoothly to growth in the number of active users or in database size. One organization utilizing a crosspoint switch array has survived, has been reported in a working paper,[1] and is the subject of the research reported below (D-2 through D-7).

This system design distributes the processing functions of the information system by making use of microprocessors. The general architectural scheme is shown in Figure 1. The user work stations and processing modules (P_n) are connected to one side of a crosspoint switch and the file control modules (F_m) and discs to another. Growth can occur in either the number of processing modules (N) or in the number of file modules (M). The modularity of the switch provides for expansion of its rows and columns. Some cells in the switch may not be implemented for reasons of economy or protection. Concurrent access to any row or column must be carefully arbitrated (D-2).

Neither the processing nor file modules communicate among themselves, but with a fully implemented switch, each processing module can communicate with each file module. An additional processor (P_o) prepares a log of all switch transactions. As the crosspoint switch has sufficiently wide bandwidth to allow transfers at main-memory rates between processing and file modules, the limiting element is not the switch and system growth can occur without performance degradation (D-3).

The proposed system design employs interpretive execution of a sequential (single sequence) application program in each processing module and multisequence execution of the database management functions in both processing and file control modules (D-4, D-5, D-6). The effect is to preserve the simplicity of sequential application program implementation and debugging, while capitalizing on the performance improvement obtainable by distributing the database functions between multiple, concurrently

executing processors. A modest experiment to study the feasibility of the proposed system has begun (D-7). Some related work on the characteristics and usage of clinical databases (D-8) and on system instrumentation (D-9) is also reported in this section.

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

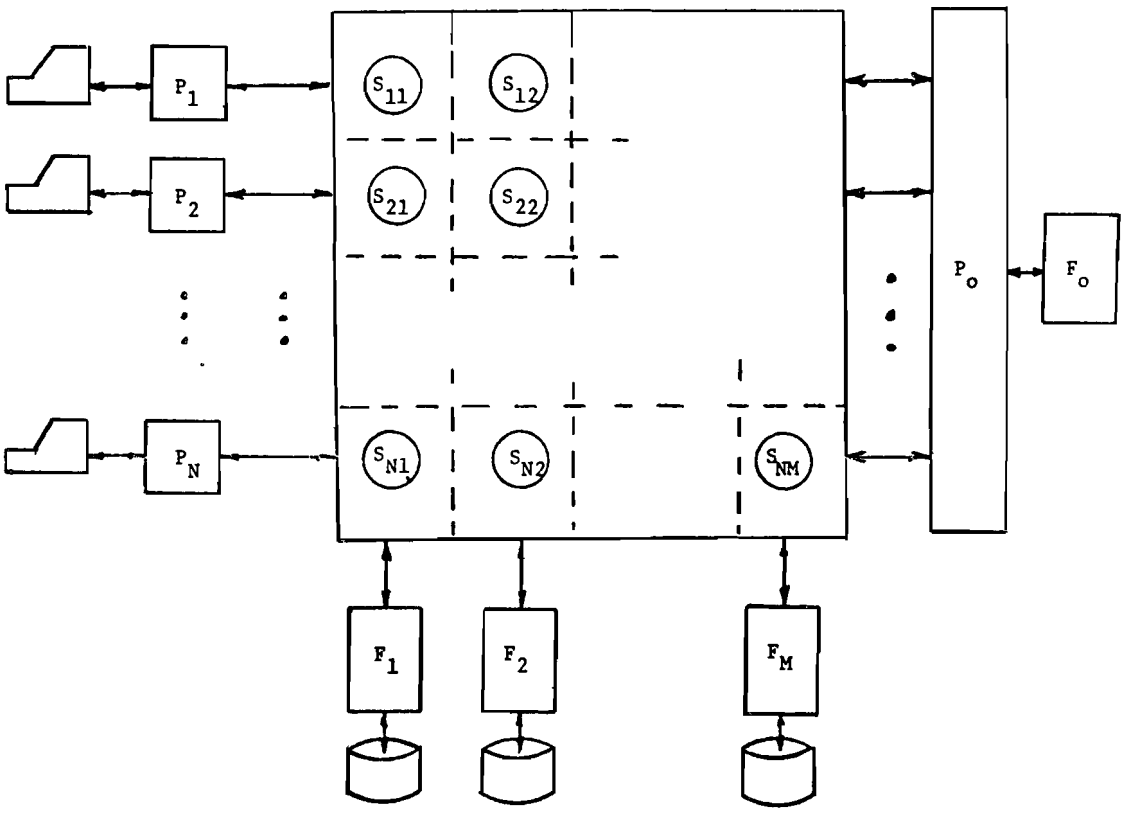

Figure 1. Block diagram of an information system based on a crosspoint switch array.

D-2. Resource Allocation in a Crosspoint Switch

Personnel: M. J. Stucki, M.S., CSL
J. R. Cox, Jr., BCL and Computer Science

Support: RR 00396
Washington University

The problem of resource allocation in the crosspoint switch array (D-1) has been studied and allocation problems arise in two contexts:

1. When more than one user-processor attempts simultaneous access to the same file.

2. When more than one file-control unit attempts simultaneous access to the same user-processor.

The crosspoint cells in the switching array must contain logic that will allocate the contested resource to one requester at a time. Further, the allocation must be done in a manner that assures that deadlock is not possible.

In approaching this design problem, we found that we could minimize the number of crosspoint cells, file units, and user-processors that could be involved in a given allocation situation by adopting the following system conventions:

1. A user-processor shall be able to receive and transmit messages concurrently. The same shall be true of file-control units.

2. A user-processor shall be able to send a message to only one destination at a time. If a message must go to more than one destination, then a separate transmission shall be made for each. The same shall be true for file-control units.

These requirements make the allocation of any resource totally independent of the allocation of any other resource. We have constructed Petri-Net models for the crosspoint cell logic needed to implement two different allocation strategies, and both are demonstrably deadlock free. The allocation problem thus appears to be quite tractable. It is true that our approach to the problem has imposed two requirements on the system, but neither of these appears to adversely affect the cost/performance factor of the system.

D-3. Simulation of an Information System Based on a Crosspoint Switch

Personnel: M. A. Franklin, Ph.D., Electrical Engineering and Computer Science
J. A. Moore, M.S., Electrical Engineering

Support: RR 00396
Washington University

A functional simulation of the information system described in the overview (D-1) has been developed. The simulation model approximates the gross functional features of the system and has been designed to help evaluate alternative system architectures and organizations.

The simulation is written in the FORTRAN-based GASP IIA[1] simulation language and runs on the local Washington University IBM System/360 Model 65 computer. Numerous inputs are available to the user of the model. These allow him to parameterize the simulation and examine how performance of the information system will vary with different organizations and loading conditions. In particular the following types of inputs must be specified for each simulation run:

1. Think Time. The mean amount of time the information system user takes in responding to information displayed on his terminal.

2. Number of Users. The number of user terminals in the system.

3. Number of Discs. The number of discs available in the system for mass storage of information files.

4. Simple/Complex Record Request Fraction. The fraction of user requests which are "simple" (i.e., require only a single record) as opposed to "complex" (i.e., require multiple records).

5. Number of Complex Records. The mean number of records required by a complex request.

6. Index Memory Design Option. A parameter which determines whether index (directory) memory is broadcast to the terminals, or represents a resource for which queuing is required.

7. Disc and Record Length Parameters. Disc parameters such as mean latency time must be set and the mean length of a record must be specified.

A number of other input parameters are also available for specifying the rates at which user errors will occur in the information system. Within the simulation program itself requests and events are randomly generated using standard random number and distribution generation techniques. The model may be run for a number of time units specified by another input parameter. As the simulation is run, generated requests

move through the modelled system with statistics generated as important events occur.

These statistics form part of an output report which is produced at the end of every simulation run. In particular the following outputs are available.

1. Time in the System. Mean time in the system for all requests and request types.

2. Queuing Times. Mean time requests spent at each queue in the system (discs, index).

3. Queue Lengths. Mean queue lengths.

4. Utilization. Percentage of time each system resource is busy.

5. Throughput. Total number of requests and the rate at which requests move through the system.

6. Statistics Verification. To verify that the random number generation procedures are operating properly, various parameter statistics are calculated as they are generated. These are printed at the end of each simulation run.

Details of the simulation model are available in a working paper.[2] The simulation has been run under a variety of input conditions. For instance, graphs have been obtained for average user wait time as a function of both number of users and number of discs. These results demonstrate the typical congestion phenomenon associated with queuing systems when overload conditions occur. Such overloading can occur under a variety of conditions. Primarily, overloading is associated with either increasing the effective input-request rate, or decreasing the effective resource capabilities of the system. The increase in request rate can occur by increasing the number of users, by increasing the percentage of requests which are complex, by increasing the number of requests generated per complex request or by decreasing the think time. The decrease in resource capabilities can occur by decreasing the number of discs available or by increasing the service time associated with each resource. Typical results indicate that if 50 percent of the users are issuing simple requests, if the number of requests generated per complex request has a mean of 20, if the think time mean is one second, then with a twenty-user, two disc system the average user waiting time will be about one second. More detailed results are available.[2]

One interesting conclusion thus far obtained concerns system scaling, i.e., how well is system performance maintained as the system grows. Indications are that system performance will not degrade as the number of user terminals increases, if the number of mass memory devices increases proportionally. Thus a fully modular system based on the cross-point switch may grow without appreciable penalty if both the vertical

axis (i.e., number of terminals) and horizontal axis (i.e., number of discs) increases at the same rate.

(1)A. A. Pritsker, and P. J. Kiviat, Simulation With GASP II, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1969.

(2)M. A. Franklin, "Simulation of an Information System Based on a Cross-point Switch," Information Systems Group Working Paper No. 2, Washington University Computer Laboratories, 1976.

D-4. Database Extensions to Procedural Languages

Personnel: F. M. Domke, BCL
W. E. Ball, D.Sc., Computer Science
D. M. Ungar, BCL

Support: RR 00396
Washington University

In order to determine the desirable programming language features for both a host language and the extensions for database management (D-1), a study of existing information systems was undertaken to draw upon experience in the Washington University medical community as well as selected segments of private industry. The following goals were identified:

1. Application-program independence from physical data-storage methods and devices.

2. Independence of each application from the database as a whole.

3. Selective access to the data giving data security and privacy.

4. Strictly logical (vs. physical) reference to the database.

5. Language constructs which are clear and easy to learn.

6. Interactive program development with strong debugging and documentation aids.

MUMPS and PL/EXUS were examined to determine their suitability as a host language. Although MUMPS has many advantages, it was found lacking in control structures, documentation aids and database independence. PL/EXUS has the advantages of PL/I's control structures and documentation aids and lacked the abundance of statement types that makes PL/I so difficult to implement. In PL/EXUS, the number of different kinds of

statements is held to a minimum, and functional extensions are realized with built-in functions and pseudo-variables. PL/EXUS' present implementation has been studied and was found to be lacking in several areas, including simplicity and ease of use. A host-language implementation based on PL/EXUS is now being studied that may overcome these shortcomings (D-5).

Database management tools have been developed by numerous vendors and research groups using a number of different methodologies. Through literature search, user survey, and conference participation the various approaches were identified and analyzed. Particular attention was given to the relational database model (typified by the work done by Codd and Date) and the CODASYL Data Base Task Group recommendations. The need for independence of each application was best satisfied by the schema-subschema concept with data definition as a distinct event performed by a database administrator. The logical relationships between data are often complex and cannot always be satisfied by a hierarchical or master-detail relationship. The CODASYL "set" relation of owner to member records was found to be flexible enough to handle very complex relationships in a straightforward and concise fashion.

After careful study, the data management capabilities of the information system have been defined. When expressed as a set of extensions to a PL/EXUS-like host language they fall into two categories: a Data Definition Language (DDL), and a Data Manipulation Language (DML).

The DDL itself is subdivided into two categories: the SCHEMA declaration, and the SUBSCHEMA declaration. The SCHEMA declaration is used by the database manager to define the structure of the whole database, while the SUBSCHEMA declaration defines the structure of a particular application's subset of a database. One of the key concepts that has been refined is the set, which allows the efficient expression of inter-record relationships.

The DML is composed of functions that manipulate special data-types, called record-instances. A record-instance implicitly contains the database key of a particular record, as well as the data. The actual data are read on demand, obviating the need for a dedicated read function. All that is necessary is a function to locate the desired record. Also, the implicit inclusion of the database key in a record-instance gives the simplicity of currency pointers without their restrictions.

D-5. A PL/I Dialect Interpreter

Personnel: D. M. Ungar, BCL
W. E. Ball, D.Sc., Computer Science

Support: RR 00396
Washington University

Since a database system must be able to use the data that it stores, a general-purpose procedural language will be used for application programs. In order to ease the development and maintenance burden typically experienced with a rapidly changing database system, this language will be executed interpretively. A PL/I dialect (PL/EXUS) was chosen for study (D-4) and was installed on the University's IBM System/360 Model 65.

Two implementations are being investigated: a virtual machine (semi-compiled) approach, and a transition diagram interpreter. In the virtual machine approach, the source code is compiled to a very high level, data-directed, stack-oriented virtual machine code. One of the advantages of this approach is that virtual machine code is so compact that large programs can comfortably reside in small memories. This is important, because the compiler can be fairly large, and still fit, as it is written in its own language. The virtual machine is simulated with an interpreter that executes the virtual machine code. Since the interpreter does not have to do syntactic analysis, it can be fast. The virtual machine approach therefore combines execution speed, compactness, ease of debugging, and portability.

A compiler has been written in PL/I to compile the new language into the virtual machine code. It is now being used to generate a compiler written in the new language. Minor changes in the new language have permitted about a four-to-one reduction in the number of statements in the syntactic routines over the PL/I version. It is estimated that the final compiler will use about 4K words of virtual machine code.

A transition diagram interpreter is under development. This approach uses a very compact and simple representation of the syntax rules, and also offers a basis for comparison with other interpreters, such as MUMPS.

D-6. Multitasking Systems Evaluation

Personnel: R. A. Dammkoehler, M.S., Computer Science

Support: RR 00396
Washington University

By definition, a multitasking system is a computational scheme which provides the programmer with explicit facilities for the dynamic initiation, termination and control of multiple, potentially concurrent or simultaneously executing programs. Typically, a multitasking system is realized by augmenting the instruction set of a computer of conventional design with a set of callable subroutines providing, in total, an environment in which multiprograms, such as operating systems, may be conveniently implemented. More importantly, in the context of the information systems project (D-1), a multitasking system provides an environment in which special purpose multiprograms, such as those which will be required to efficiently control the file processing activities, may be implemented. In order to explore this possibility, we have analyzed several extant or proposed computational schemes beginning with a specific multitasking system of local origin. Our system, referred to by the acronym MTS, is implemented on the PDP-8 and the PDP-12 as a set of core-resident programs and tables requiring a few hundred 12-bit storage words. Multiprograms running in the MTS environment are written in assembly language, PAL-8 and communicate or interface to MTS by executing any of eight special instructions which are conveniently thought of as system calls. Each computer, PDP-8 or PDP-12 is equipped with additional interrupt circuitry (the time sharing hardware modification KT8/I) which causes the transfer of control of the processor from a user program to MTS each time one of the eight special instructions is encountered in a serial instruction stream.

The objectives of the evaluation are:

1) to assess the functional completeness of MTS by comparing its capabilities with those implicit or explicit in alternative implementations,

2) to determine the time/space cost of the existing MTS, particularly version 2.6 in use at the present time, in order to develop data for performance evaluation and to identify algorithmic inefficiencies, and

3) to identify new functions and/or modifications prior to the time at which MTS may be implemented on the file processor.

