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Progress Report No. 15

Biomedical Computer Laboratory

PROGRESS REPORT

No. 15

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Biomedical Computer Laboratory

Washington University School of Medicine

700 South Euclid Ave.

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BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 15

JULY 1, 1978 - JUNE 30, 1979

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes activities during the period from July 1, 1978 through June 30, 1979. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine and its affiliated hospitals in the application of advanced computer techniques to problems in biology and medicine. This often requires work in areas stretching from basic physiology through mathematical models to equipment design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect.

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

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

For those classes of applications dominated by information processing requirements, provisions have matured from telephone lines linking our minicomputers to the IBM System/360-370 at the Washington University Computing Facilities, through development and support of a minicomputer based MUMPS system, to the establishment of an independent Medical Computing Facility to serve the local medical complex. Diverse needs continue to be met by these various options while collaborative work continues on more advanced information-processing developments.

Still another class of applications requires extensive use of large scale computational services. Many investigators are assisted in their research through the use of generalized numerical, non-numerical, and statistical routines. This work is carried out in part by staff members of BCL, but primarily by members of the Division of Biostatistics under the direction of Dr. Reimut Wette, and the University Computing Facilities whose director is Robert J. Benson.

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

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

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

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

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

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

II. SOURCES OF SUPPORT

During the period covered by this report the primary source of support for the Biomedical Computer Laboratory was a grant from the National Institutes of Health, Division of Research Resources.

RR 00396 A Resource for Biomedical Computing.

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

HL 18808 Prediction and Prevention of Sudden Cardiac Death.

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

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

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

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

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

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

Public Health Services grants.

AM 20579 Diabetes Research and Training Center,

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

EY 00256 Factors Affecting Intraocular Pressure,

EY 00336 Glaucoma Clinical Research Center,

EY 02044 Automated Digital Processing of the Human Visual Field,

HL 07081 Multi Disciplinary Heart and Vascular Diseases,

HL 13851 Cyclotron Produced Isotopes in Biology and Medicine,

HL 17646 Study of Ischemic Heart Disease,

HL 18144 Preprocessor System for Cardiograms,

HL 19537 Myocardial Injury with Ultrasound,

HL 21654 Autonomic Determinants of Arrhythmia Due to Ischemia,

HL 22517 Engineering Development of an Ultrasonic Ventilometer,

MH 31054 Mental Health in the Aged: Biomedical Factors,

NS 03856 Auditory Communication and Its Disorders,

NS 06833 An Interdisciplinary Stroke Program,

NS 06947 Bioelectric Studies of Cerebral Cortex,

NS 15070 Regeneration and Functional Recovery in Cerebral Cortex,

RR 05389 Biomedical Research Support Grant.

National Science Foundation grant.

APR 77-09776 Phase Cancellation Insensitive Receiver.

III. PERSONNEL

EMPLOYEES

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

Director

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

Assistant Directors

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

Senior Research Associate

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

Business Manager

Virginia M. Bixon, B.S.

Research Associates

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

Visiting Scientist

Harold W. Shipton, C.Eng., and Electrical Engineering

Research Assistants

H. Dieter Ambos, and Medicine (Cardiology)
Gerald L. Armstrong, B.S.
Gary H. Brandenburger, M.S.
Michael W. Browder, M.S.
Wen-Chang Chen, M.A.
Nian C. Cheng, M.S.
Kenneth W. Clark, M.S.
Stanley A. Garfield, B.S.
Alexander J. Gray, B.S.
Robert H. Greenfield, D.Sc., and Research Assistant Professor of Ophthalmology
Ronald W. Hagen, M.S., and Surgery (Cardiothoracic Surgery)
Ross K. Hartz, M.S.
Russell E. Hermes, B.S.
Richard E. Hitchens, B.S., and Lecturer in Computer Science
Janet A. Johnson, M.S.
Margaret C. Jost, M.S.
John R. Klepper, M.A.
Joanne Markham, M.S.
Charles N. Mead, M.D.
J. Philip Miller, A.B., and Assistant Professor of Biostatistics in Preventive Medicine
James K. Montrose, B.S.
Patricia Moore, Ph.D.
Nizar A. Mullani, B.S., and Research Associate in Radiology
Michael A. Province, M.A.
Kenneth L. Ripley, M.S.
J. Alan Ritter, M.S.
Kenneth B. Schechtman, Ph.D.
Sol M. Shatz, B.S.
Budimir Zvolanek, M.S.

Engineering Assistants

David M. Arbo, B.S.
Stanley R. Phillips
Don L. Rempel, M.S.
Wayne R. Roloff, B.S.
Timothy L. Weadon, B.S.

Technical Assistants

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Nicholas J. Colarelli
Joseph E. Denigan
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Patrick W. McLear
Eric G. Melanson, B.A.
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John D. Myers
Stephen J. Potter
Tamar T. Rosen
Eufaula Thornton
James S. Wallis
Kenneth G. Williams

Electronic Technicians

Theron R. Baird
George L. Bickmore
Louis F. Combrevis
Joseph H. Flacke

Librarian

Beth E. Robinson, M.L.S.
Monica W. Shieh, M.L.S.

Secretaries

Rebecca J. Bozesky
Jill D. Buchholz
Elizabeth A. Dennis
Shirley A. Gonzalez-Rubio
Betty L. Hill
Celeste J. O'Rourke
Polly E. Raith

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

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

Todd L. Carpenter, B.S.
Gary R. Cook, B.A.
Gary A. Davis

John A. Filla
John R. Hamm, Ph.D.
Paul J. Hasser
G. Howard Hays, Jr., B.A.
Frank Hummel, M.S.
Charles E. James
Thomas J. Marshall, M.S.
J. Steve Massey, B.A.
Bert H. Tanaka, B.S.
Eric Thompson, B.S.
Paul B. Webb

RESEARCH COLLABORATORS

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

J. Achtenberg, A.B., Medicine
R. L. Allen, M.S., Electrical Engineering
W. E. Ball, D.Sc., Computer Science
L. J. Banaszak, Ph.D., Biochemistry
C. D. Barry, Ph.D., Computer Systems Laboratory
D. Bauwens, M.D., Medicine
B. Becker, M.D., Ophthalmology
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R. J. Benson, J.D., Computing Facilities
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W. G. Bowen, M.D., Medicine
S. B. Boxerman, D.Sc., Health Care Administration and Planning Program
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C. A. Branyon, Ophthalmology
S. M. Brodarick, M.D., Medicine
M. E. Cain, M.D., Medicine
M. K. Campbell, R.N., Medicine
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I. Y. Christlieb, M.D., Cardiothoracic Surgery
G. L. Clark, M.D., Medicine
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W. A. Crafford, M.D., Medicine
J. E. Davis, Ph.D., Medicine
B. E. Ditzler, B.A., Ophthalmology
A. A. Ehsani, M.D., Medicine
J. O. Eichling, Ph.D., Radiology
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R. A. Ellis, M.S., Computer Systems Laboratory
R. G. Evens, M.D., Radiology

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C. Frieden, Ph.D., Biochemistry
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A. Hernandez, M.D., Pediatrics
R. R. Heye, Radiology
J. O. Holloszy, M.D., Preventive Medicine
J. T. Hood, B.S., Radiology
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L. Jarett, M.D., Pathology
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University of Nottingham, England

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A. J. Moss, M.D.

University of Texas Health Science Center, Dallas, Texas

J. T. Willerson, M.D.

University of Vermont College of Medicine, Burlington, Vermont

D. S. Raabe, M.D.

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

Mennen-Greatbatch, Clarence, New York and Hewlett-Packard, Waltham, Massachusetts - An arrhythmia monitoring 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 the laboratory space at 700 South Euclid Avenue, just across the street from the main building of the Washington University School of Medicine. During the intervening years, the floor space has been increased to 18,000 square feet by renovation and by occupation of rooms in adjacent buildings. Facilities for computational applications, laboratories, staff offices, and a WUCL reference room occupy the various BCL spaces. Other laboratory facilities include a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules, and both analog and digital tape recorders. Other space in the Medical School and Barnes Hospital Complex is frequently occupied by BCL staff members during collaborative projects.

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. That first LINC still provides a few service functions although now over 15 years old.

The current complement of computing hardware includes a variety of minicomputer systems, microcomputer systems, and data terminals for access to the Washington University Computing Facilities IBM 360/370 and the Medical Computing Facilities MUMPS system. These systems include DEC PDP-11's, Texas Instruments 980's, CALDATA 135's, Artronix PC-12's, an IBM System/7, and an MMS-X graphics system developed by the Computer Systems Laboratory. In addition to these systems under direct BCL supervision, there are installed at the Washington University Medical Center over one hundred minicomputer systems (representing twenty different makes and models) in which there is BCL interest and involvement.

V. RESEARCH PROJECTS

Introductory Summary

The goal of the Biomedical Computer Laboratory (BCL) is the application of digital computing 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. BCL's research program is organized into several major project areas with the staff grouped into teams whose interests are focused correspondingly. This year, over 80 individual projects can be categorized in the seven areas into which the body of this report is divided. For each section, a one-page overview precedes the individual project reports. What follows here is a compressed summary of BCL activities.

In the area of ischemic heart disease and ECG analysis, a new QRS detector/delineator shows major improvements in noise immunity and beat-classification accuracy; frequency-domain analysis is being applied to QRS classification; and processing strategies for detecting supraventricular dysrhythmias have been developed for a national collaborative clinical trial. Three systems for high-speed processing of recorded ECGs (Argus/2H) are in heavy use for several local and two multi-center clinical trials involving a total of 13 different institutions. Also, BCL is collaborating with the American Heart Association to develop a database of international scope, for dysrhythmia-detector evaluation. For these activities, more than 800 24-hour, dual-channel recorded ECGs have undergone detailed analysis in the past year. In the general area of ischemic heart disease, the BCL collaborates in 12 other individual research efforts with local investigators.

Work in the area of tomography embraces systems developments using two modalities (ultrasound and positron-emission) plus algorithm developments. For the ultrasound work, simultaneous time-of-flight and amplitude measurements now make possible reconstructions from both velocity and attenuation parameters. An analytic model provides important progress toward coping with signal degradation due to phase cancellation. Ray-tracing simulation algorithms are being developed for error corrections. A long-standing collaboration with the Division of Radiation Sciences has resulted in a new system for positron-emission transaxial tomography (PETT V) which has been completed and put into use. Important features include maximum circumferential detection efficiency, flexible linear and angular sampling, and data acquisition times down to one second. Meanwhile, PETT IV has been applied to clinical studies to verify infarct imaging by combined labeling of a metabolic substrate and the blood pool. Recent advances have been made in the area of fan-beam algorithms and architectures for high-speed processing as well as in fully three-dimensional tomography algorithms.

Major work in clinical pathophysiology and patient monitoring now focuses on the development of a Clinical Physiologic Research System (CPRS) which features a generalized approach to meeting a significant class of research needs with modular system elements and distributed processing. CPRS is being used to study physiologic responses to pulsatile perfusion and to acquire multiple extracellular cardiac potentials. Other work deals with the acquisition and processing of machine-readable visual-field data. Also, a recently increased commercial interest in signal processing algorithms and information processing concepts has led to extended sharing.

Several databases for disease management and research are actively supported. A BCL-initiated Glaucoma-Center Patient Registry is now self-sufficient and has moved to a separate service facility (Medical Computing Facility) which was also spawned by the Laboratory. Meanwhile, a neonatology database for clinical research is beginning to mature and it's characteristics make it especially attractive as a test for implementation of a new database model which is at the foundation of Information Systems Group work (v.i.). Five other databases maintained through BCL are specifically addressed to collaborative research projects, all of which deal with the acute and chronic manifestations of ischemic heart disease.

Our commitment to MUMPS for medical information management has been sustained and expressed through active roles of BCL personnel in the MUMPS User's Group. Close ties with the Division of Biostatistics have yielded coherent approaches to data analysis using distributed resources.

During the past year BCL's primary contributions to speech and hearing research at the Central Institute for the Deaf (CID) have been in digital instrumentation for data acquisition and analysis. Three advanced random-access, programmable digital recording systems for processing sampled speech have been installed in renovated laboratories at CID. Also, a FORTRAN package ("Speech Microscope") has been developed to support speech-signal analysis. A recently developed mechanical model of the larynx and surrounding tissues shows transfer characteristics which agree with those experimentally measured in humans. Other work explores electrocutaneous stimulation as an alternative sensory modality to hearing, the psychoacoustics of speech, and visual cues in lip reading.

In the area of central nervous system diseases and EEG analysis, the central-volume principle of tracer kinetics has been generalized to the distribution of substances with multiple chemical species, thus advancing studies of blood-brain-barrier exchange and regional brain-blood flow. On other fronts, a system for digital acquisition and analysis of VER data has been constructed and is being evaluated; for neuroanatomical studies, algorithms for autoradiographic-image processing are being studied; and work continues on an automated system for monitoring epileptic patients with indwelling electrodes.

Supporting activities span exploratory biomedical applications, system development aids, and digital hardware designs of general utility. An especially promising application is a new approach to radiation-dose calculation. It is based on a now validated mathematical model using scatter-air ratios for precise absorbed-dose computation in inhomogeneous media irradiated via irregular fields. A microprocessor support system and a high-performance digital convolution filter are examples of accomplishments in the areas of development aids and generally useful hardware designs.

Individual Projects

A. Ischemic Heart Disease and ECG Analysis

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

A real-time computer-based arrhythmia monitoring system, called Argus, in operation in the Barnes Hospital Coronary Care Unit from 1969-1975, was replaced in 1975 by "Argus/Sentinel," a commercially available version developed through collaboration with the Mennen-Greatbatch Company. The experience garnered with Argus, coupled with an evolving popularity of long-term ECG recordings from ambulant subjects, allowed us, in the early 1970's, to assemble a system, called Argus/H, for the high-speed (60 times real time) processing of those long-term recordings. Argus/H has since processed several thousand recordings for a study of ventricular arrhythmias in survivors of myocardial infarction and several hundreds of recordings for a host of other studies. Extensive evaluations have verified the integrity of the analysis algorithms, proven the value of the quantified results as compared to conventional manual-scanning techniques, and confirmed the consistency of results on reprocessing.

By the mid-1970's, it was apparent that, although we could continue to use Argus/H, that system, with special-purpose, limited, and expensive hardware, could not support rigorous algorithm development, could not efficiently process the now more-popular dual-channel recordings, and could not meet the demand for the system from the growing volume of recordings resulting from recent interest in therapeutic trials of antiarrhythmic agents and interventions designed to protect the ischemic myocardium. A newer system, called Argus/2H, emerged in 1977 and was duplicated in 1978. The two Argus/2H systems process long-term ECGs for national multicenter clinical studies of interventions to limit infarct size and of post-infarction risk stratification. For such studies, the results of processing are usually saved for subsequent statistical analyses via the University's IBM System/360-370. The systems also provide the power and flexibility necessary for work on algorithm revision and on new signal-processing strategies and they also serve the analysis and documentation needs of other internationally directed work to generate an annotated digital database for the evaluation of automated arrhythmia detectors. The Argus/H hardware and software are meanwhile being upgraded to Argus/2H status.

A-1. Argus Algorithm Development

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During the past year, Argus algorithm development has centered around continuing the revision of the original Argus processing algorithms (PR 13, A-1). Additionally, preliminary algorithmic development has been done in two related areas: 1) extraction and analysis of additional time- and frequency-domain features; and 2) detection of selected supraventricular dysrhythmias.

Argus Revision. Plans for a total revision of the original Argus ECG processing algorithms were made during the early part of 1978 and commenced with a rewrite of the Primitive QRS detector. As described in PR 13, the basis for the new Argus QRS detector was an algorithm originally written for QRS detection in the SICU.[1] The SICU detector, which was structured as a finite-state machine, had as one of its principal features Automatic Threshold Control (ATC). ATC adjusted slope-acceptance thresholds based on the amplitude of previously detected QRS complexes, giving the SICU detector increased noise immunity when compared to fixed-threshold detectors. For implementation in the Argus system, the SICU detector was substantially modified to process Aztec rather than raw sample data, and to delineate as well as detect each QRS complex. The delineation logic was written in subsections to demarcate straightforward two- and three-slope complexes, more complicated multi-sloped waveforms such as those seen in bundle branch block, and troublesome very-large-amplitude PVCs. A preliminary evaluation done on approximately 100,000 QRS complexes, showed the new algorithm to be superior to Primitive with respect to both detecting and delineating QRS complexes in the presence of baseline or muscle artifact (data loss of approximately 1% as compared with 4% for Primitive), and to false-positive PVC classification. The latter finding was particularly significant in light of the decrease in data loss and the concomitant increase in the total number of complexes analyzed. However, the new detector showed a significant (more than two times) performance degradation with respect to PVC detection. The reasons for this decreased performance centered mainly around the ATC logic. It was therefore decided to have the output of the QRS detector (now called the STAGE I detector) passed to a second detector (STAGE II). STAGE II would specifically search the STAGE I data stream for mismeasured or missed beats based on a knowledge of the types of errors of commission and ommision that STAGE I could make. Additionally, STAGE II would have access to data regarding the average Normal-Normal interval and average

Normal-QRS duration (passed from the beat classification section of the program) as an aid in determining whether a STAGE I error had occurred. The concept of a two-stage detector/delineator with communication between the second stage and the beat classification algorithms represents a fundamental departure from the original Argus implementation. However, such a departure now seems possible because of increased machine speed and memory space. At present, an extensive evaluation of the two-stage detector is underway. Preliminary results on 250,000 beats selected at random and specifically not part of the algorithm training set have shown the new detector to be at least as accurate as Primitive in PVC detection and far superior to Primitive in noise insensitivity and false positive beat classification. The final results of this evaluation will be presented at the Computers in Cardiology meeting in September 1979.

Now that the QRS detection/delineation section of Argus has been rewritten and is under evaluation, work has begun on reworking the beat classification section (Cycle). Relevant to this revision is work done on various other QRS features which might be useful in beat classification, and algorithms for atrial arrhythmias, since Cycle should be able to classify supraventricular as well as ventricular dysrhythmias.

Additional Argus Features. Mean Frequency--Cycle classifies beats as Normal, Borderline, PVC, etc. on the basis of four morphological features: duration, height, offset, and area. The original Cycle logic placed substantial emphasis on duration since this is the attribute that an electrocardiographer most readily identified as abnormal in aberrantly conducted QRS complexes. However, in automated ECG processing, it is the feature most sensitive to mismeasurement secondary to baseline or muscle artifact. A high percentage of Argus false-positive PVCs is the result of mismeasured duration. A recent paper by Kuo and Dilman[2] discussed the parameter MEAN FREQUENCY (=1/T where $T = 2\pi \Sigma|V_j|/\Sigma|V_j-V_{j-1}|$) as a rapidly calculable time-domain descriptor for ventricular fibrillation. We investigated MF to determine the utility as a feature correlated with beat width but less sensitive to noise than QRS duration. After examining several thousand QRS complexes to determine the optimal window length and beat-placement position (WL = 244 msec, BP = 48 msec from window start), we analyzed 19 one-hour recordings from 19 patients (approximately 100,000 QRS complexes). For each tape, MF for all human verified Normal and PVC complexes was plotted in histogram fashion. On 16 of the 19 tapes, MF was able to correctly separate at least 95% of the Normals and PVCs. Overlap between the two clusters occurred when the signal was heavily contaminated by low-frequency noise. The same tapes were then used to generate histograms of Normal versus PVC durations using the Argus-assigned durations. It was found that duration separated Normals from PVCs more accurately than MF on 18 of the 19 tapes. We concluded that MF was not a superior feature to QRS duration in the Argus signal processing environment.

TDIFF--Most ECG classification algorithms based on feature extraction examine only descriptors of the QRS complex per se. Lovelace et al departed from this practice by utilizing a feature called TDIFF,[3] defined as the least-squares linear approximation to a portion of the ST-T wave. Although

TDIFF ostensibly reflects activity during myocardial repolarization, it is, in fact, more exactly a measure of the relationship between depolarization and repolarization relative to a QRS fiducial point. More specifically, two QRS complexes with the same shaped ST-T wave have strikingly different TDIFF values if one complex is appreciably wider than the other since the least squares approximation is calculated for a fixed number of points beginning a fixed time interval after the maximum negative slope of the QRS (the fiducial point). We examined TDIFF for several thousand human-verified Normals and PVCs and found it to be variably effective at separating the two groups of beats. However, no single feature can ever correctly separate all Normals from PVCs and, on closer analysis, we found TDIFF to be a helpful additional feature in separating Normals from certain types of PVCs (e.g. fusion and septal PVCs). Furthermore, because the ST-T wave is a low-frequency noise event relative to the QRS, TDIFF is less sensitive to high frequency noise than other QRS features. We are currently investigating several beat classification algorithms which include consideration of TDIFF as a clustering parameter, and expect to include TDIFF in our final revision of Cycle. Because Argus processes Aztec rather than raw sample data, we have modified the calculation of TDIFF so that the least squares fit is done with Aztec data.

Additional Features--Preliminary investigation of several other features has begun. Although data on the various descriptors is at this time too sparse to draw any conclusions, promising results have been obtained with an additional time-domain feature, percent below the baseline (PBBL), and with several frequency-domain features including the First Spectral Moment of the amplitude spectrum from 6-25 Hz, the phase of the maximal power component in the same range, and the magnitude and location of the maximal power component in the lower portion of the power spectrum (2-6 Hz) (G-6). PBBL is a measure of the amount of QRS area above and below each beat's "baseline" and is thus an expansion of the concept of QRS offset. All frequency-domain features are calculated using a 512 msec FFT, thereby allowing for inclusion of the entire PQRST complex within the transform window.

Supraventricular Dysrhythmia Detection. Historically, the Argus system has not had the ability to generate data concerning the presence of supraventricular dysrhythmias (SD). However, with the start of the MILIS project (A-21), efforts were made to develop algorithms for the automatic detection of SDs. At present, a semiautomatic, interactive scheme has been developed and is in routine use. As the new version of Cycle is developed, portions of the interactive algorithm will become fully automated.

Following routine human editing of each tape, a computer search is made through the Cycle stream and all Normal beats preceded and followed by Normal complexes are analyzed. For each such beat, the ratio of the forward to backward coupling intervals is calculated (FCI/BCI). A histogram of these ratios is internally generated for each 15-minute epoch on the tape and each histogram is analyzed to determine the number of beats lying on either side of a threshold value (typically .5--1.5). In addition, the gross shape of the histogram is determined. A composite histogram for the entire tape is then printed showing the number of outlying beats per epoch,

the times of occurrence for the five earliest beats in each epoch (thereby allowing human verification and strip generation), and a shape-code letter corresponding to the dominate rhythm in each epoch (S--sinus rhythm, characterized by minimal deviation from the mode; A--sinus arrhythmia, characterized by significant deviation from the mode; F--atrial fibrillation, characterized by maximal deviation from the mode).

Before being implemented for routine processing, the algorithm was evaluated on 218 recordings of 12-24 hours in length. 79.4% of the known SDs were correctly identified with a false-positive rate of 20.6%. It should be noted that nearly half of the false-positive SDs represented PVCs missed by routine processing. The algorithm appears to be a reliable source of SD information and plans to have each machine-detected SD "edited" by a human technician in a manner similar to that of PVC verification are currently underway.

(1) C. F. Pieper and L. J. Thomas, Jr., "QRS Detection for the SICU," BCL Monograph No. 222, February 1974.

(2) S. Kuo and R. Dilman, "Computer Detection of Ventricular Fibrillation," Proceedings of the Conference on Computers in Cardiology, Stanford, California, pp. 347-349, September 1978.

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

A-2. High-Speed ECG Processing: Hardware

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The programmed input/output interprocessor link in the MILIS system (PR 14, A-2) has been replaced with a direct memory access link using DEC DA11-B/DR11-B hardware. The improved hardware considerably reduces the overhead associated with interprocessor communication in dual processor Argus (A-3).

A high performance digital convolution filter has also been added to the MILIS system. It is interfaced to the PDP-11/34 through DEC DR11-L and DR11-M modules and is used for bandpass filtering of ECG data.

Additional hardware features are planned for the IBM System/7 in order to upgrade it to two-channel processing. A 160 megabyte disk system is nearing completion (G-15). Also planned are: 1) addition of a cycle-steal analog-to-digital converter for ECG digitizing; 2) a cycle-steal tape interface to an 800/1600 bit per inch 75 inch per second tape drive; 3) upgrade of the Siemens chart recorder from two to four channels; and 4) a cycle-steal interface to the display oscilloscope.

A-3. High-Speed ECG Processing: Software

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Holter recordings are no longer analyzed by the single-channel Argus/H system (PR 11, A-4 and A-11; PR 10, A-6 and A-8) although waveforms on digital tapes created by that system may still be reviewed. The special purpose and expensive hardware used for the Argus/H system was severely limited for efficient processing of the dual-channel recordings which emerged in the early 1970's and for algorithms developed for the dual-channel Argus/2H systems. New hardware (A-2) is being added to the Argus/H system so that another Argus/2H-like system can serve the growing needs of Holter-processing activities. Since the CPU (IBM System/7) of the Argus/H system is different from the CPUs (DEC PDP-11/34s) of the Argus/2H systems, the Argus/2H software cannot be simply transferred, even though most of the peripherals are similar. In addition, the System/7 software, although it served for seven years, is not adequate for the changeover. A major software revision is planned, and work is well underway to make the new system software much more user-oriented than was the Argus/H software. Toward that end, the operating system controlling code and a file-manipulation program have been completed which, when joined with the text editor and assembler, make the creation and testing of new programs much simpler than was previously possible. New controlling routines and utility programs will be added as new peripheral devices are attached. The software for the ECG processing aspects of the System/7 are in the design phase.

Operational software for the Argus/2H systems reached a near steady-state a year ago (PR 14, A-3) and most software efforts during the past year were invested in algorithm development (A-1). The only major additions to the operational software have been (a) the printing of a special-purpose Holter recording summary for the MPIP study (A-19), (b) several additions to the edit program (PR 13, A-3; PR 14, A-3), and (c) a post-edit interactive routine which allows an editor to confirm or regroup machine-identified clusters as distinct PVC morphological groups.

MPIP summary. The Multicenter Post-Infarction Program (MPIP) study (A-19), requires 44 variables for each Holter recording analyzed. The 44 items appear on a 3-page computer-printout which is reviewed locally by a cardiologist and then mailed to the MPIP coordinating center where the data are entered into the study's database. A special-purpose summary program produces the required items: (a) name/date-of-birth code and study identification number; (b) date of the recording, the length of recording in minutes, and the amount of data loss in minutes; (c) mean and standard deviation of the normal QRS-to-normal QRS intervals; (d) number of PVCs, average and peak hourly PVC rates adjusted for data loss, the number of bigeminal PVCs and the number of PVCs in the longest run of bigeminy, and the number of PVC shapes; (e) the distribution of PVC couplets by PVC-to-PVC coupling-interval class; (f) the number of PVCs in the longest PVC run and the distribution of PVC runs by PVC-to-PVC coupling-interval class with respect to both minimum and average PVC-to-PVC intervals; (g) a binary code for the absence/presence of the occurrence of a PVC within the T wave of the previous QRS which is not a PVC and the minimum ratio of the coupling interval of a PVC to the coupling interval of the previous interval provided the two beats of that previous interval are not PVCs; (h) the average coupling interval of all PVCs preceded by nonPVCs and the distribution of nonPVC-to-PVC coupling intervals; and (i) 3-digit personnel codes of the editor/analyst and reviewing cardiologist.

Edit program additions. Following machine analysis of a Holter-recording (PR 14, A-3), a human editor verifies computer decisions via an "edit" program (PR 14, A-3; PR 13, A-3) with which PVCs are confirmed as true, false-positive PVCs are rejected, and example ECG strips are produced for documentation and subsequent review. After the routine edit session, the editor may elect options to search the disk-resident beat-by-beat data stream (called the Cycle data stream), which includes beat labels, times of occurrence, and editing decisions, for sequences of beats which suggest events of clinical interest and/or areas of questionable analysis.

One option considers only PVCs for which the editor is shown the longest and shortest coupling intervals of nonPVC-to-PVC and PVC-to-PVC, the shortest nonPVC-to-PVC interval as a function of local heart rate, the longest run, and the first episodes of bigeminy and trigeminy. A second option considers beats labeled "normal" for which the editor is shown areas of the fastest and slowest heart rates (each based on 5 consecutive normals) and the shortest and longest normal-to-normal intervals. These two options help discover possible missed beats, point out mismeasured onsets, and reveal such interesting clinical phenomena as PAT, heart block, pauses, and

supraventricular premature complexes. For any event displayed, the editor may elect to generate an appropriately annotated strip recording, disagree with the display and make any necessary changes, or simply advance to the next event.

Two other options allow the editor to look at areas where the data are questionable. The first such search looks for nonPVCs with long coupling intervals based on an absolute figure and local heart rate. Any coupling interval over 1.5 times that of a computed running average normal-normal interval or over 2000 ms is flagged and shown to the editor. Striking selected keys, the editor may insert a K beat (chaotic signal) in the middle of the interval in areas of noise, advance to the next such event, backup to the previous event or reenter the manual scan portion of the program. This has turned out to be especially useful in discovering low amplitude PVCs missed by Argus. The companion routine to the long-interval search is a routine that looks for normal beats with short coupling intervals. A normal beat is displayed if its R-R interval is less than some absolute value input by the editor. When shown such an event, the editor may strike special keys to delete either or both beats comprising the short R-R, advance to the next event, backup to the previous event or reenter the manual scan should the event require special consideration. This mode allows the editor to trim out some of the mismeasured normals and to catch APCs which may have gone undetected.

A fifth type of search shows areas of conduction defects based on 5 consecutive normal beats each with duration greater than 0.12 seconds for which appropriately annotated strip recordings may be generated. A sixth type of search, intended to expose any R-on-T phenomena, displays in sequence, the absolute shortest nonPVC-to-PVC coupling interval and the five shortest nonPVC-to-PVC intervals, each a function of local heart rate. The editor keys "yes" or "no" in response to each candidate R-on-T. The decisions are machine-recorded for future reference and strip-recordings may be generated.

Multiform PVC clustering. In order to obtain quantitative information about multiform PVCs, a true-PVC cluster routine runs after each editing session. This routine classifies true-PVCs by cluster center using morphological features similar to that of "machine edit" (PR 14, A-3). Each cluster center then undergoes human verification in order that all centers may be defined as unique. If two cluster centers appear to be of the same focus, they are reclassified as a single center. After all cluster centers have been positively identified, a printout is obtained which lists all the centers, their family members, each family's average features, and the average normal features. Also printed is a coupling interval histogram depicting the backward coupling interval distribution for each cluster. Strips are generated to illustrate a representative waveform of each cluster center.

A-4. Holter Tape Processing

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Holter tape processing facilities include 3 systems. The original system, Argus/H, processed single-channel recordings for the natural history study of sudden death (A-7). New hardware (A-2) is being added to that system and the software (A-3) will undergo an extensive revision before the system will become similar to the two Argus/2H systems. One Argus/2H system processed a number of dual-channel recordings from the sudden death study (A-7) and for a small-scale drug study of the efficacy of LB-46 (Prindolol), a cardio-selective beta adrenergic blocking agent (PR 14, A-4). The system is now used to process recordings for the Multicenter Post-Infarction Program (MPIP) (A-19), assist in the development of the American Heart Association database for automatic arrhythmia detector evaluation (A-8), and accomodate algorithm development (A-1). The second Argus/2H system is used to process recordings for the Multicenter Investigation of Limitation of Infarct Size (MILIS) (A-21). The MPIP (129 recordings) and MILIS (320 recordings) studies have predominated the Holter processing activities and their respective processing protocols are briefly described here. The protocols are extensive and involve many activities which extend over many days; a data management system (DMS), also described here, assists in the proper execution of these protocols.

MILIS Holter processing. Dual-channel 24-hour recordings are received by mail from 5 clinical units. A tape is received along with a packing slip and several ID labels. The ID labels are affixed to various forms and tapes used in routine processing. Information on the packing slip includes ID number, date and time of recording start and stop, lead placement drawing, a signature strip obtained at the time of hook-up, and a description of any problems encountered. The ID, date of arrival, start and stop dates and times, and lead placement and problem codes are logged into the DMS. Both channels of the entire recording are digitized onto disk and onto magnetic tape. The disk-resident waveform is automatically analyzed, edited, and

summarized (PR 14, A-3; A-3). The resultant beat-by-beat "Cycle data stream" is saved on magnetic tape along with the digitized waveform. The Cycle data stream is saved also with other Cycle streams on magnetic tape for the subsequent extraction of 150 relevant variables for statistical analysis (PR 14, A-6) on a larger machine. The editor/analyst notes arrhythmic findings on a review sheet and records the date of analysis, the number of the digital tape containing the Cycle data stream destined for statistical analysis, percent data loss and his initials. The ECG strips generated during editing, the printed summary produced after analysis, and the editor-completed review sheet are sent to a cardiologist as a quality control procedure. The cardiologist likewise notes on the review sheet any arrhythmic findings and the number of PVC forms (0, 1, 2, 3 or more) evident in the strips provided. Dates of processing and review, arrhythmic findings, Cycle data stream tape number, data loss percentage, number of PVC forms, and initials of the editor and cardiologist are entered into the DMS. The 150 variables extracted by the statistical analysis system and the arrhythmic findings noted by the cardiologist are distilled to 12 variables which are sent on tape to the MILIS data coordinating center at the Research Triangle Institute in North Carolina. The 12 variables are: ID; date of processing; PVC rate adjusted for data loss; number of couplets; number of runs; a flag to indicate the presence/absence of bigeminy; the number of PVC forms; the average normal-to-PVC coupling interval; average heart rate; maximum and minimum 5-minute heart rates; and a flag to indicate the presence of any of four supraventricular phenomena: atrial fibrillation, atrial flutter, an APC rate of greater than 5 per minute, or PAT at a rate of greater than 150 for 20 or more beats. A signature strip produced at the time of editing is affixed to the packing slip which accompanied the recording to BCL; presumably the waveform is similar to that on the strip produced by the clinical unit. The packing slip is signed, copied, and sent on to the data coordinating center.

All analog tapes are stored at BCL. Digital tapes containing waveform and Cycle data streams are saved until the 12 variables are sent to the data coordinating center. A folder for each recording is filed in numerical ID order by clinical center; each folder contains ECG strips, printed summaries, the editor-cardiologist review sheet, and a DMS-produced printed summary of all stages of processing. As a quality control/reproducibility measure, the data coordinating center selects some percentage of tapes to be reprocessed. In order to blind the BCL personnel, the requested analog tapes are returned to their originating clinical units, where new ID labels are affixed and the recordings remailed to BCL.

MPIP Holter processing. Dual-channel 24-hour recordings are received by mail from 9 clinical units. Half the study's Holter recordings are sent to BCL; the other half are sent to a similar processing system at Columbia University. A label is attached to each reel and specifies an ID number, a name/date-of-birth code, and date and start time of the recording. Both channels of the entire recording are digitized onto disk and onto magnetic tape. The disk-resident waveform is automatically analyzed, edited, and summarized. The Cycle data stream is saved on magnetic tape along with the digitized waveform and also accumulated with other Cycle data streams on another tape for the possibility of subsequent statistical analysis in

a fashion similar to that of the sudden death study (PR 14, A-6), although neither plans nor funding presently exists for such analysis. In addition to the printed summaries generated for any Holter recordings, MPIP or not, a special MPIP printout (A-3) serves as both a cardiologist review sheet and a transmittal form to the MPIP data coordinating center. The information which is transmitted summarizes normal-to-normal coupling intervals and ventricular ectopic activity. The cardiologist's review of ECG strips and printed summaries produced by the editor requires the acknowledgement of the presence of PVCs, bigeminy, number of PVC forms, couplets, runs, and PVC R-on-T. These decisions are entered into the DMS.

Each analog tape is returned to the data coordinating center when all steps in analysis and cardiologist review are complete. The data coordinating center may then attach a new ID label and re-mail the recording to one of the Holter processing centers for a reprocessing quality control check if the tape is returned to the same Holter processing center, or for a parallel quality control check of systems alignment if sent to the other processing center.

A digitized waveform is retained only until the analog tape is returned to the data coordinating center. A folder for each recording is filed in numerical ID order by clinical unit; each folder contains ECG strips, printed summaries, a copy of the special MPIP summary whose original cardiologist-signed record is mailed to the data coordinating center, and a DMS-produced printed summary of all stages of processing.

Data management system. The experience garnered with the Myocardial Infarction Patient Information (MIPI) system (D-2) suggested that similar data management techniques could be implemented to monitor Holter processing activities for the MILIS and MPIP studies. That same experience permitted the rapid implementation of an activity-monitoring subsystem for each multicenter study, and these data management subsystems have now proven beneficial and even crucial to the daily conduct of the Holter processing protocols. All data management subsystem routines are written in MUMPS on a time-shared terminal tied into the Washington University Medical Computing Facility.

Each subsystem retains the date and start and stop times of the recording, the recording's arrival date at BCL, the date of analysis, the date of cardiologist review, and the date of completion of total processing. These dates are used to generate internal and external management reports on systems throughput and to expose unexpected bottlenecks.

The subsystems also retain information concerning the arrhythmic content of each recording as determined by automatic analysis, editing, and cardiologist review. Searches can be made on any set of variables. For example, these subsystems can easily provide lists of recording IDs containing the more common arrhythmias; such lists may be generated for any Boolean expression of target arrhythmias.

The MILIS subsystem has several unique aspects. Unlike the MPIP study, for which only one recording is obtained per patient, the MILIS protocol dictates 3 recordings per patient. As each MILIS patient enters the study, the BCL Holter Core Lab is notified of the entry date and can therefore determine when to expect the three recordings. The Core Lab is also notified of patient termination. In that respect, work loads may be predetermined and clinical units can be contacted if recordings do not appear within some grace period of their expected dates. As each MILIS Cycle data stream is condensed into 150 variables by the statistical analysis system and several of those variables are merged with cardiologist review data to produce the 12 variables sent to the data coordinating center, the MILIS data management subsystem records the date of statistical analysis and the date on which the variables are approved for transmission to the data center. The MPIP subsystem, on the other hand, records the date on which the printed summary and analog tape are mailed to the MPIP data center.

