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Biomedical Computer Laboratory

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No. 10

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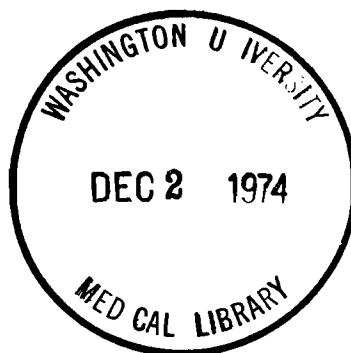
Biomedical Computer Laboratory

Washington University School of Medicine

St. Louis, Missouri

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 10

July 1, 1973 – June 30, 1974

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1973 through June 30, 1974. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine and its affiliated hospitals in the application of advanced computer techniques to problems in biology and medicine. This often requires work in areas stretching from basic physiology through mathematical models to equipment design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect.

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

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

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

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

The Computer Systems Laboratory, which is under the direction of Dr. Charles E. Molnar, is active in the design, development and evaluation of a compatible set of "macromodules" useful in the experimental design of arbitrarily large, complex, or specialized computer systems and in the continuing adaption of such systems to problems in information processing and biological research.

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

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

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

II. SOURCES OF SUPPORT

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

RR 00396   A Resource for Biomedical Computing

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

HS 00074   Technology and Health Care

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

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

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

NBS 4-35834   MUMPS Application Programs

NS 01540   Pilot Project, MUMPS Users' Group

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

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

AM 01921	Transport Processes in Mammalian Cells
AM 05248	Renal Diseases Training Program
AM 09976	Program Project - Renal Diseases
AM 15531	Membrane Transport of Amino Acid
AM 51159	Special Research Fellowship
CA 04483	Effects of X-Rays on Normal and Malignant Cells
CA 13053	Clinical Cancer Radiation Oncology Cancer Center
GM 00371	Training Program in Research Surgery
GM 01511	Training Program in Medical Genetics
GM 02016	Medical Scientist

GM 21863	Career Development Award
HL 13803	Development of a Trileaflet Aortic Valve Prosthesis
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine
HL 14147	Specialized Center of Research in Thrombosis
MH 05804	Psychiatry Basic Residency
MH 13002	Clinical and Laboratory Studies of Affective Disorder
NS 03856	Auditory Communication and its Disorders
NS 05159	The Metabolism of the Inositols and Inositides
NS 06833	An Interdisciplinary Stroke Program
NS 07498	Peripheral Auditory Mechanisms
NS 11059	Special Research Fellowship

HEW Subcontract from Harvard:

HSM-110-72-267	Development of Data Demonstrations in Training Centers

National Science Foundation:

GK 32239	Information Processing for Doubly-Stochastic Poisson Processes

Robert Wood Johnson Foundation:

189	The Development and Evaluation of a Teaching Practice of Medicine

EMPLOYEES

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

Director

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

Associate Director

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

Assistant Directors

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

Administrative Officer

Edward L. MacCordy, M.B.A.

Associate Professor

Donald L. Snyder, Ph.D., Electrical Engineering

Assistant Professors

R. Martin Arthur, Ph.D., Electrical Engineering
William F. Holmes, Ph.D., Biochemistry
Thomas F. Martin, M.D., Cardiology

Research Associates

Robert J. Arnzen, Ph.D.
A. Maynard Engebretson, D.Sc.
Sung-Cheng Huang, D.Sc.
Kenneth B. Larson, Ph.D.
John W. Lewis, Ph.D.
Floyd M. Nolle, D.Sc.
Joan Zimmerman, D.Phil.

Lecturers

W. Edward Long, M.S.
Michael D. McDonald, B.S.

Research Assistants

Philip S. Berger, M.S.
Andrew L. Bodicky, B.S.
Gary H. Brandenburger, M.S.
Kenneth W. Clark, M.S.

Christine D. Coaker, B.S.
Ola-Olu Daini, M.S.
William M. Fisher, Ph.D.
Robert H. Greenfield, M.S.
Ronald W. Hagen, M.S.
Richard E. Hitchens, B.S.
Margaret C. Jost, B.A.
William A. Lavender, B.S.
Monte D. Lien, D.Sc.
Joanne Markham, M.S.
J. Philip Miller, B.A.
Nizar A. Mullani, B.S.
James M. Pexa, M.S.
Carl F. Pieper, B.S.
Kenneth L. Ripley, B.A.
John A. Ritter, S.B.
Bernard L. Shore, B.S.
Bruce F. Spenner, M.S.
Michael D. Sutter, B.S.
Elizabeth Van Patten, B.A.
Nageswara R. Vemula, M.S.