We have specifically examined the multitasking capabilities of MULTICS as described by Dennis and Van Horn [1,2,3] and a similar set of capabilities available to the programmer at the assembly language level in the UNIX Time-sharing System.[4] In general all three systems (including MTS) appear to provide similar capabilities despite the obvious

differences in the host processing configurations.

We have also completed a detailed timing analysis of the current version of MTS identifying certain inefficiencies in the present implementation, which are for the most part attributable to the addressing scheme and architecture of the PDP-8 and the PDP-12 computers. This information, coupled with a few functional enhancements suggested by the comparisons with other systems provides the basis for the implementation of a new version of MTS for the file processing element in the information system. Additional details of this evaluation are available in a working paper.[5]

[1] J. B. Dennis, and E. C. Van Horn, "Programming Semantics for Multiprogrammed Computations," Communications of the Association for Computing Machinery, vol. 9, no. 3, pp. 143-155, March 1966.

[2] J. B. Dennis, "Segmentation and the Design of Multiprogrammed Computer Systems," Journal of the Association for Computing Machinery, vol. 12, pp. 589-602, October 1965.

[3] R. C. Daley, and J. B. Dennis, "Virtual Memory, Processes and Sharing in MULTICS," Communications of the Association for Computing Machinery, vol. 11, no. 5, pp. 306-312, May 1968.

[4] D. M. Ritchie, and K. Thompson, "The UNIX Time-Sharing System," Communications of the Association for Computing Machinery, vol. 17, no. 7, pp. 365-375, July 1974.

[5] R. A. Dammkoehler, "Multitasking Systems Evaluation," Information Systems Group Working Paper No. 3, Washington University Computer Laboratories, 1976.

D-7. A File System Prototype

Personnel: G. J. Blaine, BCL
J. Barman, B.S., Computer Science
J. R. Cox, Jr., BCL and Computer Science
R. A. Dammkoehler, M.S., Computer Science
R. E. Olson, B.S., CSL
D. M. Ungar, BCL

Support: RR 00396
Washington University

An equipment base is being assembled to provide both a facility capable of supporting specialized file-processor hardware development and a multiuser programming environment for database software development (D-1).

The file system prototype will initially consist of a minicomputer processor, memory, disc storage, and an interface to RMM (Restructured Macromodules) for initial crosspoint switch experiments. Design studies, using anticipated file processor requirements, indicate sufficient bandwidth is available to permit file processor intra-module communication via the minicomputer bus. This allows standardly available disc controllers and memory modules to be utilized in the initial prototype.

A Data 100 Model 135 minicomputer (PDP-11/35 emulator) was selected for the processor module. Both database storage and program development support will be provided by a disc controller and two Pertec disc drives, (2.4 megawords removable cartridges, 2.4 megawords non-removable cartridges). A Lear Siegler ADM-1 CRT display terminal and a Centronix Model 306C (100 char/sec, 5 x 7 dot matrix) printer were purchased to support software development. Initial checkout of the computer, CRT terminal and printer has been completed.

An effort to define the RMM direct memory access module requirements has begun with the definition of a message level protocol and a review of previous macro-modular/minicomputer interface projects.

Several operating systems were examined to determine suitability as a host for program development on the file processor prototype. A multiuser operating system, UNIX (D-6), was chosen. UNIX supports C, a high level procedural language that can produce very efficient code. File processor experiments with UNIX will begin after delivery, installation and checkout of the disc system.

D-8. Characteristics of Clinical Database Files and Their Usage

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

Support: RR 00396
HS 00074

Studies on some of the characteristics of computer databases in a clinical environment have become more sharply focused and progressed significantly since last reported (PR 11, D-2). The objective of these studies has been to highlight for the designer of database systems a number of special problems posed by the demanding characteristics of the clinical environment.

Five topics (lengths of data items, indexing methods, database aggregates and their sizes and growths, temporal relationships, and database usage) have been chosen because of their almost universal presence and because details pertaining to them often are omitted from an initial design. Thus, costly retrofits are required to make the system operate satisfactorily. Other problem areas such as response time, reliability, and security are more adequately covered in the literature and are more dependent upon implementation details than are the areas covered in this work.

Data for this study were obtained from four active databases: a bibliography system, the Glaucoma Center Registries, the Medical Care Group Information System, and the Mallinckrodt Institute of Radiology Diagnostic Computer Facility Information System.

The bibliography system was created to serve the reference needs of this study and currently contains more than six hundred literature citations dealing mostly with aspects of computerized clinical databases. This bibliography was originally conceived only to support the reference needs of this study; however, it was soon realized that it could serve admirably as an object of the study. The Glaucoma Center Registries (D-15) had as one of their reasons for creation the support of this study. This system has been very heavily instrumented to report database growth and usage. In contrast, the MCG Information System (D-11) and the MIR System act only as sources of data for this study.

This set of four databases nicely spans a good portion of medical applications as shown in the following table:

Database	Approximate Size	Time Span of Data	Usage Orientation
Bibliography	600 citations	Not applicable	Research
Glaucoma	600 patients	Very long, chronic disease	Clinical research
MCG	9,000 subscribers	Intermediate	Management and health care research
MIR	20,000 patients	Very short	Management

Data on the first four topics of investigation have been gathered, analyzed, and prepared for presentation. Data on database usage have been gathered, but have yet to be analyzed. An experiment within this larger study demonstrated that the Davidson and the Soundex phonetic key compression schemes performed similarly in obtaining extra matches on a patient name retrieval and that both outperform by a large margin an exact name match. The results also indicate that the Davidson scheme is superior to the Soundex because it produces significantly fewer mismatches.

D-9. A Hardware Monitor for the Investigation of PDP-11 MUMPS Implementation Efficiency

Personnel: J. W. Lewis, BCL and Pathology
B. K. Herres, B.S., Electrical Engineering
J. Zimmerman, BCL

Support: HS 00074
Barnes Hospital
Washington University

With the increasing popularity of the MUMPS language for time-sharing and database applications, the need for both higher performance and greater efficiency in MUMPS implementations has grown. In order to obtain detailed performance data on MUMPS-11 systems a hardware monitor has been designed and constructed. The monitor is a single board which plugs into the PDP-11 Unibus and maintains a count of the number of times either of two programmable bus addresses is accessed, or (alternatively) the number of times any bus address in a programmable region (i.e., between lower and upper limits) is accessed. Preliminary data have been obtained under Version 3 of DEC MUMPS-11 on the number of times major interpreter modules were executed when running a set of simple benchmark MUMPS routines. DEC's Laboratory Data Products group has generously made the complete source listings of MUMPS-11 Version 4 available to this project, and all subsequent data will be taken under this improved release.

A principal motivation for this project was a proposal for a small, inexpensive single-user "MUMPS Machine" based on microprocessor, flexible

disc, and possibly CCD mass-storage technologies. It is anticipated that the data and analyses produced by the hardware monitor will be useful both in design studies for such a MUMPS machine and in the improvement of existing MUMPS implementations. Furthermore, the monitor board is not restricted to use on MUMPS, and may find uses in other PDP-11 software performance analyses.

D-10. Medical Information System Applications: Overview and Support Activities

Personnel: J. Zimmerman, BCL
G. J. Blaine, BCL
J. R. Cox, Jr., BCL and Computer Science
F. M. Domke, BCL
M. Rigden, BCL
B. F. Spenner, BCL

Support: RR 00396
HS 00074
HS 01540
Washington University

The activities reported in the next nine articles demonstrate the increasing Laboratory involvement with medical information system applications. Beginning five years ago with our first work on MUMPS (PR 8, I-2) the number and diversity of our collaborations both at Washington University and nationally have grown to reflect the importance of this aspect of biomedical computing. In addition to the work reported in this section, information system activities may be found in related reports (A-1, E-4, H-16, H-17 and H-20).

The activities reported below fall into three categories: reports on systems intended primarily for the support of care for the individual patient (D-11, D-12, D-13 and D-14), reports on systems intended as registries useful in research (D-15 and D-16), and reports on national user group activities and application transfer (D-17, D-18, and D-19).

To facilitate these information system activities we have continued to increase the capacity and performance of our multiuser MUMPS system. In addition, many users have taken advantage of the new Medical Computing Facilities MUMPS system and the availability of a local commercial MUMPS service (Artronix).

Specific improvements made to the Laboratory system (Artronix PC-12/7 MUMPS) include processor memory expansion (32K words to 48K words), the addition of block-move processor hardware, and the installation of software release 2.3 of Extended MUMPS-PC. These modifications provide

increased system throughput particularly through the use of buffer pooling. The asynchronous communication interface modules were modified to provide increased frequency stability by installing a recent engineering release. The I/O ports were expanded to service eight simultaneous users:

3 auto-answer Bell Modems (300 bps)
1 auto-answer Vadic Modem (1200 bps)
4 dedicated ports (1200-4800 bps)

A second mass-storage drive unit (Artronix Model 1234) was added to increase system storage capacity (33.2 megawords to 66.4 megawords), enhance system reliability by providing a back-up for single drive failures, and enable on-site database duplication for error recovery procedures.

D-11. Medical Care Group Information System

Personnel: F. M. Domke, BCL
G. J. Blaine, BCL
M. J. Kenner, B.S., Medical Care Group
A. W. Washington, M.B.A., Medical Care Group

Support: RR 00396
HS 00074
HS 01540
Medical Care Group
Washington University

The Medical Care Group experienced substantial growth in enrollment and utilization over the last year. The number of prepaid enrollees increased from 4,500 to 10,000 and the number of patient visits also increased to an average of 3,700 per month during the last half of the fiscal year. In order to manage this volume of data, MCG began to rely heavily on the Extended MUMPS-PC information system (PR 11, D-4). Manual systems for maintaining patient population demographic information were discarded in favor of computer maintenance of these data for both patient identification and insurance reimbursement purposes. Very little reprogramming was necessary to accommodate this growth but a comprehensive set of data verification and system utilization programs were added to ensure smooth, error-free operation of the system. The previous method for producing an alphabetic inverted list for name access of the file was to regenerate this list in batch mode on a periodic basis. With the large population and frequent updates to the files, an on-line update of the inverted list offered greater currency of the data and less overhead. Therefore, all population updates which affect the inverted list now invoke routines to update it concurrently with the update of the main files.

As utilization increased, so did the need for more encounter data searches with greater sophistication in the type of searches made. Additional search routines were written which allow retrieval of patient and visit data for arbitrary Boolean criteria on the encounter parameters including the SNOP-coded patient problem lists. For the convenience of the person requesting searches, a spooling program was implemented which defines searches in the normal interactive manner but saves the parameters for overnight processing.

As the system matured, it became apparent that it was providing a necessary service to MCG and should, therefore, be under their control and supported by them. In cooperation with MCG, an analysis of the alternatives available to them was conducted. Studied in depth were two service bureau operations with experience in serving group practices, the Medical Computing Facilities of Washington University (offering MUMPS) and a commercial MUMPS vendor. In order to preserve the flexibility of the current system, provide for expansion of on-line in-house terminals, and meet budgetary requirements, the commercial MUMPS vendor was selected. To assist the vendor in the development of additional application software, portions of the system were reorganized and further generalized (particularly by use of table-driven techniques). Programmer-level documentation was also written to enhance the maintainability of the entire system.

D-12. MESCH

Personnel: J. Zimmerman, BCL
B. Karpiak, BCL
D. G. Robida, B.S., Electrical Engineering
R. K. Stimac, BCL
D. Tao, M.S., Electrical Engineering

Support: RR 00396
HS 00074
HS 01540

We are working towards the specifications of a MESCH (Multi-Environment Scheme; PR 11, D-5) for ambulatory-care. During the last year, we have concentrated upon the analysis and comparison of various ambulatory-care information systems. To facilitate this work, we divided the activities in such systems into four categories. First, there is the only essential activity, patient identification. Secondly there are those activities which primarily add new data to the information system: patient registration, patient encounter forms, physician's notes, and patient history taking. Thirdly there are the activities in which data are both added to and retrieved from the database: billing, inventory and supplies, laboratory data, paramedical guidance, patient/provider scheduling, pharmacy, physician

consultation, and X-ray data. Fourth, there are the activities which only utilize the entered data: administrative report generation, medical record inspection, patient education and counseling, research, and summaries of record sets.

A report is being prepared on one survey of patient identification methods, registration forms, and encounter forms. The variation of all three is both surprising and striking. It is not clear whether the bulk of the variation arises because each group is working independently (and is therefore unaware of the choices made by others), or because each group really does require the degree of individuality which it displays in the data types it collects. Other similar reports are being produced in conjunction with thesis projects on scheduling (Tao; D-13) and pharmacy (Robida; D-14).

With the wealth of data that is being thus amassed, we will shortly begin an organized effort to define the questionnaire-like interactions whereby an institution could specify how it wishes to have its information system handle each of these components, and will continue our work on the generation of custom-tailored code for each set of specifications.

D-13. Outpatient Appointment Systems Research

Personnel: D. Tao, M.S., Electrical Engineering
W. F. Pickard, Ph.D., Electrical Engineering
J. Zimmerman, BCL

Support: HS 00074
St. Louis City Hospital

A research and design project for the development of an outpatient appointment system has been nearly completed. The first stage (system analysis) was reported previously (PR 11, D-6) and effort in the past year has been devoted to implementing an experimental MUMPS appointment system at St. Louis City Hospital medicine clinics.

A demonstration installation of the system was operational from February 17 through June 2, 1976, after having been delayed repeatedly for several reasons: lack of response from hospital data processing personnel to administration plans to integrate the clinic appointment system with the outpatient billing system; resignations of several key administrative and data processing personnel; a nursing strike and controversy over quality of care; budget problems; and uncertainty regarding the ultimate status of the hospital. Because of these many factors, there was no possibility to convert the programs for permanent use by the hospital's UNIVAC computer, as had been originally planned. However,

useful data were gathered on the performance and reliability of the computer system; the problems associated with erratic clinic loads, widely varying rates of failure to appear among different categories of patients, and the "no cancellation" policy were documented; the interrelationship of the clinic system with other departments (medical records, radiology, laboratory, emergency, inpatient) was clarified; and the MUMPS programs were debugged and streamlined for user convenience. A detailed set of recommendations was made on improving the existing system and making it more compatible with standards that have been established in other appointment systems.

A final phase of the research, generalization of the MUMPS demonstration system into a module of the MESCH Ambulatory Care Package (D-12), was begun with preparation of an automated questionnaire for appointment system specification, based on research into a wide variety of appointment systems.[1] This was first tried using the QUEST driver,[2] and is to be revised shortly, using a more comprehensive MESCH questionnaire driver. Thus the benefits of a specific application design combined with the broad findings of other research are expected to enhance the likelihood of successful application transfer among many institutions.

[1] D. Tao, "Outpatient Appointment Systems - A Survey of Practices, Devices, Attitudes and Plans," BCL Monograph No. 283, December 1975.

[2] J. Zimmerman, and C. R. Brigham, QUEST Design Manual, MUMPS Application Design Manual for QUEST, a Simple Questionnaire Driver for Teaching and Testing Students, internal memorandum, 1976.

D-14. COMAPS: COMputer-Aided Pharmacy System

Personnel: D. G. Robida, B.S., Electrical Engineering
J. Zimmerman, BCL

Support: HS 00074

COMAPS,[1] a computer-aided pharmacy system, was developed to meet the following four objectives:

1. Meet the specific record-keeping needs of the Medical Care Group (MCG) Pharmacy.

2. Minimize the number of repetitious entries of patient and drug related information needed to maintain the pharmacy records now kept.