Although these management information subsystems are laudable in the tasks they perform, the crucial dimension to their success is the error-checking logic built onto the routines for data acquisition and activity monitoring. Nonsensical entries are disallowed and improbable entries are questioned. Various steps in processing and review may not proceed until previous steps have not only been completed but have produced meaningful results. The many details involved in paperwork, machine-processing, and internal and extramural personnel interactions are an excessive burden for manual methods.

A-5. A Low Cost System for Holter Tape Playback

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A low cost alternative to the Avionics Holter tape scanners has been developed for use as a 60-times-real-time computer input device where real-time playback, chart recording, and other features of the full Avionics scanner are not required. The playback unit is compatible with tapes recorded on Avionics Model 425 and 445 recorders.

The Ampex Model ATR-700 audio recorder/reproducer was chosen as the basis for the playback unit because of these desirable features: 1) high reliability and easy maintainability; 2) availability of 2-track heads; 3) direct-drive DC servo capstan for low wow/flutter and tape speed variations; 4) accurate elapsed time counter; 5) optional remote control; 6) ability to operate on 120/240 volts, 50/60 Hz; and 7) low cost relative to the Avionics playback units.

Several modifications have been made to the tape deck. The reproduce equalize amplifier was modified in order to give flat response (± 3 decibels) from 6 Hz to 6000 Hz (0.1 Hz to 100 Hz in real time) for constant tape flux. This was accomplished by modifying or removing the NAB frequency breakpoints. Additionally, an inverting variable-gain amplifier was added to increase the signal level to approximately one volt peak-to-peak.

A-6. Extended Analysis of Argus/H and Argus/2H Quantified VEA

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Sandoz-Wander, Inc.

Following the processing and editing of Holter tapes by Argus/H or Argus/2H (A-4) the beat-by-beat annotation of the 10- or 24-hour recordings (Cycle streams) are accumulated on industry-compatible tape and transported to the IBM System/360-370 for bulk processing of the Cycle streams in order to extract salient features of the ventricular ectopic activity (VEA).

Summary (PR 12, A-2), the PL/I program which runs on the System/360-370 to reduce the Cycle streams to variables of interest continued to be utilized for routine processing of both Argus/H and Argus/2H processed tapes. A special version of Summary which produces for each PVC a record, which summarizes features concerning the environment of that PVC, e.g., its coupling interval, family number, Argus features, several averages of heart rate preceding the PVC, and the labels of the two beats preceding the PVC was utilized in order to more fully characterize the distribution of PVC coupling intervals. The output of both versions of Summary are in turn utilized to construct a SAS database (D-10) for further analysis and for merging with other record-keeping systems.

In an attempt to describe the form of the distribution of PVC coupling intervals,[1] a set of 12 Argus/2H Cycle streams were reprocessed using the modified version of Summary. For each of the 42,089 PVCs, a record was created which was then used to create a SAS database for subsequent

analysis. Since our previous attempts had been confounded by the grouping of all PVCs on the tape, those PVCs with similar morphology (based on the four Argus features) were grouped together into clusters utilizing algorithms developed for Argus processing (PR 14, A-3).

In order to investigate the relationship between heart rate and the PVC coupling interval (CI), PVCs within a cluster were grouped into quartiles by the average heart rate (based on average N-N interval) just prior to their occurrence. The mean, standard deviation, skewness, and kurtosis of the CI was then compared across the four heart rate groups within each cluster. The mean CI (in ms) increased monotonically as the heart rate slowed (average N-N interval increased). On the other hand, the mean of the percent prematurity (i.e. CI divided by the running average of the N-N intervals) monotonically decreased with slowing heart rate, indicating that the PVC coupling interval increases with increasing N-N, but at a slow rate. Various indices created from the CI and the current average N-N interval were investigated in an attempt to find an index which would be characteristic of the particular morphology and independent of the heart rate at which it occurred. No single adjustment was found which yielded an index which was independent of heart rate for all clusters.

Within a cluster, the CI was usually not normally distributed, with most distributions being both positively skewed and leptokurtic. Utilizing a procedure based on Johnson's systems of functions,[2] an attempt was made to find a transform of either CI or the CI adjusted for heart rate which was approximately normally distributed. Unfortunately, no single transformation was found which would yield nearly normal distributions for all clusters.

Of continuing interest is the relationship of complex VEA such as runs (3 or more consecutive PVCs) to other features noted on the tape. On the basis of previous analyses of the results of Summary processing we have concluded that, contrary to conventional wisdom, runs are usually initiated by PVCs with longer coupling intervals (PR 12, A-6).[3] To understand better the characteristics which are associated with tapes with runs, we examined 1486 10-hour tapes which had one or more PVC. The tapes were classified according to the presence or absence of couplets, bigeminy, and rate (per hour) of isolated PVCs (those PVCs not contained within either a couplet or run). The percent of tapes with a run for each combination is shown below:

Isolated PVC Rate (/hr)	No Bigeminy		Bigeminy	
	No Couplet	Couplet	No Couplet	Couplet
<10	5(37/802)	8(8/106)	0(0/14)	17(/16)
10-100	2(3/168)	16(30/182)	4(1/25)	33(18/54)
>100	7(1/14)	17(6/36)	0(0/7)	42(30/72)

Twenty percent of the tapes with a couplet also had a run while only 4% of tapes without a couplet had a run. Five percent of the tapes with isolated PVC rates under 10 per hour had runs whereas it was 12% for tapes with 10-100 per hour and 29% for those with rates over 100 per hour. The corresponding figures for the percent of tapes with couplets is 12%, 55%, and 84%. Thus although there is a strong association between tapes with couplets and those with runs it may only be by virtue of their mutual association to PVC rate. The table shown above was analyzed with a multivariate logistic with the GSK approach for categorical models (D-11). This analysis demonstrated that the probability of runs on the tape was associated significantly ($P<.0005$) with both the presence of bigeminy and couplets but not to PVC rate ($P>.15$). Thus support is demonstrated for the concept that the presence of complex VEA are associated among themselves, relatively independent of the PVC rate.

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(2) J. P. Miller, "A Parsimonious Approach to Data Transformations," Proceedings of the 1977 Statistical Computing Section of the American Statistical Association, Chicago, Illinois, pp. 73-75, 1977.

(3) R. E. Kleiger, T. Pavlovic, J. P. Miller, and G. C. Oliver, "Ventricular Tachycardia and Accelerated Idioventricular Rhythm in Survivors of Myocardial Infarction," Circulation, vol. 56, p. III-182, 1977 (abstract).

A-7. Natural History Study of Sudden Death

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The natural history study of sudden death (PR 14, A-7; PR 13, A-7; PR 12, A-1; PR 11, A-1; PR 10, A-1, PR 9, B-3; PR 8, B-4) has completed the clinical and demographic data collection activities on 2175 myocardial infarction patients who have been followed at least one year after infarction. The MUMPS-based Myocardial Patient Information System (MPIP) (D-2) was instrumental in guiding study personnel through a complex protocol to collect, edit, and forward very detailed information to the study's database. The database is now being scrutinized to expose and correct lingering errors.

A major substudy, the relationship of ventricular arrhythmias to sudden death in survivors of myocardial infarction, has completed the arrhythmia analysis of some 3200 Holter recordings obtained from 738 of those 2175 infarction patients. Although the beat-by-beat (Cycle) data streams produced by automatic arrhythmia analysis have been distilled to 154 variables each (PR 12, A-2), those Cycle data streams which exhibit clinically important ectopy (10 or more PVCs, multiformed PVCs, bigeminy, couplets, runs, or R-on-T) will be reprocessed to produce some 35-40 variables for <u>each</u> PVC.

After the additional PVC information has been merged into the database and the entire database has been purged of all detected errors, statistical analysis of the database will hopefully expose risk factors and prognostic indicators of sudden death peculiar to the myocardial infarction patient.

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

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This project which has as its goal development of a database for the evaluation of automatic arrhythmia detectors (PR 14, A-8), began September 30, 1977 and has proceeded at a rapid pace during the past year. Candidates for database inclusion are 2-channel, 24-hour ambulatory ECG recordings. To date seventeen contributing institutions have submitted 396 tapes for consideration. These contributors represent major research centers and other interested institutions worldwide as indicated by the following list:

CONTRIBUTING INSTITUTION STATUS

Institution		Tapes
Alleghany General Hospital	Pittsburgh, PA	5
William Beaumont Hospital	Royal Oak, MI	24
Cleveland Metro. General Hospital	Cleveland, OH	8
University Hospital	Copenhagen, Denmark	6
Cornell University	New York, NY	9
Creighton University	Omaha, NB	90
Danbury Hospital	Danbury, CT	9
Duke University	Durham, NC	21
Kyusha University	Fukuoka, Japan	5
Louisville Jewish Hospital	Louisville, KY	20
Institute of Cardiology	Montreal, Canada	5
Lariboisiere Hospital	Paris, France	2
Thoraxcentrum	Rotterdam, Netherlands	29
University of California	Los Angeles, CA	9
University of California - V. A. Hospital	San Diego, CA	6
Washington University	St. Louis, MO	138
Yale University	New Haven, CT	10
		396

Following the processing of a 24-hour tape, results of the analysis are reviewed to identify a four-hour segment of the tape suitable for further intensive analysis. If the tape is acceptable, it is assigned to one of eight arrhythmia classes. A digital record of this four-hour segment is then submitted to the Tape Selection Committee, which consists of four leading authorities on arrhythmias and arrhythmia detection. The committee members are: Dr. Robert C. Arzbaecher, University of Iowa; Dr. Nancy Flowers, University of Louisville; Dr. J. Thomas Bigger, Jr., Columbia University; and Dr. Suzanne Knoebel, Indiana University. Individuals from this committee independently review the tape to select the three-hour portion of the tape which is to be considered for entry into the database. These three hour segments are then submitted to the Tape Selection Committee as a whole for a group review. This is the final formal review of the tape. At this point the tape may be accepted, put on hold for later consideration, or rejected. During the past year three of these group review sessions have been held. As a result of these meetings, the database arrhythmia classes have been filled as follows:

Arrhythmia Class	Tapes Selected	Tapes on Hold	Tapes Rejected
No PVCs	14	2	9
Isolated Uniform PVCs	27	2	6
Isolated Multiform PVCs	8	0	15
Bigeminy	29	0	3
Couplets	26	0	8
R-on-T	3	0	2
Ventricular Rhythms	12	2	9
Ventricular Fibrillation	3	0	0
Totals	122	6	52

The tapes accepted represent 63 percent of the needed total. Tapes for the R-on-T class and Ventricular Fibrillation class have been very difficult to obtain. The other unfilled classes are expected to be completed very soon. With some additional special effort, including the use of the MECCA system installed at Jewish Hospital (A-9), the completion of the remaining two classes should be feasible as well. The arrhythmia classes of Isolated Uniform PVCs, Bigeminy, and Couplets have been filled.

Currently, the last half hour of three-hour records in these classes are being annotated by the Committee of Expert Electrocardiographers. The members of this distinguished committee are: Dr. Charles Fisch, Indiana University; Dr. Borys Surawicz, University of Kentucky; and Dr. Richard Langendorf, University of Chicago. The last half hour of each record is annotated on a beat-by-beat basis. The annotator must also note the noise content of the signal and the background rhythms in which the ventricular arrhythmias may be embedded. Annotated strips are then compared and reconciled to create the final set of annotations for the database tape.

During the next few months the final stages of database tape processing will begin. The analysis of 24-hour tapes will soon be completed. Major emphasis will then be placed on completing the processing of accepted tapes. The completion entails stripping, annotating, and reconciling of the last half hour of all accepted tapes. Major work yet to be done includes entering final annotations to the digital tape, microfilming of each record, and documentation of each record. The anticipated completion date for the database is now December 31, 1979.

A-9. MECCA System Development and Installation

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Modification of the MECCA system (PR 13, A-14; PR 14, A-9) for use for the American Heart Association Arrhythmia Database (AHA) (A-8) and changes for improved performance have been made. The system was converted from a single channel of ECG per patient to two channels per patient. The sampling system and encoding software have been changed from a ten-bit system to a twelve-bit system. To facilitate these changes, nearly all existing data handling routines were rewritten. Enhancements of the display routines were made to display both channels of ECG simultaneously. With the addition of a third interrupt level, sample buffering is now being done to enable the system to monitor eight channels of ECG instead of the original six channels. The disk storage structure was changed to allow for maintaining a minimum of three hours of two channels of ECG for each of four patients connected to the system.

Significant hardware changes were made to accommodate the requirements of the AHA database. Among these are the addition of hardware to sense the connection of a patient to the system, addition of control logic to sense alarm button presses and turn on indicator lamps in the event that an important episode of ECG has been recorded, and expanding of the analog hardware to 32 channels with differential inputs.

As part of the American Heart Association Arrhythmia Database project (A-8), the MECCA system was configured on a refurbished PC-1200 computer system and installed in the Jewish Hospital Medical Intensive Care Unit (MICU). The PC-1200 and associated hardware was assembled into a compact and easily portable system which also allows for easy maintenance.

Installation of the system in the MICU was carried out in two phases. The first phase included the installation of cabling from fifteen patient rooms to a central computer room. A connection box with a special connector and alarm button was installed at each patient bedside. During this phase, the system was evaluated and its performance and signal quality were improved. In addition to the computer installation, four two-channel Honeywell ECG amplifiers on portable carts were prepared for patient monitoring. The nursing staff of the MICU was trained in the connection of these ECG amplifiers and in the general use and purpose of the computer system.

Following this test, training, and evaluation period, the MECCA system was moved to a new MICU in the Jewish Hospital. This second phase required the installation of cabling to seven patient rooms, installation of the computer in a new room, and a brief checkout period. The second phase has been completed and routine patient monitoring is beginning.

The system is capable of detecting when particular patients are connected to the system and then automatically begins to record the data from that patient. Upon the occurrence of an important ventricular event, a button is pressed in the patient room to cause the computer to save the patient data permanently. These data are then removed from the MECCA system on cartridge disk and transferred to magnetic tape into an Argus/2H system format for ECG analysis.

Future system improvements include additional data handling and display capabilities for greater versatility, more efficient software to increase processing speed, and improvements to the data-storage structure and Huffman encoding to increase efficiency.

A-10. Assessment of Vascular Integrity of the Myocardium Following Ischemic Injury

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Although much progress has been made in elucidating the pathophysiology of ischemic injury to the heart, several fundamental aspects of the problem remain unresolved. Among these are: (i) identification of the determinant(s) of whether sustained injury is "irreversible" and will progress to cell death, or whether it is potentially "reversible" with restoration of normal

cell function; (ii) the effects of ischemia on vasculature; and (iii) the role of compromised vascular integrity in the pathogenesis of myocardial infarction. We have initiated a program of experimental studies intended to provide some insights to these issues. Our goal is to characterize the effects of ischemic injury on the temporal evolution of alterations of the integrity and of the permeability of membranes of the coronary vasculature and musculature, and to assess the significance of observed changes in the pathogenesis of myocardial infarction. Additionally, we hope that our measurements will allow us to determine the effectiveness of pharmacological agents intended to modulate myocardial damage of the treatment of ischemic heart disease.

The approach has been to use appropriate vascular- and extracellular-space markers labeled with gamma-ray emitting radioisotopes. By using external radiation detectors, the movements of these markers in living isolated heart preparations can be monitored following their injection into the arterial inflow. Our method relies for its experimental design and for interpretation of the data on mathematical models based on established principles of tracer kinetics.[1-4]

We perform our experiments under constant-flow conditions using isolated rabbit hearts perfused with oxygenated Krebs-Henseleit buffer. A blood-gas analyzer is used to monitor arterial and venous P_{O_2}, P_{CO_2}, and pH. Radioactivity is monitored using a lead-shielded sodium-iodide scintillation detector positioned to view the entire heart. Output signals from the detector are amplified and subjected to pulse-height analysis. Data acquisition, storage, and analysis are performed with a microprocessor.

We have used ^{125}I-labeled albumin as a vascular marker and ^{131}I-iodide as a water-space marker. Measurements of the mean-transit time of the tracers enable us to compute volumes of distribution according to the central-volume principle.[1] Values of vascular volumes so obtained agree well with values obtained by independent means in the same preparations. Our preliminary experimental determinations of the mean-transit time and the volume of distribution for iodide anion suggests that this marker labels total water space and is not excluded from intracellular space, as previously thought by analogy with chloride ion. Our preliminary results with radiolabeled albumin suggest that ischemic injury brought about by interrupting perfusate flow for 30 minutes is sufficient to disrupt both endothelial and sarcolemmal integrity.

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A-11. Mathematical Models for Estimation of Infarct Size

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Although extension of infarction is well recognized clinically, its frequency has not been elucidated definitively. Since morbidity and mortality associated with myocardial infarction are related in part to the amount of damage sustained by the heart, the contributions of recurrent episodes of infarction merit consideration. Objective assessment of measures designed to prevent extension or recurrence of infarction requires delineation of the incidence, nature, and natural history of such episodes. Unfortunately, the biological significance of clinical criteria of extensions or recurrences of infarction such as chest pain, electrocardiographic changes, arrhythmia or ventricular dysfunction is difficult to assess because these manifestations may reflect either recurrent ischemia, additional infarction or both.(1-8)

In previous studies, we have evaluated the sensitivity and specificity of serial elevations of plasma MB CK activity as diagnostic marker of myocardial infarction and as an index of the extent of infarction in experimental animals and patients.(9) Release of MB CK into circulation was found to be a remarkably specific marker of irreversible, as opposed to reversible myocardial injury. Based on values from several hundred subjects, baseline MB CK values are low and confined to a narrow range (2 ± 1 (SE) IU/l). After infarction MB CK reaches peak levels within 12 to 14 hours and disappears rapidly from the circulation with values returning to baseline in 24 to 36 hours. With a log normal or gamma distribution function fitted to all the plasma MB CK values, it is possible to objectively characterize the plasma MB CK time activity curve associated with a discrete episode of infarction. The extent of deviations from the curve fit to all values provides an index of atypicality, suggestive of an anomolous pattern of release of enzymes compatible with an episode of recurrent infarction.

The present study is designed to detect and quantify apparent early and late extensions or recurrences of infarction based on serial changes in plasma MB CK activity and to assess the biological significance of the episodes recognized with the use of independent methods characterizing cardiac biochemical integrity and electrical stability, ventricular performance, myocardial metabolism, and the intensity of the inflammatory process in the heart in vivo. In addition, the apparent impact of enzymatically detected extensions on prognosis will be assessed.

Characterization of CK kinetics based on previous CK modeling studies will be utilized to evaluate procedures for estimating the extent of infarction associated with multiple episodes. In preliminary studies we have found that a scaled gamma distribution function of the form:

$$f(t) = At^{a}e^{-ct}$$

where A, a, and c are adjustable parameters, fits CK curves adequately. A more general form, the gamma distribution function convolved with an exponential, i.e.:

$$f(t) = A(te^{-ct}) * e^{-kt} = A\int_{o}^{t} e^{-kt(t-s)}se^{-cs}ds,$$

where the * denotes convolution, has been used by us as well as other investigators. Due to the large variation in plasma CK curves we will first analyze a large number of normal CK time activity curves to determine which equation is most suitable and to define potential limitations that may be required on the values of the parameters.

Initially, we will assume that CK curves associated with the initial infarction and reinfarction events are of the same functional form as curves obtained after single, discrete episodes of infarction and that the initial and reinfarction events are independent with the exception that the removal of enzyme from the blood occurs at the same rate in both cases. The plasma CK time activity curves will then be treated as the sum of two or more curves, each curve associated with a single infarction event.

Non-linear least-squares approximation will be used to fit selected curve equations to the plasma CK curves by adjusting the value of the parameters. The resulting best-fit curves will then be analyzed statistically to determine whether significant CK release occurs late in the time course of the curve, suggestive of one or more reinfarction events. Infarct size associated with each event will be calculated from the best-fit curve using the portion of the fitted equation which corresponds to each infarction event.

Since secondary elevations of plasma MB CK activity may reflect accelerated or late "washout" from zones of infarction rather than new necrosis, independent criteria, including concomitant release of myoglobin, electrocardiographic changes, and clinical symptoms, will be used to determine whether the event is associated temporally with apparent recurrent injury to the heart.

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A-12. Evaluation of Cardiac Lymph Drainage with ^{99m}Tc-sulfur Colloid

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Support: RR 00396
HL 17646

In previous studies in this project the influence of altered cardiac lymph flow on release of myocardial enzymes into the systemic blood circulation and hence upon enzymatic estimation of infarct size was characterized. The potential importance of qualitative or quantitative detection of regional cardiac lymph drainage in refining parameters used in enzymatic estimation of infarct size was therefore identified.(1) During the past year, a study was completed in which external detection of cardiac lymph flow was achieved with ^{99m}Tc-sulfur colloid injected intramurally into selected regions of the heart in 17 dogs.(2) Serial images of the chest were obtained for 24 hours with a scintillation camera after which the animals were sacrificed and the cardiac and other mediastinal nodes removed and assayed for radioactivity. Analysis of the images and counts in vitro demonstrated a consistent drainage pathway between the anterior left ventricular wall and the cardiac node. Other areas of the heart exhibited variable drainage patterns. After injection into the left ventricular wall in both open-chest and closed-chest dogs via a percutaneous, subxiphoid approach with a specially designed collared needle, the cardiac node was visualized within two minutes. Activity in the cardiac node region peaked within 40 minutes and accumulated to levels exceeding 1,000 counts/min in 5 of 6 dogs before reaching a plateau. However, in dogs with cardiac lymphatic occlusion five days prior to anterior left ventricular wall injection of the tracer, appearance of radioactivity in the cardiac node was markedly delayed and maximum activity was far less than that in controls. Thus, regional cardiac lymph flow from the anterior left ventricular wall can be assessed semi-quantitatively with a radionuclide imaging technique potentially useful in refining enzymatic estimates of infarct size.(3,4)

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A-13. Modification of Infarct Size

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Studies were performed in the Cardiac Care Unit at Barnes Hospital to assess the effect of selected pharmacological agents on infarct size, ventricular dysrhythmia and hemodynamics in patients with myocardial infarction. Infarct size was estimated from serial plasma creatine kinase (CK) changes during a 72 hour interval and results in controls were compared to that observed in the treated group. All Holter tapes were digitized and processed by the Argus/H computer system. Hemodynamics including cardiac output were determined by Swan-Ganz thermodilution technique and the effect of the drug assessed by comparing hemodynamics before and after administration. In selected cases left ventricular function was assessed by radionuclide ventriculograms before and after therapy.(1-13)

Results of the study completed in 1976 assessing the effect of dobutamine in patients with acute myocardial infarction showed dobutamine to be a potent inotropic agent with minimal chronotropic effect. Dobutamine significantly increased cardiac output and decreased the wedge pressure without deleterious effect on infarct size or ventricular arrhythmias. However, in order to obtain adequate data for prediction of infarct size, dobutamine was not administered until 12 hours after the onset of chest pain. Another study is now in progress assessing the effect of dobutamine in patients with myocardial infarction when administered immediately upon admission to the Coronary

Care Unit. Results of dobutamine on infarct size and ventricular arrhythmias will be compared to that observed in concomitant controls. Eighty patients with acute myocardial infarction have been entered into the study and results so far are similar to those obtained in the previous study showing beneficial effect on hemodynamics without deleterious effects on heart rate, ventricular arrhythmias or infarct size.

A randomized trial initiated in 1978 to assess the effect of intravenous nitroglycerin on chest pain, ventricular arrhythmias and infarct size in patients with acute myocardial infarction is progressing well. The intravenous infusion of nitroglycerin is titrated so that the systolic blood pressure does not fall more than 20% and the heart rate does not increase by more than 20 beats per minute. The drug is initiated immediately after the patient is admitted to the Coronary Care Unit and results of infarct size and ventricular arrhythmias will be compared to that of the concomitant randomized controls. So far, 90 patients have been entered into the study. Patients have tolerated the drug well without any significant side effects and in patients, particularly those with cardiac failure or pulmonary edema, marked improvement in hemodynamics has been observed without any significant increase in heart rate. It is too early to determine the effect on infarct size but preliminary results on the first 69 patients are summarized below.

Nitroglycerin has been shown to be beneficial during experimental myocardial infarction. To determine the effects in man, 69 patients (Class I-II) were randomized to control (C) (n=30) or treated (T) (n=39). Nitroglycerin was started at 10 μg/min and increased until a 10% decline in blood pressure, a 10 beats/min increase in heart rate or 200 μg/min was attained. ECGs were recorded continuously and analyzed by Argus/H computer. Frequency of PVCs in the first 12 hours was significantly higher in treated than controls (178 ± 44 (SE) vs 106 ± 31, $p < 0.05$) but not ventricular tachycardia or couplets (4.7 ± 1.5 vs 2.8 ± 1.0/12 hours). Infarct size index was similar (13 (T) vs 18 (C) CK-g-eq, NS). Severity of pain, reflected by the amount of morphine given was similar (12.4 (T) vs 13.8 (C) mg/24 hours). Slightly more lidocaine was required in the treated group averaging (1692 vs 1512 mg/24 hours, NS). Radionuclide ventriculograms showed slight improvement in ejection fraction in the treated group (n=8) (46 vs 49%, $p < 0.05$) versus controls (n=15, 34 vs 34%) but no change in wall motion abnormalities. Thus, nitroglycerin did not reduce analgesic requirements but increased ventricular ectopy despite absence of significant hypotension or tachycardia.

The role of digoxin in the treatment of cardiac failure associated with acute myocardial infarction is controversial. Accordingly, we compared the hemodynamic effects of digoxin to those of dobutamine, an inotropic agent with rapid onset of action and clearance ($t_{1/2}$=2.5 min) in 6 patients (Killip Class II-III) who were catheterized within 36 hours of acute myocardial infarction. Dobutamine (5-10 μg/kg/min) was given intravenously for 30 minutes and then discontinued until hemodynamics returned to baseline. Digoxin (0.0125 mg/kg) was then given intravenously and hemodynamics were recorded for 90 minutes. Dobutamine markedly decreased ventricular filling pressure (23.8 to 8.5 mm Hg, $p < 0.05$) and systemic vascular resistance (1624 to 1202 dyne•sec•cm^{-5}, $p < 0.05$) and increased cardiac index (2.4 to 3.2 L/min/M^2, $p < 0.001$) and stroke work index (23.7 to 35.6 g•m/M^2, $p < 0.02$)

without a change in heart rate or arterial pressure. In contrast, digoxin had no effect on filling pressure (19.0 to 18.8) or systemic vascular resistance and stroke work index (21 to 24, $p < 0.05$). Neither drug affected the incidence of ventricular arrhythmias. Thus, dobutamine increased cardiac output, decreased filling pressure and afterload as opposed to digoxin which did not affect filling pressure or afterload.

To initiate prompt and appropriate therapy in patients presenting with chest pain and to optimize utilization of Intensive Care facilities, an early and specific diagnosis is required. To assess data on selective diagnostic techniques in relation to patient turnover in a large volume of patients, we established a MUMPS database in the 15-bed Barnes Hospital Coronary Care Unit. The primary goal of the present study was to determine on a routine basis the diagnostic specificity and sensitivity of ^{99m}Tc-pyrophosphate scintigrams and ECGs compared to plasma CK isoenzymes (MB CK) in the diagnosis of myocardial infarction. The study was performed on 1733 patients with chest pain admitted to the CCU over a 2.5 year period. To collect and analyze the data we employed a MUMPS database which ran on a time shared minicomputer system. The entry procedure for this database is interactive and answers are entered in standard medical codes. As the operator enters the data all entries are checked for validity and appropriate ranges. If an error is made in data entry, the prompt for the question is repeated. Since the coded data entry is redisplayed in full context, errors are easily detected and corrected. Data in the database consist of patient identification, admission date, admitting diagnosis, length of stay in the CCU and the CCU final diagnosis. Diagnostic techniques in the database consisted of serial 12-lead ECGs, pyrophosphate scintigrams and CK isoenzymes.

Diagnosis of myocardial infarction was based on elevation of plasma MB CK activity. Out of a total of 733 patients, 674 had myocardial infarction. It is of note that in patients with myocardial infarction, only 66% developed new Q-waves. All of the patients had myocardial infarction and 90% of the patients without myocardial infarction exhibited some non-specific ST-T wave changes. In patients with proven myocardial infarction, a positive pyrophosphate scan was observed in 86% of the patients, however in patients without infarction only 9% exhibited positive pyrophosphate scans. It is worthwhile to point out though that the incidence of positive scans is 89% in patients with anterior infarction while it is only 78% in patients with inferior infarction. All of the scans were performed at 24-48 hours after onset of symptoms, the time at which myocardial uptake is maximum. Patients with myocardial infarction stayed on an average of 6.3 days in the CCU, as opposed to only 3.4 days in those patients without infarction. Patients admitted to the CCU for exclusion of infarction, whose sole symptom was chest pain, averaged only 2 days. However, patients admitted with chest pain who also had cardiac failure for causes other than acute myocardial infarction stayed on an average of 4.9 days. In the present study, with the aid of a MUMPS database, we were able to analyze a large amount of data concerning patients admitted consecutively to the Coronary Care Unit for exclusion of myocardial infarction. Plasma MB CK analysis provides for a specific and rapid diagnosis of myocardial infarction. Its use is important in facilitating efficient

CCU bed utilization and in proper utilization of highly trained personnel. The diagnostic specificity of pyrophosphate scintigrams compared to MB CK was 0.89. The development of new Q-waves on ECG is highly specific, however it is relatively insensitive since only 66% exhibited Q-waves. An ongoing study is now in progress utilizing the MUMPS system to analyze ECGs taken in the Emergency Room with results compared to diagnostic studies and patient course in the Coronary Care Unit to determine whether additional information can be obtained from the ECG to improve screening of patients for the Coronary Care Unit.

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A-14. Ischemic Heart Disease SCOR Computer System

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HL 17646

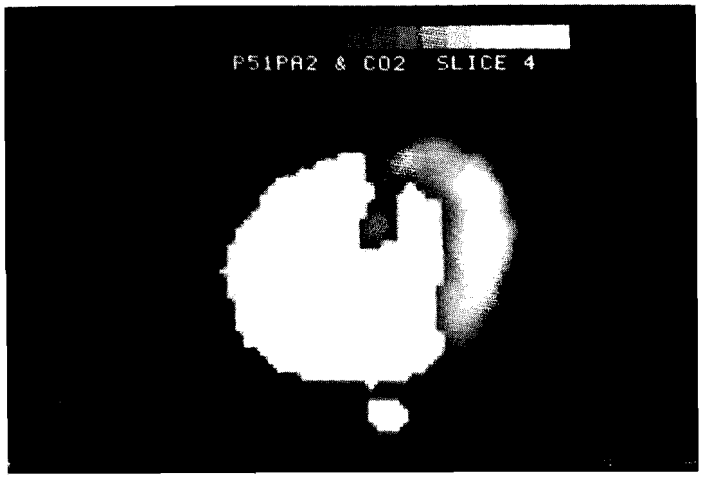
Activities associated with the maintenance and operation of the PETT IV tomographic system for cardiac imaging (PR 13, B-5) have required major efforts in both software and hardware during the past year. Thirty-six cardiac imaging studies have been performed, each study requiring several hours for data collection, processing, and display.(1-4) Calibration procedures are performed daily to ensure that the 96 photomultiplier tubes are properly adjusted and the detectors are counting approximately the same number of photons in each coincidence line.

Preliminary studies with the PETT IV indicated that the resolution of the constructed images, 1.8 cm FWHM, was not adequate for imaging the moving heart. Additional lead septa were added to the system and the sampling rate was increased, resulting in a resolution of 1.4 cm FWHM in the reconstructed images. These changes necessitated modifications in the data collection and processing programs as well as the filter function used in the filtered back-projection. The effects of various filters on the reconstructed images were investigated with the use of phantoms, and a filter which did not significantly degrade the resolution and produced images which were fairly smooth was selected for general use.

Considerable effort was expended in reducing execution time of the PETT software and improving ease of operation for clinical studies. The development of several new modes of display has aided in the detection and quantitation of infarct size in myocardial infarction patient. Sagittal and coronal sections can be generated from the reconstructed transverse slices and displayed via the Ramtek display system in either color or gray scale. Any of the slices can be plotted in gray tones on the Versatec printer/plotter with an overlaid grid. Images from different studies can be superimposed with the use of special color or gray scale schemes. Figure 1 shows an example of a blood-pool image obtained from a patient following inhalation of ^{11}C-labeled carbon monoxide superimposed on a gray-scale image obtained after intravenous injection of ^{11}C-palmitate in the same patient.

Anterior

Right



Left

Posterior

Figure 1. Superimpositions of two PETT IV transverse images obtained in a normal subject showing the distribution of ^{11}C-labeled palmitate in the myocardium (displayed in gray tones) and of ^{11}C-labeled red cells in the blood pool (displayed as a homogenous white region).

Currently, we are investigating alternative procedures for calculating correction factors which compensate for the attenuation of the annihilation photons within the subject of study. Our present procedure of using the ratio of data obtained from two scans suffers from several defects including the unavoidable fluctuation of data values due to the statistical properties of radioactive decay. As a first step, we will attempt to reduce the fluctuations in the attenuation correction factors by smoothing the projection data used to compute these factors.

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

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During the past year, studies have continued regarding the correlation of electrophysiological derangements and biochemical factors underlying malignant dysrhythmia due to ischemia. In addition, the influence of the autonomic nervous system on electrophysiological and biochemical derangements during myocardial ischemia is a major focus of the laboratory. Many patients autopsied after sudden cardiac death do not show pathological evidence of complete coronary occlusions, suggesting that vasospasm of normal or partially occluded coronary arteries, with phasic alteration in regional flow may be a major progenitor for malignant dysrhythmias associated with sudden death. Since both coronary occlusion and reperfusion initiate severe ventricular dysrhythmias in experimental animals, we have recently completed studies demonstrating disparate electrophysiological alterations underlying these two types of dysrhythmias.[1,2] Using a variety of electrophysiological

procedures, the dysrhythmias induced by coronary occlusion alone were characterized by increased conduction time through ischemic regions, asynchronous depolarization, shortening of ischemic zone refractory periods, normal idioventricular rates and exacerbation by high rate atrial pacing implicating reentry within ischemic myocardium as a major progenitor.[1] In contrast, the dysrhythmias induced by coronary reperfusion were characterized by normalization of conduction time through myocardial regions, synchronous depolarization, normalization of ischemic zone refractory periods, high idioventricular rates and consistent suppression by high atrial pacing, implicating enhanced ventricular automaticity as one possible progenitor for these malignant dysrhythmias associated with reperfusion.[1] Thus, two distinct mechanisms may underlie these two types of dysrhythmias, and since both may be potentially important in the sudden death syndrome in man, each may require different therapeutic interventions.

As an extension of previous studies pertaining to the influence of the autonomic nervous system during myocardial ischemia, studies have recently been completed demonstrating a major electrophysiological role of α-adrenergic stimulation during both coronary occlusion and reperfusion.[3-7] Alpha- compared to β-adrenergic contributions to dysrhythmias induced by left anterior descending (LAD) coronary occlusion and by reperfusion were assessed in chloralase-anesthetized cats. Alpha-adrenergic receptor blockade with either phentolamine or prazosin significantly reduced the number of premature complexes (PVCs) during coronary reperfusion (321 $\pm$ 62 PVCs to 14 $\pm$ 10, $p < .001$), abolished early ventricular fibrillation (from 25% in controls to 0%) and prevented the increase in idioventricular rate (IVR) normally seen with coronary reperfusion. However, β-receptor blockade with propranolol was without effect. Ventricular dysrhythmias induced by coronary occlusion alone (without reperfusion) were attenuated markedly by α-receptor blockade under conditions in which perfusion (measured with radiolabeled microspheres) within ischemic zones was not affected. Alternative sympatholytic interventions, including pretreatment with 6-hydroxydopamine to deplete myocardial norepinephrine from 8.8 $\pm$ 1.4 ng/mg protein to 0.83 $\pm$ 0.2 and to render the heart unresponsive to tyramine (120 μg/kg) attenuated dysrhythmia induced by both coronary occlusion and reperfusion in a fashion identical to that seen with α-receptor blockade. Although efferent sympathetic activation induced by left stellate nerve stimulation increased idioventricular rates from 66 $\pm$ 6 beats/min to 144 $\pm$ 7 ($p < .01$) prior to coronary occlusion, this response was blocked by propranolol but not phentolamine. In contrast, during reperfusion the increase in idioventricular rate induced by left stellate nerve stimulation (to 203 $\pm$ 14 beats/min) was not inhibited by propranolol but was abolished by phentolamine (71 $\pm$ 10 beats/min). Likewise, intracoronary methoxamine (10^{-7}M) in animals depleted of myocardial catecholamines by 6-hydroxydopamine pretreatment did not affect idioventricular rate prior to coronary occlusion. However, early after coronary reperfusion, regional intracoronary infusion of methoxamine increased idioventricular rate from 33 $\pm$ 7 beats/min to 123 $\pm$ 12 ($p < .01$). Thus, enhanced α-adrenergic responsiveness occurs during myocardial ischemia and appears to be a primary mediator of the electrophysiological derangements and resulting malignant dysrhythmias induced by catecholamines during myocardial ischemia and reperfusion.

Recently, studies have been initiated to evaluate the role of increased intracellular Ca^{++} in the rapid increase in idioventricular rate and dysrhythmia induced by reperfusion. Since reperfusion induces a two-fold increase in Ca^{++} within 90 sec, we are evaluating whether this increase is mediated through enhanced α-adrenergic activity and whether α-adrenergic blockade or enhancement affects accumulation of intracellular Ca^{++} in this setting.