Engineering Assistant

H. Dieter Ambos

Electronics Technicians

Roy R. Auer
Daniel J. Bax
George L. Bickmore
Kenneth L. Kunkelmann
John L. Robinson
Thomas F. Schuessler, B.S.
David T. Taylor
Richard W. Wodicker

Technical Assistants

Donald R. Bassman, B.A.
Steven H. Cooper, B.A.
Stanley A. Garfield
Betty J. Greenwood, B.S.
Susan R. Holmes, B.A.
Andrew G. Kegel
Charles N. Mead, B.S.
James B. Minard
Jeanne A. Paskowitz, B.S.
Glen Roa
Lawrence S. Sandler, M.S.
Emil D. Scheifler, B.S.
John J. Schier, B.S.
John J. Sueme

Machinist

Kenneth J. Spraul

Librarian

Loretta C. Benso, M.A.

Business Manager

Virginia M. Bixon, B.S.

Secretaries

Carol E. Benke, B.A.
Sandra Cole
Shirley Gonzalez-Rubio
Betty L. Hill
Sandra E. Katzen, B.S.
Faye L. Martin
Jeryl L. Persky, B.A.
Linda C. Stites

Summer Personnel

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

Gary A. Appel
David P. Bax
Barbara D. Eldredge
Ronald Inselberg
Edward H. Kovnar, B.S.
Eric H. Leder
Gregory W. MacCordy
Larry N. McCord
Richard V. Sanders
Robert W. Scheifler
James B. Sellinger
Alan J. Tiefenbrunn, B.A.
Daniel A. West

RESEARCH COLLABORATORS

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

Washington University

P. O. Alderson, M.D., Radiology
K. A. Arnold, M.D., Surgery
K. M. Baldwin, B.A., Medicine
W. E. Ball, D.Sc., Computer Science

M. R. Bedford, B.S., Electrical Engineering and School of Medicine
F. Bekhrad, B.A., Biomedical Engineering
D. M. Bier, M.D., Medicine
J. T. Biggs, M.D., Psychiatry
H. A. Bomze, Ph.D., Preventive Medicine
R. L. Boshans, A.B., Psychiatry
W. L. Brock, B.S., Opthalmology
E. M. Carlson, M.S., Medicine
R. E. Clark, M.D., Surgery
C. S. Coble, A.B., Radiology
T. J. Coleman, M.S., Biomedical Engineering
D. C. DeVivo, M.D., Pediatrics and Neurology
W. E. Dodson, M.D., Pediatrics and Neurology
F. M. Domke, Radiology
J. O. Eichling, Ph.D., Radiology
R. G. Evens, M.D., Radiology
T. P. Fang, B.S., Computer Systems Laboratory
P. M. Fishman, D.Sc., Psychiatry
H. Fotenos, Radiology
M. A. Franklin, Ph.D., Electrical Engineering
M. Gado, M.D., Radiology
S. Goldring, M.D., Neurosurgery
S. L. Goodwin, B.S., Psychiatry
R. L. Grubb, Jr., M.D., Neurosurgery
P. J. Haas, M.A., Medical Care Group
B. J. Halbrook, B.S., Medical Library
B. K. Hartman, M.D., Psychiatry
B. R. Hieb, M.D., Medicine
R. S. Hertert, M.S., Biomedical Engineering
R. L. Hill, M.S., Radiology
L. S. Hillman, M.D., Pediatrics
R. E. Hillman, M.D., Pediatrics
E. J. Hoffman, Ph.D., Radiology
W. H. Holland, A.B., Psychiatry
K. A. Hruska, M.D., Medicine
L. Jarett, M.D., Pathology
G. C. Johns, Computer Systems Laboratory
R. G. Jost, M.D., Radiology
I. N. Katz, Ph.D., Systems Science and Mathematics
J. Kenner, B.S., Medical Care Group
D. M. Kipnis, M.D., Medicine
S. Klahr, M.D., Medicine
R. E. Kumpf, B.S., Biomedical Engineering
K. A. Lewis, M.S., Electrical Engineering
J. J. Lobick, B.S., Electrical Engineering
T. F. Martin, M.D., Medicine
C. E. Molnar, Sc.D., Computer Systems Laboratory
G. C. Oliver, M.D., Medicine
G. D. Oliver, Ph.D., Radiology