3. Store some data previously not kept and provide summaries and managerial reports of these data.

4. Develop a pharmacy system which contributes to the design and implementation of other similar pharmacy systems elsewhere.

COMAPS was proposed after a survey failed to discover a pharmacy system which would meet these four goals. The functional capabilities of COMAPS were designed with the aid of interviews with several local pharmacists as well as a literature review. Although COMAPS was actually implemented in MUMPS-PC, the code was written for easy translation into Standard MUMPS.

An evaluation of COMAPS was carried out involving two time-motion studies. One time-motion study was conducted on the manual system of filling and refilling prescriptions and the other was conducted on the filling and refilling of prescriptions using COMAPS.

The benefits of COMAPS are:

1. Decreased prescription fill or refill transaction times.

2. Decreased paper work.

3. More effective control over patient medication compliance.

4. Increased control over the drug inventory.

5. Development of a medication database to aid in research relating medications prescribed to the patient's medical problem.

The primary disadvantage to COMAPS is its cost. The cost of block storage accounts for 50% of the total annual cost of the system and efforts will be made to redesign the global structure to reduce the storage required.

(1) D. G. Robida, "A Computer Aided Pharmacy System," Master of Science thesis, Washington University, June 1976.

D-15. Glaucoma Center Registries

Personnel: R. H. Greenfield, BCL
M. A. Kass, M.D., Ophthalmology
J. L. Livingston, B.A., Ophthalmology

Support: RR 00396
EY 00336
HS 00074

Progress on the implementation and usage of the Glaucoma Center Registry (PR 11, D-2 and D-3) has continued, and new registries have been started in this current reporting period. The original registry contains fairly complete information about subjects participating in the Center's research protocols. One new registry, started in November 1975, contains a short summary of the characteristics of private patients of the Ophthalmology staff. These summaries should prove useful in supplementing the Center's population for a particular study if the need should arise. MISAR's[1] modular construction makes the addition of new registries very easy. MISAR is also supporting a small metabolism database for the diabetes center.

Some effort has been put into adapting MISAR to our needs, but much of the original Beth Israel code remains and our version is still very similar to the original except for several additions. Since MISAR was primarily a demographically oriented database system and because our Center is concerned with a chronic disease, it was necessary to find a compact way to incorporate multiple visits into MISAR. This method inserts date and time information into a MISAR field without changing MISAR's data structure. Our need to record precisely and succinctly diagnoses and surgical procedures in our databases led us to adopt (and to expand and adapt to our needs) the ICD-9 code.[2] Since the Illinois Eye and Ear Infirmary is also using this code we plan to cooperate with them in our modifications. The database studies which are elsewhere reported (D-8), have shown the benefits of simple editing transformations applied to name and address data items. This has caused the routine usage of these transformations to be started in order to increase the uniqueness of and to decrease the space required by these items.

We found it necessary to improve and expand the MISAR documentation[3] as our system grew away from the original. MISAR came to us by a still relatively uncommon method, program transfer from another institution, facilitated by the MUMPS Users' Group (D-18, D-19). Our good experience with program transfer may be of interest to others and has been reported.[4]

Both the size and usage of the database have exhibited growth and maturation. Database size and usage have been comprehensively monitored to support the database studies which are reported elsewhere (D-8). Presently there are more than 640 subjects (out of the Center's population of 2000) represented in the computerized registry. These data require

about 260,000 characters of disc storage and approximately 560 characters for the average subject's record (representing about 11 visits over a period of seven years). Eighteen visits and 29 years are the respective maxima. Usage of the database has started to shift from pure data entry towards some information output. Fellows and some staff physicians have started to use the registry as a method of generating lists of subjects for retrospective research and for new protocols. Progress in the establishment of this Glaucoma database has been reported.[5]

Our database efforts have been synergistic with and complementary to our collaboration in the clinical evaluation of CASNET, a computerized glaucoma consultant being developed at Rutgers University which is elsewhere reported (H-20).

[1] 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.

[2] A. Colenbrander, "Classification of Disorders of the Eye: Based on the Ninth Revision of the International Classification of Diseases," prepared for the International Council of Ophthalmology, July 1975.

[3] D. Geer, and H. L. Bleich, revised and expanded by R. H. Greenfield and J. Livingston, "MISAR: A Miniature Information Storage and Retrieval System - Directions for Using MISAR," BCL Monograph No. 292, June 1976.

[4] R. H. Greenfield, "Rapid Establishment of an Ophthalmologic Data Base via Program Transfer," Proceedings of the 1975 MUMPS Users' Group Meeting, pp. 78-87, 1975.

[5] R. H. Greenfield, and M. Kass, "Progress on the Establishment of a Computerized Glaucoma Data Base," presented at an Informal Session of the Second Annual Workshop on Artificial Intelligence in Medicine, East Windsor, New Jersey, June 3, 1976.

D-16. Neonatal Database

Personnel: C. N. Mead, BCL
J. A. Johnson, BCL
R. E. Marshall, M.D., Pediatrics
M. M. Maurer, M.D., Pediatrics

Support: RR 00396
Missouri Division of Health Special Project Grant

Neonatology is a sub-speciality of Pediatrics concerned with the care and treatment of the critically ill newborn and infant through the first three months of life. Because it is a relatively new field, not nearly enough is known about many of the disease processes seen in the modern neonatal intensive care unit. Furthermore, since many of the methods employed in the treatment of the various syndromes and disease states are so new, no good follow-up data exist on their true effects (and side effects). Many carefully planned studies, both retrospective and prospective, must be undertaken in an attempt to further understand the variables involved in the treatment of the critically ill infant. Unfortunately, the traditional medical chart (a collection of doctor's notes placed on a background of rather randomly organized admission history, numerous laboratory and X-ray reports, and a discharge summary) does not lend itself to analyses of this sort.

The requirement for a database with rapid file search capacity is critical to the future design and implementation of meaningful prospective studies. To provide physicians and researchers with meaningful information organized in an easily accessible manner, a computer database system is currently being developed at the Neonatal Intensive Care Unit in St. Louis Children's Hospital. The primary goal of the system is the collection and storage of data in such a form that the database could be searched repeatedly, with reasonable response times, to locate patient groupings and outcome trends based on specific preceding conditions.

The data to be searched fall into three categories according to whether they were acquired during admission, in-hospital stay, or follow-up. Each category differs as to the amount of data and the form of data collected. The well-defined and fixed nature of the admission history and physical lends itself to the questionnaire format with multiple coded responses. The large amount of time-oriented information needed to describe a patient's in-hospital progress is better handled by a summary form which charts symptoms and treatments on a weekly basis. In the Follow-Up Clinic, where most patients are interviewed and examined for a few problems, a checklist format is probably the most desirable. This specialization of data collection techniques is reasonable since it parallels the natural progression of events. The concept of organizing the database to parallel external data collection patterns has in fact become a basic design approach for the system. The collection of admission history and physical data is proceeding with the database now containing over 250 patient files with approximately 100 searchable items each.

Collection forms and retrieval strategies for in-hospital data have been developed and are being implemented. User acceptance and cooperation have been extremely good.

All programs run on a 20-user Artronix PC-12 MUMPS system with 64K of core. The standard system software includes bit functions and buffer pooling. All communications with the system are through a remote terminal at St. Louis Children's Hospital connected to the central computer at the Mallinckrodt Institute of Radiology.

D-17. MUG/MDC: Activities of the MUMPS Users' Group (MUG) and the MUMPS Development Committee (MDC)

Personnel: J. Zimmerman, BCL
D. Bridger, M.S., Computer Science
A. Forrey, Ph.D., University of Washington
F. Sias, Ph.D., Georgia Institute of Technology
R. F. Walters, Ph.D., University of California, Davis

Support: RR 00396
HS 00074
HS 01540

The MUG mailing list has grown to over 2,300 names of people interested in MUMPS. It is believed that there are probably now about 400 institutions using MUMPS worldwide. Among the documents which MUG has produced in the last year are:

1. The Standard MUMPS Pocket Guide, a concise but complete introduction to Standard MUMPS.

2. A revision (almost complete) of the monograph on "Advanced MUMPS Techniques," written last year.

3. The Proceedings of the 1975 MUG Meeting.

4. Four quarterly issues of the MUMPS News.

5. Summaries of MUMPS applications used at various institutions.

MUG is gradually increasing the number of different ways in which it is involved in application transfer. A year ago it played only two roles:

1. MUG was a source of information about which applications existed and where they might be found. This was done mainly through the accumulation of MUMPS institution profiles.

2. MUG compiled summaries of several applications available at various institutions. This was done mainly through encouraging the institutions to submit abstracts of their applications.

During the last year, MUG has not only continued in these roles, but has also begun to:

3. Evaluate objectively various application types (such as ambulatory-care accounting).

4. Document and even modify some applications produced externally to MUG, such as CAPO (PR 11, D-7).

5. Design, encode, and document applications for the MUG applications library (D-19).

The main work of the MDC has been the completion of Standard MUMPS and its publication as a GPO document.(1) The MDC is now reviewing several of the completed and developing implementations of Standard MUMPS to encourage implementors to be thorough and to study incorporation into the Standard of some of the developing extensions.

(1) J. T. O'Neill, "MUMPS Standard Language," NBS Handbook No. 118, 1976.

D-18. MUG/MDC: Evaluation of Application Program Transfer

Personnel: J. Zimmerman, BCL
R. Parkes, Ph.D., Economics

Support: HS 01540

The transfer of MUMPS applications attempted at the Biomedical Computer Laboratory and the Washington University School of Medicine has been reviewed.(1) Seven attempts were identified involving medical records, bibliography, CAPO (PR 11, D-7), a miniature information system (MISAR: D-15), pharmacy, registry, and a questionnaire driver. Only two of these seven attempts had been completed. These two applications (the miniature information system and the questionnaire driver) were small and each transfer required only two or three weeks (a translation from one MUMPS dialect to another was necessary in each case). The success of these transfers probably resulted from the enthusiasm of those responsible for the transfer and their perceptions that the application would perform a useful service when transferred. The major problems identified in the other transfers, currently considered to be unsuccessful, were:

1. No potential source of the desired application was known to the would-be receiving institution.

2. No response to letters and phone calls was obtained from an institution known to have a desirable application.

3. No administrative summary of the application existed.

4. The application would require translation from another MUMPS dialect; although this, like several other problems listed here, is not a major hindrance, it does add resistance to attempted transfer.

5. The physical problems associated with the transfer of code and data from the originating to the receiving site.

6. The decision to redesign rather than transfer an application when there were sufficient differences at the user level in the actual and the desired functions.

Another project has been begun to evaluate the success or failure of attempted MUMPS application transfer between other institutions. We have started with the Clinical Laboratory system developed at the Massachusetts General Hospital in Boston. Over 20 institutions have received listings and documentation of this application and some have received machine-readable code. Preliminary information indicates that only about four of the attempts resulted in successful transfers, and that many of the problems listed above were also encountered.

(1) J. Zimmerman, "Attempted MUMPS Application Transfer to the Biomedical Computer Laboratory and the Washington University Medical School," internal memorandum, May 11, 1976.

D-19. MUG/MDC: Development of MUMPS Applications for Transfer

Personnel: J. Zimmerman, BCL
C. R. Brigham, BCL
A. Forrey, Ph.D., University of Washington
G. Kuthe, BCL
B. Karpiak, BCL
R. Malamud, BCL
M. Rigden, BCL
J. H. Rixleben, BCL
R. K. Stimac, BCL

Support: RR 00396
HS 00074
HS 01540

We have proposed(1) that the most important component of a MUMPS application is its Design Manual. This Design Manual should provide: an

analysis of the problem to be solved and a discussion of alternate solutions; a means for communication between the designers, programmers, management, and others involved in the solution of the problem; information useful to other groups of how problems were solved; and general information on MUMPS application design. Each Design Manual should contain two parts: the non-technical specifications of the application (purpose, background, required capabilities, logical data structure, and user interactions) and the technical specifications (constraints imposed by the MUMPS implementation, physical data structure, code structure, programming conventions, and test runs). Design Manuals have been written for the following applications:

1. QUEST, a simple but powerful questionnaire driver.

2. Person identification (partially complete), a scheme which includes each of the most commonly used means of person identification.

3. Dictionary creation and editing (partially complete).

4. Forms, a general-purpose forms driver (partially complete).

5. A package for aiding MUMPS application documentation (partially complete).

A nine-institution group has been set up to review our Design Manuals and give us feedback on their appropriateness. The first application (QUEST) is currently being transferred to the University of Washington, Seattle, where it will also be translated into Standard MUMPS.

(1) J. Zimmerman, "Plans for MUMPS Application Exchange Activities: Report #2," BCL Monograph No. 294, December 1975.

E. Cardiac Catheterization Laboratory

E-1. New Cardiac Catheterization Laboratory Computer System

Personnel: G. H. Brandenburger, BCL
S. A. Garfield, BCL
B. R. Hieb, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
P. A. Ludbrook, M.D., Medicine
G. C. Oliver, M.D., Jewish Hospital
M. Smith, BCL
B. Zvolanek, BCL

Support: RR 00396
Jewish Hospital
Washington University

The first phase of the new cardiac catheterization laboratory computer system (cath lab system) is complete, and the system is routinely used at its first installation, the Jewish Hospital Cath Lab.

In addition to all the capabilities of the original PC-12 cath lab system, the new system is now providing:

1) Simplified operation during the catheterization procedure with the data acquisition control "panel" supported by software developed to minimize the computer-user interaction. A table of procedure "protocols" is maintained with the system. Each "protocol" is a user editable sequence describing a particular catheterization procedure. During an actual procedure, a "protocol" is used to control data acquisition, automatically sequencing "panel" keys. For routine procedures the user-computer interaction is reduced to specifying when valid data is available and making minor protocol corrections. The protocol can be overridden simply by depressing a key indicating a new anatomical site. Because of the "panel" and the highly refined acquisition software, acquisition without the "protocol" or in the override mode is very simple and requires less operator attention than the old cath lab system.

2) An "initialization" option of the system permits the operator to view and edit many laboratory parameters. The pressure scales used, types of data acquisition and display hardware, recording methods, calibration level, empirical analysis constants and other system parameters are easily entered or modified. An "analysis recipe generator" permits definition of special anatomical sites along with the type of analysis to be used for each. Specialized gradients such as those encountered with coarction of the aorta can be specified to the system and appropriate gradient calculations will be performed automatically.

3) Calibrations can be corrected after data are acquired should calibration error or baseline drift occur.

4) All entered information and calculated results can be edited either during or after data acquisition to correct for inevitable operator errors and omissions.

5) Access to all cath lab system data is provided to the user under a user's operating system. User written OS/PC FORTRAN programs may access any system data by calling cath lab system subroutines provided in the user's operating system. This feature is currently being used in dye-dilution analysis research (C-4).

6) Software drivers for the forthcoming automated analysis programs (E-2) are an integral part of the "analysis executive" software already in use. As the automatic analysis programs become available, they need only be copied to the system tape/disc. Various options of the analysis driver system provide for several levels of automated analysis including a completely automatic "unattended analysis." The automated analysis driver has also simplified the manual analysis currently used.

7) Tentative flowcharts are complete for: 1) A high-speed ECG-triggered pressure sampling overlay. 2) A high-speed pressure sampling overlay for use during cine-angiography. Plans for software linkage of the cath lab system and the cine-angiography analysis system (E-3) are also complete. The high speed ECG-triggered pressure data will be used for micromanometer-tipped-catheter dP/dt measurements. The simultaneous cine-pressure measurements will be used for ventricular compliance studies in conjunction with the cine-angiography system (E-3).