Recently, we have detected accumulation of lysophosphoglycerides in ischemic myocardium early after coronary occlusion as well as in effluents from isolated, perfused hearts under hypoxic conditions. As reported in PR 14, A-15, comparable concentrations (.75 to 3.0 mM) of lysophosphoglycerides bound to albumin markedly and reversibly altered action potentials of canine Purkinje fibers in vitro using an automated system for analysis of intracellular action potentials stored on analog tape.[8] Electrophysiological alterations induced by lysophosphoglycerides include decreases in resting membrane potential, overshoot of phase 0, $\dot{V}_{max}$ of phase 0 and action potential duration.[9,10] In addition, these compounds induced fractionation of the action potential into several components, unresponsiveness to external stimulation and enhanced automaticity at normal and reduced membrane potentials, all phenomena characteristic of ischemic tissue in vivo.[9] In addition, a rightward and downward shift in the membrane response curve ($\dot{V}_{max}$ vs membrane potential) resulting in a 40-fold prolongation of conduction time together with an increase in the ratio of effective refractory period to action potential duration such that the effective refractory period persisted beyond action potential duration resulting in post-repolarization refractoriness.[9,10] Since all these alterations are peculiar to ischemic tissue in vivo, the accumulation of these metabolites may play a major role in the membrane alterations and resultant electrophysiological derangements and malignant dysrhythmia during ischemia. More recently, we have demonstrated that both lysophosphatidyl choline (LPC) and lysophosphatidyl ethanolamine (LPE) increase in ischemic tissue within three minutes, at the time of onset of ventricular dysrhythmia and that a correlation exists between the number of premature ventricular complexes and the tissue lysophosphoglyceride content ($r=.79$, $p < .01$). In addition, one major study has involved the demonstration in vivo that lysophosphoglycerides appear in venous effluents from ischemic regions within 10 minutes after coronary occlusion and may explain the known arrhythmogenic effects of venous effluents from ischemic regions in vitro.

Additional studies have been performed to determine whether free L-palmitoyl (acyl)-carnitine induces alterations similar to LPC in canine Purkinje fibers, since this amphiphilic compound also accumulates in ischemic myocardium.[11-13] Both LPC and palmitoyl-carnitine (75 μM) without albumin induced significant decreases in maximum diastolic potential (MPP), $\dot{V}_{max}$ of phase 0 and amplitude, changes identical to those induced by albumin-bound LPC (.75 mM) at ten-fold higher concentrations.[11] Thus, free LPC and acyl-carnitine induce similar electrophysiological alterations suggesting potential cumulative arrhythmogenic effects of amphiphilic compounds accumulating in ischemic myocardium in vivo.

To determine whether the electrophysiological alterations induced by LPC in vitro resulted in action potentials dependent exclusively on the slow inward current, LPC effects were examined in superfused canine Purkinje

fibers with inhibitors of fast (tetrodotoxin) and slow (verapamil or Mn^{++}) channels.[14] Verapamil (1 mg/l) or Mn^{++} (10^{-6} M) triangularized action potentials without altering MDP or $\dot{V}_{max}$ of phase 0. Subsequent superfusion with 0.2 mM LPC decreased MDP from -92 ± 5 mV to -57 ± 3, $\dot{V}_{max}$ from 660 ± 47 V/sec to 11 ± 1 and amplitude from 132 ± 2 mV to 34 ± 4 (all $p < .01$). Although at a MDP of -53 ± 3 mV the fibers were inexcitable in the presence of both verapamil or Mn^{++} and LPC, increasing $(Ca^{++})_o$ from .75 to 8.1 mM led to immediate initiation of action potentials with slow upstroke velocity (26 ± 8 V/sec) and low amplitude (48 ± 3 mV) even though MDP remained unchanged (-54 ± 1 mV). Action potentials were not affected by tetrodotoxin. Thus, low concentrations of LPC induce action potentials dependent exclusively on the slow inward current and suggest the possibility that these types of action potentials may underlie in part the abnormal electrophysiological behavior in ischemic myocardium.[14]

Initial studies have begun to determine whether the apparent alteration in β- to α-adrenergic responsiveness during ischemia and reperfusion occurs as a result of accumulation of amphiphilic metabolites. Using [^{3}H]-dihydroalprenolol (DHA) as a specific β-receptor ligand, preliminary results revealed that LPC induced a significant decrease in specific DHA binding in rat myocardial membrane preparations (68.4 to 18.1 fmoles/mg protein) suggesting a decrease in β-receptor number with no alteration in affinity for the remaining receptors (K_D 5.05 to 4.92, n.s.). Although specific binding of α-adrenergic receptors has not yet been completed, these studies might explain the mechanisms responsible for the apparent alteration in adrenergic receptors during myocardial ischemia.

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A-16. Characterization of Myocardial Properties by Ultrasonic Parameters

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The goal of this project is the implementation of a system for ultrasonic reconstruction based on measurements of regional attenuation and backscatter of normal and ischemic myocardium and of normal and atherosclerotic vascular tissue. Although initial experiments have been performed in transmission, the ultimate goal of imaging of tissue will incorporate the use of reflected ultrasound. The current research program is multidimensional in that experiments are designed for investigation of tissue properties utilizing three approaches: (1) characterization of ultrasonic and biochemical properties of tissue in vitro, (2) development of a method for the measurement of quantitative backscatter by reflected ultrasound in vivo, and (3) refinement of the data acquisition system designed by Digisonics. Within these three approaches, specific accomplishments during the past year include characterization of the dependence of the ultrasonic backscatter and ultrasound upon the myocardial content of collagen.[1-3] Specific interventions, including the use of collagenase for dissolution of collagen and variable osmolar concentrations of buffer for alteration of water content of tissue, were employed in experiments utilizing isolated, perfused rabbit hearts. Both canine and rabbit hearts have been employed in studies addressing the use of quantitative backscatter, an ultrasonic parameter measurable with the use of reflected rather than transmitted ultrasound. In these studies, we have demonstrated detectable alterations of ultrasonic backscatter from ischemic regions of canine hearts compared to nonischemic regions within two hours of coronary occlusion. Further refinements of the Digisonics Digiscan^{R} data collection system include the use of alternative methods for data analysis and display. Accordingly, manipulation of parameters utilized in data processing has improved definition of myocardial dimensional and structural characteristics.

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A-17. Real-Time Digital Echocardiography

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The digital echocardiograph designed and built for this project combined burst-analog sampling circuitry using serial analog memory and a dual Motorola 6800 microprocessor network (PR 14, A-17). It can send 256, 8-bit samples taken every 5 ms to a TI-980 computer for storage on disk in real time. This acquisition and analysis system was used to study depth compensation functions (gain applied to the ultrasonic echoes) and to develop methods for quantitatively evaluating the resolution of clinical imaging systems.

We compared conventional depth compensation techniques, automatic analog gain control methods, and digital gain control algorithms. Digital control of gain has two important advantages over the other two methods. Like automatic analog gain, the dynamic range of echo signals can be increased compared to conventional ramp functions. The response of digitally controlled gain functions, however, can be much sharper than analog AGC because it has memory of the received signal from previous echo periods. For example, the automatic digital gain function brought out about twice as many echoes in a gelatin target with a nearly uniform distribution of air bubbles as either the conventional or analog AGC methods. Similar results were obtained when imaging cardiac structures.

The digital echocardiograph is now being used to evaluate the quality of ultrasonic images. The primary limitations come from the transducer and initial stages of signal processing. We scanned the American Institute of Ultrasonics in Medicine 100-mm test object with a typical adult transducer (2.25 MHz, unfocused) using both conventional and digital AGC depth compensation functions. From digital records of both the echoes and the gain functions, the original echo strength was reconstructed to quantify the dynamic range attained with each depth compensation technique. In addition with these data we can investigate transformations from echo to display which give maximum resolution in the optical image. Effects of deconvolution filters used to sharpen the image beyond the defraction limits of the transducer are also being studied.

Other transducer effects which limit image quality have been examined. Models were implemented on the TI-980 to calculate the conversion of an electrical excitation pulse into an acoustic force on the face of the transducer and to compute the pressure patterns throughout the region insonified by circular and rectangular piston transducers given the force across the transducer face. These models will be used to simulate image generation to determine resolution limits of existing scanners, as well as appropriate design constraints for new echocardiographs.

In order to determine ultrasonic resolution in tissue, we built several gelatin models with attenuations and propagation velocities similar to those of tissue. Attenuation measured with the CUTAR scanner (PR 13, B-3) at frequencies from 4.0 to 7.5 MHz ranged from 0.3 to 1.3 db/cm/MHz. Velocities measured with the digital echocardiograph varied from 1540 to 1650 m/sec. We plan to image the test object and other known structures through well-characterized tissue models to measure the effects of tissue on resolution values predicted from simulations and tests in homogeneous media.

A-18. Interactive Digital Acquisition of Electrocardiograms

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Support: RR 00396
HL 18144
Washington University

A microprocessor-based (Intel 8080) acquisition system was previously developed to study the signal quality of 3-lead electrocardiograms stored on FM analog tape (PR 14, A-18). This system was used to evaluate both the quality of 708 pediatric vectorcardiograms and the performance of algorithms tailored to test interactively for technical problems, primarily baseline shift and excessive high-frequency noise.(1) The implementation for the FM tape study had no high-gain ECG amplifiers and no mass storage. It used a CRT for interactive displays. A number of modifications have been made to convert the acquisition system to an ECG cart.

The circuitry has been put into a portable cabinet. A 16-character self-scan display and a 3-channel strip-chart recorder have replaced the CRT. A floppy disk drive was installed for mass storage, however, the controller is not operational yet. The major change was in the addition of analog amplifiers and control circuitry for direct ECG measurement.

Design of the analog section incorporated the following features: isolated patient connections, performance exceeding American Heart Association recommendations, fixed gain, and automatic calibration and reset. Buffered

isolation amplifiers with a gain of 10 have a common-mode-rejection ratio of more than 86 db. A driven right-leg reference further reduces the common-mode signal. After an overall gain of 2000, ECGs are coupled to a 12-bit analog-to-digital converter with a ± 10 volt range. These values yield an input range of ± 5 mv with a resolution of 2.4 μV. Both the calibration procedure and baseline restoration for signals that are out of range are under the control of the microprocessor which sets the measurement protocol.

The number of ECG channels was increased from three to eight, so that either the standard 12-lead or the Frank lead signals could be taken simultaneously. The equivalent leads are calculated by the microprocessor, thus eliminating any resistor networks. The system senses which cable set is attached and processes the signals accordingly. A clinical trial of the cart is being planned.

(1)R. M. Arthur, "Assessment of Electrocardiographic Signal Quality During Acquisition," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 78CH1391-2C, Stanford, California, pp. 255-258, September 12-14, 1978.

A-19. Multicenter Post-Infarction Program

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Support: RR 00396
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The Multicenter Post-Infarction Program (MPIP) is a study of myocardial infarction patients in diverse geographical settings. Organized in 1978 and begun in 1979, the four-year study hopes to determine prognostic indicators

of sudden death from clinical and demographic information collected during the acute phase prior to hospital discharge along with telephone follow-up information. Special procedures include, for each patient, a Holter recording, ejection fraction determined by radionuclide angiography, and a low-level activity evaluation.

The various enrolling centers are located in four cities: New York City (Columbia University College of Physicians and Surgeons, Roosevelt Hospital, St. Luke's Hospital Center); Rochester, New York (Highland Hospital); St. Louis (Jewish Hospital, St. Luke's Hospital East); and Tucson (St. Joseph's Hospital, Tucson Medical Center, University of Arizona). The data coordinating center and project administrators are located at the University of Rochester School of Medicine, Rochester, New York.

One half the Holter recordings are processed by the Biomedical Computer Laboratory (A-4) and the other half by Columbia University. After analysis, the analog recordings are sent to the data coordinating center for storage. As an alignment check of the two processing systems, some recordings are sent to the processing center where they were not previously processed. As well, some recordings are sent to the same processing center to assess processing consistency.

Several local logistical problems have surfaced at Jewish Hospital. First, radionuclide angiographic equipment has been ordered but not delivered; patients consenting to the study's procedure must be transported to and from Barnes Hospital for the test. Secondly, some private physicians have been reluctant to have their patients undergo the low-level exercise test so soon after infarction. Nonetheless, of 89 patients eligible to participate in the study, 47 have been enrolled into the study from the two St. Louis hospitals.

A-20. Research Projects Utilizing the Isolated Probe Data Acquisition System

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Support: HL 13851
HL 17646

The Division of Cardiovascular Diseases is interested in the noninvasive measurement of myocardial perfusion and metabolism evaluated with positron emitting tracers. Studies are conducted in isolated rabbit hearts which allow for the precise control of many factors that modify myocardial perfusion and metabolism.

Traditionally, isolated perfused hearts (perfused retrograde via the aorta) are perfused with buffered salt solutions. Since oxygen solubility is low in these solutions, hearts require high flow rates in order to maintain adequate oxygenation. Since high flow rates decrease the transit time of an injected tracer, and may thus induce artificiality to monitored time activity curves, we have developed an isolated heart preparation that includes washed sheep erythrocytes in the perfusate. Inclusion of erythrocytes allows for adequate oxygenation of the hearts at physiological flow conditions. Furthermore hearts perfused in this fashion exhibit metabolic and ventricular performance which closely simulates that in intact hearts.(1)

The development of quantitative noninvasive measurement of myocardial metabolism in patients is dependent on adequate modeling of fatty-acid flux in the isolated heart. Currently we are injecting ^{11}C-palmitate as well as a vascular tracer (^{68}gallium-transferrin). In addition to monitoring tracer time-activity curves via coincident detection of the positron emission, a number of metabolic functions are being assessed simultaneously. In this manner we hope to be able to analyze ^{11}C-palmitate washout curves in a quantitative manner and correlate back extrapolation of the monoexponential tail to actual fatty acid extraction and oxidation.

The use of the erythrocyte-enhanced perfusion media has enabled us to evaluate certain tracers that are currently proposed as perfusion indicators, but which have not been tested in rigorously controlled systems. In a recent study $^{13}NH_3$, a positron-emitting tracer that has been used as a flow indicator, was evaluated in the isolated heart system. By comparing the results of washout curves in hearts perfused with the erythrocyte-enhanced buffer with hearts perfused with buffered salt solutions alone, and with the use of metabolic blocking of glutamine synthetase, the enzyme that is responsible

for the incorporation of ammonia into glutamine, we demonstrated that the accumulation of ^{13}N via the myocardium after a bolus injection of $^{13}NH_3$ is not, as conventionally thought, due to myocardial flow per se, but due to a large extent to the metabolic status of the myocardial cell.(2)

External assessment of perfusion has been limited in part by the dependence of tracer extraction on metabolism, lack of regional specificity, and high radiation burden. To overcome these difficulties we have been developing an approach potentially useful in the quantitative external measurement of myocardial flow. A diffusable tracer (we are currently using $H_2{}^{15}O$) is infused exponentially into the inflow of isolated hearts and time activity curves are analyzed for a parameter that approaches a constant value as a function of tracer delivery and decay while cardiac radioactivity increases. With this approach we have been able to estimate myocardial flow based on this derived steady-state function and correlate it with measured flow. We are currently pursuing this approach in the "blood" perfused isolated heart (to simulate physiological flow) and using ^{11}C-butanol, a tracer which has a lipid:water partition coefficient of approximately 1 and which should prove particularly useful as a diffusable tracer in this context.(3,4)

(1)S. R. Bergmann, R. E. Clark, and B. E. Sobel, "An Improved Isolated Heart Preparation for the External Assessment of Myocardial Metabolism," American Journal of Physiology, vol. 236, p. H644, 1979.

(2)S. R. Bergmann, S. Hack, T. J. Tewson, M. J. Welch, and B. E. Sobel, "The Dependence of Accumulation of $^{13}NH_3$ by Myocardium on Metabolic Factors and Its Implication for Quantitative Assessment of Perfusion," Circulation, in press.

(3)B. E. Sobel, "Non-Invasive Regional Assessment of Myocardium with Positron-Emitting Radionuclides," in Advances in Cardiology, vol. 26, J. H. K. Vogel, ed., S. Karger, Basel, Switzerland, pp. 15-29, 1979.

(4)M. S. Klein, R. A. Goldstein, M. J. Welch, and B. E. Sobel, "External Assessment of Myocardial Metabolism with ^{11}C-Palmitate in Rabbit Hearts," American Journal of Physiology: Heart Circulation Physiology, vol. 6, p. H51, 1979.

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

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Support: RR 00396
HV 72941
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On August 1, 1978 Washington University, in collaboration with four other centers implemented phase II of the collaborative clinical trial of therapy to protect ischemic myocardium. The overall goals of the project include objective evaluation of the efficacy of administration of hyaluronidase and of propranolol in limiting the extent of infarction among patients with acute myocardial infarction and in modifying prognosis. Data will be acquired from five clinical centers, including Washington University, Massachusetts General Hospital, The Medical Center Hospital of Vermont, Parkland Hospital in Dallas, and the Peter Bent Brigham Hospital in Boston. Each of the clinical units plans to enroll patients during a three-year interval to provide an overall sample size sufficiently large to statistically test the hypotheses being explored.

In addition to the five clinical units participating in the study, a series of core laboratories will be utilized so that objective analysis of data obtained from each unit can be performed in a blinded fashion. These core facilities include a CK Reference Laboratory (at Washington University), a Holter Recording Analysis Reference Laboratory (also at Washington University), an Electrocardiographic Reference Laboratory (at the Peter Bent Brigham Hospital), a Myocardial Infarct Scintigraphy Laboratory (at Parkland Memorial Hospital in Dallas), a Radionuclide Ventricular Function Laboratory (at the Massachusetts General Hospital), and a Pathology Core (at Duke University). During phase I the Washington University Reference Laboratories were equipped with the necessary analytical biochemical and computer equipment (PR 14, A-2; A-2). In addition, personnel were trained in procedures needed for analyzing the large number of samples that will be acquired during the course of the study. Data from each core laboratory is forwarded to the Data Coordinating Center (Research Triangle Park, North Carolina) so that objectivity in data management and statistical analysis can be assured.

The Washington University components of this project comprise the Clinical Investigation Unit, directed by the Clinical Unit Coordinator, Dr. Allan S. Jaffe, the CK Reference Laboratory, directed by Dr. Robert Roberts, and the Holter Reference Laboratory, at the Biomedical Computer Laboratory, directed by Dr. Lewis J. Thomas, Jr. During phase I, biochemical analytical techniques were verified with samples obtained from other institutions and software for the Holter Reference Laboratory developed.

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

Several endpoints are being utilized to assess the effects of therapy on the extent of infarction and on prognosis. These include enzymatic estimation of infarct size based on analysis of serial changes in plasma creatine kinase activity, the extent of infarction assessed in plasma creatine kinase activity, the extent of infarction assessed from the number of electrocardiographic leads in which initial ST-segment elevation is followed by development of criteria of transmural infarction, the distribution and extent of impairment of ventricular function assessed from radionuclide ventriculograms, the severity and persistence of dysrhythmia assessed from Holter recordings, and the distribution of infarction assessed from ^{99m}technetium pyrophosphate scintigrams. Additional endpoints include exercise tolerance tests six months after the episode of infarction, as well as clinical follow-up recorded on standardized forms developed during the planning phases of the project. Radioventriculograms are obtained three months after infarction, along with a 24-hour Holter recording. Six months after infarction myocardial infarct scintigrams are obtained, along with a repeat 35-lead precordial electrographic map and 24-hour Holter recording. A Pathology Core Lab will perform studies among patients who expire during the acute or follow-up phases of the study for whom autopsy permission can be obtained.

Since August 1, 1978 forty-two patients have been entered into the study by the Clinical Investigation Unit at Barnes Hospital. All studies during the acute phase and in follow-up have been completed according to protocol. A recent visit by the Policy Board, the Clinical Coordinating Center and the Data Coordinating Center assessed the performance of the

Clinical Unit, CK Laboratory and the Holter Laboratory as superb. A total of 192 patients have been enrolled by the five centers. The operation of the clinical centers and the core laboratories after initial problems has been extremely successful. Data bank analysis studies have been approved and initial publications should be forthcoming this year.

B. Tomography (Ultrasound and PETT)

Although ultrasound has proven to be a useful source of diagnostic information, results of examinations based on current ultrasonic methods are primarily qualitative and pictorial. To provide quantitative information in addition to a picture, a collaborative effort with the Physics Department has been undertaken to develop ultrasonic tomography to measure regional parameters of tissue. To this end, a multiple frequency-attenuation and time-of-flight transmission tomographic reconstruction system has been implemented, and the physical limitations of ultrasonic transmission tomography have been assessed. The results are being used to derive physical and algorithmic corrections to improve reconstructions. The past year has been spent improving the actual scanning system and completing the first phase of an extensive ultrasonic-measurement simulation effort. Time-of-flight measurements can now be made simultaneously with the amplitude measurements allowing reconstructions from both velocity and attenuation-related parameters. In order to provide realistic test specimens without the expense of animal studies, ultrasonic tissue phantoms have been constructed. Simulation of ultrasonic propagation models and algorithms are being evaluated using these phantoms with known, easily controlled properties and geometries.

Ultrasonic measurement, modeling, and simulation has proceeded in two parallel efforts. The problem of signal degradation by phase cancellation effects in piezoelectric receiving transducers is discussed in Section B-1. An analytic model based on a Fourier series expansion of the incident ultrasonic field has been developed and experimentally verified. A geometrical ray-tracing model based on a local solution of the eikonal equation has been developed and is discussed in Section B-2.

Stimulated by the clinical impact of the EMI transmission tomographic scanner in 1973, experimental studies were initiated in collaboration with the Division of Radiation Sciences to evaluate the positron coincidence-detection as a method for emission reconstruction tomography. This collaborative activity resulted in a prototype scanner called PETT (Positron-Emission Transaxial Tomograph). A back projection algorithm, based on a convolution approach, was implemented in a mini-computer to effect reconstruction of radioisotope activity from coincidence detections. Extensive studies in patients and animals were conducted subsequently with the PETT III scanner in collaboration with the divisions of Neurology and Cardiology. A subsequent scanner, PETT IV, utilized concepts developed with its predecessor but incorporated a novel technique for the simultaneous collection of four tomographic slices from a single set of detectors. PETT IV is now located in the Cardiac Care Unit for use in the SCOR project for the quantification of regions of myocardial ischemia and infarction in vivo in experimental animals and patients (B-3, B-4). Over the last year PETT V has been developed for rapid, high-resolution head scans. This is described in Section B-5.

Theoretical studies of various aspects of tomography systems have been pursued in the Resource since the initial projects in 1973. The most recent advances have been in the area of fan-beam algorithms and architectures for high-speed processing and in fully three-dimensional tomography algorithms. These are reported in Sections B-6 and B-7.

B-1. Ultrasonic Attenuation Tomography

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APR 77-09776
HL 19537

A. Time-of-Flight Tomography: Biomation 8100

A Biomation 8100 fast-transient recorder was interfaced to the PC-12, and a library of FORTRAN-callable subroutines was produced (G-20). Digitization with 8-bit resolution at programmable rates up to 100 MHz provides new flexibility for this research.

The Biomation 8100 was incorporated into the CUTAR scanner and CUTARSYS software (PR 14, B-1) with leading-edge waveform recognition algorithms providing 10 ns time-of-flight measurement resolution. Time-of-flight measurements are made simultaneously with amplitude measurements during the standard CUTAR scan. Time-of-flight analysis and reconstruction software is also used for concurrent development in tomographic simulation (B-2).

In addition to time-of-flight tomography, the Biomation 8100 provides a means for improved received signal analysis. The effects of refraction, pulse width, pulse gating envelope shape, and intervening attenuating media on measurements made using piezoelectric and acoustoelectric receiving transducers can be studied with the aid of computer analysis of the associated digitized waveforms. This capability is exploited in the validation of the ultrasonic simulation studies.

B. Ultrasonic Tissue Phantoms

Madsen[1] describes the use of laboratory gelatins for ultrasonic tissue phantoms. Both the ultrasonic attenuation and acoustic velocity can be adjusted, predictably, over the range of values encountered in actual tissue by the addition of varying amounts of powdered graphite and n-propanol to the gelatin solution prior to cooling. Samples of gelatin mixtures have been scanned, and the attenuation and speed of sound values reconstructed agreed well with the published values. An example reconstruction is given in Figure 1.

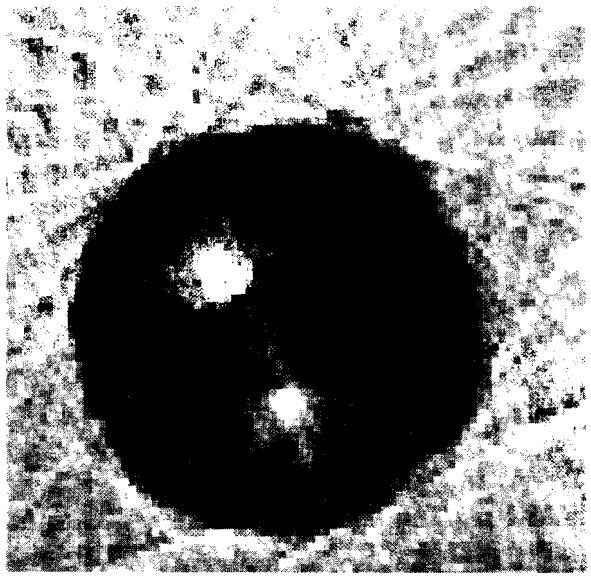

Figure 1. Time-of-Flight Tomography. A typical reconstructed time-of-flight image of a cylindrically shaped laboratory-gelatin tissue phantom with two cylindrical regions removed from the interior.

The precisely formed gelatin phantoms are providing a new means for evaluating the CUTAR scanner performance. Resolution, limitations of dynamic range, refraction effects, and effects of finite beam width may all be systematically studied. Because of the controllability of the acoustic properties of these phantoms, a quantitative measure of reconstruction degradation due to these various limitations can be made.

Comparison of measurements made using these tissue phantoms with computer simulations based on geometrical ray tracing allows verification of the accuracy of the simulations before corrective algorithm development proceeds.

C. Dynamic Range Enhancement

The overall dynamic range of the imaging system has been improved by greater than 10dB over the entire range of frequencies from 2 to 8 MHz with as much as 20 dB improvement at some frequencies. Maximum dynamic range with an acoustoelectric receiver is now in excess of 50 dB at 5 MHz. Practically speaking, the dynamic range enhancement permits more attenuating objects to be imaged without degrading the measurement signal-to-noise. The improvement in dynamic range resulted from a combination of changes in instrumentation and improvement in ultrasonic transducers.

Increased efficiency has been achieved in both ultrasonic transmission and reception. Low insertion loss broadband piezoelectric transducers have been acquired from Precision Acoustic Devices for use as ultrasonic transmitters.

These transducers have a 5dB minimum one way insertion loss as compared to the 15dB minimum one way insertion loss of the Panametrics transducers formerly used. The tradeoff is a reduction of the overall usable bandwidth; however, the kidney image (PR 14, B-1) derived from the slope of the ultrasonic attenuation as a function of frequency indicates that a 1.5 MHz bandwidth is sufficient for such images. Since these transducers have an approximate 50% bandwidth, the 3.5 and 5 MHz transducers purchased should allow frequency dependent imaging.

An acoustoelectric receiving transducer[2] has been constructed out of a single crystal of CdS expressly for use in the scanner. An improved quarter-wave matching layer has increased the receiver sensitivity by 3dB. A tungsten doped epoxy backing material provides better matching to the CdS crystal, reducing the reflected wave in the crystal. This allows the use of a longer pulse to improve sensitivity, and permits received pulse integration instead of simple peak detection. Improvements in the low pass filtering of the acoustoelectric signal has enhanced the receiver dynamic range through an improvment in signal to noise.

Several changes in instrumentation have resulted in the improvement of dynamic range. A new Wavetek Model 165 function generator replaced an HP8690A sweeper/oscillator as the master signal source. A voltage controlled oscillator provides the programmable frequency function of its predecessor while the gated mode allows generation of an integral number-of-cycles tone burst. The latter feature allows removal of mixers, and their associated distortion at high signal levels, from the system. A gated swept frequency capability may also be useful in experiments with chirp signal transmission.[3] A modification of the programmable (auto-ranging) gain module, coupled with the elimination of the gating mixers permits a wider dynamic range of transmitter drive levels without added distortion.

D. In Vitro Cardiac Tissue Studies

Canine hearts were chosen as an animal study model for ultrasonic tomography since the ultrasonic properties of dog myocardium were documented previously by other members of the Laboratory for Ultrasonics in the Physics Department. Representative results are shown in Figure 2, a series of four cross-sections of the same heart spanning the basal to apical regions of the heart. Qualitatively, these images are substantially improved over previously reported work;[4] however, quantitative results were compromised by insufficient dynamic range. The dynamic range enhancement detailed in Section C and mechanical scanner improvements detailed in Section E were made after this series of measurements. After evaluation of the scanner improvements using the tissue phantoms described in B, further cardiac tissue studies are planned.

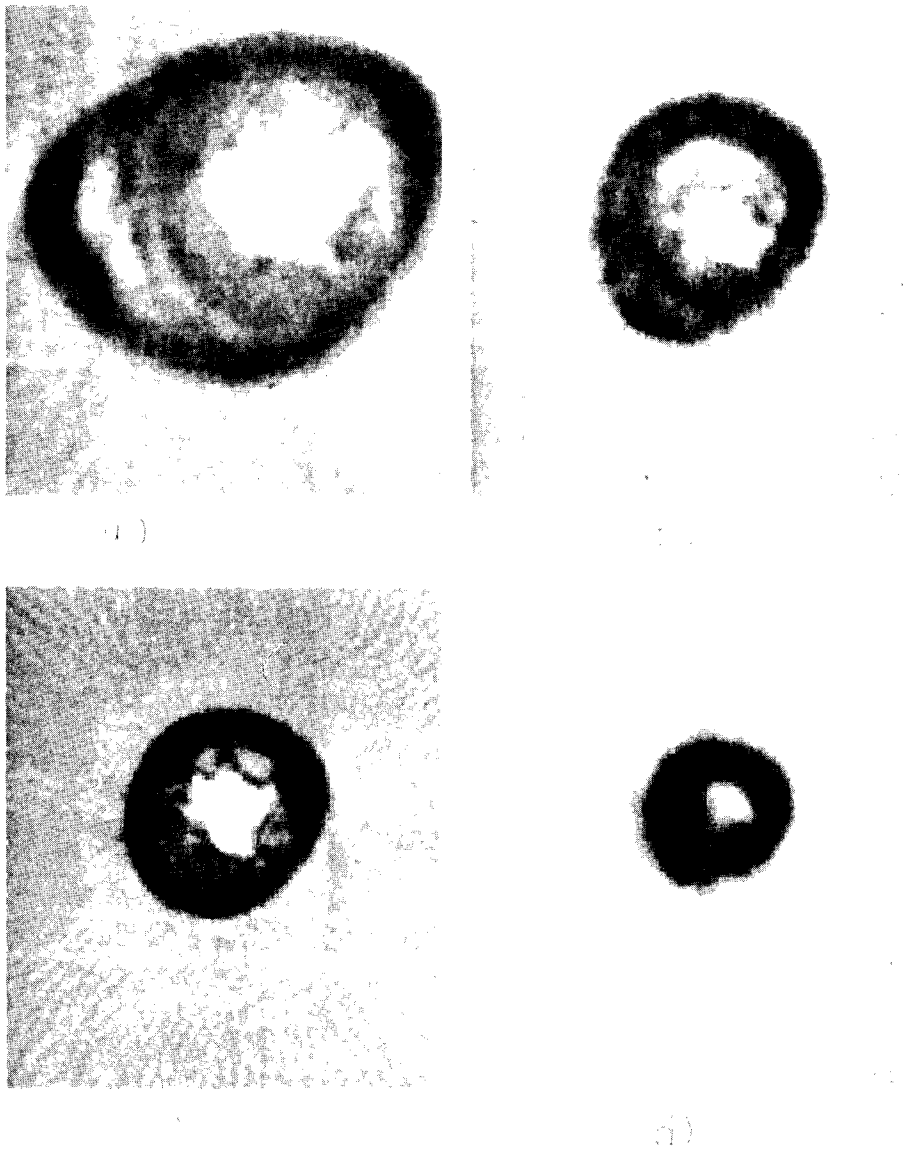

Figure 2. Reconstructed Attenuation in Canine Heart. Consecutive cross sections from a) basal to d) apical region of a single in-vitro heart.

E. Mechanical Scanner Improvements

The transducer mounting fixtures in the scanner were modified to provide a more flexible arrangement of both transmitter and receiver. The transmitter to receiver distance as well as the center of scan rotation-to-transducer distances are now adjustable to accommodate the focal length of each transducer and the size of the specimen to be imaged. Simulations and experiments have demonstrated that the receiving transducer should be located as close as possible to the object to be imaged to reduce refraction error.

F. Phase Cancellation: Analytical Model and Experimental Verification

One of the primary problems with computed ultrasonic attenuation tomography is the limitation of dynamic range. It has been shown[2] that ultrasonic amplitude measurements made with piezoelectric transducers are substantially degraded by phase cancellation effects; thus, the phase insensitive acoustoelectric transducer has been used in our effort with an accompanying reduction in the dynamic range of the imaging system. Although significant improvements have been made in dynamic range with the acoustoelectric transducer and efforts to further improve its characteristics are being carried out in the Laboratory for Ultrasonics,[5] analytical modeling of phase cancellation was pursued with the objective of identifying a method for deconvolving the phase cancellation to provide accurate attenuation measurements. Such a model is important in the design of a system that would use the more sensitive piezoelectric receiver.

We first considered the simple case of a plane wave perturbed harmonically in space in a direction perpendicular to the direction of propagation. Analytic solutions for this case were derived for receiving transducers of rectangular and circular aperture. An approximate form of these solutions exists that is independent of the size and shape of the receiving transducer in many experimental situations. Under such conditions, a generalized solution for arbitrarily shaped wavefronts was derived based on a two-dimensional Fourier series expansion of the wavefronts.

An experimental verification of one of the major predictions of this theory is presented in Figure 3. Results of substitution-technique experiments in a water bath performed on acrylic plexiglass samples with machined surface corrugations are reported. To determine the magnitude of phase cancellation that occurs in measurements with piezoelectric receivers, such measurements are compared with measurements made on the same samples with a phase insensitive CdS acoustoelectric receiver.

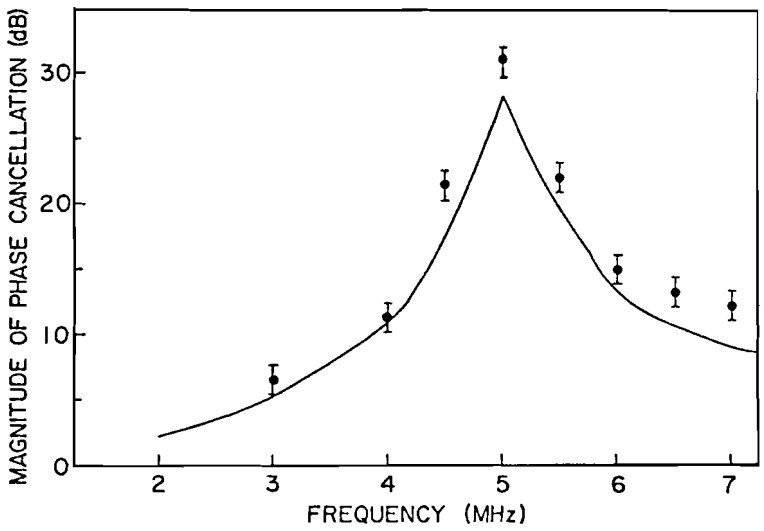

Figure 3. Phase Cancellation Measures in Transmission. Comparison of the excess signal loss measured with a piezoelectric receiving transducer (Φ) to the theoretical prediction of the magnitude of phase cancellation (-). Plane ultrasonic waves were transmitted through an acrylic plexiglass sample with machined surface corrugations to provide a known distortion of the ultrasonic wavefronts.

(1) E. L. Madsen, R. A. Zagzebski, R. A. Banjavie, and R. E. Jutila, "Tissue Mimicking Materials for Ultrasound Phantoms," Medical Physics, vol. 5, no. 5, pp. 391-394, September/October 1978.

(2) L. J. Busse, J. G. Miller, D. E. Yuhas, J. W. Mimbs, A. N. Weiss, and B. E. Sobel, "Phase Cancellation Effects: A Source of Attenuation Artifact Elimination by a CdS Acoustoelectric Receiver," in Ultrasound in Medicine, vol. 3B, D. White and R. E. Brown, eds., Plenum Press, New York, pp. 1519-1535, 1976.

(3) Interim Progress Report, NSF Grant APR77-09776, January 1, 1979.

(4) J. R. Klepper, G. H. Brandenburger, L. J. Busse, and J. G. Miller, "Phase Cancellation, Reflection, and Refraction Effects in Quantitative Ultrasonic Attenuation Tomography," Proceedings of the IEEE Ultrasonics Symposium, no. 77CH1264-ISU, 1977.

(5) L. J. Busse and J. G. Miller, "Broadband Acoustoelectric Receivers that Eliminate Phase Cancellation Effects," Third International Symposium on Ultrasonic Imaging and Tissue Characterization, NBS, June 1978 (abstract).

B-2. Simulation of Ultrasonic Wave Propagation in the Context of Ultrasonic Imaging

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Support: RR 00396
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HL 19537

As demonstrated in earlier ultrasonic tomography experiments (PR 14, B-1) the imaging limitations stemming primarily from acoustic velocity inhomogeneity can be severe. Imaging limitations, in the context of transmission tomography, are manifest in two general categories:

a) Instrumentation-related errors such as phase cancellation in piezoelectric receiving transducers, or dynamic range limitations.
b) Deviations from the assumptions underlying tomographic reconstruction algorithms, including:
   1) deviation from straight line transmission due to refraction;
   2) deviation from strict line-integral-derived measurements, for example, reflections at acoustic impedance discontinuities;
   3) complicated geometry of the finite-width transmitted beams.

The initial thrust of this effort has been to gain a clearer understanding of the above limitations through development of models and simulation algorithms. Besides establishing practical ultrasonic imaging performance limitations, a goal of this research is the development of error correction algorithms. A refraction-correction tomographic reconstruction algorithm based on sampled-beam ray tracing has been developed. This algorithm will be tested as soon as results from the simulation algorithms are validated.

During this year, a set of algorithms to simulate acoustic beam transmission were developed in conjunction with geometrical ray-tracing algorithms. The algorithms permit transmission attenuation and time-of-flight measurement simulation for finite width (focused or unfocused) beams traversing inhomogeneous objects by appropriately summing the amplitude and phase of the traced rays. Propagation through elliptically bounded regions can be simulated. The superimposed-ellipse geometries are also easily fabricated as laboratory gelatin phantoms (B-1) and laboratory validation of the algorithms is underway.

Simulations include: 1) ultrasonic propagation effects such as:

a) Refraction (ray path error and beam distortion);
b) Reflection (non-unity transmission coefficients and total internal reflection);
c) Frequency dependent finite beam widths and shapes;

and 2) instrumental effects such as:

a) Piezoelectric receiving transducer phase cancellation errors;
b) Peak detector error due to arrival time skew;
c) Scanner-centering error.

The simulation algorithms are an integral part of the CUTARSYS software on the PC-12. Simulated tomographic scan data files are generated as though they had been acquired by the CUTAR scanner. Simulated data may be subject to the identical processing used on actual scan data. Intermediate simulation stages can be output or subject to analysis as needed. Software generation for refraction correcting tomographic reconstruction, an outgrowth of the simulation, has already begun as part of CUTARSYS.

Figure 1 graphically illustrates the development of the simulation method. To simulate transmission acoustic imaging measurements, algorithms were developed based on an "iso-index" region model. Inhomogeneous objects were modelled as superpositions of regions, each described by unique acoustic velocity, attenuation, and density. Algorithms trace rays through the object to be imaged from transmitter to receiver keeping track of signal loss, refractive bending or total internal reflection, and lapsed time (or phase). Ray-summing algorithms were employed to accumulate the signals from bundles of rays simulating the finite-width transmitted beam (Figure 1B, 1C). Transmitted beam geometry, such as focusing, was simulated by appropriate amplitude, phase, and launch angle from the transmitting transducer (Figure 1D). Piezoelectric receiving transducers of finite width and particular aperture (circular or rectangular) were modelled by appropriate phase cognizant processing (Figure 2) with resulting reconstructions shown in Figure 3.

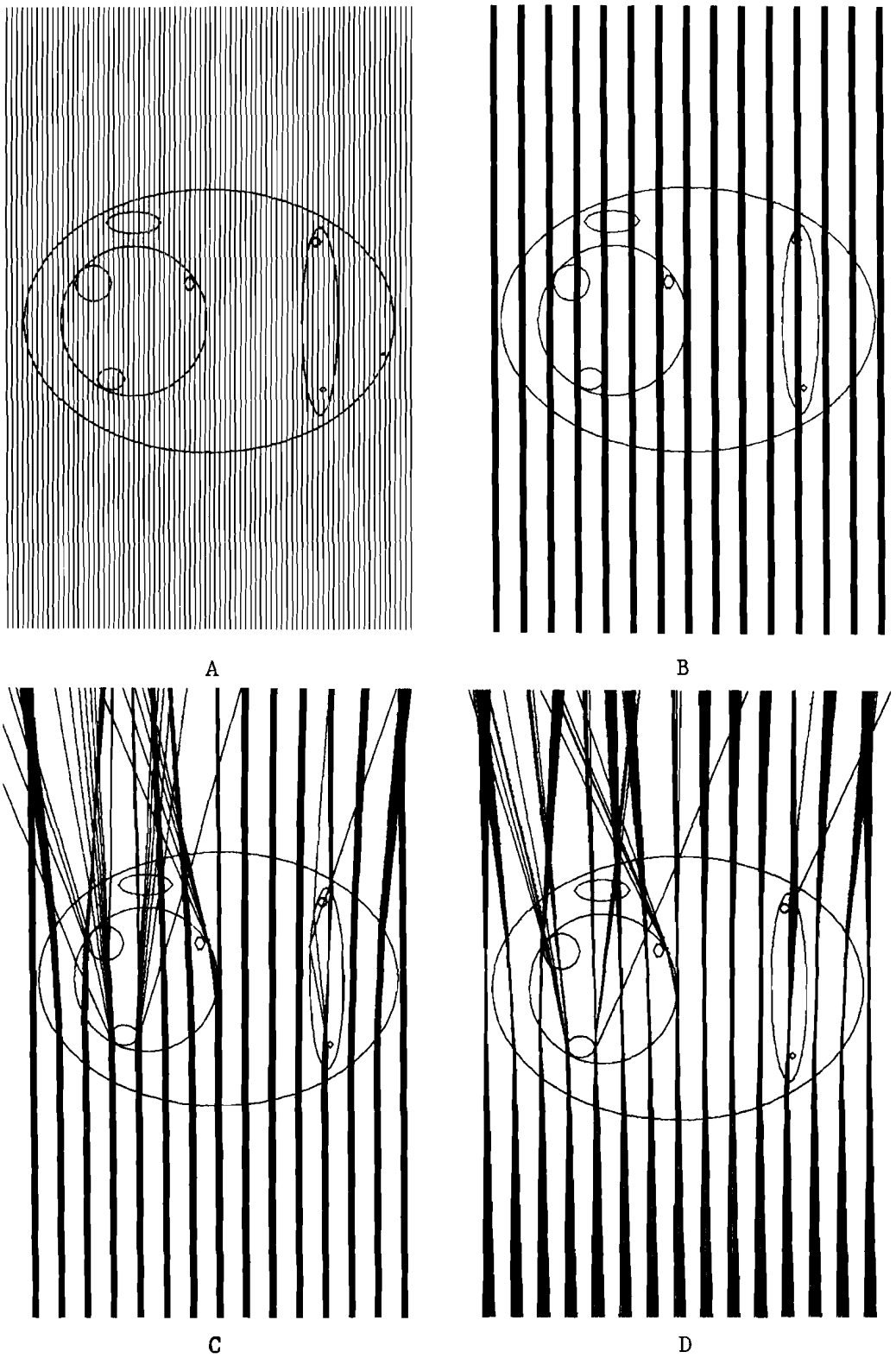


Figure 1. Development of Ray Tracing-Based Simulation.

A: Infinitesimal-width acoustic beam, non-refracting object
B: Finite-width collimated beam, non-refracting object
C: Finite-width collimated beam, refractive index: 1.05
D: Focused beam, refractive index: 1.05

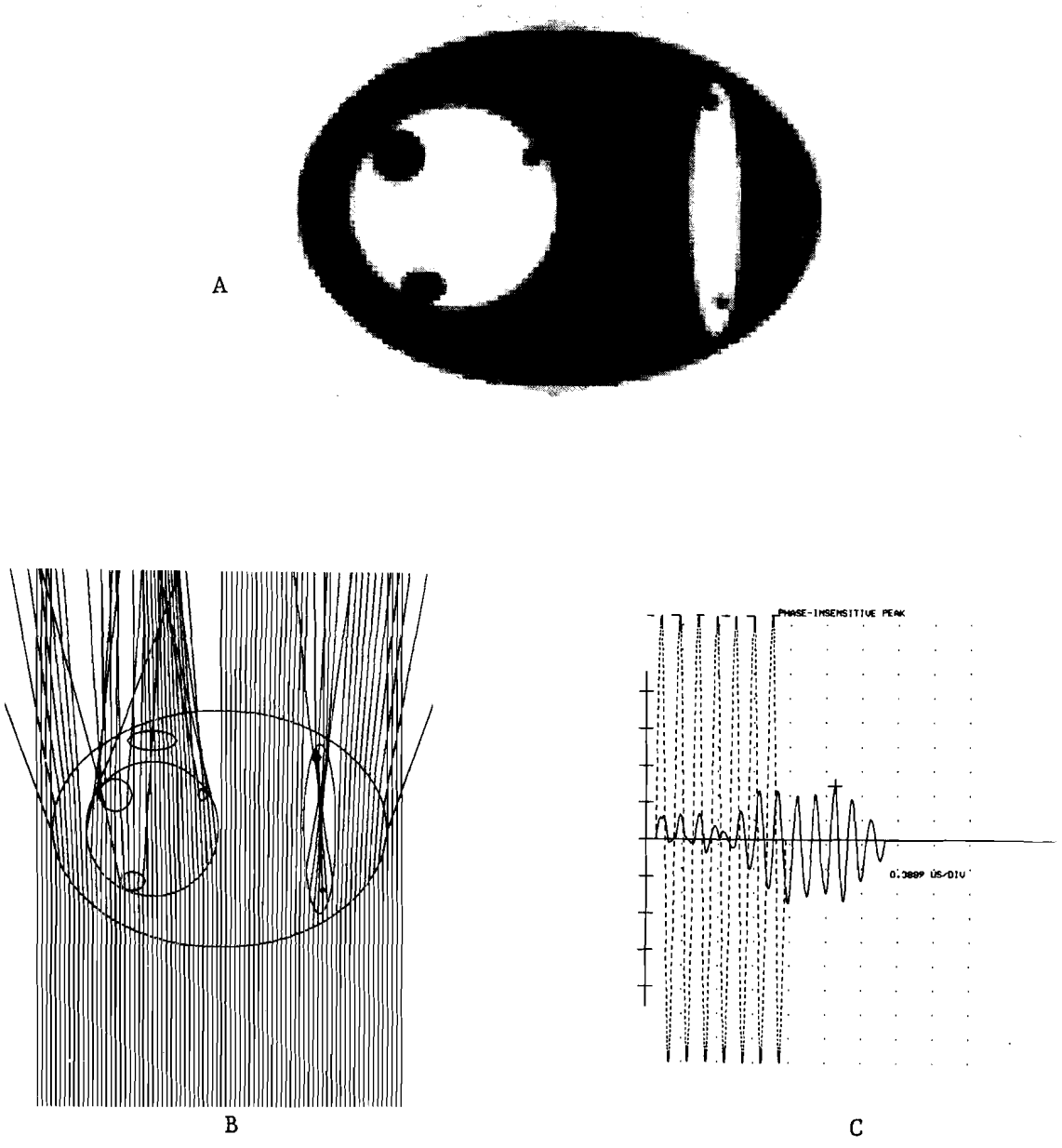
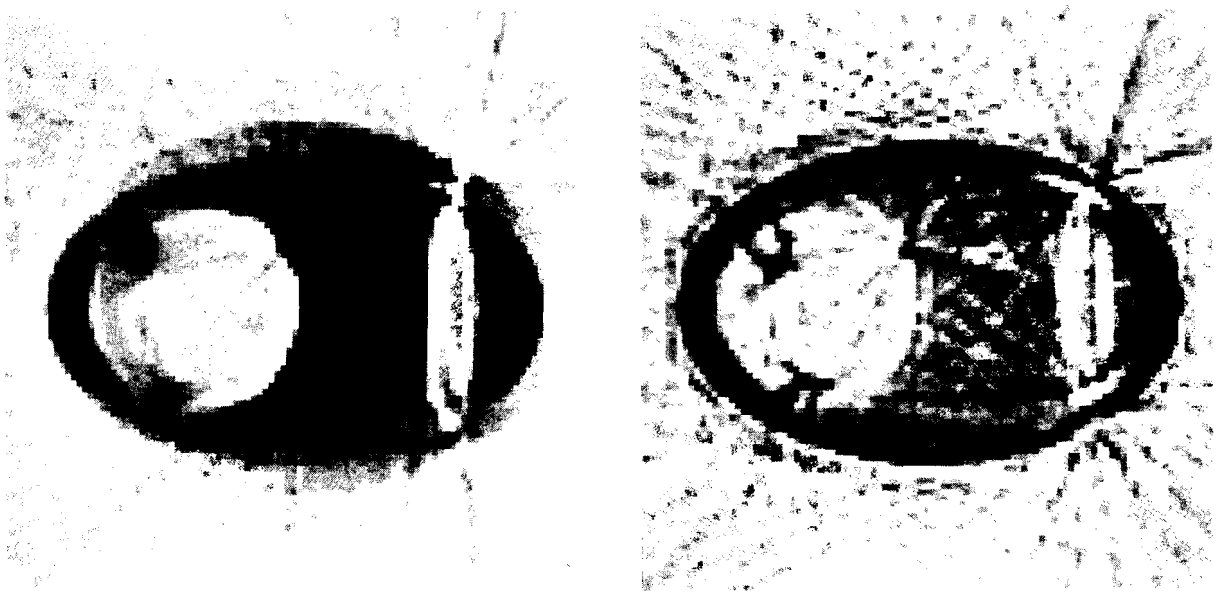


Figure 2. Ray Tracing-Based Heart Simulation.

A: Reconstructed attenuation from infinitesimal-width beam simulated scan of non-refracting heart.
B: Graphic illustration of the effect of the refracting medium (refractive index: 1.05).
C: Simulated example of phase cancellation in a piezoelectric receiver;
Dashed line: Desired phase-insensitive received signal.
Solid line: Actual phase-sensitive received signal suffering pulse-lengthening and phase cancellation due to multiple-path arrival time skew.



A B

Figure 3. Simulated Heart: Reconstructions of Refracting Object.

Reconstructions from collimated beam data assuming refractive index of 1.05.

A: Time-of-flight reconstruction.
B. Reconstructed attenuation slope with respect to frequency simulating a circular aperture piezoelectric receiving transducer.

B-3. External Detection and Tomography of Ischemic Myocardium

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Support: RR 00396
HL 13851
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The overall goal of this project is to define and quantify regional myocardial metabolic rates and zones of impaired biochemical integrity by external detection of positron-emitting radionuclides. A subsidiary goal is to assess regional perfusion quantitatively with appropriately selected tracers.[1,2] Previously we demonstrated that administration of ^{11}C-palmitate to isolate perfused hearts led to a characteristic time-activity curve which permitted estimation of extraction fraction of tracer and global metabolic rate of oxidation of fatty acid initially incorporated into lipids. Results were compared to rates of $^{14}CO_2$ production from prelabeled myocardial lipid stores and to arteriovenous differences of fatty acid concentration. In addition, we found that reduction of perfusion to such preparations led to impaired uptake, trapping, and accumulation of exogenous labeled fatty acid with retained fractions diminishing from approximately 40% to 3%. These observations were extended to intact dogs in which the accumulation of intravenously administered ^{11}C-labeled palmitate was quantified externally with a positron-emission transaxial tomograph (PETT III). Zones of prolonged ischemia were delineated in animals subjected to occlusion of the left anterior descending coronary artery 48 hours prior to administration of ^{11}C-palmitate and were found to correlate closely with zones of infarction detected at necropsy by enzymatic analysis of the myocardium, morphometric determination of the extent and distribution of the infarction, and concomitant changes in the myocardial content of ^{14}C-palmitate administered intravenously in the same animals prior to sacrifice. In a preliminary previous study, we demonstrated with PETT IV that zones of infarction could be identified in patients as well.

During the past year several studies have been completed in conjunction with this project. An improved isolated heart preparation was devised and validated to permit characterization of regional myocardial metabolism under conditions in which bulk flow was comparable to that in vivo. Generally, isolated perfused heart preparations incorporate a hemoglobin-free perfusion

medium. Hence, flow must be several fold greater than physiological flow in vivo in order to provide adequate oxygenation of the tissue. To facilitate characterization of myocardial metabolism with the use of positron-emitting tracers, we developed an isolated heart preparation designed to simulate physiological levels of flow in substrate extraction. Isovolumically beating hearts were perfused retrograde and without recirculation at 60 mm Hg with Krebs-Henseleit solution enriched to hematocrit of 25 or 40% with washed sheep red cells (for which the oxyhemoglobin dissociation is independent of DPG concentration). Under conditions in which coronary perfusion was comparable to that in vivo, the preparation was stable for several hours with left ventricular systolic pressure averaging 98 when the hematocrit was maintained at 40 and with left ventricular dP/dt, pressure-time index, and directly measured oxygen consumption being comparable to values in vivo. Fatty acid extraction was several fold higher in hearts perfused with red cell-enhanced media compared to those perfused with buffer alone even under conditions in which the buffer-perfused hearts were well oxygenated. This preparation avoids intrinsic limitations encountered with buffer-perfused hearts in studies in which radiolabeled tracers are employed to characterize metabolism and in which time-activity curves must be evaluated under conditions of flow comparable to those likely to be encountered in vivo.(3)

With this preparation, studies were undertaken to characterize the relationship between flow and retention of $^{13}NH_3$, since this tracer has been used in vivo as an indicator of perfusion. The study was performed because of our concern that metabolic factors might markedly influence the relationships between retention of ammonia and flow and that accordingly, quantitative delineation of perfusion with ^{13}N-labeled ammonia would not be possible even if the detection system employed permitted quantitative delineation of the distribution of the radionuclide. The residual fraction of ^{13}N-labeled ammonia was evaluated in isolated perfused rabbit hearts under conditions in which flow and cardiac metabolism were selectively and independently controlled. In 13 hearts perfused with buffer alone, the residual fraction of ^{13}N counts was not altered significantly when flow was decreased by 75% from the control rate of 4.2 ml/g/min (residual fraction = 17.9 $\pm$ 2.7, mean $\pm$ S.E. (%) under control conditions to 18.4 $\pm$ 1.2 under conditions of low flow). In 12 hearts perfused with red-cell-enhanced media, residual fraction was not altered despite marked ischemia when flow was diminished by 75% from control values of 1.4 (residual fraction = 54.6 $\pm$ 2.4% under control conditions and 58.1 $\pm$ 4.4 in the face of ischemia). In hearts perfused with red-cell-enhanced media containing methionine sulfoxamine, a glutamine synthetase inhibitor, myocardial retention of ^{13}N counts was reduced by more than 60% despite constant flow. The results obtained indicate that retention of ^{13}N activity by myocardium is markedly influenced by the metabolic state of the tissue and that accordingly, relationships between extraction and retention of tracer and flow per se are complex and preclude direct estimation of perfusion from the amount of tracer sequestered by the myocardium.

In view of these limitations of conventionally used perfusion indicators, studies were undertaken to determine whether perfusion could be assessed quantitatively in such preparations with the use of programmed exponential infusions of tracer. Exponential infusions of $H_2{}^{15}O$ were administered to

isolated perfused rabbit hearts with Krebs-Henseleit buffer alone or Krebs-Henseleit enriched with red cells to a hematocrit of 40%. With flow varied from 1.2 to 5 ml/g/min actual and estimated flow correlated closely (r = .95, n = 52 determinations). The method employed permits quantification of flow by exponential infusion of a diffusible tracer and analysis of a parameter that approaches a constant value rapidly as a function of tracer delivery rate and decay constants while tissue radioactivity increases monotonically. Since time-activity curves with tracers such as ^{11}C-palmitate in isolated perfused hearts presage regional changes detected by positron tomography in vivo, the results with exponential infusions of tracers suggest that such approaches will permit regional quantification of myocardial perfusion in vivo as well.

In additional studies, the applicability of quantitative delineation of regional metabolism with ^{11}C-palmitate was assessed in rabbits in vivo. The animals were given intra-atrial injections of ^{11}C-palmitate (100 μCi) and cardiac time-activity curves monitored with two NaI(Tl) crystals with a field of view encompassing the heart. In the same animal under constant physiological conditions, the rate of decline of cardiac ^{11}C-palmitate counts remained constant (.009 $\pm$ .002 SE ln counts/min, n = 4). In contrast, mono-exponential clearance, reflecting oxidation varied directly with tension time index (range = 1,000 to 2,850 mm Hg·sec, r = .96) and peak dP/dt (1,000 to 5,550 mm Hg/sec, r = .84) among different animals. Simultaneous injection of ^{14}C- and ^{11}C-palmitate led to a prompt decline of counts from blood in contrast to the heart. Thus, persistent, circulating tracer did not distort results. These results indicate that external detection of cardiac ^{11}C-palmitate metabolism quantitatively reflects myocardial oxygen requirements in vivo and may permit assessment of regional metabolism in man with disappearance of tracer monitored by positron emission transaxial tomography.

An additional study was performed to characterize the distribution of labeled palmitate in lipid extracts from control and ischemic isolated hearts and to determine whether the nature and extent of labeled fatty acid uptake within minutes after its administration would impair accurate delineation of infarction by positron emission tomography. Perfused hearts were exposed to ^{14}C-palmitate complexed to defatted albumin in conditions of high (20 ml/min) or low (5 ml/min) flow -- conditions providing adequate and impaired oxygenation respectively. After 5 minutes of perfusion with tracer, hearts were removed quickly and flushed with perfusate free from tracer to clear the vascular space of residual ^{14}C-palmitate. For subsequent radiochemical analyses, myocardial samples were taken from the interventricular septum in order to avoid inclusion of epicardial fat, frozen in liquid nitrogen, and stored at -70°. Lipid extracts were prepared in methanol:chloroform, and radioactivity in short-chain fatty acid metabolites (in the upper phase) assayed by liquid scintillation spectrometry. Radioactivity in long-chain fatty acids and acyl CoA and other neutral and phospholipids was assayed by evaporation of the lower phase to near dryness, dilution with chloroform, and chromatography on silicic acid columns. Additional aliquots were evaluated by two-dimensional thin-layer chromatography on silica gel plates. Results indicated that the percentage of radioactivity in neutral lipids was higher in ischemic than in control hearts (75 $\pm$ 3.3 versus 41 $\pm$ 3.3%) but that the

percentages of radioactivity in polar lipids were similar. Counts recovered in the upper phase represented 40% of total extractable radioactivity in control hearts but only 6% in ischemic hearts. This reflects the lack of degradation of long-chain acyl groups to short-chain, aqueous soluble metabolites of oxidation in the ischemic hearts. Although the percentage of tissue radioactivity in triglycerides was higher in ischemic than in control hearts (36 $\pm$ 2.3% versus 20 $\pm$ 1.5%), the total amount of radioactivity per gram of tissue was significantly less in the ischemic than in the control hearts (19,150 $\pm$ 5,922 dpm/g compared to 38,048 $\pm$ 5,891). These results indicate that despite the altered metabolism of fatty acid evident in ischemic tissue with preferential deposition in neutral lipids, net accumulation of radiolabeled exogenous fatty acid decreases in ischemic myocardium. Accordingly, the relative increase in deposition of fatty acid in neutral lipids does not obscure detection of metabolic consequences of ischemia based on diminished uptake of labeled fatty acid. As described in (B-4), application of some of these approaches to studies of myocardial infarction in man with regional radioactivity detected by positron emission tomography has been accomplished.

(1) B. E. Sobel, "Non-invasive Regional Assessment of Myocardium with Positron-Emitting Radionuclides," Advances in Cardiology, vol. 26, J. H. K. Vogel, ed., S. Karger, Basel, Switzerland, pp. 15-29, 1979.

(2) M. S. Klein and B. E. Sobel, "Fatty Acid Uptake and 'Metabolic Imaging' of the Heart," Cardiovascular Clinics, A. N. Brest, ed., F. A. Davis Company, Philadelphia, pp. 165-176, 1979.

(3) S. R. Bergmann, R. E. Clark, and B. E. Sobel, "An Improved Isolated Heart Preparation for External Assessment of Myocardial Metabolism," American Journal of Physiology: Heart and Circulatory Physiology, vol. 5, pp. H644-H651, 1979.

B-4. PETT IV Cardiac Studies

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This project is designed to determine whether positron emission transaxial tomography (PETT) permits delineation of regional myocardial metabolism in vivo with particular emphasis on delineation of zones of jeopardized ischemic myocardium and infarction. Its overall objective is to provide a diagnostic modality of superior quality to conventional procedures and to provide an investigative tool that will permit objective assessment of the efficacy of potentially therapeutic interventions in diminishing the progress of ischemic injury to myocardial necrosis. Previously (B-3) we have demonstrated that ^{11}C-palmitate is a particularly useful radionuclide for assessment of myocardial metabolism externally. Fatty acid is the preferred substrate of the heart for a variety of reasons, including the high cytoplasmic ratios of carnitine to CoA which leads to conversion of activated fatty acids to species that can ingress into the mitochondria where oxidation takes place. In our previous studies we demonstrated, using isolated perfused hearts, that the reduction of ^{11}C-palmitate accumulation detectable externally correlated closely with hypoxia and its metabolic sequelae despite the maintenance of constant flow. In addition, we found that the distribution and extent of myocardial infarction detectable tomographically with ^{11}C-palmitate administered intravenously into intact dogs correlated closely with myocardial infarction quantified morphometrically at necropsy and delineated with the use of enzyme assays applied to contiguous cross sections of the heart. A series of studies has defined the consistency of lipid pools in heart muscle, the relationships between altered retention of ^{11}C-palmitate and metabolic integrity reflected by generation of CO_2, and physiological determinants of myocardial oxygen requirements in relation to oxidative rates of ^{11}C-palmitate detected externally.(1-4)

In this project, the feasibility of tomographic delineation of myocardial infarction was demonstrated initially with PETT III in patients with remote myocardial infarction.(1-3) In the initial study it was demonstrated that the distribution of ^{11}C-palmitate in cross sections of the heart from normal subjects was homogeneous but that zones of diminished uptake characteristically occurred in patients with pre-existing myocardial infarctions in locations corresponding to the electrocardiographic loci of infarction. In a study completed very recently, PETT IV was used to image myocardium after intravenous

injection of ^{11}C-palmitate to delineate zones of jeopardized or irreversibly injured tissue and after inhalation of ^{11}CO to image the cardiac blood pool with ^{11}CO-hemoglobin. Twenty-eight patients with suspected myocardial infarction were studied (21 with electrocardiographically documented transmural infarcts and 7 in whom the diagnosis of infarction was ultimately excluded based on enzymatic and electrocardiographic criteria). To assess reproducibility, 4 patients were studied on two occasions one month apart. Inferior and apical infarcts were readily localized with sagittal and coronal reconstructions as opposed to transaxial reconstructions. Complete electrocardiographic and tomographic concordance was observed for the loci of all transmural infarcts. Reproducibility of tomographic estimates was within 10%. Tomographic estimation of the extent of infarction with ^{11}C-palmitate in a subset of patients in whom right ventricular contributions to overall enzyme release could be excluded was facilitated by delineation of the endocardial border with ^{11}CO-hemoglobin cardiac blood pool images in each of the planes for which ^{11}C-palmitate images of myocardium were obtained. The correlation between enzymatic (serial plasma MB CK method) and tomographic estimates was close ($r = .92$). Thus, as has been demonstrated previously in experimental animals, positron emission tomography with ^{11}C-palmitate permits quantification and localization of myocardial infarcts in patients. Future directions in this project include the anticipated use of rapid scan instruments that will permit detection of regional metabolic rates of oxidation of initially incorporated ^{11}C-palmitate based on serial analyses of selected tomographic regions of interest within the left ventricle. In preliminary experiments in animals, we have demonstrated that the rates of decline of ^{11}C-palmitate activity within regions of the left ventricle are virtually identical in hearts from normal animals, and that the rates of decline are markedly increased when metabolic demand of the heart is increased by acceleration of heart rate after administration of atropine. Accordingly, it appears highly likely in patients that homogeneity of metabolism of ^{11}C-palmitate will be characteristic in normal hearts, that variation in regional metabolic rate will be a manifestation of differential nutrition and oxygenation, such as that occurring in association with coronary artery disease, and that evaluation of regional metabolism will provide a sensitive index of occult coronary artery disease in patients studied at rest or during physiological stress. An additional future direction involves clinical application of procedures, developed in our studies of ischemic myocardium in experimental animals (B-3), for quantification of regional perfusion based on exponential infusion of positron-emitting radionuclides. Again, rapid scan instrumentation will be required, gating of the tomographic system to the cardiac cycle, and an interpretation of results will depend on verification with other biological sequelae of regional ischemia.

(1) B. E. Sobel, E. S. Weiss, M. J. Welch, B. A. Siegel, and M. M. Ter-Pogossian, "Detection of Remote Myocardial Infarction in Patients with Positron Emission Transaxial Tomography and Intravenous ^{11}C-Palmitate," Circulation, vol. 55, pp. 853-857, 1977.

(2) B. E. Sobel, "External Quantification of Myocardial Ischemia and Infarction with Positron-Emitting Radionuclides," Advances in Cardiology, vol. 22, J. H. K. Vogel, ed., S. Karger, Basel, Switzerland, pp. 110-129, 1978.

(3) B. E. Sobel, "Non-Invasive Regional Assessment of Myocardium with Positron-Emitting Radionuclides," Advances in Cardiology, vol. 26, J. H. K. Vogel, ed., S. Karger, Basel, Switzerland, pp. 15-29, 1979.

(4) M. S. Klein and B. E. Sobel, "Fatty Acid Uptake and 'Metabolic Imaging' of the Heart," Cardiovascular Clinics, A. N. Brest, ed., F. A. Davis Company, Philadelphia, pp. 165-176, 1979.

B-5. PETT V

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PETT V[1,2] is a high sensitivity, seven slice positron emission tomograph designed for the imaging of the human brain. The design concepts incorporated in PETT V, such as maximum circumferential detection efficiency, flexible linear and angular sampling, high and low resolution, and minimum data acquisition times of one second, enable it to be used in a low resolution dynamic mode or a high resolution static imaging mode. The detector system of PETT V consists of a circular array of 48 NaI(Tl) scintillation detectors, each fitted with two photomultiplier tubes, with one dimensional positioning capability. Angular sampling is achieved by the rotation of the circular array of detectors and the linear sampling is obtained by a unique wobbling motion of the detectors. A detailed description of PETT V has been published.[1,2] PETT V has been built and tested and has been used in both animal and patient studies. Work is still in progress in improving the performance of PETT V with the aid of phantom studies and new software.

(1) M. M. Ter-Pogossian, N. A. Mullani, J. T. Hood, C. S. Higgins, and D. C. Ficke, "Design Considerations for a Positron Emission Transverse Tomograph (PETT V) for Imaging of the Brain," Journal of Computer Assisted Tomography, vol. 2, pp. 539-544, 1978.

(2) N. A. Mullani, M. M. Ter-Pogossian, C. S. Higgins, J. T. Hood, and D. C. Ficke, "Engineering Aspects of PETT V," IEEE Transactions on Nuclear Science, vol. NS-26, no. 2, pp. 2703-2706, April 1979.

B-6. Algorithms for Tomography Systems Having Fan Beam Geometries

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As reported last year (PR 14, B-3), we have derived a fan beam reconstruction algorithm for a geometry in which the detector rotates with the source. This algorithm can be implemented by adaptive transversal-filter technology to achieve a very high processing speed. The relationship between the number of source angles, number of taps in the transversal filter, number of detectors, image resolution, and the reconstruction time has now been established. We have also derived a fan beam algorithm for a geometry in which a ring of fixed detectors surrounds the object.

For the rotating detector geometry (PR 14, B-3), we have established the following relationship: $N_\alpha \approx N_\beta$, where N_α is the number of source angles, and N_β is the number of detectors in the fan. In the case where the image pixels are distributed Δr apart on concentric circles with Δr radical increment, the total reconstruction time T is given by:

$$T = \frac{4\pi}{f_B} \left(\frac{L}{\Delta r}\right)^2,$$

or alternatively by:

$$T = \frac{N_\alpha^2}{\pi f_B},$$

where L is the radius of the object, and f_B is the bandwidth of transversal filter. The number of taps in the transversal filter, N_t, is given by:

$$N_t = 4\pi \frac{L}{\Delta r}.$$

The fan beam reconstruction algorithm for a fixed detector geometry is a weighted sum of filtered detector outputs. Each detector output is filtered independently but the filter function is the same for all the detectors. The algorithm is based on the relation that if:

$$M(\psi,\xi) = \int_{\xi-\beta_m/2}^{\xi+\beta_m/2} m(\alpha,\xi)\ g(\psi-\alpha/2)d\alpha$$

then

$$\mu(r,\theta) = \int_0^{2\pi} W(r,\theta,\xi)\, M(\psi,\xi)d\xi$$

where

$$\psi = \tan^{-1}\left\{\frac{r \sin (2\theta-\xi)/2 - r \cos \xi/2}{R \sin \xi/2 - r \cos (2\theta-\xi)/2}\right\}$$

$$W(r,\theta,\xi) = [R^2 + r^2 + 2\, r\, R \sin (\theta-\xi)]^{-1}$$

α = source angle,
ξ = origin-detector angle,
β_m = total fan angle,
(r,θ) = location of a point in the reconstruction image in polar coordinates,
R = origin to source distance,
$g(\cdot)$ = filter response used in the parallel beam algorithm,
$m(\alpha,\xi)$ = data at source angle α, origin-detector angle ξ,
$\mu(r,\theta)$ = attenuation density at (r,θ).

B-7. Algorithms for Three-Dimensional Tomography

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Let $a(\underline{x})$ be the density of a three dimensional object to be reconstructed from projection data; here $\underline{x}$ is a point in the three dimensional object space. Let $\underline{e}$ be a unit vector of arbitrary orientation. A projection of $a(\cdot)$ on the line $t\underline{e}$ is defined by:

$$m(t\underline{e}) = \int_{P(t\underline{e}^{\perp})} a(\underline{x})ds,$$

where $P(t\underline{e}^{\perp})$ is a plane perpendicular to $\underline{e}$ and at a translation distance t from the origin, and where ds is a differential area in this plane. The three dimensional reconstruction problem is to determine $a(\underline{x})$ for all $\underline{x}$ in terms of $m(t\underline{e})$ for all t and $\underline{e}$. If $\underline{e}$ in polar coordinates is denoted by $(1,\theta,\phi)$, we find that:

$$a(\underline{x}) = \frac{1}{2\pi} \int_{-\pi/2}^{\pi/2} \int_{-\pi/2}^{\pi/2} g(\underline{x}^T \underline{e}, \theta, \phi) \sin \phi \, d\phi \, d\theta$$

where

$$G(f,\theta,\phi) = \int_{-\infty}^{\infty} g(t,\theta,\phi) \exp(-j2\pi ft)dt = |f|^2 M(f\underline{e})$$

and where

$$M(f\underline{e}) = \int_{-\infty}^{\infty} m(t\underline{e}) \exp(-j2\pi ft)dt$$

is the one dimensional Fourier transform of $m(t\underline{e})$. This equation can be interpreted as a "filtered back projection" that generalizes the usual parallel beam back projection in two dimensions by using projection data $m(t\underline{e})$ resulting from integration over planes $P(t\underline{e}^{\perp})$ rather than lines, employing a one dimensional filter with an $|f|^2$ response rather than an $|f|$ response, and by back projecting as a constant over planes $\underline{x}^T\underline{e}$ = constant rather than lines.

In an emission tomography system having detectors distributed on a cylinder, $m(t\underline{e})$ is obtained by appropriately summing all detection events occurring in detectors intersected by the plane $P(t\underline{e}^{\perp})$. With this algorithm, there appears to be a potential for rigorously accommodating data that are obtained in planes other than those perpendicular to the cylindrical axis of the system; such "cross plane" data are presently ignored or treated in an ad hoc manner. The practicality of this is an issue under current investigation.

C. Clinical Pathophysiology and Patient Monitoring

BCL activities addressing clinical pathophysiology and patient monitoring began in 1970. In 1973 a minicomputer-based patient monitoring system was installed in the Cardiothoracic Surgical Intensive Care Unit (SICU) at Barnes Hospital. After nearly seven years of continuous use, this highly regarded system will be replaced by a commercial monitoring system that incorporates several of the novel features found useful in the existing SICU patient monitoring system. The presence of the SICU system has heightened the awareness of clinical investigators to the value of on-line digital signal processing in their research. In general, the computer is now seen as an important tool in a continually increasing number of biomedical research activities. These demands for digital computing have stimulated us to develop more flexible and enduring solutions to better satisfy pathophysiologic research needs. The Clinical Physiologic Research System (CPRS) offers a generalized approach to meeting a significant class of such needs with modular system elements and distributed processing. In addition to providing a methodology for implementing instrumentation systems in a local environment, the CPRS concept may provide a convenient means for interfacing instrumentation systems to more global networks where expanded computational and data storage capacity reside.

During the past year, several research activities have dealt with the development of new and enhanced instrumentation and measurement techniques needed to make important clinical measurements. Included in these activities is the development of a system for acquiring serial left-ventricular angiograms that are subsequently analyzed to evaluate and improve ventricular boundary extraction algorithms. The objectives of the ultrasonic flowmeter and cardiac output studies are to enhance the clinical measurement of respiratory gas flow and cardiac output respectively. Instrumentation systems which have the promise of providing information that will contribute to a better understanding of glaucoma have been implemented in collaboration with the Department of Ophthalmology.

Research activities have applied mathematical methods in the statistical analysis of factors contributing to the risk of visual-field loss associated with glaucoma. The detection of high risk individuals is essential for the early institution of appropriate therapy. A multiple logistic function was used to assess the relative contribution to risk of multiple factors acting in concert. Another activity seeks to refine the mathematical model of fluid and exhaust mechanisms via the canal of Schlemm by measuring the temporal response of intraocular pressures following sudden displacements of the fluid.

Pathophysiologic research activities which initially focus on new instrumentation techniques or employ mathematical methods to answer important biomedical questions through modeling and statistical analysis have clinical application as an ultimate objective. The prototype SICU monitoring system has contributed to the clinical application of physiologic patient data and the SICU signal processing algorithms have been translated for use in clinical applications of the CPRS.

C-1. Clinical Physiologic Research System

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The Clinical Physiologic Research System, CPRS, results from a search for a reasonable and systematic approach to the application of microcomputers in meeting biomedical instrumentation needs. The CPRS demonstrates a practical methodology for integrating commercial instruments with distributed modular elements of local design in order to make facile responses to changing instrumentation needs in medical research laboratories and clinical environments.