8) A unique feature, the pullback linkage, has already proven to be valuable for gradient analysis. During pressure acquisition, a panel key (pullback) may be used to indicate that sequentially acquired pressures are to be treated as simultaneous during analysis. A special multiple time shift feature permits individual beats to be shifted into temporal alignment should the pressures have occurred with different heart rates.

While numerous small changes and software errors are undergoing correction, the new cath lab system has seen routine clinical use since June, 1976. Extensive evaluation has begun.

The Cath Lab System development group has been involved in general catheterization laboratory support and improvement. Included in this work are:

1) Addition of a digital read-out to an analog oximeter at the Jewish Hospital Cath Lab.

2) The COMVAS ventricular volume analysis system (E-3) used at the Washington University Catheterization Laboratory is to be upgraded with the addition of a sonic x-y position transducer tablet (SAC GP-3 from Science Accessories Corporation). The BCL-designed interface for the

tablet is undergoing revision and will be operational by July 1976.

3) Construction of a PC keyboard cable switch and a video switch has begun. The keyboard switch will simplify operation of the PC from the two remote sites at the Jewish Hospital Cath Lab. The video switch will permit the Cath Lab computer system video displays to be viewed on the fluoroscope monitors between fluoroscope operations.

4) Specification and initial design of a low-speed single-frame video A/D converter based on the PEP 400-R video system are nearly complete. The system will be used in research conducted by Jewish Hospital on computerizing ultrasonic cardiac measurements.

5) The PEP 400-R grey-scale display for the PC-12 has proven valuable in video-angiographic pattern recognition studies (PR 11, E-1) and in ultrasound reconstruction research (H-13). The scan converter is an integral part of the new cath lab display system. A preliminary PEP 400-R interface has been in operation for 10 months; an expanded version has been built and is presently undergoing evaluation.

6) The data acquisition control "panel" electronics and the PC-12 data bus extension (PR 11, E-4) have been in use for several months in the "multi-Patient System for Retrospective Retrieval of ECG Episodes" (A-19). PC-12 data bus extensions have also been installed at the Jewish Hospital Catheterization Lab for the new cath lab system and at BCL for the ultrasound research (H-13).

E-2. Automatic Pattern Recognition of Left Ventricular Pressure Waveforms

Personnel: R. G. Lagler, M.S., Biomedical Engineering
F. D. Biggs, M.D., Jewish Hospital
G. H. Brandenburger, BCL
V. R. deMello, M.D., Jewish Hospital
R. E. Eggebrecht, M.D., Jewish Hospital
B. R. Hieb, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
G. C. Oliver, M.D., Jewish Hospital
R. Ruffy, M.D., Jewish Hospital
A. Salimi, M.D., Jewish Hospital

Support: RR 00396
Jewish Hospital

A large fraction of the data obtained during cardiac catheterization consists of pressure waveforms collected from different anatomical sites. One of the goals of the new FORTRAN cath lab system (E-1) was to automate pattern recognition procedures. Automatic processing of the left ventricular (LV) pressure waveforms was chosen as a prototype project. The experience gained from this endeavor will then serve as a basis for extending the automatic pattern recognition process to other types of waveforms. The database for this project consisted of approximately 400 catheterization cases on file in the Washington University Catheterization Laboratory at Jewish Hospital. From this database a training set and a test set were constructed containing 46 and 53 LV waveforms respectively. In order to determine the inter-physician variability in left ventricular pressure waveform analysis, each of eight cardiologists independently analyzed the left ventricular waveforms in both the test and training sets.

A review of the literature revealed several algorithms which had been applied to left ventricular pressure analysis by other investigators. Three of these were implemented and applied to database waveforms. All were found to be unacceptable due to occasional large discrepancies between the end-diastolic and systolic pressure values determined by each algorithm and the corresponding values determined by the eight cardiologists. It was decided therefore to develop a more satisfactory algorithm building on the experience from the analysis of the training data. The completed algorithm utilizes a 7-point convolution procedure to obtain a smoothed first derivative of the pressure waveform. It then determines the maximum positive derivative for each beat. The value of this derivative and the pressure scale at which the waveform was acquired are used to select a derivative criterion which is then used to search for the end-diastolic pressure. Systolic pressure is obtained by averaging all data points within 20 milliseconds of the peak pressure value. The pressure data points within 10 msec of the peak value are then examined and the value closest to the average is taken

as the systolic pressure. Using the training database, this algorithm was tuned to perform optimally when compared with the results of the eight cardiologists. The algorithm was then tested against the cardiologists using the independent test set, for which the correlation coefficient for a total of 410 observations was greater than 0.99. This algorithm will be embedded in the new FORTRAN cath lab system and will serve as a basis for pattern recognition of other pressure waveforms.

E-3. A Computerized Ventricular-Contour Analysis System

Personnel: B. R. Hieb, M.D., Jewish Hospital
G. C. Oliver, M.D., Jewish Hospital

Support: RR 00396
Jewish Hospital

A software system has been developed for the storage and analysis of left ventricular contours. The system permits entry of single-plane ventricular contours from the projected angiographic image using a rho-theta transducer (BCL Monograph No. 55). Each contour is permanently stored using a data compression technique which permits a seven-fold reduction in the amount of computer memory required.[1] The system is designed to permit entry of either diastolic-systolic contours or sequential contours obtained from cineangiographic data. Provisions are also made for storage of demographic data. The stored serial contours can be analyzed to determine regional indices of myocardial contractility.

Modifications to this system during the past year have included the following: 1) Addition of the ability to skip specified frames in a sequential series of contours. This permits the operator to ignore frames which are unacceptable due to insufficient contrast, noise, poor development or other technical problems. Any skipped frames are excluded from computations of contractility indices. 2) The system has been expanded to permit analysis of the stored ventricular contours using a variety of orthogonal and radial grid systems. Analysis is performed such that the same contour series can be analyzed using any or all of the various grid systems. Once analysis has been completed using a particular grid system the results can be output using either the Tektronix 611 storage oscilloscope or the Centronics 306 line printer. 3) Several additional types of analysis output have been added to the system. 4) The patient information section has been rewritten to utilize the new FORTRAN Q and A routines. This simplifies editing the demographic data concerning a given series. 5) A new method of calculating X-ray magnification has been incorporated. This technique is much less sensitive to variations in the optical system used to project the angiograms and

minimizes errors arising from improper positioning of the patient relative to the angiographic apparatus. The new magnification algorithm has been demonstrated to be simpler to use than the previous method and to yield more precise results.

(1) B. R. Hieb and G. C. Oliver, "Compact Digital Storage of Sequential Left Ventricular Contours," Computers and Biomedical Research, vol. 9, no. 1, pp. 1-6, February 1976.

E-4. A Program for Calculating Relevant Parameters Derived from Catheterization Results

Personnel: B. F. Spenner, BCL
H. D. Ambos, BCL
T. A. Gillespie, M.D., Medicine
P. A. Ludbrook, M.D., Medicine

Support: RR 00396

Manual calculations of derived cardiac catheterization parameters are now performed by a FORTRAN program currently executed with the PC/12 computer system located in the Barnes Hospital Coronary Care Unit computer room.

Raw data are entered and edited, by Barnes Hospital Cardiology Fellows, with the use of an alphanumeric keyboard and display device. Derived parameters such as circumferential fiber shortening velocity, stroke work index, ejection fraction, and valve areas are obtained by the cardiologists in a form suitable for inclusion in patient record files.

F. Laboratory Biochemistry

F-1. A Developmental Microcomputer System for Biochemical Instrumentation

Personnel: M. C. Jost, BCL
P. S. Berger, BCL
W. F. Holmes, BCL

Support: RR 00396

The goal of this project is the development of a flexible set of computer modules and systems software suitable for general use with analytical instrumentation. The applications typically require on-line data acquisition and control with modest speed requirements. Most applications involve 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. Typical applications include automation of control, data acquisition, and/or data processing for amino-acid analyzers (F-2), gas chromatographs, spectrophotometers (F-3), and assay systems requiring variable quantities of reagent addition.

Components needed in most systems include:

1. A central processor. Any one of a number of currently available 8 or 16-bit microprocessors has adequate speed and a sufficiently comprehensive instruction set so as to be suitable for use.

2. RAM memory at the 1, 4, or 8K word level.

3. ROM memory for permanent program storage, preferably reprogrammable ROM.

4. A small alphanumeric printer (15-20 characters wide).

5. An alphanumeric keyboard having a reasonable number of special-function keys. The printer and keyboard permit the user to select run parameters and data-processing modes. A monitoring panel with status lights and LED displays is also quite important.

6. An analog input module with a wide range (1 mv to 10 v full scale) variable-gain amplifier and multiplexed analog-to-digital converter.

7. A digital I/O module, for control of relays, valves, DC motors, and stepping motors.

8. A programmable clock.

Certain applications may require floppy disc or cassette tape units for on-line or long-term data storage, or for program storage. An inexpensive TV-based graphic terminal would also be quite useful to most applications.

After consideration of commonly available 8 or 16-bit microprocessors and microcomputers, a Digital Equipment Corporation LSI-11 microcomputer was selected. The basic computer module includes a 16-bit central processor with fixed and floating-point arithmetic capability and 4K of 16-bit RAM memory. In addition, the (mobile) developmental computer system, which can be moved to the site of the instrument for testing, will have two DEC serial interface modules, two 16-bit dual input/output modules, and 4K of 16-bit core memory. An inexpensive, integrated circuit 12-bit analog-to-digital converter, 18-column alphanumeric printer, and an alphanumeric keyboard with 18 special function keys have also been selected for use. Design of interfaces for these components is now in progress. Program development initially will be done using the LSI-11 paper-tape software package loaded from a Teletype. In the near future, a dual floppy disc system with the RT-11 operating system will be available for use and will greatly simplify program and system development. The software for the initial project, processing the output of a new amino-acid analyzer (F-2), has been specified to the detailed flowchart level.

To minimize the cost of individual instrument processors, low-cost modules will be developed to replace the relatively expensive DEC I/O and memory modules. Using new LSI interface circuits which have been developed for microprocessors, the common data-acquisition and control functions can be placed on a small number of inexpensive modules. Thus, most new instrument applications will require little or no digital design, allowing concentration on the software. Programs will be stored in erasable ROM's after completion. The core memory in the development system will serve as a conveniently alterable substitute during checkout of a new instrument processor.

F-2. A Microprocessor Controller for Amino-Acid Analysis

Personnel: S. R. Holmes, B.S., Biochemistry
L. J. Banaszak, Ph.D., Biochemistry
G. R. Barbarash, B.S., Biochemistry
P. S. Berger, BCL
W. F. Holmes, BCL

Support: RR 00396
GM 13925

A small MCS-4 microprocessor system originally designed for monitoring the output of a liquid chromatograph (PR 11, F-7) has been adapted for use with a new amino-acid analyzer designed to extend the chemical characterization of proteins to much smaller samples. The microprocessor acts as a programmed controller for the motorized buffer-switching valve that determines the sequence and duration of buffer solutions pumped through the analyzer column. The new analyzer achieves faster separations and works with much smaller quantities of amino acids than standard analyzers, but requires more care in the adjustment of buffer switching times to produce routine, quantitative separations.

Modification of the MCS-4 system required little change to the basic hardware, which has several unused I/O parts prewired. A three-channel solid-state switching box was designed for controlling 110 VAC devices by means of microprocessor output commands. One channel goes to a motorized six-way valve, which was modified so that a single adjustable power pulse, nominally one second, could switch the valve to the next setting. A manual override switch was also provided. The second channel is used to automatically turn off the pumps, water bath, and recorder at the end of an analysis. The third channel controls a pneumatic valve which will be used for switching another detection solution into the output stream during elution of proline.

BCD thumbwheel switches are used to set the dwell time in 0.1-minute units for each position of the six-way valve. LED displays allow verification of these settings, should the user wish to adjust some of them before a new analyzer run. During the analysis, the time remaining at the current valve setting is displayed so that the progress of the analysis can be visually monitored. After the analysis is complete, including reconditioning of the column, the six-way valve is reset to the starting position, ready for a new run. The program is controlled by four switches which are coded for the user as, 1) turn/keep power on, 2) set timers, 3) examine timers, 4) start run. The MCS-4 system itself is never powered down, so that the timer settings, which reside in semiconductor memory, are always set to the last values entered. The program itself resides in erasable ROM. The output of the amino acid analyzer will be processed by a new LSI-11 microprocessor system under development (F-1). The sensitivity of the new analyzer causes amino-acid peaks imposed on large and noisy baselines of complex shape, sometimes containing false peaks. Thus, detection methods used on standard analyzers

will not be sufficient, and may require signal processing techniques similar to those under investigation for gas chromotography mass spectrometry (F-4).

F-3. Cary Spectrophotometer Paper-Tape Punch Interface

Personnel: M. C. Jost, BCL
W. F. Holmes, BCL
C. M. Jackson, Ph.D., Biochemistry

Support: RR 00396
HL 12820
HL 14147

The kinetics of activation of several blood clotting factors are under study using a Cary double-beam scanning spectrophotometer. Since the blood clotting system has many components, kinetic analysis of the data is underway using a PDP-12 computer equipped with a floating-point processor. The spectrophotometer is capable of generating a large quantity of data, thus a convenient method for computer input has become quite important. Using the digital panel meter output of the spectrophotometer, a punched-paper-tape interface has been designed. In a later design phase, this interface will be adapted to an LSI-11 microcomputer system (F-1) which will provide direct digital control of the spectrophotometer along with preliminary data processing.

Using control lines from the digital panel meter of the spectrophotometer, the interface initiates analog-to-digital conversion of the spectrophotometer's output. Upon completion of this conversion, the interface reads the binary-coded-decimal data and status outputs from the digital panel meter which are converted to 8-bit ASCII code and sent serially at 110 baud to a Teletype equipped with a paper-tape punch. The spectrophotometer data are followed by the output from a binary coded decimal counter within the interface which indicates the relative sample time since data acquisition began. The resulting punched paper tape will provide input to the PDP-12 computer. Using this interface, data may be acquired from the spectrophotometer at the rate of one sample every 0.8 seconds, which is adequate to study the kinetics of blood clotting.

F-4. Parameter Estimation for Mass-Spectrometry Data

Personnel: P. M. Fishman, BCL
W. F. Holmes, BCL
J. Markham, BCL
D. L. Rempel, M.S., Biochemistry
W. R. Sherman, Ph.D., Psychiatry
D. L. Snyder, BCL

Support: RR 00396
Washington University

Shortly, there will be four gas chromatograph mass spectrometers in use at the Washington University Medical Center for the identification and quantitation of small amounts of compounds in biological fluids and tissue samples. Many problems arise in data analysis of mass spectrometer output due to partial separation of the mixtures by the gas chromatograph plus a variety of noise sources, some chemical and some electrical. We have begun to investigate the applicability of signal processing techniques to such data. This effort was judged to be particularly inviting since on-line computers are already in use to automate the data-collection process. Our effort up to now has consisted of a literature search to determine what the current state of signal processing technology is in this area, and also of a number of formal and informal meetings with various users of the mass spectrometers to determine what they felt to be outstanding problem areas in their own research. Broadly, the following areas have been identified as potentially fruitful for BCL participation: (1) automatic library identification of unknown compounds from their spectra, (2) extraction of pure spectra from mixtures of unknown compounds, (3) precise measurement of the relative amounts of known compounds using selected masses which are unique to the compounds. We have decided at present to concentrate our efforts on the last problem because it is most easily described in terms of mathematical models, and because its resolution is of importance to a number of ongoing research efforts at Washington University. We are now implementing a number of straightforward statistical techniques, and are also obtaining a physical characterization of the GC-MS system and its limitations. Such a characterization will be of use in deciding between alternative approaches to processing the data.