The changing needs that characterize clinical research instrumentation systems are not unique. This dynamic situation prevails in most active research environments where biomedical instrumentation is employed. Our experience indicates that these systems evolve in such a way that new needs are determined by the outcomes of current experiments making it impossible to predict long-range requirements satisfactorily. In the past, a degree of flexibility was gained through the introduction of minicomputers into medical research activities. Since the beginning of the "microprocessor revolution," the microcomputer has been applied either as a less expensive and less powerful substitute for an instrumentation system's centralized minicomputer or as an inaccessible component embedded within a particular instrument. Through experience in applying microcomputers, another role for this new tool has emerged. The CPRS concept embodies this new role in that it depends on a distributed set of programmable microcomputers packaged in function-specific modules which communicate over a standard digital bus. Through this approach, the implementation of biomedical instrumentation systems can be effectively addressed.

The scheme adopted for the CPRS is general enough to enable the addition of both experimental and established measurements to previously configured systems. While the required transduction techniques and control devices may differ from application to application, many research applications have common underlying needs for signal acquisition, feature extraction, information display, information storage and control. The processing power that can be economically focused on these common needs continues to increase as the offerings of electronic component manufacturers improve almost daily. However, the low-cost virtue of microprocessors cannot be realized until a substantial investment has been made in support equipment, support personnel and an implementation procedure.

The CPRS design focuses on a modular approach which spans hardware, software and packaging as reported in PR 14, C-2. This enables instrumentation

systems to be configured appropriately for each particular application while maintaining the flexibility necessary to change with needs. Each hardware module is tailored to provide a specific function. Although each module is functionally different and operates independently in time, they are coupled to one another through a standard communications pathway. Because the functional portion of each module is isolated from the common pathway, the design of new modules is not constrained, allowing the designer of new modules to take advantage of current hardware and software offerings, while remaining compatible with previously designed modules. Software modularity is achieved through the use of a microprocessor-development system. It contains a growing library of subprograms written in assembly language. The application program for a particular functional module is constructed by linking together the appropriate subprograms using the development system described in G-1.

During the past year the CPRS has been used in a pulsatile perfusion study (C-2), a data acquisition system (C-3), and a patient monitoring application. To date, five different module designs have been packaged in Tektronix TM 500 blank plug-in kits. In order to expedite module construction, a wire wrap panel with an on-board switching regulator was designed to substitute for the kit's circuit board. Plans call for the extension of the existing wirelist program (G-14) to accomodate this wire-wrap panel. General software modules have been written to provide the listener, talker, and controller capabilities for the IEEE standard 488 bus using the M6800 microcomputer chip set. The physiologic signal processing algorithms, long employed in the Surgical Intensive Care Unit (PR 14, C-1), were translated into M6800 assembly language and reside as software modules in the microprocessor development system for use in CPRS applications. Two commercial devices compatible with the IEEE standard 488 bus have been readily incorporated into CPRS implementations during the past year. In order to expand intermodule communication capabilities, new hardware offerings are being surveyed. Of particular interest are offerings which will permit the efficient transfer of bus control from module to module. Direct memory access and dual-ported memories need to be examined as means for reducing bus transaction times and task coupling. It is expected that the CPRS will provide the flexibility necessary to adapt to changing instrumentation requirements in the existing applications as well as general enough to be appropriate for use in new applications such as the intraocular-pressure measurement system (C-4).

C-2. Pulsatile Perfusion System

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BCL, in collaboration with the Division of Cardiothoracic Surgery, has continued the development and testing of a pulsatile perfusion system. Using the Clinical Physiologic Research System (C-1) modular approach, a new pulsatile perfusion system has been implemented. A block diagram of this system is shown in Figure 1. Three CPRS hardware modules are used as well as several standard software modules. A user interface module is used for parameter input to control the pumping cycle and volume to be pumped, a controller module is used for communication control between modules, and a signal processing module is used to detect QRS complexes from the ECG and to control the occlusive-roller pump operation by providing the QRS-synchronized signals required by the motor driver. A standard QRS detection algorithm is used along with several standard mathematical routines. The use of the CPRS modular approach greatly enhanced our ability to implement a new pulsatile perfusion system, requiring the construction of three standard hardware modules and the incorporation of the software necessary to control user input and pump operation.

Several animal experiments have been successfully completed. During the next year reliability testing will continue in preparation for the introduction of the pulsatile perfusion system into the cardiothoracic-surgery operating room.

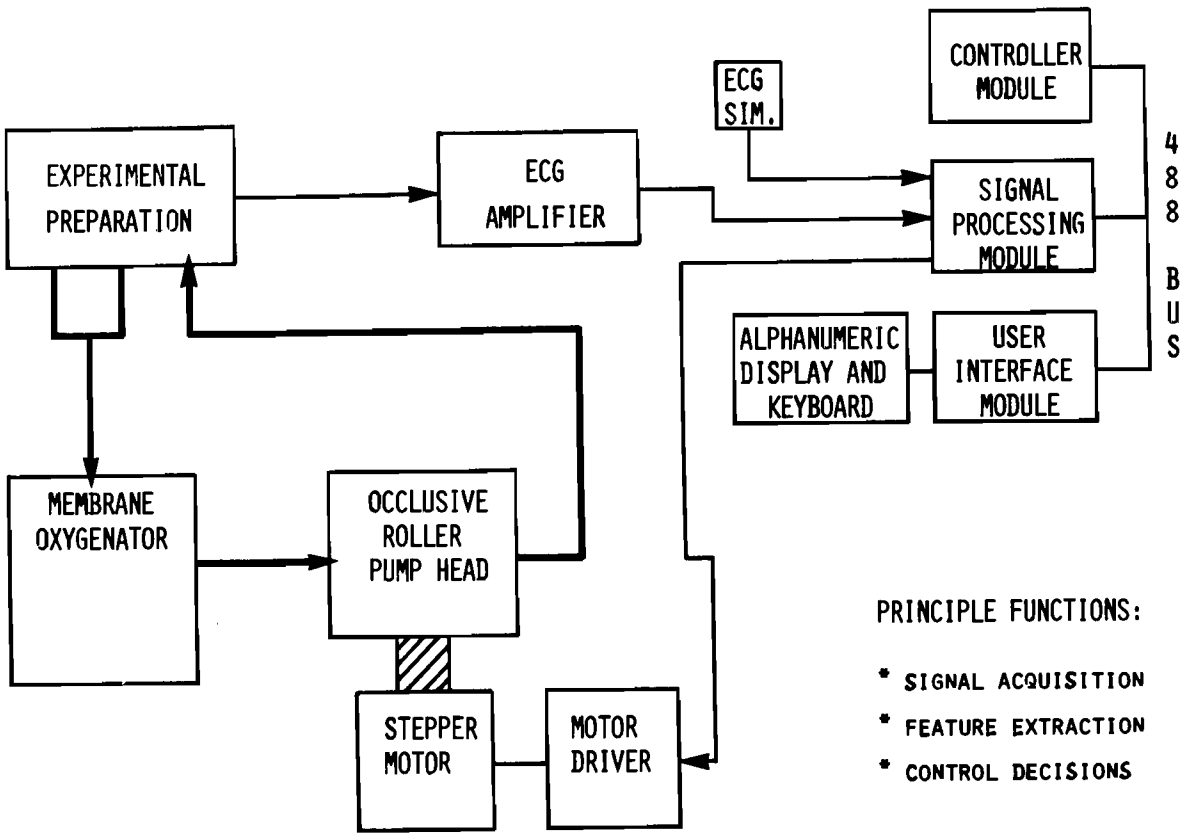

Figure 1. Pulsatile Perfusion System

C-3. Data Acquisition System for Extracellular Cardiac Potentials

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Support: RR 00396
American Heart Association, Missouri Affiliate, Inc.
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Changes in left-ventricular myocardial activation are known to correlate with the development of ventricular tachycardia and/or ventricular fibrillation (VT/VF) during acute myocardial ischemia, but little quantitative information is available regarding the electrophysiologic precursors of VT/VF. The study of the time course of the changes in several characteristics of multiple left-ventricular epicardial and endocardial electrograms induced by acute coronary artery occlusion in the dog necessitates multichannel acquisition of high-bandwidth analog data.

A system has been designed to address the signal-acquisition requirements of these electrophysiology experiments. A modular approach, based on our CPRS development activities (C-1), provides the high-speed sampling, digitization, storage and display capabilities commensurate with the requirements of a flexible experimental protocol, laboratory space and economic constraints. The data collected using the acquisition system are to be transported via flexible diskette to a minicomputer system for feature extraction and analysis.

A 4-channel analog burst-sampling module (ASM), a control/display module (CDM) and a data-storage module have been defined. The IEEE-488 bus provides the modular interconnection which facilitates system expansion. The ASM can be initialized via the interconnect to select sampling rate (10 Hz to 20 kHz), delay after trigger (1 to 200 msec) and sampling window (1 to 100 msec). The ASM contains 8K bytes of local memory to store the burst of digitized (8-bit) samples. A prototype ASM is currently operational.

A small computer system, of the "personal" computer class, the "PET" (Commodore, Inc.), is being evaluated for use as the control/display module. The capability to program in BASIC, the video graphics for prompting protocol specification, a pseudo-IEEE-488 interface port and low cost allow many of the CDM needs to be easily addressed. Resolution of the PET graphics is inadequate for display of digitized/reconstructed waveforms. Plans now include a separate display module for sampled-waveform review.

The DSM is based on a floppy disk controller/drive with an IEEE-488 interface. The DSM design capitalizes on components developed locally (G-3).

The prototype DSM has been constructed and preliminary testing has been completed. System level routines to allow ASM acquisition and transfer to the DSM have been written and testing is in progress.

The prototype configuration consisting of a single ASM (4 channels), the PET and a Tektronix storage oscilloscope to address the CDM requirements, and the floppy-disk-based DSM is to be evaluated under experimental conditions in the electrophysiology laboratory before construction of those modules required to support sixteen-channel experiments.

C-4. Intraocular Pressure Measurement

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Support: RR 00396
EY 00256

Supporting effort has continued in collaboration with researchers in the Ophthalmology Department of Barnes Hospital for measurement of the temporal response of the intraocular pressure following a sudden displacement of fluid. Study of this behavior will assist in the refinement of physiological models of the fluid-generation and exhaust mechanisms via the canal of Schlemm which play a central role in the development of glaucoma.

Hardware preparation to carry out these experiments has been completed. The system consists of a chart-recorder pen motor coupled to an LVDT tonometer. The footplate of the tonometer is placed against the cornea and the pressure within the cornea is measured. Current, flowing through the pen motor, can be accurately monitored and used as a direct measure of the torque produced by the motor. The tonometer, driven by the pen motor arm gently pushes against the cornea causing a volume of fluid to be displaced as flattening occurs. By continuously measuring pressure and total force, the area of flattening can be maintained constant. This procedure will be carried out automatically with a TI-980 computer which will have direct control over the current supplied to the pen motor.

Through the course of the experiment a Universal Storage Device (G-3) will collect pressure and force data that will be subsequently used in the development of a physiological model. Furthermore, the USD will act as a means to bootstrap the applications program into the TI-980 computer that will be used for controlling the experiment.

Currently, all hardware needs for this system have been completed and verified; and a FORTRAN program for monitoring and controlling the experiment is under development. Results from this experiment should contribute to the verification and refinement of algorithms which will ultimately be written for CPRS modules (C-1). These modules will be employed in the clinical environment where their discreteness will be needed for routine diagnostic work with glaucoma patients.

C-5. A Microprocessor-Based Data-Acquisition System for the Goldmann Perimeter

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Support: RR 00396
EY 00336
EY 02044

A prototype microprocessor-based system has been developed to obtain computer-readable visual-field data at the time of patient examination (PR 13, I-2; PR 14, C-12). This system permits the use of existing examination techniques and is designed to allow easy attachment to a Goldmann perimeter. The instrument contains five major peripherals: 1) a keyboard with an alpha-numeric display, 2) point-location and stimulus-setting transducers, 3) an oscilloscope display, 4) a floppy-disk drive, and 5) a serial-communication link to a host minicomputer. Operation centers about a menu that permits push-button selection of all major functions:

A. Calibrate the location transducer,
B. Start a new examination,
C. Edit the textual data,
D. Edit the field data,
E. Display the field for each eye as a set of closed contours,
F. Save the data on the floppy diskette,
G. Obtain an index of the examination,
H. Retrieve an examination from the diskette, and
I. Communicate with a central computer.

The mechanical attachments to the perimeter have been refined and the system has been packaged as a portable desk-unit. The serial communication protocol has been modified to be compatible with a PDP-11/34 using RSX-11M. In addition, this protocol has been improved so that the user is only responsible for understanding the acquisition system. The user is given the option of transfering the entire contents of the diskette or paging through the examinations and performing selected transfers.

A calibration procedure has been formalized and added to the menu. The instrument has been moved to a clinical environment and a perimetrist has been trained in its use. A user's manual is being prepared and will soon be released as a monograph. A number of patient studies using the instrument are planned (C-6).

C-6. Visual Fields and Ocular Hypertension

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Work has continued on the quantitative evaluation of visual field data obtained from patients with known or suspected glaucoma.[1] Prior work, using retrospectively obtained data recorded with a PC-1200, established the presence of quantitative though "nonspecific" pressure related changes in the visual field prior to the onset of typical glaucomatous visual-field defects. During the past year the visual-field programs have been transferred to a dedicated mini-computer (PDP 11/34A) located in the Department of Ophthalmology. Data are recorded by two methods. In the first, visual field charts are traced directly using a magnetic graphics tablet (Tektronix 4953). The second method employs a microprocessor-controlled recording device for the Goldmann perimeter (C-5). All programs have been modified to be compatible with the new operating system (RSX 11M), and the necessary software has been written to permit graphic output to both display terminals (Tektronix 4010) and a matrix printer-plotter (Versatec 1200-A).

Data are stored on disk in patient-specific files, permitting real-time retrieval of all data at the display terminals. In addition, graphic records can be obtained in a condensed hard-copy form for inclusion in physical charts (see Figure 1).

Automated pattern analysis techniques have been developed for the detection of specific topographic features characteristic of glaucomatous visual field defects.[2] Detection strategies employ isopter and sector-area computations, angular orientation of connecting line segments, changes in orientation at each point of an isopter contour, and a generalized shape feature (P2/A) that quantifies any deviation from a generally circular contour. Thus, enlargement of the physiologic blind spot, the presence of central or paracentral scotomata, significant constriction of central or peripheral isopters, altitudinal patterns of field loss, and "nasal steps" may all be detected and quantified for any of a large number of

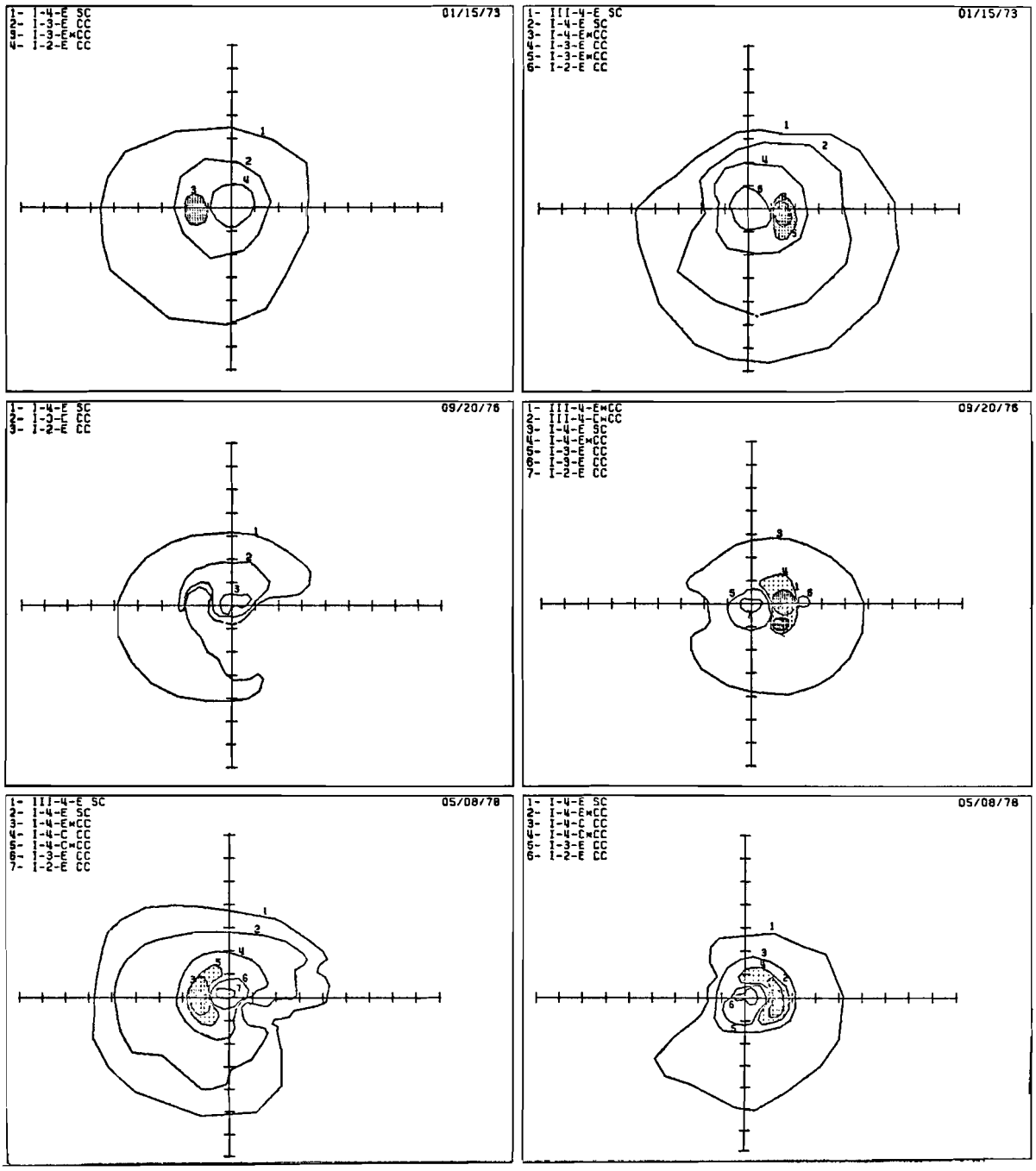

Figure 1. Visual Field Summary

visual-field records. It is intended that this will permit cross sectional studies on large numbers of subjects in the Glaucoma Center, using objective criteria for the description of visual-field defects.

Additional work reported this year involved the statistical analysis of factors contributing to the risk of visual-field loss among subjects with ocular hypertension.[3] The detection of individuals felt to be at high risk prior to the actual development of visual loss is essential for the early institution of appropriate therapy. A multiple logistic function was used to assess the relative contribution to risk of multiple factors acting in concert. Those factors found to have the greatest predictive value included mean intraocular pressure, age, cupping of the optic disk and a positive family history of glaucoma.

During the coming year attention will be given to correlation of quantitative visual field changes with electrophysiologic testing (visual evoked response) being carried out in parallel studies on the Glaucoma Center population. The automated feature-detection algorithms will be refined, and two-dimensional surfaces will be used to improve appreciation of complex topographical features in pathological visual fields.

[1] W. M. Hart, "Computer Applications to Visual Fields," Computers in Ophthalmology 1979, St. Louis, Missouri, April 5-6, 1979, in press.

[2] W. M. Hart, R. K. Hartz, G. J. Blaine, and L. J. Thomas, "Automated Pattern Analysis of Visual Fields," presented before the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 1, 1979.

[3] W. M. Hart, M. Yablonski, M. A. Kass, and B. Becker, "Multivariate Analysis of the Risk of Glaucomatous Visual Field Loss," Archives of Ophthalmology, vol. 97, pp. 1455-1458, 1979.

C-7. Ventricular Boundary Extraction

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Support: RR 00396
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The closed-circuit TV (CCTV) video-image acquisition hardware/software system (IMSYS) (PR 14, C-9) was completed and used to digitize and store several left ventricular (LV) serial angiograms from a video tape recorder (VTR). While VTR instability complicated the digitization procedure, a number of digitized LV images were produced for automated boundary detection algorithm performance evaluation.

The performance evaluation of the LV image acquisition system (IAS) revealed the VTR as the largest source of signal degradation within the IAS chain.[1] The peak-to-peak signal noise ratio ($SNR_{pp/pp}$) achieved from VTR images was 18 dB, equivalent to 3-bit image grey-level quantization. In addition, the VTR noise levels dominated the 23 dB $SNR_{pp/pp}$ noise levels inherent in the X-ray fluoroscopy system (XFS). The video digitizer system (VDS) noise measurements indicated the $SNR_{pp/pp}$ of 47 dB, or 8-bit quantization reliability. Hence elimination of the VTR from the IAS chain would result in the digitized LV image noise being solely dictated by the XFS noise levels and the inherent biological noise. In addition to high levels of noise, the VTR contributes significantly to the non-linearity of the IAS transfer characteristic. The full-scale non-linearity of the VTR was determined to be about $\pm$ 1% as compared to $\pm$ 0.3% for the VDS. Finally, measurements identified the VTR to be the greatest source of image-edge position jitter. As fractions of the horizontal and vertical image-sampling periods, the jitters were determined to be $\pm$ 11% and $\pm$ 33%, respectively. The horizontal and vertical jitters for the VDS were determined to be $\pm$ 17% and negligible, respectively.

To assess the implications of the digitized LV image noise on the performance of LV boundary extraction algorithms the noise was characterized as a random process.[1] The digitized noise levels were observed to be independent of the digitized signal levels, indicating additive noise. Flat-field grey-level scatter diagrams showed the noise samples to be highly uncorrelated, thus indicating the noise spectral density approximation of a white-noise (wide-band) random process. The scatter diagrams and

grey-level histogram distributions were strong indications that the noise was a Gaussian random process.

The performance analysis of a digitized-image edge extractor was accomplished by modeling a one-dimensional edge profile as a known deterministic function corrupted by an additive, Gaussian, white-noise random process. A non-linear, single-parameter estimation procedure resulted in deriving a matched filter followed by a maximum-value detector as an optimum edge-position estimator. The estimator performance was assessed by a theoretical lower bound (minimum value) for an expected root-mean-square (rms) error. The lower bound was inversely proportional to the ratio of the peak edge signal to rms noise ($SNR_{p/rms}$), the constant of proportionality being dependent on the selected edge-transition model.

For left-ventricular edge recognition, both the Latter-Day-Saints Hospital (LDS) algorithm[2] and the algorithm of Modestino[3] were investigated in great detail and comparisons were made between these approaches. Although radically different, both use a comparable number of empirical constants. The LDS algorithm was chosen for the initial implementation, and the requisite software is 50% completed. Plans have been made for future implementations and performance comparisons with the Modestino and other possible algorithms. For algorithm experimentation, the LV image data acquired by IMSYS will be used. To be able to study the differences between image row and column boundary search directions, a fast row-column matrix-transposition algorithm[4] has been implemented.

The new BDOS file access routines (G-2) have substantially simplified the software to process the vast (approximately 10^5 words) image-sequence files. The graphic tablet for manual LV boundary tracing has been built and can now be used in conjunction with the boundary extraction algorithm development.

[1] B. Zvolanek, "Video Digitizer System for Acquisition of Cardiac Left-Ventricular Images: Design, Implementation, and Performance Evaluation," BCL Monograph No. 365, May 1979.

[2] P. D. Clayton, L. D. Harris, S. R. Rummel, and H. R. Warner, "Left Ventricular Videometry," Computers and Biomedical Research, vol. 7, pp. 369-379, 1974.

[3] G. P. Ashkav, and J. W. Modestino, "The Contour Extraction Problem with Biomedical Applications," Computer Graphics and Image Processing, vol. 7, pp. 331-355, 1978.

[4] J. O. Eklundh, "A Fast Computer Method for Matrix Transposing," IEEE Transactions on Computers, vol. C-21, pp. 801-803, July 1972.

C-8. Ultrasonic Gas-Flow Instrumentation

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Support: RR 00396
HL 22517

Our interest in ultrasonic gas-flow instrumentation began several years ago during the development of a physiologic monitoring system which was implemented to assist clinical personnel in caring for post cardiothoracic surgical patients (PR 14, C-1). Since these patients are usually supported by mechanical ventilation, an objective was to provide reliable, long-term monitoring of respiratory flow in the patient-ventilator circuit. In measuring this flow, ultrasonics offered several potential advantages over alternative methods. Commercial ultrasonic flowmeters were evaluated and found to be unsuitable. An effort to design an ultrasonic flowmeter was initiated and resulted in a prototype instrument described in PR 14, C-6.[1] The discrepancies which exist between the theoretical models of sound-flow interaction within this transducer and experimental results limit the understanding of transducer design trade-offs and component specifications. The mathematical modeling of sound-flow interaction has been given considerable attention during the past year and should lead to a better understanding of transducer behavior.[2]

In addition to developing an improved theoretical model of the transducer, plans include an evaluation of polyvinylidene fluoride (PVDF) films as a piezoelectric transceiver element. Poled and stabilized PVDF is reported to possess several characteristics which may be useful in gas-flow transducer applications.[3] These characteristics include a very broad-band frequency response and flexible fabrication into different geometries.

[1] R. W. Hagen, L. J. Thomas, Jr., and M. L. McCartney, "An Ultrasonic Ventilometer," Proceedings of the 31st Annual Conference on Engineering in Medicine and Biology, Atlanta, Georgia, vol. 20, p. 232, October 21-25, 1978.

[2] R. D. Livengood, "Mathematical Modeling of the Sound/Flow Interaction of an Ultrasonic Flowmeter," Master of Science thesis, Department of Electrical Engineering, Washington University, St. Louis, Missouri, August 1979.

[3] P. E. Bloomfield, R. A. Ferren, P. F. Radice, H. Stefanou, and O. S. Sprout, "Piezo- and Pyroelectricity in Poly (Vinylidene Fluoride)," Naval Research Reviews, pp. 1-15, May 1978.

C-9. Thermodilution Cardiac Output Studies

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Thermal dilution studies during the past year have focused on signal processing strategies for evaluating cardiac output in anesthetized dogs. In earlier experiments, reported in PR 14, C-7, it was observed that the constant infusion of room temperature saline solution into the right ventricle produces changes in an animal's pulmonary artery blood temperature, T_{pa}, which may be described by a function of the following form:

$$T_{pa}(t) = T_{baseline} + B(1-e^{-at}) + \frac{C}{2}[t-t_1 + |t-t_1|] \qquad (1)$$

These experiments suggested that temperature effects due to recirculation are significant but can be expressed as a linear function with slope C, beginning at time t_1, as shown in the last term of the preceding equation. The first term in this equation is the average baseline blood temperature prior to indicator infusion. The middle term describes the transient exponential change in T_{pa} resulting from the constant infusion of thermal indicator.

Data were collected during animal experiments using the Universal Storage Device (G-3). Equation 1 was fit to the temperature data collected from the pulmonary artery by varying the four parameters B, a, c and t_1 to obtain a best fit according to least-squares criterion. An iterative procedure based on a method developed by Marquardt[1] was used to minimize the least-squares problem. Figure 1 shows a typical T_{pa} curve with the fit curve superimposed.

The steady-state temperature change in the pulmonary artery when a constant infusion of thermal indicator is added to the blood returning to the right atrium is expressed as parameter B. Once B is determined by the curve fitting procedure, the cardiac output may be estimated using an equation based on conservation of thermal energy (PR 14, C-7). During the experiments, an independent measurement of cardiac output was obtained from an electromagnetic flowmeter.

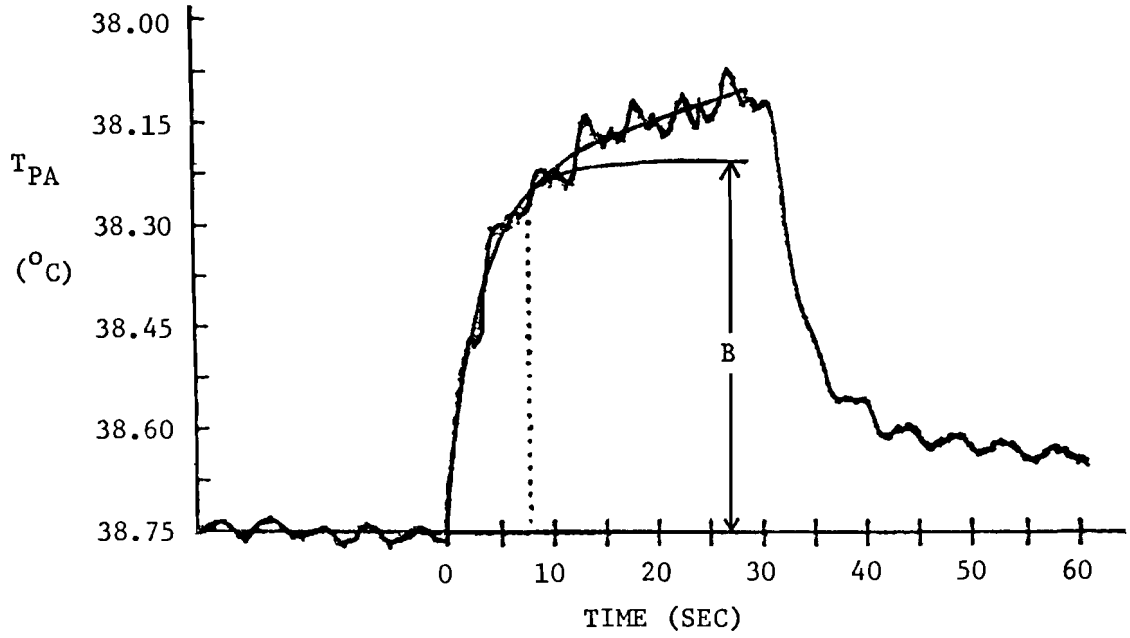

Figure 1. Time course of pulmonary artery temperature (T_{pa}) during constant infusion of thermal indicator.

The results indicate that the described procedure consistently underestimates parameter B, producing overestimates of cardiac output. Limiting the ranges of the curve fitting parameters needs to be evaluated as a means for improving the accuracy of parameter B estimates. In addition, the validity of the assumed model must be verified. The underestimated value of parameter B, may result from the exchange of thermal energy between the blood/indicator mixture and the walls of the right atrium and ventricle through which the mixture passes prior to reaching the T_{pa} measurement site. This assumption, crucial to the viability of all thermal indicator techniques, needs to be examined in animal experiments.

(1) D. W. Marquardt, "An Algorithm for Least-Squares Estimation of Nonlinear Parameters," Journal of the Society for Industrial and Applied Mathematics, vol. 11, no. 2, pp. 431-441, June 1963.

C-10. West Pavilion Planning

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Support: RR 00396
Barnes Hospital

During the past year BCL has continued to address the patient monitoring needs in Barnes Hospital's West Pavilion through staff appointment to the hospital's Patient-Monitoring Committee. The anticipated monitoring needs in the West Pavilion were documented in a request for proposals (RFP) as reported in PR 14, C-5. Five vendors developed proposals in response to the RFP. These proposals were evaluated in order to determine the degree to which each satisfied the monitoring needs. A survey of each vendor's installed systems provided additional information regarding the performance of the proposed monitoring systems. Selected components were tested by Barnes Hospital's engineering staff. Proposed systems which satisfied the need and performance criterion were then evaluated with respect to cost. This procedure resulted in the selection of patient monitoring system suppliers in the fall of 1978.

The first patient care area to be opened this fall in the West Pavilion will be a new cardiothoracic surgery facility. This new facility will replace and expand the existing surgical intensive care unit (SICU) and the patient monitoring system in the SICU will be retired after 6.75 years of successful operation (PR 14, C-1). The commercially available monitoring system in the new cardiothoracic surgery facility incorporates many of the features developed for the prototype SICU monitoring system.

D. Databases for Disease Management and Research

The need for database facilities in several BCL projects became compelling in the early 1970s. The quantity and diversity of data for these projects had grown unmanageable by manual methods. Prior experience underscored the desirability of interactive data entry in order to assure adequate quality and to provide easy access to up-to-date information. Primarily through external funding a minicomputer-based system (MUMPS) capable of supporting database activities was imported, rewritten for the PC-1200, and applied in radiation oncology. This application has developed into an installation, the Oncology Data Center, (ODC), located within the Mallinckrodt Institute of Radiology. A fee-for-service installation, the Medical Computing Facilities (MCF), was organized within the Medical School to provide MUMPS service to those who do not desire to operate their own installations. BCL, itself, operated a MUMPS facility for training purposes and investigation into database characteristics until 1978. By that time the applications still operating on the system were deemed mature enough to migrate to either the MCF or ODC installations.

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

Following a long-standing tradition of the laboratory, an increasing emphasis has been placed on allocating the appropriate computer resource to each information processing task. As the databases which are described in this section mature their analyses become of increasing importance. Because of the richness of the software development and because of the overall suitability of a general-purpose large-scale computer for analysis tasks, they have been performed largely on the University's IBM System/360-370. SAS, a popular statistical-analysis/data-management package, has provided the primary vehicle for the analyses of databases managed on other computing systems.

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

D-1. Glaucoma Center Registries

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Support: RR 00396
EY 00336

In 1974 investigators in the Glaucoma Center initiated automation of their records to facilitate clinical research. From BCL's interest in characterizing clinical databases and their usage,[1] a collaborative effort emerged. Rather than design a new information system, MISAR[2] was imported (PR 12, D-15). Since then the registries have grown and their supporting programs have been improved. The registries have facilitated both clinical and database research.[3-6] Approximately 1900 of the Glaucoma Center's estimated 2400 charts have been completely entered into and kept current in the computerized registry. These data are represented in approximately three million bytes (March 1979) and utilize a total of 13.1 million bytes including registry data, auxilliary data, pointers, programs, and overhead. The three million bytes represents a growth of one million bytes over the approximately two million bytes stored in May 1978.

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

Improvements to the database included the addition of a ZIP code directory, and creation of a registry of approximately 200 referring MDs and ODs. Both changes increased data quality and reduced storage requirements. Reminder slips which are created using the computer database and inserted into the subject charts, prompt the physician to update historical data, such as family history of glaucoma and diabetes, and to perform tests that the subject has not recently had. This reminder system has greatly improved the completeness of both the written chart and the computerized summary.

The second major statistical study using data from the glaucoma registry was initiated. In April approximately 880,000 bytes of data (30 fields from 248 subject records) were transferred to the IBM System/360-370 computer on the Hill Campus for statistical analysis of diurnal variations of intraocular pressure. The data were successfully transferred via magnetic tapes, SAS data sets were created, and the data were verified and checked for correctness using SAS.

The Glaucoma database has been supported by MUMPS-based computer services available through the Oncology Data Center (ODC), Mallinckrodt Institute of Radiology. System availability forced a reevaluation of our needs, resulting in a selection of the MUMPS-based computer services provided by the Medical Computing Facilities (MCF). The programs to store and access the Glaucoma registries are currently being rewritten for the new environment.

(1)R. H. Greenfield, "Characteristics of Clinical Data Bases and Their Usage," D.Sc. Dissertation, Sever Institute, Washington University, St. Louis, Missouri, December 1976; also available as BCL Monograph No. 303.

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

(3)R. H. Greenfield, "Evolution of an Ophthalmologic Data Base," Proceedings of the 1978 MUMPS Users' Group Meeting, San Francisco, California, pp. 67-75, 1978.

(4)M. A. Kass and R. H. Greenfield, "Glaucoma Report: Computers in Patient Care and Clinical Research," Annuals of Ophthalmology, vol. 10, no. 12, pp. 1693-1694, December 1978 (editorial).

(5)R. H. Greenfield and M. A. Kass, "A MUMPS Data Base to Facilitate Glaucoma Research," in Computers in Medicine: Proceedings of the Scientific Forum of the Society for Computer Medicine, November 1978, T. C. Gabriele, ed., Raven Press, New York, New York, in press.

(6)R. H. Greenfield, "Ophthalmologic Information Systems," presented at the Computers in Ophthalmology Meeting, St. Louis, Missouri, 5-6 April 1979, proceedings in press.

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

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During the past year the MUMPS-based MIPI system (PR 12, A-1; PR 13, D-2; PR 14, D-2) has supported the activities of the Sudden Death Study in three areas: 1) the gathering of data and the passage of coded data to a SAS database (D-10) for statistical analysis, 2) the notification of patients and physicians concerning Holter recordings, the termination of the study, and the study's progress, and 3) the definition and performance of "cleanup" tasks which are needed to convert free-text responses to coded format. Unless further tasks for the database are defined, it will cease to function in the coming year since all data will have been sent to the SAS database or archived on tape.

The gathering and management of data for the study can be classified into three categories: 1) the recording of CCU admissions for Barnes and Jewish Hospital patients (10/27/75 - 03/31/78) and the gathering of relevant clinical data for all myocardial infarction (MI) cases, 2) the scheduling of Holter recordings and the acquisition of related data elements, and 3) the follow-up done on all surviving MI patients.

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

For patients recruited into the Holter monitoring program two recordings were made, the first 10-14 days post-MI and another 2-3 months post-MI, and then, for qualifying patients the recordings were continued at three month intervals for a minimum of one year. The MIPI system noted patients to be scheduled and generated applicable correspondence. The diverse sources of data for each recording included: 1) forms completed at the time of recording, 2) the digitization and Argus/H edit of the tape (A-4), 3) the cardiologic review of the Argus/H edit results, 4) serial reading of the 12-lead ECG taken at the time of the Holter recording, 5) successful passage of Cycle-save data to the IBM System/360-370 and subsequent recycling of digital tapes, and 6) data collected for a special lipid research project. As with the in-hospital phase of the system, tracking records controlled the entry of data, related the status of any file, and allowed the generation of work lists and management reports.