F-5. Computer Simulation of the Kinetic Properties of Enzymes

Personnel: C. Frieden, Ph.D., Biochemistry
P. E. Bock, Ph.D., Biochemistry
W. F. Holmes, BCL

Support: RR 00396
AM 13332
GB 26483

The PDP-12 computer simulation system (PR 9, G-12) has been used for analysis of: 1) full time stopped-flow data obtained with isozymes of malate dehydrogenase,[1] 2) coupled enzyme systems and 3) the pH, temperature and ligand induced inactivation and reactivation of phosphofructokinase.[2-4] In all cases the fits are made by assuming a mechanism which is consistent with all the data obtained, and visually matching the real data with the simulated kinetic curves using an interactive display.

[1] C. Frieden and J. Fernandez-Sousa, "Kinetic Studies on Pig Heart Cytoplasmic Malate Dehydrogenase," Journal of Biological Chemistry, vol. 250, p. 2106, 1975.

[2] P. E. Bock and C. Frieden, "Phosphofructokinase I. Mechanism of the pH Dependent Inactivation and Reactivation of the Rabbit Muscle Enzyme," Journal of Biological Chemistry, in press.

[3] P. E. Bock and C. Frieden, "Phosphofructokinase II. Role of Ligands in pH Dependent Structural Changes of the Rabbit Muscle Enzyme," Journal of Biological Chemistry, in press.

[4] C. Frieden, H. R. Gilbert and P. E. Bock, "Phosphofructokinase III. Correlation of Regulatory, Kinetic, and Molecular Properties of Rabbit Muscle Enzyme," Journal of Biological Chemistry, in press.

G. Speech and Hearing

G-1. A Two-Dimensional Model of Cochlear Mechanics

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

Support: RR 00396

A two-dimensional model of cochlear mechanics has been developed with the structure of the cochlea represented by two fluid-filled rectangular-chambers separated by a partition defined by its specific acoustic impedance. The symmetry of the two rectangular-chambers, about the partition, allows the model to be reduced to a single-chamber fluid system bounded on one side by a partition with appropriately redefined impedance characteristics. A further reduction of model complexity is accomplished by considering separately the properties of the partition and the fluid. Energy loss as well as kinetic and potential energy storage are considered for the partition but only kinetic energy storage is included for the fluid. Neglecting both the loss and potential energy storage of the fluid is equivalent to neglecting its viscosity and compressibility and leads to a mathematical description in terms of Laplace's equation.

The mathematical development of the model produces a closed-form expression describing the motion of the fluid and partition at their adjoining boundary. Such an expression requires that both the fluid system and partition have a compatible relation between pressure and acceleration along this boundary. The fluid system relation is found by solving Laplace's equation for the acceleration distribution along the partition boundary resulting from a pressure source located on the same boundary. Laplace's equation is solved with the aid of Green's theorem and a well-defined mathematical approximation. This approximation imposes a spatial frequency constraint on the solution, but has the advantage of producing a spatially-discrete model. A second relation which defines pressure in terms of acceleration is derived directly from the impedance of the membrane.

This second relation is then combined with the fluid relation to form a time-dependent expression that models the operation of the partition boundary. Solution of this time-dependent expression has been accomplished in the time domain using discrete integration techniques and in the frequency domain using Gauss elimination.

The development of this model was motivated by desires to study the effect of introducing partition non-linearities, and to analyze the cochlear response to stimuli such as speech. The model allows the introduction of partition non-linearities because the solution of the fluid system is independent of the partition characteristics. The analysis of speech and other temporally complex sounds is facilitated by the time-domain solution.

G-2. The PC Speech and Hearing System

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
D. H. Eldredge, M.D., Central Institute for the Deaf
S. A. Garfield, BCL
M. T. Hakkinen, BCL
J. D. Miller, Ph.D., Central Institute for the Deaf
D. A. Ronken, Ph.D., Central Institute for the Deaf
J. W. Sharp, Central Institute for the Deaf
N. R. Vemula, BCL

Support: RR 00396
NS 03856

The speech and hearing computer system continues to provide support for various research activities including a number of on-going studies that use the system on a daily or weekly basis. These are MEGS test evaluation (G-7), glottal wave studies (G-4), experiments with electrotactile stimulation (G-6), signal calibration and data analysis of CM experiments in the Physiology Laboratory (G-8), studies of LP analysis and a model of the vocal tract (G-5). Numerous sets of stimulus sounds have been synthesized from "prescriptions" in the form of functional block diagrams of synthesis models and parameter traces. These include synthesis of a set of noise pulse stimuli, a BA-DA-GA series, and a series of male, female, and children vowels and dipthongs.

The capability for programming a variety of speech models has proven useful in relating the results of new experiments in speech perception to the results of older studies reported in the literature. For example, a version of the Haskins Speech Synthesizer has been implemented. Since subtle differences in the implementation can influence the experimental results, an attempt was made to simulate the circuitry of the Haskins synthesizer exactly. Characteristics such as gain factors, time constants, and frequency response measurements at intermediate points in the circuit were compared with measurements taken at Haskins. The similarity of the sounds recorded at Haskins and here, using the same parameter tables, were evaluated through listening tests and comparison of spectrograms and waveforms. Except for slight differences in the waveforms (relative phase of components), the sounds are identical. Using this model, several stimulus sets, including BAE-DAE-GAE, KA-GA, PA-BA, and TA-DA series, have been synthesized for use in comparative psychoacoustic experiments at CID.

A second disc drive has been added to the system to make it possible to use one removable cartridge as a system disc, one removable cartridge as a data disc, and have two fixed discs available as temporary storage buffers. To accomodate this change all programs and subroutines which use the RAP format were modified to use the second disc drive as the RAP disc and to allow all 812 tracks to be accessed. Library utility routines were improved and updated, and several new commands, programs, subroutines,

and functions were added to the library. The two-channel analog system (8 inputs and 4 outputs per channel) that has been designed and built over the past year will be checked out and added to the system this summer. The increased analog capability will make it possible to accomodate binaural experiments at a 20 kHz sample rate and applications involving multiple analog inputs and outputs at reduced sampling rates.

The macromodule display controller used with the system is scheduled to be replaced in the near future by a microcomputer system consisting of an LSI-11 microprocessor with 12K of memory for program and display storage and a two-channel DAC interface.

G-3. A Computer System for Auditory Research

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

Support: RR 00396
NS 03856

An outgrowth of the CID-BCL collaborative project is the development of an overall plan for economical deployment of small computer systems in the Research Department of CID. This plan includes the installation of a central computer system that will be shared by the various individual laboratories and a number of simpler, but compatible, lab systems that will be installed in each laboratory.

In addition to providing programming support for the lab systems, the central system will have additional features to support other types of research tasks such as data analysis and display and model simulation. The lab systems are an extension of the RAP concept (PR 9, G-1; PR 10, G-1) and will be used primarily for on-line data collection and stimulus control.

G-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

Support: RR 00396
NS 03856

In the past, accurate investigation of the glottal source has been limited to several complicated and difficult procedures, such as inverse filtering or high-speed photography of the vocal folds themselves. A much simpler method[1] was used in a preliminary investigation of the voice-source characteristics of deaf and normally-hearing children. In the preliminary study, the measuring device was a three-foot hollow tube, one inch in diameter, into which a wedge was placed. The subjects were asked to intone a long neutral vowel (schwa) into the open end of the tube, and the sound was picked up by a microphone fitted into the middle of the tube. The tube acts as a reflectionless extension of the vocal tract and has the effect of almost totally eliminating the vocal-tract resonances.

In this preliminary study, the glottal source of 28 hearing-impaired and five normally-hearing adolescents were compared with respect to waveshape and spectrum. Significant differences between the deaf and normal talkers were observed in: (1) waveshape appearance, (2) phase spectrum, and (3) intensity spectrum. The normal glottal wave appeared to have a long opening phase and a sharp and abrupt closing phase. For some of the deaf subjects, the waveshape appeared reversed with respect to normal: the opening phase was abrupt and the closing phase was long and gradual in slope. It was noted that for the typical normally-hearing subject, the second component was nearly 180 degrees out of phase with the fundamental, while for many of the deaf subjects the fundamental and the second component were nearly in phase. The intensity spectrum of the normal glottal source typically falls off at a rate of -12 dB per octave, whereas the intensity spectrum for many of the deaf subjects falls off at a much steeper rate, e.g., -15/-18 dB per octave or greater. Period abnormalities (recurrent abnormal periods), which would appear to indicate diplophonia, were noticed in two of the deaf subjects but in none of the normal subjects.

Recently, we have improved significantly on the reflectionless tube used as a measuring device. A new tube, six feet long, was constructed that can be disassembled into two parts to facilitate handling and cleaning. It was discovered that the best material for construction of the acoustic wedge is polyurethane foam. The wedge itself is three feet long, and although it is physically wedge-shaped, it acts in reality as a combination spatial/density wedge, since it is squeezed tightly into the tube at the farthest end. Using this foam wedge, we obtain a frequency response that is flat ($\pm$ 1.2 dB) from 20 Hz to 10,000 Hz.

In addition to the improvement of the reflectionless tube, the experiments have been moved to the sound booth near the Speech and Hearing computer system so that the glottal signals can be sampled on-line. This eliminates the tape recorder that was necessary before the change was made and improves the low frequency characteristics of the overall recording system. Analysis of the glottal-wave data is done with the assistance of the speech-examiner program (PR 11, G-5).

At present, glottal source data are being collected from normally-hearing male and female adults. Each subject is asked to phonate in the following ways: (1) normal voice; (2) loud voice; (3) soft voice; (4) rising and falling glides (approximately "words" with interrogative and declarative intonation respectively); (5) three-syllable "words" containing one stressed and two unstressed syllables each; (6) falsetto and "creaky" voice. The glottal wave data are analysed in terms of (1) waveshape characteristics; (2) frequency and runs intensity; (3) phase and intensity spectra. With regard to the above characteristics of the glottal wave, the following questions are asked: (1) what happens to the glottal wave when speakers change fundamental frequency or change intensity; (2) what happens to the glottal wave when speakers produce a stressed rather than an unstressed syllable; (3) what kinds of glottal wave differences obtain between males and females.

While the results of the study cannot all be summarized in this report, the following preliminary generalizations appear warranted: (1) for all speakers, there appears to be a range of fundamental frequency over which the closing phase of the glottal wave maintains a relatively fixed time interval and over which the closing phase of the wave consequently increases as a percent of the total period with increasing fundamental frequency; (2) the spectral slope of the glottal wave typically falls off more steeply than the -12 dB/octave cited in the literature. In fact, in most conditions of phonation, the slope of the glottal wave changes with frequency in such a way that the actual spectral envelope tends to remain constant in the presence of frequency change; (3) dips in the spectrum often appear at 800-900 Hz, 1300-1600 Hz, and 2400-2600 Hz. The slope of the spectrum falls off less steeply below 1000 Hz and more steeply above 1000 Hz; (4) male-female differences in glottal wave characteristics appear to be similar to differences of lower versus higher frequency of phonation in the male.

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

G-5. Speech Modeling (LP Analysis and Vocal Tract Model)

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

Support: RR 00396
NS 03856

The evaluation of a linear prediction method of speech analysis as a possible training-aid display for the deaf is continuing. A major drawback of the method seems to be the inadequacy of the linear prediction speech model in describing pathological speech. Accurate vocal tract area-function estimation depends strongly on removing the glottal source and lip-radiation functions from the vocal tract transfer function. For a reasonable class of speech sounds spoken by normal talkers these contributions can effectively be removed by a 6 dB/octave preemphasis of the speech wave. In doing so it is presumed that the glottal source spectrum decreases 12 dB/octave and that the lip radiation adds a rising 6 dB/octave slope to the overall speech spectrum.

Recent measurements of glottal waveforms (G-4) suggest that the source characteristics of deaf talkers can deviate significantly from the idealized 12 dB/octave spectral slope and that the source characteristics for normal talkers are also variable, but less so. We will continue to study the errors introduced into the linear prediction analysis by source function variations as more data are available from glottal wave measurements.

A related study that has been started is the implementation of a vocal tract speech model that includes a self-oscillating glottal source. The model will be used in an attempt to associate variations in glottal waveforms that are observed for hearing and deaf talkers with physiological changes for the model such as subglottal pressure, vocal cord stiffness and tension and degree of vocal cord separation.

In the model, the masses representing each vocal cord are parts of mechanical oscillators with springs and damping. The springs have nonlinear characteristic and represent the tension of the cords. The contact force at the collision of the vibrating cords during the glottal closure is similarly modeled by a nonlinear spring. Damping is assumed to be piecewise linear, increasing step-wise on the glottal closure, corresponding to the stickiness of the soft and moist contacting surfaces. The masses are internally coupled by a linear spring representing the flexural stiffness in the lateral direction.

The vocal tract is represented by a transmission line consisting of N cylindrical hard-walled sections. The sectional areas of these N sections approximate the continuous tract shape. The inductances and capacitances are taken to be those of cylindrical pipes and the resistances corresponding to the viscous loss at the pipe wall. A multiplicative coefficient is applied for the resistances to produce formant bandwidths that are natural in human speech. The transmission line is terminated in a

radiation load equal to that of a circular piston in an infinite baffle. In order to synthesize unvoiced sounds, every section in the tract is provided with a random noise source. The pressure and resistance of each noise source is a function of the volume velocity and cross-sectional area of each section.

The model is simulated on the speech and hearing computer system. As a practical matter of implementation, the differential equations representing the cord and tract behaviour are transformed into first backward-difference equations. N independent random number generators with uniform probability distribution over [-1,+1] are employed to simulate the turbulent sources in the N sections. In our simulation N varies from 4 to 18 sections. For stability, two identical equivalent circuits are taken, each representing the cords and the tract. The first circuit has the subglottal pressure as the source and generates only voiced sounds, whereas the latter circuit has random noises as the sources and generates only unvoiced sounds. The resultant pressure at the lips is equal to the sum of those from the voiced and unvoiced circuits.

Our experience shows that the model duplicates the cord and tract behaviour realistically. Glottal area and volume velocity waveforms obtained from the model are consistent with the earlier experiments elsewhere. Studies of the variation of the waveforms in the model with respect to the parameters such as cord stiffness, quiescent position and tension of the cords, tract shape and subglottal pressure have begun. In the near future we plan to make modifications in the simulation to incorporate the nasal tract, the effect of the yielding side wall of the tract, which in reality vibrates with the sound pressure in the tract, and the radiation of sound from this side wall.

G-6. Experiments in Tactile Loudness with a Single Channel Electrocutaneous Device

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

Support: RR 00396
NS 03856

A single channel version of the electrocutaneous sensory aid developed by F. A. Saunders at the Smith Kettlewell Institute in San Francisco has been built and is presently being used with a bipolar concentric silver skin electrode supplied to us by Dr. Saunders. This device has been interfaced to the Speech and Hearing system which is programmed to deliver a series of N biphasic constant current pulses per burst, at a burst rate of R bursts/sec. The maximum value of N is limited so that no more than half the burst interval is filled with pulses. Pulses occur every 0.1 msec, R is usually about 100 bursts/sec, and N varies between 1 and 50, depending on the sound stimulus intensity.