All surviving MI patients were followed at six-month intervals to document their post-MI status. Presently a last follow-up effort is underway to determine each patient's status as of March 1, 1979. Final results are still needed for 25 Study I and 9 Study II patients. The MIPI system aids the follow-up process. A periodic computer listing of patients to be contacted is made. Since the previous source of contact is included the nurse conducting the follow-up can decide upon one of several methods of contact: 1) a computer generated letter to the private physician which contains data specific to the particular patient, 2) a computer-generated letter to the patient or some other contact, or 3) a telephone conversation with the patient or some other contact. A computer generated log containing appropriate names, phone numbers, and addresses is used to keep track of attempts to contact by phone. For patients who have expired, a blinded summary of the circumstances surrounding death is prepared and coded.

Data from all three phases of the project are transferred to the project's SAS database via tape in a multi-step process. Data are transferred according to the form on which they appear. Qualifying forms are rechecked since edits have been updated as the study progressed. Data from error-free forms are reformatted into records suitable for SAS using table-driven routines. Errors are corrected by rekeying data or by running one of several automatic conversion programs. When the data have been recorded in the SAS database, forms which contain no free-text items and/or items needed to make future decisions about a patient are removed from the MIPI database.

All data relating to the in-hospital phase of the study have been passed to the SAS database except for CK values. The entry and passage of these data to SAS was delayed until the protocol under which the CK measurements were made was carefully defined. Since the task has been accomplished these data are being entered into the MUMPS database and will be sent to the SAS database soon.

Data collected concerning the Holter monitoring phase of the study have also been passed to SAS with the exception of the 12-lead ECG form. When comparisons were made between various responses on these forms, some discrepancies were noted. The pertinent ECG's are being reviewed. After updates are made to the database, these data will be sent to the SAS database.

The latest version of the follow-up data are sent when they are needed for a particular analysis. When the follow-up phase of the project is complete, the latest version of the data will be sent to SAS. At that time patient identification data will be saved on tape and the MIPI system should no longer be needed.

The data collected for the Sudden Death Study can be summarized as follows:

	Barnes	Jewish
Patients Admitted	2734	2736
Diagnosis of Definite MI	610	469
In-Hospital Data Forms Entered	17963	17055
Holtered Patients	235	206
Holter Recordings	592	579

The main uses of the MIPI system over the past year were the "cleanup" of data and its passage to SAS. The system has generated lists of data collected in free-text so coding schemes could be developed. Some of the more interesting areas include diagnoses, concurrent problems in CCU, death complications, exercise, and 12-lead ECG features. All free-text data have been converted using special update procedures. A great deal of effort was devoted to the development of an editing scheme for drug prescriptions. Codes were assigned to drugs by their generic name and reason for prescription. Common brand names, dosages, and schedules were included in an online medication table. All drugs recorded in the system were checked using these criteria and any problems were corrected.

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

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

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The MUMPS-based PIM system (PR 13, D-3; PR 14, D-3) coordinates the double-blind propranolol intervention study for the reduction of infarct size run by St. Louis University and two collaborating institutions, St. John's Mercy Medical Center and Veteran's Administration Hospital. Since the enrollment of patients in this study was terminated March 31, 1979 the system has been serving a dual role. In addition to monitoring the continued collection of data, it has also aided the coding of data and its passage to the statistical database. All in-hospital data concerning study patients have been entered into the system and verified. It is estimated that in-hospital data for all patients will be entered and verified as of August 1, 1979. Based on this assumption all of these data will be coded and sent to the SAS database by September 1, 1979. The system will continue to receive follow-up data and send it to the statistical database until all follow-up visits have been completed.

The data collection protocol for this study is complex. Data are collected concerning the hospital and especially the CCU stay of any patient admitted to one of the three participating CCU's to rule out an MI. The forms completed documenting the patient's stay are determined by classifying the patient's case into one of four categories: 1) recruited for study, 2) eligible but not recruited, 3) not eligible but MI was diagnosed, or 4) not eligible and no diagnosis of MI.

The major thrust of the system revolves around recruited patients for whom a minimum of sixty-five forms are completed. Besides data similar to that obtained by the MIPI system (D-2) hemodynamic measurements are made for 72 hours, metabolic measurements for 4 days, propranolol blood levels for 10 days, and CK measurements for a maximum of 126 hours. Thallium, pyrophosphate, and HSA scans are made at various scheduled intervals during the hospital stay and 6 Holter recordings are taken. All medications administered during the first 14 days of the hospital stay are recorded with a code number indicating reason for administration and the dosage. Any significant events occurring during that time are noted by time of occurrence and a numerical code. All in-hospital data, except scan data which are keypunched, are entered into the system upon receipt, verified, coded where needed, and then sent to the statistical database for analysis.

Recruited patients are scheduled for follow-up visits at 3, 6, and 12 months post-MI, at which time five procedures are done (stress test, HSA scan, ECG, Holter recording, and chest x-ray) and a follow-up form is completed. All data except data relating to HSA scans are entered and, as with the in-hospital data, when a file is completed the results are printed for review by the study's investigators and then formatted for passage to SAS (D-10).

As in the MIPI system the PIM system manages and controls the entry of data forms once the patient is initiated in the system via tracking records. These tracking records are used to produce ad hoc lists of "things-to-do" and weekly management reports which are distributed in order to encourage the prompt completion of incomplete files. Of particular importance is a recently produced report which documented incomplete files and the number of days the system has awaited their completion. One improvement to the information system has been the development of a series of programs which perform time-consuming edits and tracking of data not done when data are entered. Responses on various forms can then be cross-matched. Any files requiring attention are saved until time is available for inspection by the data entry clerk or research nurse.

Most software development during the previous year has centered around further edits of the data, the coding of free-text data, and the passage of all data to the statistical database. Although data had been passed to the SAS database for analysis, no data were removed from the MUMPS database since free-text items had not been coded and some data items required further clarifications. In support of this "cleanup" effort routines were written to print and/or change data items based on user-specified parameters. This listing capability was especially advantageous for the conversion of free-text items and the display of questionable data items. The proper codings of free-text items were marked on these listings by a research nurse and then keyed by the data entry clerk. All of the entered codings were verified by concurrently displaying the free-text and coded data on either the terminal or printer. This conversion effort has run smoothly since list generations and changes to the data are all handled by table-driven routines. The medication edits and code lists developed for the MIPI system were used to handle some of the data conversion problems. However because of the variety of free-text items in this study new coding schemes were also developed.

At this time most of the data specific to the in-hospital stays of the study patients have been passed to the SAS database. The follow-up data are being coding so permanent versions of these data can replace the temporary SAS files. After these data are sent to SAS, data relating to the registry of all patients will be sent.

There are 2983 patients registered in the PIM system. Of these, 743 are documented MI's and 132 met the entrance criteria for the propranolol intervention study. Ninety-seven patients were recruited into the study. Follow-up data have been collected concerning 206 visits made on 83 patients.

D-4. SCOR Patient Information Database

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Support: RR 00396
HL 17646

The SCOR database currently contains information on 543 patients. The discrete variables contained therein describe the patients' cardiovascular history, in-hospital physical condition, and long-term progress as assessed through follow-up interviews and examinations. The data records are entered onto disk with the use of the Interdata computer and then written onto magnetic tape. Tapes are transported to the IBM System/360-370 and maintained as a permanent SAS database. The database has been used in several studies concerned primarily with the relationship between infarct size and long-term survival after myocardial infarction.

A subset of 173 patients who had no evidence of prior myocardial infarction, who survived acute infarction for at least 24 hours, and who were 65 years of age or less was studied.[1] Mean infarct size index (ISI) of those who succumbed was significantly larger than that of survivors (46.5 $\pm$ 5.8 (SE) vs 21.1 $\pm$ 1.4 CK-g-eq, $P < .01$). Overall survival was significantly better after small (ISI < 15) or moderate infarcts ($15 \leq ISI \leq 30$) than after large infarcts ($ISI \geq 30$) ($P < .05$). Regardless of the locus of infarction, patients with small infarcts had a significantly lower long term mortality rate and fewer premature ventricular contractions evaluated with follow-up Holter recordings than those with large infarcts ($P < .05$). Late mortality was comparable after transmural and subendocardial infarction but higher after anterior than inferior infarction. Of the 10 clinical and hemodynamic variables investigated, the most important predictors of mortality were ISI and congestive heart failure present at the time of hospital admission.

Based on data from 356 patients (256 with initial and 100 with repeat infarction), the prognostic import of ISI in patients with prior infarction was investigated.[2] ISI was less with repeat compared to initial infarction (15 ± 1 vs 22 ± 1). Nevertheless, those with prior infarction had a significantly lower ($P < .01$) 1 year survival rate (64%) than those without prior infarct (77%). In contrast to the case with patients with initial infarction, mortality in patients with repeat infarction was not closely related to ISI, probably because of the overriding importance of the cumulative extent of earlier injury.[3-8]

(1) E. M. Geltman, A. A. Ehsani, M. K. Campbell, K. B. Schechtman, R. Roberts, and B. E. Sobel, "The Influence of Location and Extent of Myocardial Infarction on Long-Term Ventricular Dysrhythmia and Mortality," Circulation, in press.

(2) E. M. Geltman, K. B. Schechtman, A. A. Ehsani, R. Roberts, and B. E. Sobel, "The Influence of Infarct Size on Prognosis Among Patients with Repeat Infarction," American Heart Association 52nd Scientific Sessions, in press (abstract).

(3) E. M. Geltman and B. E. Sobel, "Modifications of Infarct Size: Physiologic and Therapeutic Implications," Current Concepts in Evaluation and Management of Coronary Disease, in press.

(4) D. W. Snyder, D. J. Sheridan and B. E. Sobel, "PVCs: Therapeutic Dilemmas and Decisions," Advances in Cardiology, in press.

(5) B. E. Sobel, J. K. Kjekshus and R. Roberts, "Enzymatic Estimation of Infarct Size," in Enzymes in Cardiology: Diagnosis and Research, D. J. Hearse and J. DeLeiris, eds., John Wiley and Sons Limited, Chichester, pp. 257-289, 1979.

(6) G. G. Ahumada, R. P. Karlsberg, A. S. Jaffe, H. D. Ambos, B. E. Sobel, and R. Roberts, "Reduction of Early Ventricular Arrhythmia by Acebutolol in Patients with Acute Myocardial Infarction," British Heart Journal, in press.

(7) B. E. Sobel and E. Braunwald, "Management of Acute Myocardial Infarction," Heart Disease, in press.

(8) A. L. Gutovitz, B. E. Sobel and R. Roberts, "Progressive Nature of Myocardial Injury in Selected Patients with Cardiogenic Shock," American Journal of Cardiology, vol. 41, pp. 469-475, 1978.

D-5. Neonatal Database

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

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

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

Over an 18 month period admission data were collected on over 800 patients and the coding structure for admission data was improved and stabilized. At the same time methods were developed which allowed for the consistent coding of free-text in-hospital data by neonatologists.

The system for collection of admission data was then transferred to the ODC Artronix MODULEX system and software was developed to support the collection and manipulation of in-hospital data. The same design criteria were followed for the in-hospital phase of the system. Admission and in-hospital data were recorded in this new system for patients admitted to the NICU after July 31, 1977. Patient data stored on the PC-1200 was not transferred. In addition to these two data types, lab data could be entered on patients where desired.

The entry of a patient's entire file into the system is a multi-step process. The hospital's daily census sheet is checked for any NICU admissions by the data-entry clerk and all new NICU patients are registered into the system. Thereafter, the system ensures the computer entry of all required data. Admission data are collected and coded by an LPN, reviewed by the neonatologist, which serves as a quality control, and then entered. Data are edited as they are entered and more complex edits are performed later.

After the entered data are verified and approved they are added to the inverted file and can be searched. When the census sheet is checked for admissions, hospital discharges are also noted, so the system can generate lists of charts to be reviewed by the neonatologists during their periodic coding sessions. Final disposition and in-hospital data are coded by the neonatologists with a problem/concurrent event/complication approach. Each date of onset is noted and in some cases termination dates are also recorded. The in-hospital data are recorded according to 17 major classifications, 1) pulmonary, 2) infectious disease, 3) cardiovascular, 4) G.I. disorders, 5) endocrine, 6) hematology, 7) tumors, 8) metabolic, 9) neurology, 10) fluids and electrolytes, 11) immune disorders, 12) renal -- G.U., 13) skin, 14) orthopedics, 15) ophthalmology, 16) diagnostic procedures, and 17) events of interest. All data which are entered into the system are reviewed by the data-entry clerk and then printed out and checked by other personnel for typing errors. A copy of the in-hospital data is printed after this review and placed in each patient's chart and the data are added to the inverted file for searching.

All patient data collected for this system are stored in both a master file and an inverted file. Data are stored in this manner so the database can be rapidly searched by physicians using criteria they have specified. In addition to searches of the database, the inverted files can be used to produce histograms and cross-reference tables. An automatic report generator which tallies according to user criteria either year-to-date or six-month data also utilizes the inverted files. Data are stored in the master file so that printouts of patients' files or subsets of patients' files can be produced easily.

If desired laboratory data can be entered and then printed via tabular displays, plots over time, or X-Y plots. Various simple statistics on the data can be done. In the future these data will be "searchable" and can be displayed in conjunction with certain in-hospital occurrences.

Operational problems with the ODC MODULEX system resulted in a decision to transfer the entire database, which contains data on 953 patients, to the TANDEM system operated by the Pathology Department of St. Louis University Medical School. The goals of the new system are the same as those previously stated. Because bit functions do not exist in the version of MUMPS being utilized, the development of an alternative method to quickly search the database is being developed. A system will be coded in MUMPS which will allow fairly rapid searches. It will then be evaluated to see if part of the system must be developed in a different language. The current transfer effort offers the opportunity to extend the system to include the ability to search the in-hospital data for complications which occurred according to certain rules of precedence and/or time constraints, and to allow the addition of follow-up data. General data entry schemes will be developed to allow the quick incorporation of other data and the development of related databases.

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

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Support: HL 18808
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The feasibility of computerization of cardiology reports was demonstrated as a pilot project (PR 13, D-6) and currently is in the process of being implemented on a production basis at the Washington University Medical Computing Facility (PR 14, D-6). The system was designed to meet the following goals: 1) provide accurate data regarding all interactions of individual patients with the Cardiology Division, 2) reduce the professional and secretarial time required to generate clinical reports, 3) establish a database in a computer readable form to facilitate data management and clinical research, and 4) be economically viable as a clinical tool, paying for itself from savings in secretarial and professional time as well as reduced copying costs for the multiple reports. It was designed to be operated by the divisional secretaries rather than a specialized computer technician. All of the routine cardiology reports are planned to be implemented through this project. Implementation of the stress test report generation was completed June 1977 (PR 14, D-6). Echocardiographic reports were implemented March 1979, and catherization-coronary angiography reports were implemented in June 1979. Details of the latter two reports are as follows. The echocardiogram reports are entered from a check-off sheet by the fellow and checked by the supervisor. Individual comments are entered in code and expanded into full sentences by the computer for the report. Diagnosis and comments are entered both in code and free text to permit ultimate flexibility of expression. Final diagnosis and indications for study are stored "on line." Simple searches on staged diagnosis can utilize MUMPS programs. The complete report will be transferred to tape in a form readable by SAS (D-10). Extensive searches for all details of the program as well as statistical analysis will be possible "off line" utilizing SAS on the IBM System/360-370.

The basic coronary angiography and cardiac catheterization reports have been implemented and are presently functioning. The report consists of sections entitled Demographic Information, Clinical Summary, Procedure, Hemodynamics, Coronary Vessel Description, Description of Angiography, Findings, and Recommendations. The Procedure section can be entered as a) "standard procedures" where entire stereotyped procedures described in multiple sentences can be entered with a single code, b) "coded procedures" where individual codes are expanded into complete sentences describing the procedure in chronological order and also any comments which can be stereotyped, and lastly, c) free text which allows for unusual situations. Both the Findings and Recommendations sections permit coded entries for ease of entry and potential

retrieval as well as free-text entries for maximum expressive flexibility. The Coronary Vessel Description is entered separately and permits the generation of sentences describing the name of the vessel, its size, the location of the lesion in the vessel or vessel segment, (origin, proximal or distal section), the type of lesion, (focal or diffuse) and its severity. Each part of these descriptive sentences can be entered by a code. In addition, the presence or absence of collaterals and their source is easily specified by a short mnemonic code. There is provision for free text description as well. Any number of vessels or vessel segments can be coded. In addition, uncoded vessels can also be described with the same format. Description of Angiography is also entered separately. The details of the left ventriculogram are entered in short codes and translated into sentences. Free text description is also available. Each of these three sections of the completed report can be entered separately at different times if convenient. They are then combined by the program into one report. A special feature of the entire system is the flexibility of adding new coding. Codes consist of eight letter alpha-numeric entries which can be entered directly. New codes can be assigned or the text changed easily by the physician to permit ample opportunity for full expressiveness. Correction of errors is facilitated by provisions for addressing directly those responses which are incorrect and changing them. This part of the report has been operational since June 1979. The system is still being phased in so that full benefits cannot yet be evaluated, but comprehensive and detailed reports which are searchable have already been produced. Additional parts to the cath report are being implemented. A standard letter, including the findings from the report as well as recommendations will be generated. The letter will utilize files of the addresses of referring physicians for automatic addressing which should greatly minimize time spent addressing letters. In addition, we currently send photographs of the coronary angiogram to referring physicians. The computer can generate descriptive sentences which are placed on the sheet to refer to these pictures enhancing their value as a teaching aid. Presently there are plans to generate computerized reports of cross-sectional echocardiogram and Holter monitors, and it is expected that these will be working within the year. It is also anticipated that the SAS search programs will be operational by June 1980. Overall the acceptance of the computerized reporting for stress tests and echocardiograms has been excellent. The cath report has not been operational long enough to permit evaluation.

D-7. Information Systems Group: Experimental System

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Support: RR 00396
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A modest experiment was defined to study the feasibility of a proposed high-performance information system configuration.(1) The experimental implementation consists of four physically distinct processing units and a 2 × 2 crosspoint interconnect implemented with restructured macromodules (RMMs). The processing units (2-LSI-11, 2-PDP-11/34) utilize RMM compatible controllers to support a speed-independent, delay-insensitive communication discipline. Two of the processing units (PDP-11/34 based) are equipped with 80 Mbyte disk storage units to support database storage.

The configuration has been utilized as a facility for time/space cost evaluations of the multitasking system software developments and system instrumentation. As a result of the evaluations, a design modification was made to the RMM controllers to improve processor efficiency by eliminating the need for message assembly into a continuous block before transmission. Review of system power and reset criteria established the need for independent AC power for the processing unit and the RMM controller and separation of the power-on reset. This change allows a processing unit to power on/off without requiring a system-wide reset.

Preliminary studies were conducted to establish feasibility of expansion beyond the 2 × 2 configuration. The speed-independent delay-insensitive discipline can be preserved using a very-local interconnect based on the bus within the RMM crate. The RMM bus allows ready expansion to 31 processing units. An equivalent interconnect bandwidth of approximately 50 megabits/second should be achievable. A CATV-like coaxial cable approach(2) is being explored to provide a local-area interconnect which permits assimilation of processing units geographically distributed within the Medical Center.

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

(2) N. B. Meisner, D. G. Willard, G. T. Hopkins, "Time Division Digital Bus Techniques Implemented on Coaxial Cable," Proceedings of Computer Networking Symposium, December 1977.

D-8. MUMPS Users' Group and Application Transfer Activities

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Support: RR 00396
The MITRE Corporation

Support by The MITRE Corporation of the MUMPS Users' Group (MUG) continued from the previous year (PR 14, D-9). MUG's activities were coordinated by Chairman Jeffrey Rothmeier and Executive Director Richard Zapolin. Joan Zimmerman became Chairwoman of MUG's Education Committee (EC). The major EC projects during the year were:

1. MUMPS programmer certification. Collaboration of MUG with the Institute for the Certification of Computer Professionals (ICCP) is possible, with MUG developing a specialty exam in MUMPS that would be taken in conjuction with the ICCP's core exam on programming technique.

2. Curriculum development. The EC is collaborating with the ACM and other groups to define curricula for (a) an advanced degree in medical informatics and (b) informal training for clinical chemists and pathologists.

3. MUMPS tutorials. Programming tutorials were arranged for the annual MUG meeting and other conferences.

4. The "Introduction to Standard MUMPS" (a document intended as a complete and clear first book about programming in MUMPS) was drafted.

A follow-up study was made of the 27 recipients of QUEST, DOC, and the Standard MUMPS teaching program (PR 14, D-10). Of the 22 contactable recipients, 16 (73%) had completed the transfer successfully. Problems had been experienced by 6 (38% of 16), mostly concerning needs for data reformatting. QUEST had been used by 4 (25% of the 16), DOC by 5 (31%), and the teaching program by 11 (69%). Experiences of the 22 contacted recipients have been reported.(1) Use of the teaching program by novice programmers shows considerable variation in the speed and skill of learning but also indicates that the students do remember much of what they learn from the program because they were able to perform better on repeating the material some days later.(2)

(1)J. Zimmerman and R. K. Stimac, "Follow-up Study on Transfer of Applications, Particularly Those Developed for the MUG Application Library," Proceedings of the 1979 MUMPS Users' Group Meeting, Atlanta, Georgia, June 6-8, 1979, in press.

(2) J. Zimmerman, "Use of an Interactive Teaching Program to Teach Medical Workers About MUMPS Programming," Journal of Medical Informatics, in press.

D-9. MESCH and Computers for the Physician's Office

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Support: RR 00396
HS 02760

Our studies of procedures for specifying and building primary-care medical records arose from concerns about (1) difficulties and problems experienced by primary-care physicians and their administrative staff in defining and using automated record systems, (2) high costs of record-system development, and (3) difficulties in transferring medical applications between institutions. To address these problems, we:

1. Surveyed existing primary-care automated medical records.
2. Synthesized these data in state-of-the-art reports.(1,2)
3. Tested the COSTAR automated record system.(3)
4. Reviewed the potentials and problems of microcomputers in primary care.(4)
5. Designed and began the implementation of a computer-based Multi-Environment Scheme (MESCH) that could guide representatives of the primary-care practice through the analysis of their present and future needs and the selection of suitable features of an automated medical-record system.(5)

(1) J. Zimmerman, R. S. Gordon, D. K. Tao, and S. B. Boxerman, "The Acceptability of Computer Applications to Group Practices," Journal of Medical Systems, vol. 2, no. 1, pp. 15-24, 1978.

(2) J. Zimmerman and A. L. Rector, Computers for the Physician's Office, Research Studies Press, Forest Grove, Oregon, 1978.

(3) J. Zimmerman, "Report on Oxford Work: 17 May 1978 to 15 July 1978," BCL Monograph No. 354, December 1978.

(4) J. Zimmerman, S. B. Boxerman, and A. L. Rector, "Personal Computing - Appropriate for Your Practice?", Journal of the American Medical Association, in press.

(5) J. Zimmerman, "Specification and Building of Ambulatory-Care Records: Final Report," in preparation, 1979.

D-10. SAS as an IBM System/360-370 Data Management Tool

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M. A. Province, BCL and Biostatistics

Support: RR 00396
AM 20579
EY 00336
HL 17646
HL 18808
HV 72941
HV 62960
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The utilization of minicomputers under MUMPS as an environment for the interactive data acquisition and management of the information gathering process has been quite successful for a number of projects involving the study of chronic diseases (A-21, D-1, D-2, D-3, D-4). However for analytic tasks requiring the processing of large sets of patient data, the application of more computationally burdensome statistical procedures, or the production of large reports, the general-purpose IBM System/360-370 environment operated by the Washington University Computing Facilities (WUCF) has provided a more hospitable environment.

Because of its strong data management components SAS(1) has continued to be the chief tool for the analyses of databases gathered with these other computer systems (PR 14, D-12). By providing the necessary tools for the listing, creation and deletion of data sets within a SAS database, SAS removes the user from much of the administrative burden associated with database management on a large IBM system. The release during the past year of SAS 79

has significantly augmented these facilities and has added facilities for other utility functions so that many users need to only use SAS for their IBM System/360-370 data management. Indeed, several other studies utilize SAS exclusively for their data management requirements,[2] and SAS tape datasets were chosen as the medium of data exchanged for the results of Holter tape processing for the MILIS study (A-21).

Industry-compatible tape has continued to be the primary mode for interfacing the SAS system to the data collection computers, including the MCF machine (D-2, D-3), the SCOR computer system (A-14, D-4) and the ODC MODULEX (D-1). Other studies utilizing similar approaches include the Diabetes Education and Training Center's Patient Registry, and a study of the familial transmission of alcoholism and related disorders as part of the Alcohol Research Center. The interface between DATA3, a MUMPS-based table-driven interactive data-entry and management system, and SAS has facilitated several of these studies. It provides a three-stage semi-automatic process which utilizes the same tables as those used to drive the data-entry/retrieval operations.[3]

Work during the past year has been concentrated on the final transfer of information for studies already completed (D-2, D-3) and on data for the analysis of an ongoing patient registry (D-1). As the coding of items originally entered as free text is completed, checks are performed in MUMPS for each form. Additional checks are made, especially those requiring extensive cross-form criteria after the forms are transferred to SAS.

During the last year the WUCF has installed MUSIC,[4] an interactive system operating on one of the IBM System/370s. MUSIC has allowed the simplification of interactive JCL generation for the submission of SAS jobs, thereby reducing the necessary training needed to utilize SAS efficiently in the WUCF environment. It has also allowed the installation of a CAI course on SAS.[5]

[1] J. T. Helwigh and K. A. Council, eds., SAS User's Guide, 1979 Edition, SAS Institute, Raleigh, North Carolina, 1979.

[2] J. P. Miller, "The Role of SAS in the Support of Clinical Studies in Medicine," in Proceedings of the Fourth Annual Conference of the SAS Users' Group International, SAS Institute, Raleigh, North Carolina, pp. 300-305, 1979.

[3] J. Achtenberg and J. P. Miller, "Interfacing a MUMPS-based Data Entry System to SAS," in Proceedings of the Third Annual Conference on the SAS Users' Group International, SAS Institute, Raleigh, North Carolina, pp. 161-167, 1978.

(4) McGill University, MUSIC: McGill University System for Interactive Computing, McGill University, Montreal, Canada, 1978.

(5) D. A. Glenn and I. H. Cockrell, "Conversational Instruction in the Statistical Analysis System," in Proceedings of the Third Annual Conference of the SAS Users' Group International, SAS Institute, Raleigh, North Carolina, pp. 93-96, 1978.

D-11. Methodological and Technical Developments for Risk Function Analysis

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

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

Efforts during the past year have been directed towards implementing software to evaluate several statistical models for risk function analysis (PR 13, D-18; PR 14, D-13) that are being applied to the database accumulated for the study on the natural history of sudden death (A-7). SAS procedures for the solution of the Cox model for the multivariate analysis of survival distributions were obtained from the Mayo Clinic[1] and Duke University.[2] SAS 79 contains a program (PROC FUNCAT) for the analysis of multivariate categorical data utilizing the GSK[3] approach. While the GSK approach is asymptotically equivalent to the log-linear models (PR 14, D-13) it is a more natural technique for risk function analysis in that it is formulated in terms of the relationships between a dependent variable (e.g. death) and a set of independent variables (e.g. risk variables) utilizing techniques which are analogous to those utilized for analysis of variance.

We utilized a log-linear model in order to clarify the relationship between nontransmural myocardial infarction and in-hospital prognosis.[4] Previous reports had attributed both a more favorable and an equivalent prognosis to patients with nontransmural MI. Since several authors had commented on the relationships between nontransmural MI and serum enzyme elevations (which are thought to reflect the amount of myocardial damage) it appeared that the observed more favorable prognosis of nontransmural MI might be simply a reflection of the better prognosis of patients with less myocardial damage. Log-linear models were fit predicting a number of endpoints (death, cardiomegaly, congestive heart failure, cardiogenic shock, and presence of PVCs). In each case the peak serum SGOT level was significantly related to the endpoint ($P < .001$) and type of MI (transmural vs nontransmural) was not ($P > .05$).

[1] T. M. Therneau, "Procedures for the Analysis of Survival Data," in Proceedings of the Fourth Annual SAS Users' Group International Conference, SAS Institute, Raleigh, North Carolina, pp. 116-120, 1979.

[2] F. E. Harrell, Jr., "The PHGLM Procedure," Division of Epidemiology and Biostatistics, Duke University Medical Center, Durham, North Carolina, 1979.

[3] J. E. Grizzle, C. F. Starmer, and G. C. Koch, "Analysis of Categorical Data by Linear Models," Biometrics, vol. 25, pp. 489-504, 1969.

[4] S. Thanavaro, R. J. Krone, R. E. Kleiger, M. A. Province, J. P. Miller, V. R. deMello, and G. C. Oliver, "In-Hospital Prognosis of Patients with First Nontransmural and Transmural Infarctions," Circulation, in press.

E. Speech and Hearing

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

The RAP-I system has been invaluable in the study of speech waveforms, the evaluation of hearing aids, and the study of speech perception with infants, adults, hearing-impaired subjects, and animals. The RAP-II system has greatly enhanced the LINC facility with the addition of quickly accessible mass storage for physiological data and program overlays and a high-quality analog subsystem for playback and recording of arbitrary auditory stimuli.

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

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

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

2) The measurement of glottal source characteristics of normal and deaf talkers. This study has involved developing glottal tube instrumentation and supporting computer programs. Additional work in this area of interest includes a study of the acoustic transmission properties of the throat wall near the glottis, the development of a physically-based model of the throat wall, and the study of the human vocal tract using an input-output procedure.

3) Psychoacoustic studies related to questions of speech perception. Simplified speech-like sounds and exemplary speech sounds have been generated and used for testing human adults and infants and chinchillas. A major focus of these studies is to understand the acoustic and neural transformations that are important in speech perception that occur in the cochlea and other parts of the auditory system.

4) The development of methods for generating rapidly changing visual displays that can be used in lipreading studies. This work was started in an attempt to delineate the facial cues that are important in lipreading.

E-1. Computer System for Auditory Research

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Checkout of the third free-standing satellite computer has been completed. These RAP-III systems are part of a laboratory renovation at Central Institute for the Deaf that has been described in PR 13 and 14.

This last system is to be installed in the Psychoacoustic Laboratory and will be used for general applications of sound recording and editing and for stimulus generation, experimental control, and data collection in a variety of psychoacoustic experiments.

The second RAP system has been installed in the Comparative Psychoacoustics Laboratory for use in studies of auditory learning and perception by animals.

Four subject stations have been added to the Eclipse central system. Each station consists of a video display, keyboard, and earphones. Each display can be independently controlled to provide instructions and response feedback to the subjects.

The stereo earphones are driven from the two analog channels of the system. Cue lights are included at each station that can be programmed to indicate the beginning of a trial or a response interval.

Other work that has been completed includes: 1) the addition of a line printer and an eight-channel attenuator to one of the RAP systems and 2) the development of a three-channel, infrared light-beam sensor for monitoring the animal's position in order to automatically determine behavioral responses.

E-2. Speech Microscope

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Our interests in the study of speech production and perception have recently led us to need a means of precise measurements and analysis of acoustic details of the speech waveform. Our research has required accurate information about spectral, temporal and amplitude parameters of speech for steady state as well as dynamic portions. Examples of such information are the measurements of formant transitions, fundamental frequency of vowels, and power spectra of vowels, stop consonants and voiceless fricatives. Such measurements require a computer based system for efficiency, flexibility and ease of operation. The system should also have a high speed (analysis in seconds, not minutes) and should be easy to use by researchers not necessarily familiar with computer programming.

"Speech Microscope" is such a system developed over the past year, and presently in use at the laboratory.[1] It is a software system, written in FORTRAN language, for the PC-1200 based Speech and Hearing computer system. The system is designed to conveniently record, store, display, playback and analyze speech signals. It can be considered as an expanded version of the "Interactive Speech Wave Examiner System" (PR 10, G-5). The speech microscope system is highly interactive, allowing a variety of controls by the user through a keyboard and a storage display scope. Because of the small memory size of the machine (16K), the system is divided into about 50 overlays. About 75 subprograms, in addition to the standard ones provided with the operating system have been written to make the system convenient to use. The system has three main parts: the display window, the analysis window, and the utility programs.

The display window can bring the waveform of a recorded sound onto the scope with a variable window width (from a fraction of a millisecond to 1000 msec) and a variable amplitude scale, both under the keyboard control. The window provides a number of controls, enabling the user to essentially "walk through" the sound, and examine its successive segments. The window acts as a "temporal microscope" showing the whole syllable at a time, or a fraction of it. Pressing a single key can cause the waveform to be viewed on the scope in successive segments, allowing the user to sequentially scan the whole sound, forward or backward; this can be done automatically, or under frame-by-frame, manual control. Once a portion of the sound is selected for closer attention, the user can adjust the display time and amplitude parameters and "zoom in" on the waveform with the help of knob-controlled cursors, much as one can increase a microscope's "viewing field." The display window can also playback the cursor-selected segment of the sound on the speaker, for audio feedback.

The analysis window performs spectral or Linear Predictor (LP) analysis on a selected segment of the waveform. The "zoom in" capacity is still available in the analysis window, allowing detailed examination to help decide exactly which portion will be analyzed. The window offers an option to select the cursors at the zero crossings of the waveform. This option is useful, for example in selecting a period of the wave for analysis. A rectangular, Kaiser-Bessel or cosine pedestal window can be applied to the signal before analysis. Once the analysis key is pressed, the system quickly performs the analysis, and the results are displayed on the scope. The available display frames are: (1) waveform and linear frequency DFT, (2) waveform and log frequency DFT, (3) waveform and phase spectrum, (4) waveform and interpolated, smoothed spectrum obtained by evaluating the z-transform of the signal along the unit circle in the z-plane, (5) phase spectrum and linear frequency DFT, (6) locations of the poles of the LP filter in the unit circle in the z-plane and the values of the formants, bandwidths and the signal energy levels at the formant frequencies, (7) waveform and LP magnitude transfer function, (8) an approximation to the tract shape, (9) waveform, log frequency DFT, and LP magnitude transfer function superimposed on the DFT, and finally, (10) waveform and a display of the energy levels in the 1/3 octave filter bands. The system also prints out the values of the DFT components, tract model sectional areas, and the energy levels in the 1/3 octave filter bands.

The utility programs have options to record the samples of a sound, up to 1 sec, through a 12 bit A/D converter at a 20 kHz sampling rate, to playback the recorded sound repeatedly until a key is struck, to save the sound on RAP disk (PR 11, G-1), to display the stored signals, to playback RAP tracks, and to read stored data from the disk for analysis.

We are currently using the system for the following purposes: study of voice source characteristics (E-4), spectral analysis of noises of different durations for research on the psychoacoustics of sound sequence identification, duration measurements for components of consonants for a study on identification of sub-phonetic speech sounds, and description of acoustic characteristics of English consonants as a basis for synthesis of a continuum of approximations to speech. The goals of speech microscope and its methods are not original, but its modular programming design, applicability to the study of a wide variety of acoustic signals, flexibility and ease of use have made it a basic tool for our research on complex sounds.

(1) N. R. Vemula, A. M. Engebretson, R. B. Monsen, and J. L. Lauter, "A Speech Microscope," ASA 50 Speech Communication Preprint Experiments, Cambridge, Massachusetts, pp. 71-74, June 12-16, 1979.

E-3. Models for the Human Throat-Wall and a Study of the Vocal Tract from Input/Output Measurements

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Support: RR 00396
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Work is continuing on the study of the throat-wall and the vocal tract from input/output measurements. A lumped-parameter mechanical model for the throat-wall has been developed based upon the physiology of the larynx, anatomical data for the larynx, and existing data on the characteristics of the laryngeal muscles and ligaments. The elements in the model have a one-to-one correspondence with the laryngeal cartilages, muscles and ligaments. Each cartilage is represented as a mass element, and muscle or ligament as a pair of compliance and viscous loss elements. The soft tissue on the inside and outside surfaces of the wall are represented as mass-compliance-viscous loss elements based on the work done by Ishizaka et. al.[1] The transfer function of the model seems to agree well with the passive acoustic transfer function characteristic of the wall, measured experimentally by giving an external force with a vibrator and measuring the inside wall volume velocity while the subject has held the glottis closed articulating a neutral vowel without phonation. The inside response is measured with a reflectionless terminator tube at the lips.

The throat-wall, during phonation, is modeled as a 3-port network with an "acoustic port" corresponding to the supraglottal pressure excitation of the wall, a "mechanical port" representing the excitation due to the net dynamic force exerted by the vibrating vocal folds on the posterior surface of the thyroid cartilage, and an "output port" where the external transducer is affixed on the wall to measure the wall vibration. It is assumed that the wall is reciprocal, looking from these ports. Therefore, the 3×3 network matrix relating the port variables becomes symmetrical, leaving only 6 unknown elements. One of these corresponds to the above measured passive acoustic transfer function characteristic. A second element, corresponding to the input impedance at the output port, is experimentally determined by giving an external force on the wall and measuring the velocity of the outside surface. The remaining 4 elements are evaluated from a computer simulation of the above lumped-parameter physiological model, because of the inaccessibility of the mechanical port.

The transfer characteristic of the throat-wall (supraglottal sound pressure resulting from a force applied on the external surface of the neck) is determined experimentally and is represented as an autoregressive moving average (ARMA) model. Using a Maximum Likelihood approach, the parameters of the model are estimated from the measured samples of the external force and the inside wall response, where the response samples are corrupted by

a predominantly low-frequency noise in the tract. Using this model and also the measurements of the inside pressure and the external vibration during phonation of a neutral vowel into the glottal tube, it has been determined that the mechanical component of vibration is about 3-7 times larger than the acoustic component, depending upon the pitch and intensity of phonation.

The tract shape is determined from the measurements of the microphone pressure at the lips and the acceleration of the external surface of the neck near the glottis. The ARMA model for the throat wall characteristics is used to calculate an approximation to the supraglottal pressure. Preliminary results indicate that the input/output procedure gives reasonable tract shapes for vowel phonation at normal pitch and intensity, even though the details of the shapes do not seem to be accurate. The procedure has also been tested by introducing controlled changes in the tract shape, for example inserting a wooden piece of known dimensions into the tract and taking it out, creating a tongue hump toward the front and removing the hump, etc. Analysis of these measurements show corresponding changes in the computed tract shapes.[2]

[1]K. Ishizaka, J. C. French, and J. L. Flanagan, "Determination of the Vocal Tract Wall Impedance," IEEE Transactions on Acoustics, Speech and Signal Processing, vol. ASSP-23, no. 4, pp. 370-373, 1975.

[2]N. R. Vemula, A. M. Engebretson, and D. L. Elliott, "Models for the Human Throat-Wall and a Study of the Vocal Tract from Input/Output Measurements," Proceedings of the 1978 IEEE Conference on Decision and Control, San Diego, California, pp. 946-948, January 10-12, 1979.

E-4. Voice Source Characteristics

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NS 03856

In continuance of this project (PR 14, E-4), newly designed equipment for the measurement of the glottal wave has been used to study the effect of hearing impairment on the generation of voice and to study the characteristics of various functional voice disorders, such as hoarseness or breathiness. In previous studies, the reflectionless tube had been used to collect data

from normally hearing adults. These data were used to establish what the characteristics of the glottal vibration are in the normally functioning larynx. By comparing such data with synthetic glottal waveforms generated by the Ishizaka-Flanagan 2-mass model of vocal-fold vibration, the relative participation of vocal-fold tension and subglottal air pressure as the controlling parameters in voice production were indirectly inferred. A detailed description of the method and the conclusions reached concerning the normal characteristics of glottal vibration may be found in the published sources.

The equipment has not been altered since previous reports. When phonation is examined by use of this device, we find that the glottal waveform has an appearance basically similar to those observed by other methods. For male speakers and for females who phonate at a relatively low fundamental frequency, the waveform is distinctly triangular and somewhat humped. In most cases, a well-defined closed period does not occur, whereas measurement of the glottal waveform by other methods usually shows a fairly clear and flat closed period. To some extent, this is due to the phase response of the system at low frequencies. Therefore, we have added a correction for the phase response of the system by applying the inverse of the phase response curve to the recorded samples. This has the effect of making the observed waveforms more nearly resemble the "textbook" variety of triangular pulse. However, an additional possible explanation for the general appearance of the observed waveforms is that when the vocal folds are tightly closed, the system (from the glottis to vocal tract to reflectionless termination) is then effectively terminated at one end with a high acoustic impedance, and thus some reflections may be present. We believe this is the case because we can observe some traces of formants in the glottal spectrum when a subject phonates in the "loud" voice mode, a mode in which the vocal folds presumably collide forcefully with each other and remain rather tightly together during the closed portion of each cycle. Formant traces are usually difficult to observe in normal voice phonation and are not at all apparent in soft voice. In summary, when a subject phonates in a soft voice, neat closed periods in the glottal volume velocity waveform are not observed because there may not be any; in the loud voice or normal voice mode, we observe a hump in the opening phase of the waveform, and this hump we believe may lie astride the closed portion of the waveform.

During the past year, the new reflectionless tubes were used to gather glottal waveform data from a group of 20 hearing-impaired adolescents. The subjects each provided samples of phonation in normal and soft voice modes and in a three-syllable word with primary stress on the medial syllable. Analysis of these data in comparison with the characteristics of phonation produced by normally-hearing subjects indicates that deafness affects primarily the time-varying characteristics of the glottal source. Among the hearing-impaired subjects the following abnormalities were noted: higher-than-normal rates of jitter and shimmer (frequency and intensity perturbations) for some subjects; diplophonia and creaky voice episodes at the onset or middle of phonation; and irregular patterns of change in the frequency and intensity of the glottal waveform. Deafness does not appear to prevent a speaker from producing a glottal pulse whose shape and spectrum are similar or identical

to normal, but may prevent a speaker from learning the phonatory consequences of the muscular gestures which maintain and alter vocal-fold tension (as well as subglottal air pressure) in the production of speech.

Recently, a study of functional voice disorders among the normally-hearing was begun by recording samples of abnormal voice simulated by a speech pathologist. Functional disorders with simulated abnormalities were chosen (1) to assure that there is no accompanying organic abnormality, and (2) so that the differences observed are not attributable to differences in subjects. The following types of voice were recorded and analyzed: (1) normal, soft, very soft, and loud voice; (2) soft-breathy voice; (3) breathy voice; (4) dry-hoarse voice; (5) ventricular-hoarse voice; (6) harsh-hoarse voice. These samples of functionally-deviant voice were compared with normal in several different ways: the appearance of the waveform, the amount of perturbations of frequency and intensity, including diplophonic perturbations, and the amount of noise in the spectrum. The glottal waveforms of these voice types are all recognizably different one from the other by either the appearance of the waveform, the periodicity of the waveform, or the amount of noise in the spectrum.

On the basis of the appearance of the glottal waveform, it is possible to distinguish between normal voice on the one hand and either breathy voice types or hoarse voice types on the other. The waveforms of breathy voice types are roughly similar to normal, except for the superimposed presence of noise. In contrast, the hoarse voice types are all diplophonic, which is indicated in the waveform by the regular alternation of longer and shorter pitch periods.

The period-to-period fluctuations of frequency are the greatest for breathy voice, and less for soft-breathy voice. Diplophonia is a particular extreme kind of pitch-period alternation, and the nature of the diplophonia appears to distinguish well between the different types of hoarse voice. To see this relation, it is necessary to distinguish between major and minor pitch periods. For dry hoarse voice, the major period is relatively stable at 83 Hz (well below the subjects' normal voice phonation range of 120-140 Hz), and the two minor periods alternate regularly between 176 and 155 Hz. For harsh-hoarse voice, the major period is erratic, and has an average frequency of about 132 Hz. The minor periods are also erratic, and span a range of about 100 Hz, from 220 to 320 Hz. For ventricular-hoarse voice, the major period has considerable frequency fluctuation, and centers around 115 Hz, while the minor periods are quite regular and alternate between 210 and 250 Hz.

The amount of noise in the spectrum was measured in the following way: five successive periods were selected, and the amplitude spectrum of each period was calculated. In each of these five successive spectra, the level of each individual harmonic was compared to that of the fundamental. We assume that if there is little noise in the spectrum, then the level of a given harmonic will be relatively constant from one period to the next with respect to the fundamental. If, on the other hand, there is considerable

noise present in the spectrum, then the level of a given harmonic will vary considerably from period to period due to the randomness of the noise sample. The statistical variance of the level of the first five harmonics was calculated for each of the different voice types. As expected, the variance of the level of harmonics in normal voice is quite low, indicating quantitatively that the noise is low. The average variance of the first five harmonics for normal voice was 0.8 dB; for soft-breathy voice, the average variance was 13.4 dB; for breathy voice, the average variance was 22.3 dB. According to this measure of noise, the hoarse voice types are not particularly "noisy," but this measure of noise was applied only to the major periods. It is interesting that the spectra of successive minor periods in the diplophonic hoarse-voice samples are very different from each other, and the regular repetition of such periods may well be a primary source of the roughness of the hoarse voice types.

The reflectionless tube appears from these studies to be a useful tool for investigating voice disorders, and it perhaps can be put to diagnostic use as well.

E-5. Identification of Changing Elliptical Shapes in Relation to Lipreading

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Support: RR 00396
NS 03856

In an effort to increase our understanding of perception of changing mouth openings during speech, we examined subjects' identification of elliptical shapes differing only in maximum vertical size. An analog circuit was used to present an elliptical lissajous pattern on an oscilloscope screen. The horizontal and vertical extension of the ellipse were under computer control. Using the PC-1200 based Speech and Hearing computer system, a visual identification experiment was programmed. Between trials, a static shape remained on the screen (e.g. a 48 mm horizontal line to mimic a closed mouth). During each trial, the line "opened" to an ellipse and then closed again to the line configuration. The observer's task was to label the extent of maximum opening with an assigned number. Several different stimulus durations were tried, as well as different ranges of ellipse size and vertical spacing. In later experiments, a duration of 200 msec was used, and the 48 mm wide ellipse opened and closed according to a raised cosine function with no intermediate steady state. Twelve maximum vertical openings were presented, spaced logarithmically from 2 to 24 mm. After about 100 trials with feedback, two observers each were processing about 2.3 bits ($=\log_2 5$) of information. That is, it is predicted that they would have identified all shapes correctly if only 5 alternate sizes had been presented over the same range of openings.

Elliptical stimuli of longer duration were easier to label, and up to 3 bits of information (8 alternatives) could be processed. When linear increments in vertical size were used, the overall difficulty of the task was comparable, but the smaller shapes were easier to identify because of the larger proportional steps. This perceptual task, in general, may be closely related to the ability to identify front (spread) vowels in /b/ context (e.g. /i, I, E, ae, a/). Further studies of shape identification as it relates to lipreading of vowels awaits analysis of films of talker articulation.

E-6. Further Development of Computer-Drawn Faces for Lipreading Research

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NS 03856

Present available facilities do not permit computer generation of animated faces in real time. Nevertheless, we decided to use the FORTRAN graphic capability of the Speech and Hearing computer system to display a rather detailed "face." One reason was that availability of a synthetic "face" would assist in developing computer-aided methods for analysis of films of talker articulation. Once oral/facial dimensions were entered into the computer, either as a table of numbers or from a graphic tablet, a "face" generated with those dimensions could be compared immediately with the original film image for confirmation. A second purpose was to determine the fewest straight line segments (vectors) required to produce a satisfactory "face," below which number it would be apparent to an observer that straight lines had been used in synthesis. This finding would aid in estimating future computer needs.

A face synthesis program has been written. The synthetic image, which appears on an oscilloscope screen, depicts head and jaw outline, eyes, eyebrows, nose, and mouth. The mouth details include inner and outer lip edges (with philtrum) and two straight horizontal lines representing tooth edges. All curved face components are based on ellipses, but in reality are constructed from straight-line segments, and a common cosine/sine table subroutine is used to specify x/y locations of the vector endpoints. The basic elliptical curvature is altered as needed by raising the sine values to a predetermined exponent between 0.35 and 2.3, the former for the head outline, and the latter to define lip borders. A 60-vector approximation to the largest border (a life-size head and jaw outline) could not be distinguished from any approximation composed of more vectors. When all vectors are considered, less than 200 are needed for the (variable) lower half of the "face," and fewer than 400 are needed for the (fixed) upper half.

E-7. General Software Development

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Support: RR 00396
NS 03856

Several routines have been written in FORTRAN language, and added to the software library for the Speech and Hearing system. They can be divided into (1) scope display routines, (2) mathematical routines, (3) signal processing routines, and (4) waveform synthesizers.

The scope display routines can be used to read a disk file of sampled data, to modify systematically the number of samples to fit the data into the available memory, and to display the signal between specified initial and final times. The signal is appropriately scaled along the time and the amplitude axes, and the axes are marked conveniently. Other routines display the magnitude transfer function characteristic of a digital filter, the magnitude and the phase information of the discrete Fourier transform of a signal on linear or logarithmic frequency scale, a specified RAP track of data, the location of poles and zeros of a digital filter in the unit circle in the z-plane. A variety of types of lines can be specified such as: solid, dotted, dashed, dashed with dots in between consecutive dashes, and dashed with alternating long and short dashes. Other routines are available to display pointers that are controlled from knobs on the keyboard.

The mathematical routines do the following operations: simulation of discrete time systems, analysis and synthesis of digital and analog filters, and matrix inversion to solve a set of algebraic equations.

The signal processing routines apply a Kaiser-Bessel window, a Hamming window, a cosine pedestal, or a 6 dB/octave pre-emphasis characteristic on a given signal. The routines also can be used to process a given signal through a specified pole-zero digital filter. The routines can determine the zero crossing points of a signal. This is useful in selecting one period of a periodic wave for analysis. Other routines have been written to synthesize a variety of waveforms such as: triangular waves, an impulse train differenced a specified number of times, or any periodic wave for which the fundamental frequency and the amplitudes and the phases of the fundamental and the harmonics can be specified.

F. Central Nervous System Diseases and Electroencephalogram Analysis

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

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

Research efforts at BCL in application of computers and mathematical models to CNS disease management and EEG analysis, reported last year in PR 14, have continued to be productive and this year's results are summarized here. Progress has been made in projects previously described: in regional in-vivo studies of hemodynamics and metabolism in brain and in development of computerized systems for automatic processing and monitoring of signals generated in the neurophysiology laboratory and during neurosurgical procedures. Additionally, the two new projects reported for the first time last year have each made impressive strides: (a) the visually evoked-response data-acquisition instrument has been constructed and is undergoing evaluation tests, and (b) control algorithms for the autoradiographic-image-processing system have been completed and their performance characteristics are being investigated.

F-1. Visual Evoked Response

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Support: RR 00396
MH 31054

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

A system consisting of a programmable acquisition instrument for on-site use in the visual evoked response laboratory and a minicomputer-based editing facility for off-line data analysis are being developed. The programmable acquisition instrument samples, digitizes and averages two channels of EEG data. The instrument provides artifact rejection and randomization of stimuli triggers as well as spectrum analysis for the resting EEG signals. The instrument can be preprogrammed for a multi-step clinical protocol to eliminate "knob-and-dial" manipulations of various parameters which vary with the protocol. Both an oscilloscope display and an x-y recording capability are provided for on-site monitoring of evoked responses. A floppy-disk storage unit is used to store the averaged evoked responses, the Fourier coefficients of the resting EEG and test-specific information. The acquisition instrument implementation, which is based on an M6800 microprocessor, is currently in the test-and-evaluation phase of development.

The minicomputer system is configured to accept digitized data from the remote acquisition instrument and to provide a computer-assisted editing facility, thereby enabling the clinical investigator to specify the latencies for the selected waves in the evoked response.

The VER editor is an interactive system that allows the operator to review the VER features identified by the VER automatic feature-extraction program. Through a set of single-key commands, the operator has the ability to examine each response, and, if desired, to modify the latencies of the points of interest of the responses presented. A typical output is shown in Figure 1. When editing is complete, the results may be printed or plotted if so desired. All results will be stored on nine-track

magnetic tape for transport to the main-campus computing facility. This will facilitate incorporation of the VER results in the long-term temporal study of the senile dementia syndrome.

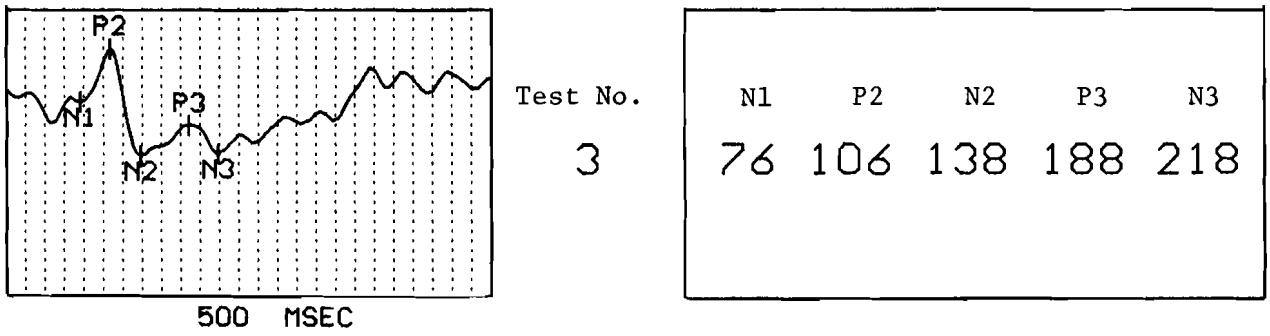

Figure 1. Sample VER output.

A brief pilot study was conducted to compare bipolar derivations obtained from locations O1-Cz, Cz-A2 and O1-A2. The study was facilitated through the use of a universal storage device (G-3) to acquire and digitize the three EEG channels as well as a fourth channel containing a stimulus reference marker. The results suggest that the best choices are the O1-Cz and the O2-Cz bipolar derivations for recording P2, N2, P3 and N3 latencies. The Cz-A2 derivation exhibits lower amplitude potentials than any of the other derivations tested. Monopolar derivations using either the ear ipsilateral or the ear contralateral to the stimulated eye as reference give lower amplitudes than does the O1-Cz bipolar derivation. This is true for the responses to both checks and flashes. Our characterizations of these electrode locations are consistent with the results of investigations of other workers, e.g., the field studies of Fender and Santoro.[1] Given the limited number of channels, however, the choice of electrode site is arbitrary and largely dictated by considerations of convenience and reproducibility. Similarly, the limited spatial resolution achievable with the small number of electrodes employed makes the choice between bipolar and unipolar configurations a matter of personal preference.

[1] D. H. Fender and T. P. Santoro, "Spatiotemporal Mapping of Scalp Potentials," Journal of the Optical Society of America, vol. 67, pp. 1489-1494, 1977.

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

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Support: RR 00396
NS 06947
Washington University

Development of the crosspoint switching matrix (PR 14, F-2) has continued with its expansion to 48 inputs by 64 outputs. Completed are the previously proposed patient-protection circuits, calibration circuits and auto-testing circuits. Hardware and software have been expanded to permit gating of the stimulus voltage to the desired electrodes during direct cortical stimulation. Several schemes to reduce EEG amplifier saturation during direct cortical stimulation have been considered; their realizations have been constructed and are currently under evaluation. The system has been used successfully with several patients, both in the operating room and during extended bedside recording.

The augmented output capacity will be used to drive additional EEG amplifiers currently under development. These additional amplifiers will permit collection of the averaged sensory evoked response to median nerve stimulation without interruption of patient monitoring. The gain and filter settings will be controlled by the microprocessor, thereby preserving the system's keyboard-oriented character.

F-3. In-Vivo Measurements of Regional Blood Flow and Metabolism in Brain

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Support: RR 00396
HL 13851
NS 06833
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We have continued our previously reported efforts in the study of central-nervous-system hemodynamics and metabolism. Our immediate objective has been the development of techniques employing biochemically significant compounds labeled with cyclotron-produced isotopes (PR 14, F-4), suitable external-radiation-detection systems (PR 14, B-4, B-5; B-5), and appropriate mathematical models (PR 14, F-4) for the in-vivo and regional study of basic biological processes and pathology within brain. Our ultimate goal is to use these techniques to provide the quantitative physiological and biochemical measurements in humans necessary to understand central-nervous-system disease, as well as to formulate specific therapies and monitor their results.

Our previously reported studies of glucose metabolism (PR 13, H-1; PR 14, F-4) have been complemented by quantitative measurements in the rhesus monkey of brain-tissue acid-base status employing ^{11}C-labeled carbon dioxide and ^{15}O-labeled water. Measurement of the mean-transit times of these two tracers, together with prior knowledge of the partition coefficient of water, enable us to derive the partition coefficient of total carbonate (i.e., dissolved carbon dioxide plus bicarbonate anion). This determination, in turn, has enabled us to obtain, for the first time, in-vivo values of total-carbonate concentration in brain. Our method of computing the total-carbonate partition coefficient is based on a mathematical model that shows under what conditions the central-volume principle of tracer kinetics,[1,2,3] which had previously been derived only for a single labeled species, can be generalized to include the case of a tracer distributed among several species that are locally in mutual chemical equilibrium within vascular and extravascular spaces.

Our previously reported studies of ammonia uptake and metabolism (PR 14, F-4) have also progressed. The observed blood-pH dependence of ^{13}N-labeled ammonia extraction from blood into brain has allowed us to

derive values for the blood-brain-barrier permeabilities of both the uncharged and the anionic species. We have interpreted our data on the basis of a mathematical model that is a dynamic distributed-parameter representation of the vasculature. With it, we have shown that the classical outflow-detection method of measuring capillary permeability[4] can be suitably modified for use with radioactive tracers detected externally.

[1] P. Meier and K. L. Zierler, "On the Theory of the Indicator-Dilution Method for Measurement of Blood Flow and Volume," Journal of Applied Physiology, vol. 6, pp. 731-744, 1954.

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

[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] D. G. Levitt, "Evaluation of the Early-Extraction Method of Determining Capillary Permeability by Theoretical Capillary and Organ Models," Circulation Research, vol. 27, pp. 81-95, 1975.

F-4. Studies of an Image-Processing System for Neuroanatomy

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Support: RR 00396
NS 15070

One of the more important research techniques used in neuroanatomical studies is autoradiography. This is a technique by means of which spatial distributions of radioactively labeled compounds in central-nervous-system tissue can be inferred in specially prepared tissue samples as a result of the action of the radioactivity on photosensitive materials. Exposure to the ionizing radiation causes the formation of silver grains, whose distribution density reflects that of the radiolabel. The latter can, in turn, be interpreted on the basis of appropriate models to provide information

on the spatial distributions of rates of physiological processes of interest. Examples of such processes are blood-flow and metabolism.

Since manual analysis of autoradiographic material is tedious and conducive to error, automatic or semiautomatic counting techniques can be of potential value. For this reason, a semiautomatic grain-counting system was developed at Washington University in the mid-seventies. This system consisted of a PDP-12 computer, a plumbicon TV camera, and some special-purpose hardware. Recent increases in the volume of autoradiographic image processing have led to the development of a second-generation grain-counting system. The experience gained in building and operating the original device, as well as contemporary advances in microelectronic components, have been strong incentives in this undertaking.

Of primary importance in the design of the system is the degree to which it can be "human-engineered." Thus, criteria such as modularity, flexibility, and maintainability have been central considerations in shaping system architecture. As presently envisioned, the automatic grain-counter consists of several independent processors, each performing a specific task. This partitioning of functions allows a high degree of parallelism and hence high counting speed: we hope to achieve a complete count of two or more video frames per second.

The system consists of a stage-control processor that positions the microscope stage, a video processor and image analyzer (VPIA) that accepts video data from the imaging device and extracts grain counts and other image parameters, and a supervisory processor and mass-storage manager. The supervisor controls overall system coordination, mass-storage management, and all high-level user interaction. It will be programmable in a high-level language. These modules are interconnected by means of an IEEE-488 bus. All elements are software-controlled; the bus is generalized, allowing a high level of flexibility to be achieved. Of special interest is the use of a solid-state charge-coupled-device (CCD) TV camera instead of the more conventional tube-equipped type. The CCD camera exhibits much better lag, burn, and shading characteristics than tube cameras and is very easily interfaced to digital hardware.

The new system incorporates several features not found on the original system, including automatic segmentation-threshold selection, improved graphics capability for enhanced data presentation, an improved focusing algorithm using an image-sharpness criterion, and user-prompting single-stroke key selection for most system interaction. Finally, provisions are made to allow portions or all of the system to be changed, improved, or deleted with few, if any, hardware changes and minimal software side effects.

Algorithms to accomplish automatic microscope focusing, dynamic thresholding, and grain counting are being evaluated on the DECSYSTEM 20 at the Engineering School utilizing data acquired through the video digitizing system (C-7) at BCL. The microscope and scanning stage have been delivered and the CCD camera will be in hand shortly.

An operational specification for the completed system which delineates performance and user interface details, has been developed in collaboration with the ultimate users.

F-5. A Correlation Technique for the Study of Visually Evoked Responses

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Support: RR 00396
Washington University

Classical studies of visually evoked responses (VER) have used flash stimulation and simple response averaging. These choices were largely dictated by convenience. While VER studies have yielded clinically significant information (F-1), they have not yet contributed much to the knowledge of the functional anatomy of the visual system. Recently, in an effort to enhance VER as a research tool for visual neurophysiology, stimuli thought to be more physiologically plausible than brief light flashes have been introduced. An example is the "checkerboard" light pattern.

We have performed preliminary experiments to devise more controllable and presumably more appropriate visual stimuli. In order to provide sequential stimulation of different parts of the retina believed to have different thresholds, stimuli consisting of expanding and contracting circles or arcs are being tried. These patterns, displayed on a cathode-ray tube, are generated in such a way as to be confined to any desired quadrant of the visual field. A suitable stimulus generator has been designed and built in "bread-board" form. In the expectation that responses to this type of stimulation will be relatively sharply localized, a correlation technique has been implemented using a "hard-wired" digital correlator.(1) Responses and ongoing background activity are correlated with a saw-tooth waveform whose amplitude is a linear function of the stimulus diameter. The equipment is operational and a few preliminary experiments have been performed.

(1) J. W. Emde and H. W. Shipton, "An On-Line Correlator for Electroencephalography," Electroencephalography and Clinical Neurophysiology, vol. 33, pp. 527-529, 1972.

F-6. Design and Construction of an Emde Low-Level Calibrator

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The low-level time-locked calibrator described by Emde[1] is of value in the interpretation of visually evoked responses. The calibration pulses are generated at biological levels and in series with the recording electrodes. In use, a square pulse of known amplitude appears at a fixed point after the stimuli. Deviations from the nominal "square-wave" shape indicate high and/or reactive electrode impedances. In the presence of residual noise, the confidence with which the amplitude may be estimated is an indicator of the reliability of the averaged signals.

The system as described by Emde, while fundamentally sound, dates from the vacuum-tube era. A solid-state version has been designed, built and evaluated.

[1] J. W. Emde, "A Time-Locked, Low-Level Calibrator," Encephalography and Clinical Neurophysiology, vol. 16, pp. 616-618, 1964.

G. Supporting Activities

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

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

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

The digital hardware designs reported in this section are frequently one-time, special purpose designs. The design of electronic switching equipment for peripheral access fits this description. In contrast, other designs may have wide appeal and construction of multiple copies can easily be envisioned. The USD (Universal Storage Device) is such a design and is widely applied by users with a need for off-line data acquisition and local mass storage.

G-1. Microprocessor Development Support

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Support: RR 00396

Our microprocessor development support includes a FORTRAN-based cross-assembler, FOCRAS, intelligent console, InC, and a small library of "standard" M6800 system modules. At present FOCRAS provides cross-assembler support for the 6800, 8080, and 6502 instruction sets and is currently operational on Texas Instruments Model 980B, Artronix Modulex, and Digital Equipment Corporation Model PDP-11 minicomputers. A collection of generally useful subroutines into a shared microprocessor library which is accessed by the FOCRAS linking loader has been established. The Intelligent Console is itself a microprocessor-based instrument which is used to assist both hardware and software development of systems based on the 6800 and 8080 microprocessors.

Minor extensions to both the InC and FOCRAS were made to allow programming of the type 2716 (2K byte) EPROM. Memory test programs[1] were written to aid in the identification of random access memory (RAM) failures at the chip level. Nonfunctionality, faulty write recovery, access time deficiency and addressing problems are included.

Preliminary studies have been initiated to determine feasibility of extending both InC and FOCRAS support to the 16 bit microprocessors such as the 6800 and the 8086, and to examine commercially available software for high-level language support for both 8 and 16 bit microprocessors.

[1] J. K. Montrose, "User's Guide for Memory Test Programs: M6800," BCL Monograph 364, May 1979.

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

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Support: RR 00396

Final versions of OS/PC and BCL/LIB (PR 14, G-2) were released in August, 1978. Development of a new operating syytem then began. The new system is called BDOS, for BCL Disk Operating System. It represents a merger of OS/PC and BCL/LIB with extensive modifications, enhancements, and additions. The major motivating factors for the new system were:

1) OS/PC commands and routines did not incorporate the bank structure of the BCL disk.

2) OS/PC files could not be longer than 1019 blocks.

3) Redundant copies of OS/PC were required on the BCL disk, thus filling it needlessly.

4) OS/PC could not search more than one index for a file.

5) The OS/PC date code would expire at the end of 1979.

The design objectives for BDOS were:

1) All commands and routines should be able to access the full disk by adding bank arguments.

2) Files should not be restricted in length, but should be segmented to allow easy backup on LINC tape.

3) Compatibility with OS/PC file structure should be maintained.

4) Commands should appear to work the same way as they did in OS/PC through the use of appropriate default actions.

5) Only one copy of the operating system should be required on a disk.

6) Files should be allowed to reside anywhere on a disk and should be searched for by the operating system.

7) The system date should continue beyond 1979.

8) Performance of the system should be improved in speed, memory usage, functionality, and ease of use.

BDOS was first released in January 1979. A second release came in April, 1979. BDOS requires a PC-1200 with a floating point unit and 12K words of memory. It makes full use of the BCL disk but does not require such a disk. BDOS can run on LINC tape, LINC DISK, or diskette. The system is supplied on two LINC tapes and there is also a separate documentation tape.

Some of the key features of BDOS are:

1) All relevant commands and routines have a bank argument.

2) A search table defines the order in which indexes are searched for a file.

3) Module lists allow arbitrarily large files to exist.

4) A base year allows years through 1999.

Major changes made to OS/PC include:

1) The ability to print a file while simultaneously using the text editor was added.

2) The FORTRAN compiler now optionally produces in-line one-dimensional subscripting and has four new format types.

3) The linking loader now links two to three times faster and can find relocatable modules on any set of units by using the search table.

4) BCL/LIB has been added.

The system is configured as follows:

I. Commands (46)

A. Programming

1. Text editor and overlapped print utility
2. FORTRAN compiler
3. Assembler
4. Linking loader

B. System

1. Batch monitor
2. Exit
3. Set date
4. Set memory site
5. Set monitor
6. Install disk bootstrap
7. Install resident monitor
8. Set search table

C. File

1. Save file
2. Copy file or blocks
3. Compact/update, copy unit
4. Module list copy/delete
5. Library merge/split
6. Dump/edit
7. Compare files or blocks

D. Index

1. Index display, file deletion
2. Index information
3. Index concordance
4. Index update
5. Create, destroy, rename index
6. Rename, update, delete, allocate index entry

E. Manuscript

1. Print
2. List all
3. Update
4. String substitute

F. Search

1. Find all occurrences of file
2. Search for manuscripts
3. Help (list documentation)
4. Load programs

G. Special

1. Floating point conversion
2. Display converted knob values
3. Display hardware configuration
4. Disk formatter
5. Create loadable tape
6. Mag tape map
7. Mag tape dump
8. Mag tape read
9. Mag tape write
10. Mag tape plot
11. Universal storage device read
12. Plot vector file
13. Text formatter

II. Runtime library (303 entry points, 207 relocatable modules)

A. Inline (6)
B. System (28)
C. Index (9)
D. Overlay (3)
E. File I/O (12)
F. Peripheral and Control (11)
G. Character I/O (33)
H. Character String Processing (11)
I. Scope Display (13)
J. Logical (6)
K. Mathematical (63)
L. Data Conversion (23)
M. Data Storage (15)
N. Keyboard Handler (4)
O. Mag Tape (3)
P. Universal Storage Device (1)
Q. Terminal (4)
R. Pen Plotter (25)
S. Versatec Generation Phase (25)
T. Versatec Plot Phase (8)

III. Work Areas (4)

A. Editor text
B. FORTRAN compiler output
C. Assembler output
D. Linking loader output

IV. Documentation (46 files)

One of the major areas of effort was the software package for use of the Versatec printer/plotter. This package allows users to produce plots by using calling sequences analogous to those used for scope displays. A file containing vectors is created in a user program. It can then be sorted, rasterized, and plotted using the plot command. Plots can be directed to the scope or to any model of Versatec plotter up to 20 inches wide.

BDOS has been well-received and is now in use at BCL, Radiology, and at Jewish Hospital. Conversion from OS/PC has been relatively painless and has provided few obstacles to using BDOS.

G-3. A Universal Storage Device

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Support: RR 00396

During the past year, several medical research activities have utilized the Universal Storage Device (USD) as a convenient tool for acquiring, storing, and transferring information. In two situations, the USD was applied to the crucial first step in synthesizing instrumentation systems when medical objectives are transformed into a set of system problem definitions. The problem definitions become the basis for algorithm definitions. The degree to which these definitions reflect the real medical objectives has much to do with an activity's ultimate success. The analog acquisition capabilities of the USD were used to refine those initial system definitions for both the Visual Evoked Response and Thermodilution Cardiac Output activities as reported in F-1 and C-9 respectively. The USD's analog signal acquisition feature enables the user to store digitized analog signals on floppy disk media for subsequent retrieval over a standard RS-232 serial communications interface. In the two projects just mentioned, analog signals were acquired using existing laboratory instrumentation. These data are then retrieved by a minicomputer system in order to analyze and refine problem and algorithm definitions for new and ongoing research activities.

The Intraocular Pressure Measurement activity, described in C-4, applies the USD in two roles. The first role is as a bootstrap loader for the TI-980 series minicomputer. Through the use of the USD's digital data acquisition, storage, and retrieval features, application programs are transferred from a program development system to a distant instrumentation system. When the instrumentation system is completed, the USD's analog signal acquisition and portability features will be used to transfer experimental information from an ophthalmology laboratory to one of BCL's minicomputer systems where physiological modeling work will be carried out.

The past year has seen the construction of five USD's using new dual-sided, double-density floppy disk drives. The new drives have doubled the USD's storage capacity. Two USDs are fully operational while the remaining three await the delivery and evaluation of alternate power supplies. Packaging and weight considerations suggested modifications in the original power supply configuration. A checkout procedure has been perfected which, in addition to reducing checkout time, revealed minor hardware and software problems that were subsequently corrected. Instrument documentation has improved. A User's Guide to the Universal Storage Device has been prepared and will soon be released as a BCL Monograph. The disk controller design in the USD was utilized in the implementation of instrumentation systems for the study of Visual Evoked Responses and Extracellular Cardiac Potentials as reported in F-1 and C-3 respectively.

During the next year we plan to continue media compatibility testing. Early results indicate that USD-to-USD, floppy disk media compatibility may be realizable within this set of instruments. A minor change to USD software was recently completed. This change enables the USD to respond to the ASR33 paper tape loader that is resident as firmware in TI-980s. As a result, first bootstrap and then application programs can be loaded into stand alone TI-980s. Suggestions for other enhancements which make the USD a more useful tool in support of specific activities are encouraged and will be considered for future incorporation.

G-4. Radiation-Treatment Planning

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Support: RR 00396
Washington University

We have completed our validation of the mathematical model[1] that is the basis of our method of calculating absorbed dose in the presence of inhomogeneities (PR 13, I-3; PR 14, G-6). For this purpose, we compared our computed values of absorbed dose with the published experimental results of Young and Gaylord,[2] who used 5-cm absorbing blocks of widely varying electron densities in a water phantom to simulate the effects of inhomogeneities. Since our intent was to verify the physical validity of our dose-calculation model, we employed exact analytical expressions rather than numerical approximations for evaluating attenuations of primary and scattered radiation along ray paths in the absorbing media and in water. The measurements of Young and Gaylord[2] used in our previously reported validation work (PR 13, I-3) were those taken along the central axis of a 10- by 10-cm ^{60}Co gamma-ray field at varying depths below inhomogeneity blocks spanning the entire field. The average fractional deviation between their data and our results calculated for points on the central axis was 0.2%. Our subsequent validation calculations, the results of which we report here, correspond to their measurements in which blocks spanned only one-half the radiation field and with dosimetry points off the central axis. As was the case for the whole-field central-axis results, those for the less symmetrical configurations also show excellent agreement with the published values.

After confirming the physical validity of our absorbed-dose model, we next wished to determine whether an exclusively numerical implementation of it, which would be obligatory for actual clinical use, would lead to unacceptable degradation of accuracy in the computed results. We therefore wrote a program for the PC that employs stepwise summations of incremental attenuation for three-dimensional electron-density matrices of arbitrary shapes, sizes, and density distributions. When we tested this numerical implementation of our model against both the symmetrical and the asymmetrical Young-Gaylord phantom data, we found relative numerical concordance of very nearly the same quality as that achieved with the analytical implementation. The largest discrepancy between experimental and theoretical results was 1.7%; this occurred with the asymmetric configuration for a point 2.5 mm from the edge of the inhomogeneity shadow, and is probably attributable to the dispersive effect due to the finite size (8-mm diameter) of the ionization chamber used for the dosimetry.(2)

Because of the success in validation and numerical implementation of our model, we expect it to perform well in actual clinical use, and are encouraged to proceed with investigation of special-purpose high-speed digital hardware to render the method practical.

(1)K. B. Larson and S. C. Prasad, "Absorbed-Dose Computations for Inhomogeneous Media in Radiation-Treatment Planning Using Differential Scatter-Air Ratios," Proceedings of the Second Annual Symposium on Computer Applications in Medical Care, IEEE Computer Society, Long Beach, California, pp. 93-99, 1978.

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

G-5. Physiologic Signal Processing

Personnel: R. E. Hitchens, BCL
J. S. Cheng, BCL
C. N. Mead, BCL
B. F. Spenner, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

Work has continued on investigation of the characteristics of electrocardiograms (ECG) in the frequency domain (PR 14, G-7, A-1). Additional signal processing techniques have been used to extract features in order to classify individual QRS events. Troublesome baseline shifts and high

frequency noise are now removed from the ECG using a finite impulse response bandpass filter (1-30 Hz) implemented with a hardware convolution filter (G-6). Several features of the amplitude spectrum have shown promise for the detection of PVCs: 1) the "first spectral moment" of the normalized spectrum from 6 to 24 Hz, 2) the value of the maximum coefficient of the normalized spectrum, 3) the location of the maximum coefficient of the spectrum from 2 to 6 Hz, 4) the location of the maximum coefficient of the spectrum from 6 to 25 Hz, and 5) the phase of the maximum coefficient. Several one hour segments of ECG recordings have been analyzed using these features with encouraging results.

We are continuing to gather statistics on the use of these features for PVC detection by analyzing a diverse set of one hour ECG recordings.

G-6. A High-Performance Digital Convolution Filter

Personnel: J. A. Ritter, BCL

Support: RR 00396

Recent interest in digital signal processing has resulted in several applications requiring rapid convolution capabilities. Even with hardware arithmetic instructions, performing convolution in software is prohibitively slow for many applications. The desire for higher speed prompted the development of a hardware realization of the traditional digital convolution algorithm:

$$Y(i) = \sum_{j=1,2,\ldots} H(j) * X(i-j)$$

In this expression, the H(j) are a set of fixed coefficients, and the X(i) and Y(i) are the input and output signals, respectively.