Present experiments are directed at measuring how the loudness sensation varies with N. In a preliminary experiment the subject's ability to absolutely identify N during a half-second stimulation period was measured. For these experiments, R was 156 bursts/sec and N was varied randomly from 1 to 16. The electrode was placed on the back of the hand between thumb and forefinger. The subjects were instructed to initially set the pulse duration so that, with N=1, the stimulus was just above threshold. With this technique low values of N could be easily distinguished from one another (e.g., N=1 was almost never confused with N=2), but as N got larger, the degree of confusion got larger (e.g., values of N between 12 and 16 were readily confused).

In a second experiment a third parameter, P, the probability of occurrence of a pulse at any time that a pulse would normally occur was included in addition to N and R. In this way, a stimulus with fractional N (=P×N) could be produced. In addition the identification paradigm was abandoned and a cross-modality matching (CMM) of the loudness of the tactile stimulus to that of an auditory pure tone was used. The basic task was to preset P and R, and have the subject adjust the intensity of an alternating pure tone for equal loudness as a function of N.

The function relating N to pure tone intensity could be obtained quickly (less than an hour for two repetitions of 10 values of N) and reliably. It gave us a measure of the dynamic range of the tactile stimulus. For example, the matching tone covered a 70 dB dynamic range with the electrode placed on the hand and N varied from 1 to 32. However, the jump in sensation from N=1 to N=2 accounted for almost 40 dB of this

70 dB range. Indeed it was possible to obtain intermediate sensations between those of low, whole numbered N using the P parameter. However, a similar result was obtained by simply having the subject reset his threshold at an N of 3 instead of the previous value of 1. The 40 dB change in tone intensity was now covered when N changed from 3 to 6, so that intermediate N gave intermediate loudness sensations.

Using this CMM procedure, loudness growth at three body sites were compared: the back of the hand between thumb and forefinger, the abdomen, and the earlobe. The latter location involved an ear-ring arrangement with the active and ground electrodes on outer and inner surfaces of the lobe respectively. A tone could be reliably matched at all three sites. However the tone-matching range varied considerably: 70 dB for the hand, 50 dB for the abdomen and 30 dB for the earlobe.

G-7. MEGS: A System for Speech Reception Testing

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

Support: RR 00396
NS 03856

The MEGS system (PR 11, G-7), has been tested further using two normally-hearing high-school students as subjects. Each subject was tested at nine different signal-to-noise ratios (-12 dB to noise off) on three sets of English speech sounds. The three sets were: (1) an exhaustive set of final consonants and consonant clusters (55 total), (2) an exhaustive list of final syllabic clusters (62 total), and (3) a list of vowel nuclei (20 total). All three tests showed subject 1 to be slightly worse than subject 2. The results also showed the vowel nuclei test to be the easiest. The final syllabic ending test was more difficult and the final consonant and cluster test was most difficult.

The system has been further validated by showing that small differences in subjects' speech reception capabilities can be seen with several different sets of speech sounds.

G-8. Analysis of Cochlear Nonlinearities Through Study of Microphonic "Signatures"

Personnel: D. A. Ronken, Ph.D., Central Institute for the Deaf
D. H. Eldredge, M.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

Cochlear microphonic (CM) as recorded using gross differential electrodes, provides an important indicator for auditory processing along the basilar membrane that precedes the transduction to neural responses. The principle objective of this project has been the measurement of frequency-dependent nonlinearities in the cochlear microphonic responses of the chinchilla. Recent experiments have been directed towards examining distortion products that are known to be present in the responses of individual auditory nerve fibers and are perceptible to human listeners.

To study these distortion products, three pairs of differential electrodes are used to measure responses from the basal (CM_1), second (CM_2), and third (CM_3) cochlear turns. The signals most frequently used have been complexes of two tones with equal sound pressures, with fixed phases, and at moderate intensities. The stimulus waveforms are synthesized digitally with corrections incorporated to compensate exactly for the frequency characteristics of the recording system, the transducer, and the acoustic coupling into the animal's ear including effects of acoustic resonances peculiar to the ear canal and tympanic membrane of individual chinchillas.

The nature of the preliminary results is as follows. The major properties of CM responses[1] are confirmed. The relatively linear CM_1 responses at moderate levels serve as good controls and place the source of these interesting nonlinearities in the cochlea. The nonlinear responses from the second and third turns are similar but occur at appropriately different frequencies. Two-tone interference is a prominent feature of many components of the responses.

A two-dimensional frequency space is required to characterize the set of two-tone combinations used for signals. Thus a third dimension is required to characterize the magnitude of any component of the CM response as functions of the two-dimensional frequency space. Such functions can be generated for the set of higher primary frequencies, for the set of lower primary frequencies, for any order of harmonic or combination tone, or for the sets of phases for any of these and each such set can be viewed as a three-dimensional surface. These surfaces for most components are complex when compared to the pure-tone response and the complexities appear to relate to two-tone interferences. The phases for many nonlinear components are often not simply predicted from knowledge of the phases of the primary tones. Because these responses defy simple interpretation we have started complementary projects in which CM sources in selected regions of the cochlea are suppressed by exposures to noise or altered in other ways.

Current emphasis is on experiments designed to analyze individual complexities in the observed responses. Since the CM voltages are small for the moderate sound pressure levels used in the experiments, a number of responses are averaged for each stimulus condition to enhance the S/N. As a consequence of working with such low-level responses, it was necessary to test the procedure to determine if any direct coupling from the transducer to the electrodes was contaminating the results. Experiments with two different sound sources (one located a considerable distance from the animal) verified that no significant transducer artifacts are present in the CM responses.

Within the past year, a new laboratory facility for these experiments has been completed. Because the classic LINC computer available near the animal preparation is not able to meet the data processing requirements, the Speech and Hearing System is used for stimulus preparation and for data retrieval, analysis and display. Actual data collection in the laboratory is controlled by the LINC, which is interfaced to a disc (mRAP) that has removable disc cartridges. In addition, mRAP has an 8k-word memory accessible to the LINC and its own A/D and D/A converters. These features are needed for current experiments where the data rate is 240,000 bits per second and more than a million words of data storage are required.

To obtain valid stimulus and response representation, it has been found necessary to use double-precision addition for signal-to-noise enhancement. Response waveforms normalized to 12 bits are obtained by the LINC and stored in disc cartridges for subsequent analysis. Previous experience has shown that the waveform analysis by Fast Fourier Transform methods must be done in floating point form. Since these computations are impractical on the LINC, analysis is done off-line on the Speech and Hearing System. Waveform synthesis is also done on this system, using inverse Fast Fourier Transforms weighted by transfer functions that are used to standardize the acoustic input for each individual animal. Communication between the two computers is principally by exchange of disc cartridges. However, a phone line communication link is available for certain applications. Using these signal processing procedures, a 60 dB signal-to-noise ratio is attained for the precisely controlled arbitrary sounds.

(1) D. H. Eldredge, "Inner Ear - Cochlear Mechanics and Cochlear Potentials," Handbook of Sensory Physiology, W. D. Keidel and W. D. Neff, eds., Berlin, Heidelberg, New York; Springer:Verlag, pp. 549-584, 1974.

(2) D. A. Ronken and D. H. Eldredge, "Retrieval of Data by Attribute Using Parameter-Flagged Data Storage," Chapter 27, Computer Technology in Neuroscience, Paul B. Brown, ed., Hemisphere Publishing Corporation, Washington, London, 1976.

H. Supporting Activities

H-1. Microprocessor Development Support: Overview

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

Support: RR 00396

The utility of microprocessors has resulted in their application to both clinical (A-18, H-7) and laboratory (F-2, H-5, H-8) projects. However, if the microprocessor is to become the basis of an increasing number of designs, then the complexity of implementing a microprocessor system must be reduced. A microprocessor properly configured in a system rarely provides adequate capability to support program development or a console to facilitate hardware/software debugging.

Commercially available support systems are typically designed to operate with a limited set of available microprocessors. As their cost range is between $2,000 and $10,000, the impracticality of purchasing a large variety of support systems tends to constrain applications to the utilization of a particular microprocessor.

Our efforts have been directed toward the development of a support capability which should allow us to capitalize on the rapid evolution of microprocessor technology. The components of the support system, a FORTRAN-based cross-assembler, FOCRAS, (H-2), an intelligent console, InC, (H-3) and a ROM programmer (H-4) are currently available.

H-2. Microprocessor Development Support: Software

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

Support: RR 00396

A structured FORTRAN-based cross-assembler, FOCRAS, has been developed to facilitate software support for a variety of microprocessors. The modular construction of FOCRAS minimizes the programming effort required to generate cross-assemblers for different microprocessors' order codes and addressing modes.

A variety of languages for writing cross-assemblers was explored, including assembly language, MUMPS, and FORTRAN. Comparisons of the approaches and a detailed description of FOCRAS are available.[1] A brief comparison of execution times for a sample microprocessor program follows:

Table 1.

Execution Time Comparisons for Three Cross-Assemblers

	ASSEMBLY LANGUAGE		MUMPS		FORTRAN	
	TIME (MIN:SEC)	LINES/SEC	TIME	LINES/SEC	TIME	LINES/SEC
PRINT (1)	1:20	0.95	15:10	0.084	3:15	0.39
PRINT TO DISC(2)	0:04	19.0			2:33	0.50
PRINT TO DUMMY(3)	0:02	38.0				
NOLIST(4)					0:57	1.33

(THE ABOVE TIMES ARE FOR A TYPICAL PROGRAM OF 76 STATEMENTS.)

For all options, object is output to disc file:

(1) Hardcopy listing on a Centronics 101, (165 char/sec. max. rate).

(2) Output listing to a cartridge disc file.

(3) Output listing to dummy device.

(4) By-pass listing routine.

FOCRAS cross-assemblers currently support Motorola M6800, Intel 8008, and Intel 8080 microprocessors, and are operational on Texas Instrument 980B and Interdata Model 70 minicomputers.

(1) D. Ungar, G. J. Blaine, and B. F. Spenner, "Microprocessor Development Support: Software Viewpoint," BCL Monograph No. 291, June 1976.

H-3. Microprocessor Development Support: The Intelligent Console

Personnel: B. F. Spenner, BCL
G. J. Blaine, BCL
R. K. Hartz, BCL

Support: RR 00396

The development of microprocessor-based equipment requires the use of support systems which allow program execution to be controlled and monitored. Because of the operational restrictions and relatively high cost of specialized support systems, once a particular processor is chosen and a support system is purchased, it becomes difficult and expensive to justify a future selection of an alternative processor, even if it would be otherwise more appropriate. The Intelligent Console (InC) was designed to remedy this situation by providing a device capable of operating with any one of a number of different microprocessors.

The InC can be defined in terms of its three functional components: a user's console, which consists of hexadecimal input switches and hexadecimal LED displays; a plug module, which is inserted between the subject-microprocessor and its connection with the subject system; and the InC microprocessor, which controls the operation of both the console and the plug module. Initial plans for the InC are to establish its operation with the Motorola M6800 microprocessor, while future plans will see the InC operating with both Intel and National microprocessors.

One of the InC's principal features is its ability to retrieve the contents of the subject microprocessor's internal registers, without requiring the subject system to execute an interrupt or provide memory space for special console programs. A technique defined as "out-of-line programming" allows the InC, rather than the subject-system memory, to define the instructions which are to be executed by the subject microprocessor. Using this technique, the InC causes the subject microprocessor to sequence through a set of operations where the microprocessor's internal registers are made available externally. After acquiring the contents of the internal registers, the out-of-line program places the subject microprocessor into the same state as was present prior to the execution of the out-of-line program.

Combination of the InC, the PROM programmer (H-4), and software support facilities (H-2) provides a complete microprocessor development support system.

H-4. Microprocessor Development Support: Erasable ROM Programmer

Personnel: R. D. Camuto, B.S., Electrical Engineering
R. M. Arthur, BCL
D. R. Jones, B.S., Electrical Engineering

Support: RR 00396
Washington University

A programmer for Intel type 2704 and type 2708 erasable read-only memory has been designed and constructed as a peripheral for a Texas Instruments 980 computer.[1] The programmer is interfaced to the TI 980 via a 16-bit digital input/output module. Eight bits of the output port are used to transfer information to be programmed into either the 512-byte 2704 or the 1024-byte 2708. The data to be programmed are connected to the EROM through a latch circuit. Ten bits of the output port are used to transfer the address in the EROM where the data are to be stored. Additional output bits are employed to control discrete components which apply programming and chip-select pulses to the EROM. The input port is used to read EROM contents to verify the programming process.

Software developed for the TI 980 regulates the duration and sequence of events in the programmer. The EROM is first tested to be sure it has been properly erased. After programming, all EROM locations are read and their contents compared to the data which were supposed to be stored. An error message is displayed if the EROM was not erased before programming and another is seen if errors occurred during programming. A list of errors and their location in EROM is also produced.

The procedure for operating the programmer is simple. Tasks are executed under the MIST operating system on the TI 980 via a single BATCH instruction in which the object file to be stored in EROM is specified. The object file is produced by the FOCRAS cross-assembler (H-2). The entire process takes 3 minutes for type 2704 and 5 minutes for type 2708 EROM. Both are erased by 20 minutes exposure to ultraviolet radiation.

[1] R. D. Camuto and R. M. Arthur, "Programming Type 2704/2708 Erasable Read Only Memory," BCL Monograph No. 286, June 1976.

H-5. A Microprocessor Laboratory Unit for Signal Processing

Personnel: A. L. Bodicky, BCL
G. J. Blaine, BCL
J. A. Ritter, BCL
B. F. Spenner, BCL

Support: RR 00396

A microprocessor configuration, utilizing the Motorola M6800 microprocessor, was designed and implemented to act as a useful tool for digital signal processing experiments and to gain experience with microprocessor support problems. Analog signals can be sampled, digitized, stored, digitally processed, and reconstructed.

The signal processor includes integrated-circuit active filters for both presample filtering and reconstruction. A fast integrated circuit sample-and-hold amplifier, a 12-bit 10 microsecond analog-to-digital converter and a 12-bit digital-to-analog converter are controlled by the M6800 microprocessor.

A separate analog comparator amplifier is included to allow analog-to-digital conversion under program control, thus providing a demonstration facility for converter techniques such as ramp, and successive approximation. For this purpose, amplifiers are also included to allow the use of a microphone for input and a speaker for output. Speech and/or audible tones are useful to demonstrate frequency-folding effects in sampling and reconstruction.

The signal processor laboratory unit currently supports 256 bytes of random-access memory, 512 bytes of read-only memory and 512 bytes of EPROM.

H-6. An Emergency Unload Fault Monitor for the Pertec Disc

Personnel: S. R. Phillips, BCL
B. F. Spenner, BCL

Support: RR 00396

With sixteen Pertec disc drives now in operation in BCL-related computer systems, it became desirable to be able to detect which of nine potential fault conditions is responsible for an emergency unload action. A fault monitor was designed and constructed which senses and stores any combination of faults through a cable which connects to an existing socket in the disc drive. The fault conditions thus stored, are displayed by LED lamps on the fault monitor control panel. This information allows quick assessment of many fault conditions which are present for only a short time before emergency unload occurs.

H-7. Optical Pen Reader for Diagnostic Radiology

Personnel: M. C. Jost, BCL
R. M. Arthur, BCL
R. G. Jost, M.D., Radiology

Support: RR 00396
Washington University

Further studies have been done with the minicomputer and microprocessor-based bar-code reader systems described previously (PR 11, H-7).[1] Using the minicomputer-based system, experiments have been carried out with 25 subjects to observe individual variations in sweep speed, acceleration, and pen tilt angle. A RS-232C driver module has been incorporated into the microprocessor-based bar-code reader to permit transmission of serial ASCII output of the decoded characters to a central computer (PDP-11/40). Provision has also been made for using this microprocessor-based decoder unit in conjunction with a standard computer terminal. In this way a keyboard is provided for manual entry of patient identification and function information whenever necessary, and messages from the central computer may be received and displayed.