As implemented, the DCF can be programmed to perform convolutions of up to 1023 points. For generality, the coefficients are stored in read/write memory, providing the user with a flexible tool. The DCF performs convolutions at the rate of 200 nanoseconds per iteration. Therefore, a 256-point convolution is performed in approximately 51 microseconds, while a full, 1023-point, convolution requires about 205 microseconds.

Two applications are currently being explored. First, a DCF interfaced to the Argus/2H system is being used to digitally filter electrocardiographic signals before processing (A-2). A second, planned application is to use the DCF in back-projection reconstruction of ultrasonic images (B-1).

G-7. Digital Data Communication

Personnel: D. L. Snyder, BCL
G. J. Blaine, BCL

Support: RR 00396
Washington University

Substantial experience with many aspects of digital data communication has been gained over the years in various Resource projects. For example, source digitization, source compression, error control, and local networking techniques were important facets of projects spanning high speed electrocardiographic processing, patient monitoring in the surgical intensive care unit, and medical information systems. This experience is presently being transferred to seniors and graduate students in Electrical Engineering and Computer Science through a course, EE 420, Digital Data Communication. The topics include source digitization, source compression for efficient transmission and storage of data, error control for reliable transmission and storage of data, data transmission standards and protocols, and data transmission architecture. Course notes are being written in collaboration with Professor James Massey of the University of California at Los Angeles.

G-8. Raster Scan Video Technology

Personnel: V. W. Gerth, Jr., BCL
G. H. Brandenburger, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

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

Raster scan video technology is attractive for a number of reasons. The cost of a raster scan monitor is considerably less than a comparably sized x-y monitor of similar video bandwidth. Another economic factor is a result of the mass production of CCTV transmission hardware and related accessories. Also, as a result of the widespread use of the CRT terminal as a computer peripheral, integrated circuit manufacturers now provide LSI chips which greatly simplify the design and lower the cost of new systems.

The added dimension of color display, made practical by the home entertainment industry, is another motivation for considering raster scan video technology for new display systems. Color display in x-y systems is limited almost exclusively to beam penetration tubes which are both expensive and critical in adjustment while providing only a limited range of color. The continuing reduction in price of digital memory devices also affects the cost of a raster scan display system in a favorable way. Because of the refresh requirement on a rigid schedule, virtually all raster scan systems employ integral memory in order not to burden the computer main memory with significant overhead.

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

Many of the design features employed in the BCL systems for display of physiologic waveforms are now present in commercial systems. The color display system mentioned above, in fact, is being transferred and integrated into the new Barnes Hospital West Pavillion operating room complex for cardiothoracic surgery. It is with some satisfaction that we note that this system, designed over five years ago, is still considered to be state-of-the-art by the users.

The general purpose display system (G-9) under development last year is now reported separately and has met all expectations. A few of the I/O options remain to be completed, but the system in its current state is being used in support of Ultrasonic Tomography (B-1).

As suggested earlier, the discrete nature of raster scan displays is responsible for potentially annoying artifact. Even if wideband monitors are used to allow good response along a scan line, the finite number of scan lines imposes a type of "sampling" process on an arbitrary image. The nature of some of these artifacts and potential means of reducing them are being investigated. One approach under consideration utilizes beam shaping by Z-axis modulation derived from an algorithmic procedure accomplished dynamically and, if successful, would trade high speed hardware for the large memory requirements of a high resolution bit map architecture.

The CCD array camera being applied to the silver grain counting project (F-4) and being considered for use in the image acquisition system (G-16)

is a development which promises to become a useful tool in raster scan technology. It overcomes most of the problems inherent in vacuum tube imaging devices and, as resolution improves, will satisfy most of the currently envisioned needs.

G-9. A General Purpose Digital Display System: Digivision

Personnel: W. A. Roloff, BCL
G. H. Brandenburger, BCL
T. J. Marshall, BCL
B. Zvolanek, BCL

Support: RR 00396

A recent survey of the Washington University Medical Center revealed a wide range of need for alphanumeric-graphic displays. Detailed analysis of the survey indicated that a particular subset of needs was common to a substantial number of applications and could be met by a modest video-graphic device with gray-scale display capability. A vendor survey revealed that while all the observed needs could be met with commerically available devices, a device fulfilling our particular set of minimum requirements would necessarily contain many unwanted features, and at a very large cost (>$10,000).

A final survey revealed a growing number of vendors supplying digital memory modules capable of providing continuous readout at rates compatible with the refreshed-video resolution required: 512 by 512 display elements. The 512 by 512 by 1 bit memory modules chosen were inexpensive and required only modest external logic to generate standard composite video signals.

The resulting requirements to be fulfilled by the new video display system (Digivision) are briefly outlined below:

I. Video Requirements

   A. 512 by 512 picture element resolution (512 horizontal by 480 vertical for standard 525 line video).

   B. Gray-scale capability expandable in 1-bit increments to 8-bits resolution.

II. Interface Requirements

   A. General purpose medium speed (<60μs per command) intelligent parallel I/O port.

   B. Low speed RS-232 intelligent I/O port for standard interfacing common to most host computers.

C. Low speed IEEE-488 (GPIB) bus intelligent port.

D. Medium speed (1.6μs per command) parallel I/O port.

E. High speed video-rate input (for use with video-rate A/D converters).

III. Graphic Support Intelligence (supports IIA through IIC).

A. Vector generation.

B. Character and page-formatted character handling.

C. Gray-scale raster generation with programmable pixel size.

D. Electrostatic (Versatec 1200 compatible) plotter hard copy output.

E. Programmable and front panel controlled diagnostic routines.

IV. Cost approximately $5,000 for basic 4-bit gray scale resolution.

The video display with 4-bit resolution using the medium speed parallel I/O port (see II-A) has been used extensively in the ultrasonic tomographic scanner (B-1, B-2). Digivision has been incorporated successfully in the PC-12 Versatec software package (G-2). Implementation of the remaining I/O ports and software is underway.

Future applications at this laboratory include:

I. Real-time digital echocardiography (A-17).
II. Ventricular boundary extraction (C-7).

Other future applications include use in electron microscopy and computer-assisted neurological research.

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

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

Support: RR 00396
CA 04483

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

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

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

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

The fabrication of all hardware and the adaptation of the microscope and automatic stage for limit switches is complete. Most of the software modules have been designed, coded, and tested. The final software employing the tested modules is nearing completion. The camera has been designed and major sub-assemblies tested. Final assembly is now in progress and the entire system should be ready for operational testing in the very near future.

G-11. A Microprocessor-Based System for Time-Lapse Film Processing

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

Support: RR 00396
CA 04483

In order to provide a convenient means for the processing of 16 mm film generated by the Time-Lapse Cinemicrography system (G-10), a system has been designed which employs an M6800 microprocessor as a control element to generate signals for moving the film through a developing tank and opening and closing valves for filling and draining developing solutions. The timing is also under control of the processor.

The mechanical system is now under construction and the microprocessor architecture has been specified and the detailed design is nearing completion.

G-12. Computers in Ophthalmology Meeting

Personnel: R. H. Greenfield, BCL
A. Colenbrander, M.D., Pacific Medical Center
W. M. Hart, Jr., M.D., Ph.D., Ophthalmology
M. A. Kass, M.D., Ophthalmology
C. A. Kulikowski, Ph.D., Rutgers University
B. H. McCormick, Ph.D., University of Illinois at Chicago Circle
A. M. Potts, Ph.D., M.D., University of Louisville
D. R. Reddy, Ph.D., Carnegie-Mellon University
A. Safir, M.D., Mount Sinai Medical Center
C. Y. Suen, Ph.D., Concordia University
L. J. Thomas, Jr., BCL
J. T. Wilensky, M.D., University of Illinois at the Medical Center

Support: IEEE Computer Society
Washington University

The first "Computers in Ophthalmology" meeting was held at Stouffer's Riverfront Towers, in St. Louis on 5-6 April 1979. One hundred and twenty-five people attended from the U.S., Canada (6), England (2), Germany (1), and Italy (1). Eight sessions (Clinical Data Bases, Perimetry, Human Factors & Coding Schemes, Automated Patient Testing, Computer Based Decision Making, Devices & Computer Aids, Image Processing, and Delivery of Ophthalmic Services) were sequentially presented in two days. Each session had a session keynote lecture and from four to six papers, for a total of 48 presentations including an after-dinner meeting keynote lecture on "Knowledge Based Systems and Medical Signal Processing" by Raj Reddy. After the meeting, short tours of BCL and Ophthalmology labs were conducted. Proceedings of the meeting are being published by the IEEE Computer Society.

G-13. An LSI-11 Microcomputer System for Laboratory Automation

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

Support: RR 00396

This project is concerned with the development of a flexible set of hardware and software modules for use in automation of control, data collection, and data processing for certain analytical instruments used routinely in biochemical research, such as amino acid analyzers, gas chromatographs, spectrophotometers, and ultracentrifuges. These applications typically require on-line data acquisition and control with modest speed requirements.

Most applications require relatively simple on-line data reduction, although some require more sophisticated post-run calculations. Costs must generally be kept to a few thousand dollars, even less for the simpler instruments.

Previous reports (PR 12, F-1; PR 13, F-1; and PR 14, G-12 and G-19) have described the selection of system components and the development of hardware and software modules for analog input, keyboard entry, and printer and plotter output. To permit quick and easy development and testing of hardware and software modules, we have assembled a dual floppy disk-based development system housed in a 24½ in. × 25½ in. × 36½ in. mobile cart. A sliding shelf holds the Keytronic C-1400 alphanumeric keyboard, Bowmar TP-3100 Thermal Printer, and Axiom EX-810 plotter. A specially-designed computer drawer immediately below the sliding shelf contains the LSI-11 central processor, RAM and core memory, parallel and serial I/O modules, the floppy disk interface, and interfaces for analog input, the keyboard, printer, and plotter. The Charles River Data Systems FD11 Dual Floppy Disk unit is housed below the computer drawer, with system power supplies located on the base of the cabinet. The DEC VT55 CRT terminal is placed on the top of the mobile cart, and terminals for connecting a Teletype are provided at the rear of the computer drawer. This cart may easily be moved to the site of the laboratory instrument, and is of a size and shape which should permit on-site system development, maintenance, or improvement without interfering excessively in routine laboratory and instrument operation.

Once an application is complete, hardware for that application will be housed in a box with a control and monitoring panel on the front and connectors in the rear for analog and digital I/O and whatever peripheral devices are required, e.g. keyboard, alphanumeric printer, and/or plotter. This dedicated system will be left at the instrument site.

Additional software modules have been written for data acquisition and for graphic display on the VT55 terminal. During data acqusition the digitized signal can be presented simultaneously on any combination of the Bowmar printer, the Axiom plotter, and the VT55 terminal, yielding both immediate observation of data collection and a hard copy plot of the values obtained.

We are beginning work on our first application, a high speed, sensitive amino acid analyzer developed in Dr. Leonard Banaszak's laboratory, and now used routinely by Dr. William Frazier. A very recent development has greatly broadened the potential impact of our laboratory automation projects. The Department of Biochemistry has just been awarded funds for a DEC VAX 11/780 computer to serve as a departmental resource. This computer will function as a large multiuser system with adjustable access priorities. Adequate memory, disk, and tape storage will be available to serve the needs of the many departmental users. The VAX is not designed for high speed real-time data acquisition or control. Thus on-line instruments must have a data buffer with preprocessing, and a controller. The LSI-11-based systems will meet this need, and quite inexpensively, since minimal memory and no mass storage will be required, the VAX supplying the additional storage. Thus a two level hierarchy of computers will be developed to serve these instrumentation applications.

G-14. A Wiring List System for Augat Hardware

Personnel: J. A. Ritter, BCL
M. W. Browder, BCL

Support: RR 00396

Originally developed in 1976, the wiring list system was rewritten in DEC Standard MUMPS in 1978. In the fall of 1978, several users expressed interest in being able to use the wiring list system for design configurations other than the Augat cards for which it was originally structured. A set of utilities was developed to allow the user to create a cross-reference dictionary between the desired configuration and an analogous Augat configuration. The user can then enter and output the wiring list in a translated format, with the full capabilities and error checking of the normal Augat wiring list system.

G-15. Biological Amplifiers: A Reappraisal

Personnel: H. W. Shipton, BCL

Support: RR 00396
Washington University

Most biological amplifiers are variations on the so-called "Differential Amplifiers," described first in the 1930's. These have been adapted to use solid state devices, which in this application, are not always superior to vacuum tubes.

The use of computers to process biological signals argues for signal conditioning amplifiers that are computer controlled and which can serve, without modification a wide range of applications. An experimental study is in progress to develop a "Universal" amplifier. Gain and bandwidth are set by standard logic levels and several modes of operation are possible. In the "AC coupled" mode only a single time constant, outside the signal loop is used. Quasi D.C. (Clamped) and automatic compensation for offset potentials can be selected as operational requirements dictate.

G-16. Design Study for an Optical Data Acquisition Module

Personnel: J. S. Massey, BCL
G. J. Blaine, BCL
V. W. Gerth, Jr., BCL
M. J. Schlesinger, Ph.D., Microbiology and Immunology

Support: RR 00396

The acquisition and processing of optical data are used in a number of biomedical projects. Such data may be classified as either image data or photometric data.

One technique which uses photometric data is the enzyme-linked immunosorbent assay (ELISA),[1] which operates on a principle similar to the radioimmunoassay (RIA). In the ELISA, enzymes are linked to antibodies or antigens to form a complex which has both immunological and enzymatic activity. The enzyme labels are detected by the addition of a chromagenic or fluorogenic substrate, and the amount of color change or fluoroscence provides a measure of the quantity of antigen or antibody present.

Image data are generally involved when some form of linear or spatial measurement is being made. The analysis of angiographic data (C-7) is one such project which has been pursued at BCL.

Other applications use both types of optical data. One example is autoradiographic analysis (F-4) which can be done with photometry or silver grain counting techniques. Another is banded-chromosome karyotyping, in which chromosomes are classified by size, shape, and intensity profile. In fluoroscent antibody techniques, the fluoroscent intensity of a specified area (e.g. a cell nucleus) provides a measure of the amount of antibody present.

Acquisition of photometric and image data with a single system poses a variety of problems. Conventional television cameras and flying spot scanners have photometric response curves which are far from ideal, and tend to show shading, a variation of response across the image area. Such devices require considerable modification to make them acceptable for photometric data acquisition.

Photodetectors used to acquire image data, on the other hand, must detect the light from one small portion of the sample at a time, and this requires using highly sensitive detectors. A sophisticated mechanical stage is used to move the sample, and some means of keeping track of the stage position is also necessary. All of these features make such systems expensive, as well as considerably slower than optical scanning systems.

Television cameras with solid state imaging devices have been introduced in the past few years, and several of the newer ones have image resolutions approaching that of conventional television cameras. The image sensors

are fabricated on a single piece of silicon and are scanned using solid state techniques, which results in good photometric response and virtually no problems with shading. In addition, one such camera is available with a digital data output, eliminating the need for high-speed analog-to-digital converters when the data are to be digitally processed.

In June, we began a design study for a general-purpose optical data acquisition module which will use a solid state array video camera. The module will be able to capture and store a video frame from the camera, perform a limited amount of preprocessing, and transfer the data to a host system, storage, or display device.

We are examining a variety of potential applications, such as those listed above, so that we may draw up a list of desirable features for the module. Such features include preprocessing algorithms, the amount and type of operator interaction, and the ability of the module to interface with various systems, such as the Clinical Physiologic Research System (C-1). These features will be evaluated in light of engineering constraints such as computational power, memory size, speed, and cost, before design of the module begins.

(1) A. H. W. M. Schuurs and B. K. van Weemen, "Enzyme-immunoassay," Clinica Chimica Acta, vol. 81, pp. 1-40, 1977.

G-17. An 160 Megabyte Disk Interface for the IBM System/7

Personnel: R. E. Hitchens, BCL

Support: RR 00396

The design of an interface between the System/7 channel interface and a System Industries Model 9500 disk system has been completed (PR 14, G-15). Construction of the interface is finished, and testing is partially complete. The second 80 megabyte drive has been added, allowing a second digitized ECG channel to be stored.

G-18. Implementation of an Instructional Model of Pulmonary Mechanics for Teaching

Personnel: R. D. Livengood, B.S., Electrical Engineering
L. J. Thomas, Jr., BCL

Support: RR 00396
Washington University

A computer-aided instructional program was added to the Physiology Department's CAI system. The program provides an educational tool for first year medical students to assist them in learning some of the concepts of respiratory mechanics with emphasis on factors affecting uneven ventilation and "alveolar diadapace." Lung resistance (R), lung compliance (C), and respiration rate are the variable inputs to a "two-lung" model in the CAI program. For each set of lung conditions, two types of output results are produced. One is a numerical display of the amplitude of breathing and the alveolar pendelluft and total ventilations which attend the RC properties specified for the two lungs individually. The other is a pictorial display of circles changing shape to simulate, in real time, the volume changes of the lungs during respiration.

G-19. Electronic Switching for Peripheral Access

Personnel: S. R. Phillips, BCL

Support: RR 00396

Since the cost of peripheral devices represents a significant portion of most minicomputer systems, there is a desire to share peripherals where feasible. This sharing requires a means of switching the peripheral between two or more computers. During the past year, three such systems have been implemented and electronic rather than electromechanical switching was employed for reasons of reliability and maintainability. Each unit also employs its own internal power supply so no external power is required from either peripheral or computer. Peripheral drivers are used where long cable runs are needed to bridge the distance between computers and peripherals.

One of the units is used to allow the sharing of a Centronics printer between multiple computers. Another unit allows the sharing of a Versatec Printer/Plotter as well as a Centronics printer. The third unit provides for the connection of a TI-980 to either a Centronics printer or a Versatec Printer/Plotter through an RS-232 translator unit.

G-20. General Purpose High Speed Digitization System for the PC-12

Personnel: G. H. Brandenburger, BCL
J. R. Klepper, BCL

Support: RR 00396

A Biomation 8100 fast-transient-recorder was interfaced to the PC-12 in conjunction with the CUTAR ultrasonic tomographic scanner (B-1). The Biomation/PC-12 interfacing was expanded and fully supported with a FORTRAN-accessible software library to form a general purpose programmable high speed data acquisition system.

The full repertoire of Biomation 8100 remote control functions is supported by FORTRAN-callable subroutines. The system functions include:

1) 8-bit resolution analog-to-digital conversion of waveforms up to 20 MHz, with sampling rates up to 100 MHz.

2) Conversion bursts programmable from 1 to 2024 samples and buffered in the Biomation 8100 internal memory.

3) Programmable:

   a) input range and offset (.05 volts to 5 volts),
   b) sample interval: .01μsec to 5 seconds,
   c) trigger range, offset, slope and coupling,
   d) dual time base rates and dual trigger delays.

The currently available software library consists of the following FORTRAN-callable subroutines and BDOS commands (G-2):

1) Sample buffer read subroutine (transfers 2000 samples in 120 ms).

2) Biomation 8100 status-read subroutines.

3) Programmable-function preset and control subroutines.

4) Digital oscilloscope command with keyboard and knob control and digital sample value display.

5) Waveform spectrum analyzer command with graphic and tabulated output.

6) Biomation 8100 (8-bit two's-complement) to PC-12 (12-bit one's complement) high speed conversion subroutine.

Algorithms are available to: 1) increase resolution to 12-bits and 2) reduce the inherent $\pm$ .01μs sample jitter. Both algorithms employ averaging techniques.[1]

[1] R. K. Elsley, "Accurate Ultrasonic Measurements With the Biomation 8100 Transient Recorder," abstract in "Program and Abstracts, Third International Symposium on Ultrasonic Imaging and Tissue Characterization," National Bureau of Standards, Gaithersburg, Maryland, p. 176, June 1978.

VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Industrial collaboration provides an additional outlet for laboratory developments and benefits the staff by keeping it abreast of the practical considerations of reliability, maintainability, and cost. Progress being made in this important phase of the laboratory's activities is summarized here.

A. Arrhythmia Monitoring. Following evaluation of the Mennen-Greatbatch ARGUS/SENTINEL computerized arrhythmia detection system, it was installed in the Barnes Hospital Coronary Care Unit. Subsequent to the successful completion of a battery of acceptance tests administered by BCL, it was released to CCU personnel for clinical use. The system has been in routine clinical use for over three years. This collaboration has continued through sharing algorithm improvements of mutual interest. During the past year, algorithm sharing has been focused on the new PRIMITIVE QRS detector reported in project A-1. (BCL personnel: K. W. Clark, C. N. Mead, L. J. Thomas, Jr.)

B. Collaborative Drug Study. A research project has been in progress during the past three years with Sandoz-Wander Inc., for a pilot study to evaluate the safety and efficacy of a new beta-adrenergic antagonist, LB-46, on ventricular irritability. Following FDA approval of the experimental design the study was initiated in May, 1976. This Phase II study consists of a double-blind crossover against placebo, of four weeks duration for each of twenty ambulatory patients with twenty or more premature ventricular contractions per hour. In addition to the appropriate clinical observations and laboratory tests, seven 24-hour Holter tapes have been collected and, as planned, three for each patient have been analyzed via Argus/H. Beyond a substantial participation in the study design, the primary role of the laboratory is analysis of the Holter tapes. Analyses have included time-of-day independent PVC rates, as well as frequencies of couplets, runs, and early PVCs. Preliminary analyses of variance have considered as dependent variables the number of couplets, runs, or early PVCs per 24-hour period, and the sources of variation as treatment, order of treatment, and patients. The advisability of processing the remaining four tapes per patient before completing the statistical analyses, is now under consideration. (BCL personnel: K. W. Clark, J. P. Miller, G. C. Oliver, L. J. Thomas, Jr.)

VII. TRAINING ACTIVITIES

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

Introductory MUMPS Programming Course for Beginners, Fall 1978.

A high-level programming language (Massachusetts General Hospital Utility Multi-Programming System - MUMPS), especially well suited for medical information systems and other textual and database applications, was presented by Joan Zimmerman, D.Phil. An Interactive MUMPS teaching program and access to a computer which supports Standard MUMPS were provided for laboratory exercises.

Attending the course were:

Jone M. Chen, M.S.	Immunology
William Chen, M.S.	Biomedical Computer Laboratory
Thomas J. Dill, B.S.	Informational Resource Electronics Corp.
Russell L. Gerber, B.S.	Radiology
Eugene Goldsand, B.A.	Surgery
Marshall Goren, M.D.	Laboratory Medicine, Barnes Hospital
Jim Hanson	Radiation Oncology
Julio Happa, B.S.	Surgical Pathology
Barbara Hayes, B.S.	Rehabilitation
Petie Heaton, B.A.	Surgery
Antonio Hernandez, M.D.	Pediatrics
Sharon Jackson	Health Care Research
Stephen M. Johnson, B.S.	Allergy & Immunology
William R. Johnson	The Jewish Hospital of St. Louis
Nancy Beth Leon	Radiation Oncology
Angelita Lim, M.S.	Lipid Research Center
Claudia Long	Clinical Research Center
Dianna Losh	Ophthalmology
Martha McCrate, B.S.	Biostatistics
Bertha L. McKinnis	The St. Louis Children's Hospital
Doris S. O'Connor	Gastroenterology
Macon Paine, B.A.	Biostatistics
Georgia Parkes, M.Mus.	Rehabilitation
Faye Marie Peats	Milliken Communication Corp.
Pat Polhman	Radiology-Physics
Beth Robinson, M.L.S.	Biomedical Computer Laboratory
Dave Sandel	Radiation Oncology
Daniel Santa Cruz, M.D.	Surgical Pathology
Sol Shatz, B.S.	Biomedical Computer Laboratory
Hai-Mei Wang, M.S.	
Oliver Wever	The Jewish Hospital of St. Louis
Carol M. Wincek	Psychiatry

Introductory MUMPS Computer Programming Course for Programmers, Fall 1978

An introductory course for those having prior knowledge of a MUMPS dialect or another higher-level computer programming language was presented by Dr. Robert H. Greenfield. DSM-11 (Digital Standard MUMPS), a popular dialect of Standard MUMPS, was used. Study notes and problems were provided. Access to Standard MUMPS was provided by the Medical Computing Facilities, Washington University School of Medicine for the purpose of completing the assigned programming problems. Attending the course were:

Cathrine A. Branyan	Computer Science and Electrical Engineering
R. Pat Bucy, B.A.	Medical Scientist Training Program Student
Kristin E. Carey, B.A.	Psychiatry
Jone Min Chen, M.S.	Immunology
James L. Daly, M.S.	V. A. Medical Center
Nelda E. Gooch	V. A. Medical Center
Mike H. Huang, D.Sc.	V. A. Medical Center
Mary C. Kramer, B.S., ASCP	Microbiology, Barnes Hospital
Georgia A. Parkes, M.Mus.	Rehabilitation
George E. Short, Jr., M.S.	V. A. Medical Center

Introduction to Programming the Laboratory Computer, Spring 1979

Students were introduced to computers, hardware terminology, and programming. Topics covered included a comparison of different types of computers, examples of computer applications, introductory programming concepts, and use of a computer operating system. Programming was done using the PC-1200 computer with the BDOS operating system and its FORTRAN compiler. The course was taught by Mr. Stanley A. Garfield.

Attending the course were:

Lori Adams, M.S.	Obstetrics/Gynecology
David Albee, B.A.	Central Institute for the Deaf
Chris Anderson-Protzel, M.D.	Pathology
Steve Bergmann, Ph.D.	Cardiology
Isabelle Bohman, M.S.	Physical Therapy
Chuck Boylan, B.A.	Pathology
Barbara Clark, B.S.	Diabetes Center
Lloyd Cook, M.D.	Pathology
David Doran, M.A.	Washington University Book Store
Loretta Findysz, M.S.	Pediatrics
Al Fischer, M.S.	Pathology
Howard Gebel, Ph.D.	Pathology
Glenn Glasgow, Ph.D.	Radiology
Marc Goldford, B.S.	Medicine
Lisa Grundhauser, B.A.	Central Institute for the Deaf
Jason Gutenschwager	High School Student
Mike Hartman, B.A.	Pathology
Stephen Johnson, M.S.	Immunology

Ram Kakaiya, M.D.	Pathology
Phil Kelley, M.A.	Immunology
Silvia Lipkin, M.S.	
Steven Luepker, B.S.	
Steve Monroe, B.S.	Immunology
Don Murch, B.A.	Pathology
Barbara Nash, M.S.	Physical Therapy
Patrick Rice, B.S.	Washington University Technology Associates
Helen Sullivan, M.S.	Central Institute for the Deaf
Joseph Udell, B.S.	Pathology
Joe Venverloh, B.A.	Medicine

VIII. SEMINARS

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

"System Design for Data Acquisition and Imaging in Neuroanatomy" January 16, 1979	Dr. Donald Woodward University of Texas Health Science Center Dallas, Texas
"Introduction/Software Views -- Microprocessor/Microcomputers" April 11, 1979	Dr. G. James Blaine Mr. Stanley A. Garfield Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"The Tandem Computer System" April 19, 1979	Mr. David A. Bridger Department of Pathology St. Louis University Medical School St. Louis, Missouri
"Support -- Microprocessor/ Microcomputers" April 26, 1979	Dr. R. Martin Arthur Mr. Michael A. Browder Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Aboard the Bus with the M6800 and the PET" May 3, 1979	Mr. Ronald W. Hagen Mr. Wayne R. Roloff Mr. Sol M. Shatz Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Chips/Cards - 16 Bits and Beyond" May 10, 1979	Dr. Robert J. Arnzen Computer Systems Laboratory and Mr. Richard E. Hitchens Biomedical Computer Laboratory Washington University St. Louis, Missouri

"BDOS: The BCL Disc Operating System"

May 17, 1979

Mr. Stanley A. Garfield
Biomedical Computer Laboratory
Washington University Medical School
St. Louis, Missouri

"A Survey of Word Processing Systems"

May 31, 1979

Dr. Barry R. Hieb
Jewish Hospital
St. Louis, Missouri

"CPRS: Clinical Physiologic Research System"

June 7, 1979

Mr. Michael A. Browder
Biomedical Computer Laboratory
Washington University Medical School
St. Louis, Missouri

"Pitfalls in the Development of a Large Microprocessor-based System"

June 21, 1979

Mr. Ross K. Hartz
Biomedical Computer Laboratory
Washington University Medical School
St. Louis, Missouri

"MIST-980 Revisited"

June 28, 1979

Mr. Gerald C. Johns
Computer Systems Laboratory
Washington University
St. Louis, Missouri

IX. PUBLICATIONS AND ORAL PRESENTATIONS

Abbrecht, P. H., Cox, Jr., J. R., and Ferguson, F. P., "Future Directions for Biomedical Engineering Research: Recommendations of an Evaluation Workshop for the NIGMS Physiology and Biomedical Engineering Program," IEEE Transactions on Biomedical Engineering, vol. BME-25, no. 6, pp. 490-493, November 1978.

Ahumada, G. G., Karlsberg, R. P., Jaffe, A. S., Ambos, H. D., Sobel, B. E., and Roberts, R., "Reduction of Early Ventricular Arrhythmia by Acebutolol in Patients with Acute Myocardial Infarction," British Heart Journal, in press.

Ambos, H. D., Moore, P., and Roberts, R., "A Database for Analysis of Patient Diagnostic Data," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 78-CH1391-2C, Stanford, California, pp. 365-368, September 12-14, 1978.

Ambos, H. D., Sampathkumaran, K. S., Jones, S. A., and Hitchens, R. E., "A Gated Radionuclide Cardiac Imaging System," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 78-CH1391-2C, Stanford, California, pp. 423-424, September 12-14, 1978.

Arthur, R. M., "Assessment of Electrocardiographic Signal Quality During Acquisition," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 78-CH1391-2C, Stanford, California, pp. 255-258, September 12-14, 1978.

Arthur, R. M., Hermes, R. E., Thomas, Jr., L. J., Geselowitz, D. B., and Oliver, G. C., "Status of the American Heart Association Database," accepted for presentation at the IEEE Conference on Computers in Cardiology, Geneva, Switzerland, September 26-28, 1979.

Bauwens, D., O'Donnell, M., Miller, J. G., Sobel, B. E., and Mimbs, J. W., "Quantitative Alterations in Ultrasonic Backscatter in Ischemic Myocardium Induced with Collagenase," Clinical Research, vol. 27, p. 152A, 1979 (abstract).

Bergmann, S. R., Clark, R. E., and Sobel, B. E., "An Improved Isolated Heart Preparation for External Assessment of Myocardial Metabolism," American Journal of Physiology: Heart and Circulatory Physiology, vol. 5, pp. H644-H651, 1979.

Bergmann, S. R., Hack, S. N., Tewson, T. J., Welch, M. J., and Sobel, B. E., "Limitations in the Use of $^{13}NH_3$ for Measurement of Myocardial Perfusion," Clinical Research, vol. 27, p. 437A, 1979 (abstract).

Bergmann, S. R., Sanofsky, S. J., Clark, R. E., and Sobel, B. E., "An Improved Isolated Heart Preparation for External Assessment of Metabolism," Clinical Research, vol. 26, p. 219A, 1978 (abstract).

Bergmann, S. R., and Sobel, B. E., "Salutary Performance of a Sanguinous, Perfused, Isolated Heart Preparation," Physiologist, vol. 21, no. 4, p. 8, 1978 (abstract).

Biello, D. R., Ambos, H. D., Sampathkumarin, K. S., and Hitchens, R. E., "A Cost Effective, Portable, Digital Data Collection System," Journal of Nuclear Medicine Technology, vol. 7, in press.

Branconi, J. M., Bowen, W. G., Cain, M. E., Goldstein, R. A., Brodarick, S. A., Ambos, H. D., Jaffe, A. S., and Roberts, R., "The Effect of Intravenous Nitroglycerin on Pain and Ventricular Arrhythmias in Patients with Acute Myocardial Infarction," Clinical Research, vol. 27, p. 156A, 1979 (abstract).

Byrne, J. D., and Ludbrook, P. A., "Cardiovascular Division, Washington University School of Medicine, St. Louis, Missouri, Facility Report," Analyzer, vol. 9, pp. 12-17, 1979.

Cain, M. E., Sobel, B. E., Snyder, D. W., and Corr, P. B., "Similarities Between Electrophysiological Changes Induced by Lysophosphoglycerides and by Ischemia," American Journal of Cardiology, vol. 43, p. 350, 1979 (abstract).

Cheng, N. C., and Snyder, D. L., "A New Algorithm and Architecture for Fan Beam Tomography," presented at the SPIE's Technical Symposium East and Exhibit '79, Washington, D. C., April 19, 1979.

Clark, K. W., "Arrhythmia Analysis of the Long-Term Electrocardiographic Recording: Its Role in the Assessment of the Clinical Effectiveness of Antidysrhythmic Drugs," presented at the Midwest Biopharmaceutical Statistics Workshop, Ball State University. Muncie, Indiana, May 22, 1979.

Clark, K. W., "Ambulatory ECG Monitoring in Clinical Trials," presented at the Symposium on Optimal Use of ECG Processing Systems in Clinical Trials and Epidemiological Studies, Dalhousie University, Halifax, Nova Scotia, June 4, 1979.

Clark, K. W., Hitchens, R. E., Moore, S. M., Potter, S. J., Ritter, J. A., Mead, C. N., and Thomas, Jr., L. J., "Argus/2H," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 78CH1391-2C, Stanford, California, pp. 397-398, September 12-14, 1978.

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Clark, R. E., and Swanson, W. M., "Durability of Prosthetic Heart Valves in Vitro and in Vivo," Medical Instrumentation, in press.

Clark, R. E., Swanson, W. M., Hagen, R. W., and Beauchamp, R. A., "Durability of Prosthetic Heart Valves," Annals of Thoracic Surgery, vol. 26, pp. 323-335, 1978.

Corr, P. B., Cain, M. E., Witkowski, F. X., Price, D. A., and Sobel, B. E., "Potential Arrhythmogenic Electrophysiological Derangements in Canine Purkinje Fibers Induced by Lysophosphoglycerides," Circulation Research, vol. 44, p. 822, 1979.

Corr, P. B., and Gillis, R. A., "Autonomic Neural Influences on the Dysrhythmias Resulting from Myocardial Infarction," Circulation Research, vol. 43, pp. 1-9, 1978.

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Corr, P. B., and Sobel, B. E., "The Importance of Metabolites in the Genesis of Ventricular Dysrhythmia Induced by Ischemia," Modern Concepts of Cardiovascular Disease, in press.

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Cox, Jr., J. R., Bridger, D. A., Ripley, K. L., and Zacher, R., "Computers in Medicine," in Computer Science and Engineering Research, B. Arden, ed., in press.

Ehsani, A., Campbell, M. K., Sobel, B. E., and Roberts, R., "The Relative Roles of Infarct Size and Conduction Defects as Determinants of Long Term Mortality," Clinical Research, vol. 26, p. 645A, 1978 (abstract).

Engebretson, A. M., and Vemula, N. R., "Some Effects of Deafness on the Generation of Voice," Journal of the Acoustical Society of America, in press.

Erber, N. P., Sachs, R. M., and DeFilippo, C. L., "Optical Synthesis of Articulatory Images for Lipreading Evaluation and Instruction," in Advances in Prosthetic Devices for the Deaf: A Technical Workshop, National Technical Institute for the Deaf, Rochester, New York, in press.

Geltman, E., Campbell, M., Ambos, D., and Roberts, R., "One Year Follow-Up on the Control of Refractory Ventricular Arrhythmias with Oral Aprindine," Circulation, vol. 58, supplement II, p. II-101, 1978 (abstract).

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Goldstein, R. A., Klein, M. S., and Sobel, B. E., "Distribution of Exogenous Labeled Palmitate in Ischemic Myocardium: Implications for Positron Emission Transaxial Tomography," in Advances in Cardiology, J. H. K. Vogel, ed., S. Karger, Basel, Switzerland, in press.

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Hagen, R. W., Thomas, Jr., L. J., and McCartney, M. L., "An Ultrasonic Ventilometer," Proceedings of the 31st Annual Conference on Engineering in Medicine and Biology, Atlanta, Georgia, p. 232, October 21-25, 1978.

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Hart, W. M., Yablonski, M., Kass, M., and Becker, B., "Quantitative Visual Field and Optic Disc Correlates Early in Glaucoma," Archives of Ophthalmology, vol. 96, pp. 2209-2211, 1978.

Hartz, R. K., Hart, Jr., W. M., and Blaine, G. J., "A Microprocessor-Based Data Acquisition System for the Goldmann Perimeter," Computers in Ophthalmology 1979, St. Louis, Missouri, April 5-6, 1979, 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.

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354	Zimmerman, J.	Report on Oxford Work: 17 May 1978 to 15 July 1978	12/78

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356	Arthur, R.M.	Assessment of Electrocardiographic Signal Quality During Acquisition	9/78
357	Moore, P. Miller, J.P. Oliver, G.C. Thomas, Jr., L.J.	Task-Oriented Management Information Systems for Clinical Studies	9/78
358	Mead, C.N. Moore, S.M. Spenner, B.F. Hitchens, R.E. Clark, K.W. Thomas, Jr., L.J.	Detection of Multiform PVCs Using a Combination of Time-Domain and Frequency-Domain Information	9/78
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361	Mead, C.N. Ritter, J.A. Moore, S.M. Potter, S.J. Clark, K.W. Thomas, Jr., L.J.	Argus Algorithm Development	9/78
362	Ambos, H.D. Sampathkumaran, K. Jones, S.A. Hitchens, R.E.	A Gated Radionuclide Cardiac Imaging System	9/78

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364	Montrose, J.	User's Guide for Memory Test Programs: M6800	5/79
365	Zvolanek, B.	Video Digitizer System for Acquisition of Cardiac Left-Ventricular Images: Design, Implementation, and Performance Evaluation	5/79