A preliminary design of a multiplexer capable of handling 64 of the microprocessor-based pen-reader units, each transmitting simultaneously at 2400 baud, has been completed. This has permitted comparison of the performance of a system where decoding is done at the pen-reader terminals with that of commercially available systems where decoding is done at a multiplexer servicing several pen-reader terminals.

[1] M. C. Jost, R. G. Jost, R. M. Arthur, R. L. Hill, and R. G. Evens, "The Use of Optical Bar Codes in Radiology," presented at the 61st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, December 1975.

H-8. A Universal Storage Device

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

Support: RR 00396

The need has been identified for a portable stand-alone device which is capable of recording analog signals for later analysis using a digital computer. The design of the Universal Storage Device attempts to satisfy

these recording needs in both the laboratory and clinical environments, while providing the facility for replaying the recorded data in digital form to any computer equipped with an asynchronous serial interface port. The issue of providing replay data in a form acceptable to most computer systems is therefore resolved by establishing the device as one which relies on plug compatibility rather than media compatibility. The Universal Storage Device assures plug compatibility with most computers by using the RS-232 asynchronous serial interface specifications to define the operation of the storage device's plug.

The analog section of the storage device consists of four analog input channels multiplexed into one channel which is then connected to a 12-bit analog-to-digital converter. The digital data coming from the analog-to-digital converter are stored on a dual-density floppy-disc drive, which provides a total unformatted storage capacity of 6.4 Mbit. The data transfer rate and access time provided by the floppy disc require that the sampling rate of the analog-to-digital converter be limited to 1024 samples per second. The user of the storage device has console controls which allow him to: start and stop the recording process, select the number of analog channels to be recorded, and specify the rate at which the analog channels are sampled. Control functions necessary for the operation of the Universal Storage Device are provided by a Motorola M6800 microprocessor.

Table 1 lists some sampling rates and corresponding record times available from the Universal Storage Device.

Table 1. Some Sampling Rates and Corresponding Record Times

Sampling-Rate	Record Times	Channel
1 s/s	94. hrs.	1
1 s/s	23. hrs.	4
256 s/s	22.2 min.	1
256 s/s	11.1 min.	2
256 s/s	5.5 min.	4
1024 s/s	5.5 min.	1

H-9. AUGAT-Card Wiring-List Program

Personnel: J. A. Ritter, BCL

Support: RR 00396

In the fall of 1975, BCL began using wire-wrap cards manufactured by AUGAT. Unlike the Cambion cards previously in use, these do not use discrete sockets for each component, but instead have a .100" by .300" matrix of individual socket-wire-wrap pins already installed. These are labelled according to an X-Y cartesian coordinate system. Wiring lists must be generated to conform to this X-Y coordinate system, and the process of translating from a pin-number-on-package designation to a pair of coordinates is extremely tedious when done by hand, and introduces many opportunities for error.

A set of programs was developed to automate this translation process. Because of the amount of data and the character-string manipulations involved, MUMPS was chosen as the most convenient language in which to implement the programs. The programs include the capability to enter the necessary layout information, enter the wiring list itself, output the list in both translated and untranslated form, and update either layout or wiring list as necessitated by engineering changes.

To facilitate rapid generation of wiring lists, the program maintains a database containing layout information for the commonly used integrated circuits. In addition, the program cross checks the input against the previously entered pins in the wiring list, effectively eliminating the common errors of wiring two chains together, or unintentionally tying a chain to power or ground. At the same time, the program checks for entries which conflict with the layout information for packages and I/O connectors, preventing references to undefined packages or references to a pin number greater than the number of pins on a package or I/O connector.

The software has been operational since January, 1976. It has been used extensively and has proven to be a valuable tool both in detecting initial errors and in simplifying the debugging of complex assemblies.

H-10. OS/PC LIBRARY: Utility Programs for the PC/12

Personnel: S. A. Garfield, BCL
G. H. Brandenburger, BCL

Support: RR 00396

OS/PC LIBRARY consists of sixteen new OS/PC (PC/12 operating system) commands and forty-five FORTRAN-callable subroutines. The function of the commands and subroutines are divided as follows:

1) Pertec disc (PR 10, I-6) support software facilitating intra-disc data manipulations and overlay swapping.

2) Mathematics subroutines including fast Fourier transformation, statistics, linear equation solution, and random number generation.

3) Upgrading and enhancement of OS/PC and the FORTRAN subroutine library with: plotting routines, scope graphics and character display routines, a keyboard dispatcher subroutine, file and array manipulation and data conversion subroutines, and patches correcting errors in several subroutines supplied with OS/PC.

A local central library of PC/12 software is also being created to promote software sharing and eliminate duplicate programming efforts by PC users.

H-11. PC-1200/System 7 Communications Routines

Personnel: B. F. Spenner, BCL
K. W. Clark, BCL

Support: RR 00396

The need for a simple technique which allows information to be transferred from LINC tape to industry compatible 9-track tape has led to the development of a set of programs which allow data to be easily transferred between the PC-1200 with LINC tape, and the IBM System 7 with 9-track tape. As seen from the PC-1200, the communication routines provide a FORTRAN IV-callable subroutine which permits data to be written to or read from a 9-track tape unit. The design of both the PC-1200 and the System 7 programs attempts to make the required communications protocol and tape operations transparent to the user of the PC-1200 FORTRAN IV subroutine.

The communications protocol used to operate the 9600-baud serial data path provides both inter-machine synchronization and transmission error

detection. This protocol and the data-path baud rate allow the communications system to operate at a speed by which a 1024-block LINC tape can be transferred to 9-track tape in approximately 10 minutes.

H-12. Remez Filter-Design Program for PC-1200

Personnel: R. E. Hitchens, BCL

Support: RR 00396

A general purpose technique for designing optimum minimax, finite impulse response, linear-phase digital-convolution filters[1] has been adapted to PC-1200 FORTRAN. The program can design several filter types, including low pass, high pass, band pass, and differentiators, using the Remez exchange algorithm. Plots of frequency and impulse response of the optimum design aid in interactive use of the program, and make it a good demonstration of this technique. The maximum length of the impulse response is limited to 32 sample points by PC-1200 memory size and use of single-precision (24 bit mantissa) arithmetic. An IBM 360 version of the program is available for impulse responses of up to 256 sample points in length.

[1] L. R. Rabiner, J. H. McClellan, and T. W. Parks, "FIR Digital Filter Design Techniques Using Weighted Chebyshev Approximation," Proceedings of the IEEE, vol. 63, no. 4, April 1975.

H-13. Ultrasound Explorations

Personnel: G. H. Brandenburger, BCL
J. R. Cox, Jr., BCL
R. E. Hitchens, BCL
J. R. Klepper, M.S., Physics
J. G. Miller, Ph.D., Physics
D. L. Snyder, BCL

Support: RR 00396
Washington University

This work is the beginning of a collaborative effort between BCL and the ultrasound research team at the Washington University Department of

Physics. The principal objective is an accurate characterization of tissue pathology from ultrasonic attenuation and velocity measurements. Initially, characterization of myocardial tissue, differentiating normal, ischemic and necrotic tissue, is the principal area of concern.

The work completed thus far has been implementation of an in vitro ultrasound transmission tomographic scanner. The scanner will hopefully provide high-speed generation of a two dimensional array of ultrasonic attenuation and propagation velocity of freshly excised dog hearts prior to CPK infarct-size estimation. Tissue sampling for CPK measurements must be completed within 30 minutes of excision; the scanner should make thorough ultrasound measurements possible well within this limited time.

Thus far, the scanner has been operated manually with data printed on paper tape and, more recently, stored directly on LINC tape with the LINC-tape analog recording system (PR 11, H-6). Reconstructions on the PC-12 are performed using the standard back-projection method (BCL Monograph No. 273). The PEP 400R scan converter (E-1) is used to generate grey-scale displays of the reconstructions. Smaller intervals of the grey-scale can be expanded, as is done in X-ray tomographic systems, to overcome the dynamic range limitations of the video monitor. Software has also been written to randomly perturb simulated data to simulate errors incurred in the ultrasound measurements.

A phantom consisting of four plastic rods has been manually scanned. The reconstruction was poor due to the inadequate sample imposed by manual operation (5 cm translations and 5 degree increments). Circularly symmetric phantoms consisting of rings of castor oil are presently being scanned at a single angle with finer (2 mm) translational sampling.

Stepping motor drives for the scanner are being built, and the motors will be driven by a PC-12 interface currently being designed.

Errors expected in the ultrasound reconstructions using attenuation measurements are believed to arise from two sources:

1) Phase cancellation across the face of the piezoelectric receiver. This effect is attenuated by reducing the receiver aperture. The CdS acousto-electric receiver currently under development by the Physics Department can be made to respond to the average power of the received acoustic energy and is, therefore, phase insensitive. A CdS transducer for the reconstruction scanner is presently under construction.

2) Beam dispersion and reflections constitute a random additive term in the log of the received ultrasound signal. This term is less sensitive to frequency than the attenuation through a tissue specimen, hence, attenuation measurements are made at two distinct frequencies. Reconstructions of the difference of the measurements are presently being compared with reconstructions of single frequency data. Too few data have been gathered to judge the effectiveness of this method.

H-14. Analysis of Archaeological Dental Specimens

Personnel: B. R. Hieb, M.D., Jewish Hospital
D. G. Gantt, M.S., Anthropology
S. A. Garfield, BCL

Support: RR 00396
Jewish Hospital
Washington University

A software system for graphic analysis of archaeological dental specimens has been developed. The system is designed for use as part of a graduate student project in the Washington University School of Anthropology. The project involves analysis of archaeological tooth specimens which have been longitudinally sectioned and then magnified by graphic techniques to a scale suitable for analysis. The quantities of interest in these specimens are: 1) the area of the enamel surface, 2) the area of the dentin pulp, 3) the fraction of the total tooth area occupied by each of these entities, and 4) the ratio of the enamel to dentin areas. In order to facilitate obtaining these parameters on multiple specimens a modification of the computerized ventricular analysis system (E-3) was performed to make it suitable for use on dental specimens. The modification permits the user to enter the contour enclosing the enamel area and then the contour enclosing the dentin area. The computer then calculates the area of the two enclosed figures and prints the desired areas and ratios on the line printer together with appropriate identification data. The use of this system on an initial series of several dozen dental specimens has demonstrated the usefulness and accuracy of the modified ventricular analysis system for the analysis of dental specimens.

H-15. Survival of Irradiated Tumor Cells

Personnel: C. A. Perez, M.D., Radiology
H. Z. Hill, Ph.D., Radiology
J. Markham, BCL

Support: RR 00396
CA 13053

The survival of irradiated B-16 tumor cells was studied in order to measure the resistance of the cells to radiation. Mouse tumor cells in suspension were irradiated and the number of live cells counted at various times. The time curves of the number of live cells were then analyzed on the PC-1200 computer by fitting the data to three equations derived from three different models of cell survival. The parameters of survival determined from the equation which best described the data differed from those obtained by other investigators. Previous work had suggested that B-16 tumor cells were

highly resistant to radiation; the results of this study did not support this conclusion.

H-16. Digital Storage and Analysis of Visual Field Data

Personnel: W. M. Hart, Jr., M.D., Ph.D., Opthalmology
G. H. Brandenburger, BCL
R. H. Greenfield, BCL

Support: RR 00396
EY 00336
Washington University

Initial program development is underway to write interactive programs for the PC-1200 to record clinical visual fields. The Rho-Theta position transducer is being used to trace the contours of static and kinetic clinical visual fields. The digitized data are to be stored on magnetic media for later retrieval. Computation of areas of isopters on kinetic fields and profiles on static fields will permit a quantitative statistical analysis of visual field changes in normal subjects, and in subjects with ocular hypertension.

A retrospective study will be undertaken using visual fields recorded in the charts of patients followed in the Glaucoma Center of the Department of Ophthalmology. An extremely large body of data has been collected over the past two decades in the Glaucoma Center, but quantitive analysis of the visual field data has heretofore been unavailable. It is intended that qualitative interpretation of visual field changes can be supplanted by objective, quantitative analysis.

H-17. Library System - Medline Link

Personnel: P. Moore, BCL
G. J. Blaine, BCL
L. M. Calcaterra, BCL
R. H. Greenfield, BCL
M. F. Johnson, Jr., M.L.S., Medical Library
J. P. Miller, BCL

Support: RR 00396
HL 18808
Washington University

The goals of this project which is still in a development stage are two:

1) Using a terminal connected to the MCF MUMPS computer system, the user will be able to perform MEDLINE searches. When the user has decided upon a particular subset of journal articles, it will be stored in temporary storage on disc to be edited and printed or stored in the user's permanent data base of library materials. Currently a method of making this connection via the TYMNET system is being investigated in preference to a sophisticated switching-box strategy.

2) Programs will also be developed allowing the user to manipulate the data he has stored in his library database. Searches will be made, data will be printed out, and, besides material obtained from MEDLINE, the user will be able to add and update data directly via his MUMPS terminal. The routines have been defined and will be written once the strategy to handle item one has been established.

H-18. RTOXY: A pH Data Acquisition System for the PC-12

Personnel: G. H. Brandenburger, BCL
W. F. Boron, Ph.D., Physiology and Biophysics
S. A. Garfield, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
Washington University

Records of pH values traced by a chart recorder for periods of many hours and requiring computer analysis necessitated a new software system (RTOXY) for the PC-12 using the Rho-Theta transducer. RTOXY permits digitization of arbitrary continuous curves of up to 1023 points and includes a filing system and provisions for storage oscilloscope or line printer tabulation of the data. Data may be stored using the RTOXY filing system for analysis by PC-12 programs. Alternatively an ASCII file tape compatible

with a PC-12 to remote computer transmission installation can be generated by the system. The ASCII file tape can include a stream of keypunch-card images containing IBM 360 JCL and FORTRAN sources, as typed by the user. In addition to the Rho-Theta transducer and Computek graphic tablet, RTOXY will support the GP-3 graphic tablet (E-1) when it becomes available.

H-19. IDAS Processing Software

Personnel: C. F. Pieper, M.S., Neurosurgery
W. G. Clark, Neurosurgery
S. A. Golden, B.S., Neurosurgery

Support: RR 00396
NS 06947
Washington University

IDAS is a LINC-based averaging system capable of digitizing and summing two analog sources (250 points/channel) at a frequency of up to 1 KHz. The sums are time-locked to an external signal which may be displaced forward in time from the start of the average. The Department of Neurosurgery is currently using IDAS to aid investigation of the "Motor Potential," a potential variation of cerebral origin time locked to a movement, an attempted movement, or an anticipated movement. Included in the investigation are measurements of extracellular K^+ and activity of individual neurons (units). Data generated by IDAS are stored on LINC tape and transported to a PC-1200 for further processing and display.

An operating system has been developed in PC-1200 FORTRAN to ease scaling and calibration of data. High quality graphs are obtained from the Versatec Matrix plotter (H-22) and may be first smoothed by fitting with sinx/x functions according to the sampling theorem. A filtering package currently under development takes the Fast Fourier Transform of the raw data, removes selected frequencies and performs the inverse. An addition/subtraction package allows the addition or subtraction of two curves to enable transformation from bipolar averages to monopolar and vice versa. The result may be saved in the IDAS format to allow spacially contiguous averages to be processed sequentially. Finally, a program has been written to compute a two dimensional current source density about a point from four bipolar averages.

Future developments will provide for rastering sequential averages, a useful technique for the study of unit data. The filter package will be expanded to include time-domain first and second order, low and high pass digital filters and a notch filter.

H-20. Clinical Evaluation of CASNET

Personnel: R. H. Greenfield, BCL
M. A. Kass, M.D., Opthalmology
C. A. Kulikowski, Ph.D., Rutgers University
J. L. Livingston, B.A., Ophthalmology
S. M. Weiss, Ph.D., Mt. Sinai School of Medicine

Support: RR 00396
EY 00336
Rutgers University
Stanford University

At the Glaucoma Center the clinical evaluation of the Rutgers University CASNET (Causal-Association Network Systems) program has continued. CASNET performs as a consultant for management of the glaucomas. Washington University is one of the five clinical centers which is providing medical feedback to the system implementors. BCL continues to provide technical assistance on computer usage to the Glaucoma Center as well as recommending program changes to improve the person-to-machine interface. This work was previously reported in PR 11 (D-3).

H-21. Analog Input-Output System for Interdata Model 7/16

Personnel: D. C. Ficke, BCL

Support: RR 00396
HL 17646

A general purpose analog input-output system is being developed for use with the Interdata Model 7/16 computer used for the Ischemic Heart Disease project (A-12). The primary objectives of the system are to display computer generated data on conventional analog devices, digitize analog signals for computer analysis, and input real-time parameters for control applications.

The analog processor consists of the following major components:

1) An eight-channel Data Acquisition System (DAS) to perform 12-bit A/D conversion in a random or sequential mode.

2) A 64x16 FIFO memory for block transfers from the DAS to the computer on an interrupt request basis.

3) An eight-channel Data Distribution System (DDS) to perform 12-bit D/A conversion in a random or sequential mode.

4) A 64x16 FIFO memory for block transfers from the computer to the DDS on an interrupt request basis.

5) A programmable sample interval generator to control the sampling periods of the DAS and DDS.

Preliminary design of the processor and the interface to the Interdata computer is complete and construction has begun.

H-22. PC-FORTRAN-Callable Versatec Plotter Subroutine

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

Support: RR 00396

A Versatec matrix plotter interfaced to a PC-1200 was seeing suboptimal use for want of convenient plotting routines to cope with the awkwardness of raster-scan plotting. In response to the needs of several potential users, a PC-FORTRAN-Callable subroutine was written to provide flexible use of the Versatec plotter for generating high-quality plots of both graphic and alpha-numeric information. The subroutine is written almost entirely in assembly language (for speed and compaction). It occupies just under 4K of memory with about 1K for the setup and plotting routines, 1K for a text buffer, and the remaining 2K for character patterns. Characters are generated on a 16 x 24 matrix (including intercharacter and interline spacing) to provide "publication quality" alphanumerics. The full PC-keyboard 64-character set is provided and provision is made for character modification to suit the user's whims. Flexibility is accomplished by providing four independent calling modes for entering text, entering graphic data, requesting individual scans, and advancing the paper. Documentation and instruction in use of the routine are available as BCL Monograph No. 293.

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 below.

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 now been in clinical use for several months and is used routinely by CCU nurses and doctors.

In collaboration with Hewlett-Packard, BCL is currently conducting a comparative evaluation between the HP78220 computerized arrhythmia detector and ARGUS/H (A-17). Hewlett-Packard has supplied an ECG data base (15 minutes on each of 14 patients) in analog form. The 78220 has processed this data previously and computer annotations also have been supplied. This evaluation is intended to clarify performance-related questions for the two systems which have been designed according to very similar philosophies. (BCL personnel: H.D. Ambos, R. M. Arthur, G. C. Oliver, L. J. Thomas, Jr., K. L. Ripley, J. A. Ritter)

B. Reconstructive X-Ray Tomography. The work previously reported in collaboration with the Picker Corporation (PR 11, VI-B) has been completed. A comprehensive report of all phases of the work has been completed and delivered to Picker. (BCL personnel: R. J. Arnzen, J. R. Cox, Jr., P. M. Fishman, V. W. Gerth, Jr., R. E. Hitchens, J. A. Ritter, D. L. Snyder)

C. Collaborative Drug Study. A research protocol was developed during the past year 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 and will continue into next year. 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 will be collected and analyzed via Argus/H for each patient. Beyond a substantial participation in the study design, the primary role of the laboratory will be analysis of the Holter tapes. Provision has been made for optional analyses to include time-of-day-dependent PVC rates as well as frequencies of couplets, runs, and early PVCs. Initial analyses of variance would then consider dependent variables being either the number of couplets, runs, or early PVCs per 24-hour period and the sources of variation being treatment, order of treatment, and patients.

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. 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, T. F. Martin, J. P. Miller, G. C. Oliver, L. J. Thomas, Jr., P. W. Webb)

VII. TRAINING ACTIVITIES

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

Programming for Medical Information Systems, Fall, 1975

A high-level programming language (Mass. General Hospital Utility Multi-Programming System - MUMPS) designed for medical information systems was presented with programming examples from hospital and ambulatory care settings. The course was presented by Fred Domke. Attending the course were:

C. R. Brigham, B.S.	Medical Student
A. G. Cave, B.S.	System Sciences and Math Student
M. J. Haubenstock, M.S.	Computer Science Student
M. A. Kass, M.D.	Ophthalmology
E. L. Poe, B.S.	Technology Health Care Student
J. B. Rapp, B.S., B.A.	Central Institute of the Deaf
F. K. Thomas, M.S.	Computer Science Student
S. I. Waldman	Computer Science Student
K. F. Wong, M.S.	Computer Science Student

Introduction to Programming the Laboratory Computer, Spring, 1976

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

T. R. Baird	BCL
L. L. Brandenburger, R.N.	Medical Computing Facilities
M. Clarke	Nuclear Medicine
P. J. Hasser	BCL
S. E. Katzen, B.S.	BCL
J. R. Martin	Radiation Sciences
R. Moroni	BCL
P. E. Raith	BCL
C. Weller	High School Student
R. Zeitinger	High School Student

Survey of Biomedical Computer Techniques, Fall, 1976.

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, architectures of computers and computer systems, pertinent number systems, logical design of digital computers, programming techniques including elements of machine, assembler, and higher level languages, input and output devices, information systems, application techniques as exemplified by existing systems (e.g. clinical and laboratory research systems, patient monitoring, molecular modeling, and patient information systems). Presentations were given by: BCL staff members, R. M. Arthur, K. W. Clark, J. R. Cox, Jr., F. M. Domke, V. W. Gerth, Jr., W. F. Holmes, N. Mullani, D. L. Snyder, B. F. Spenner, L. J. Thomas, Jr., and J. Zimmerman; C. D. Barry of CSL and R. J. Benson of the Main Campus Computing Facility. Attending the course were:

A. Assimacopoulas, M.D.	Pathology
J. Beguelin, M.D.	Private Practice
R. Bhola	BCL
P. J. DeWeer, Ph.D.	Physiology
R. S. Greenwood, M. D.	Neurology
B. R. Hieb, M.D.	Jewish Hospital
M. A. Kass, M.D.	Ophthalmology
J. P. McMahon, M.D.	Neurology
S. I. Meyers	Medical Student
S. R. Phillips	BCL
R. San Antonia	Medical Student
R. W. Sutherland, B.A.	BCL

VIII. SEMINARS

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

"The Cal Data 135 Computer" July 24, 1975	Mr. Ken Omohundro Chief Design Engineer California Data Processors Santa Ana, California
"The Johns Hopkins Microbiology System in MUMPS" September 3, 1975	Mr. John Merillat Department of Laboratory Medicine Johns Hopkins Hospital Baltimore, Maryland
"The Washington University Medical Computing Facilities" September 9, 1975	Dr. Simon Igielnik Medical Computing Facilities Washington University Medical School St. Louis, Missouri
"Terminal Data Communications and Network Planning at MCAUTO-HDS" (jointly sponsored by Computer Systems Laboratory) September 26, 1975	Mr. Don Hirst Hospital Services Division McDonnell-Douglas Automation Company St. Louis, Missouri
"Resource Sharing Networks" (jointly sponsored by Computer Systems Laboratory) October 3, 1975	Dr. G. James Blaine Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"The MUMPS Users' Group, MUMPS Application Transfer, and the International MUMPS Scene" October 7, 1975	Dr. Joan Zimmerman Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Extended MUMPS on the PC12/7 and Its Applications in the Washington University Medical Community" October 14, 1975	Mr. Fred Domke Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri

"Datran: A Digital Circuit-Switching Communications System" (jointly sponsored by Computer Systems Laboratory) October 17, 1975	Mr. Ned Farinholt Manager of Market Planning Datran Vienna, Virginia
"Argus/H: A Computer System for the Processing of Single-Channel, Long-Term Electrocardiograms" October 21, 1975	Mr. Kenneth Clark Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Data Communications in the Bell System" (jointly sponsored by Computer Systems Laboratory) October 24, 1975	Mr. Ralph Freivogel Marketing Data Specialist Southwestern Bell Telephone Company St. Louis, Missouri
"Hardware and Software Plans for a Dual-Channel Version of Argus/H" October 28, 1975	Mr. Richard Hitchens Mr. Kenneth Ripley Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"A Primer on Data Link Protocol" (jointly sponsored by Computer Systems Laboratory) October 31, 1975	Dr. G. James Blaine Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"What Hath Argus Wrought?" November 11, 1975	Mr. J. Philip Miller Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Basic Queuing Theory for Communications Engineering" (jointly sponsored by Computer Systems Laboratory) November 14, 1975	Dr. Mark Franklin Department of Electrical Engineering Washington University St. Louis, Missouri

"A Proposed MIS to Achieve Timely Collection, Storage, Retrieval, and Flow of Data in a Decentralized Environment" November 18, 1975	Dr. Patricia Moore Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"IBM's SDLC: A Bit-Oriented Data Link Control" (jointly sponsored by Computer Systems Laboratory) November 21, 1975	Dr. Marco Hurtado Computer Systems Laboratory Washington University St. Louis, Missouri
"Cardiac Catheterization Laboratory Data Acquisition and Analysis System" December 2, 1975	Mr. Gary Brandenburger Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Computer Network Design" December 5, 1975	Mr. Robert Hedderig Computer Communications System McDonnell-Douglas Automation Company St. Louis, Missouri
"New Methods for Quasi-Static and Dynamic Routing in Computer Networks" December 9, 1975	Dr. Adrian Segall Department of Electrical Engineering and Computer Science Massachusetts Institute of Technology Cambridge, Massachusetts
"Computer Controlled Gas Chromatograph/Mass Spectrometry" December 16, 1975	Dr. William Holmes Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Legal Liability of Users and Managers of Computerized Medical Records" January 21, 1976	Mr. James P. Chandler Associate Professor of Law Washington University School of Law St. Louis, Missouri
"Technology for High-Performance Information Systems - Part II" March 4, 1976	Dr. Jerome R. Cox, Jr. Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri

"Introduction to the M6800: System Overview"

March 16, 1976

Mr. Andrew Bodicky
Mr. Bruce F. Spenner
Biomedical Computer Laboratory
and
Mr. Robert Ellis
Mr. Richard Olsen
Computer Systems Laboratory
Washington University
St. Louis, Missouri

"Introduction to the M6800: Input/Output"

March 17, 1976

Dr. G. James Blaine
Mr. Bruce F. Spenner
Biomedical Computer Laboratory
and
Dr. Marco Hurtado
Mr. Richard Olsen
Computer Systems Laboratory
Washington University
St. Louis, Missouri

"Introduction to the M6800: Software Support"

March 18, 1976

Mr. David Ungar
Biomedical Computer Laboratory
and
Mr. Robert Ellis
Computer Systems Laboratory
Washington University
St. Louis, Missouri

"Features of Automated Ambulatory Medical Record Systems"

March 26, 1976

Mr. Gio C. M. Weiderhold
Office of Medical Information Systems
University of California
San Francisco, California

"A Two Dimensional Model of the Cochlea"

May 13, 1976

Mr. Bruce F. Spenner
Biomedical Computer Laboratory
Washington University Medical School
St. Louis, Missouri

"MUMPS in a Family Practice Center"

June 23, 1976

Dr. Mark L. Braunstein
Department of Family Practice
Medical University of South Carolina
Charleston, South Carolina

IX. PUBLICATIONS AND ORAL PRESENTATIONS

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Bock, P. E., and Frieden, C., "Phosphofructokinase I. Mechanism of the pH Dependent Inactivation and Reactivation of the Rabbit Muscle Enzyme," Journal of Biological Chemistry, in press.

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Corr, P. B., and Sobel, B. E., "Automated Data Processing: An Essential Decision Making Aid in the Treatment of Acute Myocardial Infarction," in Advances in Cardiology, in press.

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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
220	Schuessler, T. F. Thomas, Jr., L. J.	User Manual for Computer-Based Surgical Intensive-Care Monitoring System	6/76 (Revised)
221	Schuessler, T. F. Hagen, R. W.	Technician Manual for Computer-Based Surgical Intensive-Care Monitoring System	6/76
277	Vaca, M. V. Snyder, D. L.	Estimation and Decision for Observations Derived from Martingales: Part 1, Representations	8/75
278	Alderson, P. O. Jost, R. G. Strauss, A. W. Boonvisut, S. Markham, J.	Radionuclide Angiocardiography Improved Diagnosis and Quantitation of Left-to-Right Shunts Using Area Ratio Techniques in Children	6/75
279	Oliver, G. C. Cox, Jr., J. R. Thomas, Jr., L. J.	Sudden Cardiac Death and the Onset of Myocardial Infarction. Relationship of Ventricular Arrhythmias to Sudden Death in Survivors of Myocardial Infarction	7/75
280	Snyder, D. L. Rhodes, I. B. Hoversten, E. V.	An Exact Estimator-Controller Solution to a Stochastic Optimal-Control Problem with Point Process Observations	9/75
281	Snyder, D. L.	Point Process Estimation with Applications in Medicine, Communication, and Control	11/75
282	Fishman, P. M. Othmer, E.	An Algorithmic Description of the SLEEP Program for the Analysis of Sleep Polygraphic Recordings	6/76
283	Tao, D.	Outpatient Appointment Systems, A Survey of Practices, Devices, Attitudes and Plans	12/75

Monograph Number	Author(s)	Title	Date
285	Ripley, K. L.	Mecca, A Computerized System for Capturing Transient Electrocardiographic Data	5/76
286	Camuto, R. D. Arthur, R. M.	Programming Type 2704/2708 Erasable Read Only Memory	6/76
287	Ripley, K. L. Arthur, R. M.	Evaluation and Comparison of Automatic Arrhythmia Detectors	10/75
288	Mead, C. N. Ferriero, T. Clark, K. W. Thomas, Jr., L. J. Cox, Jr., J. R. Oliver, G. C.	An Improved Argus/H System for High-Speed ECG Analysis	10/75
289	Brandenburger, G.	Rho-Theta Data Logging System	6/76
290	Garfield, S.	OS/PC Utilities	6/76
291	Ungar, D. Blaine, G. J. Spenner, B. F.	Microprocessor Development Support - Software Viewpoint	6/76
292	Geer, D. Bleich, H. L. Revised by: Greenfield, R. H. Livingston, J.	MISAR: A Miniature Information Storage and Retrieval System - Directions for Using MISAR	6/76
293	Thomas, Jr., L. J.	PC-FORTRAN-Callable Versatec Plotter Subroutine	6/76
294	Zimmerman, J.	Plans for MUMPS Application Exchange Activities: Report #2	12/75
295	Zimmerman, J.	The MESCH (Multi-Environment Scheme) Computer-Based Approach to the Creation of All Ambulatory Care Record Systems	7/75