G. T. Perkoff, M.D., Medical Care Group
R. R. Pfeiffer, Ph.D., Electrical Engineering
M. E. Phelps, Ph.D., Radiology
W. F. Pickard, Ph.D., Electrical Engineering
W. E. Powers, M.D., Radiology
J. A. Purdy, Ph.D., Radiology
D. P. Ragan, Ph.D., Radiology
M. E. Raichle, M.D., Radiology
R. Roberts, M.D., Medicine
L. S. Sandler, M.S., Electrical Engineering
J. J. Schier, B.S., Surgery
L. G. Sharpe, Ph.D., Psychiatry
W. R. Sherman, Ph.D., Psychiatry, Biochemistry
B. A. Siegel, M.D., Radiology
E. Slatopolsky, M.D., Medicine
B. E. Sobel, M.D., Medicine
M. G. Straatman, B.S., Radiology
J. S. Strauss, Ph.D., Computing Facilities
P. S. Tchang, Ph.D., Pediatrics
M. M. Ter-Pogossian, Ph.D., Radiology
L. J. Tolmach, Ph.D., Radiology
A. N. Weiss, M.D., Medicine
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Surgery
R. Wette, D.Sc., Biostatistics
J. Wiecko, Ph.D., Psychiatry
P. B. Zwart, Ph.D., Computer Science

Central Institute for the Deaf, St. Louis, Missouri

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

Cornell University, New York, New York

J. J. Corona, M.D.

Jewish Hospital, St. Louis, Missouri

J. L. Dregalla, B.A.
M. L. Dunne
A. S. Geha, M.D.
J. Haddad, M.D.
D. G. Hagenlocher
Y. Hamuth, M.D.
R. E. Kleiger, M.D.

R. J. Krone, M.D.
L. T. Lim, M.D.
D. K. McDermott, B.S.
B. A. Sandefur, B.A.
R. W. Sutherland, B.A.
D. P. Wheeler

Methodist Hospital, Houston, Texas

M. E. DeBakey, M.D.
D. H. Glaeser, Sc.D.

Research Triangle Institute, Durham, North Carolina

T. J. Odiorne, Ph.D.
D. W. Rosenthal, Ph.D.

St. Louis University, St. Louis, Missouri

R. L. Burse, Sc.D.
G. C. Kaiser, M.D.
A. R. Lind, D.Phil. and Sc.D.
J. S. Petrofsky, Ph.D.

Stanford University Medical Center, Stanford, California

E. L. Alderman, M.D.

University of Chicago, Chicago, Illinois

H. A. Fozzard, M.D.

University of Missouri, Columbia, Missouri

G. S. Lodwick, M.D.

Worcester Polytechnic Institute, Worcester, Massachusetts

C. L. Feldman, Ph.D.

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

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

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

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

IV. PHYSICAL RESOURCES

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

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

An IBM System 7 was installed at the laboratory in April, 1972 to become a major component of a system for the high speed analysis of electrocardiograms. (A second IBM System/7 was added in November, 1973.) 1972-73 also marked the beginning of routine use of the inventory of Macromodules for significant work supporting research in hearing and speech, high speed ECG processing, and higher-level language performance improvements. Other laboratory facilities include a data transmission distribution system, a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules, and both analog and digital tape recorders.

During the past nine years the laboratory space has been increased by 1526 square feet in the basement, 2762 square feet on the ground floor and 3171 square feet on the second floor of 700 South Euclid, and by 3463 square feet on the second floor and 1257 square feet of the basement of the building just south of the original space. Facilities for computational applications, laboratories, staff offices and a WUCL research library are provided in these

acquired spaces. Direct communications with the IBM 360 Model 65 at the Washington University Information Processing Center is provided via phone lines, Programmed Consoles and LINC's.

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

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

The SPEAR PC in the Cardiac Catheterization Laboratory was replaced in September, 1973 by a new Artronix PC-1200 System housed in newly renovated space for Catheterization Laboratory instrumentation.

In May, 1973 a Texas Instruments TI980 Computer was acquired which is being used as a major element in a satellite patient monitoring system.

V. RESEARCH PROJECTS

Summary

The goal of the laboratory is the application of computer techniques to problems in medicine and biology. This often requires work in areas stretching from basic physiology through mathematical models and frequently to the design of specialized equipment. The laboratory's research program has traditionally been organized into several major project areas with many of the laboratory's staff grouped into teams whose interests focus in one of these project areas. The oldest such project, Radiation Therapy, has now graduated and, in most respects, is separated from other laboratory activities. Six to eight years ago Radiation Therapy occupied a major share of our attention. The transition to the present state has been accomplished through the growth of the commercial firm producing the system we designed and through the growth of a staff of computer professionals in the Division of Radiation Therapy. The heading, Radiation Therapy, will no longer appear in our Progress Report, but the change does not diminish our enthusiasm for the accomplishments of our colleagues who continue this important work.

A. <u>Electrocardiographic Rhythm Monitoring</u>. Production operation of the Argus/H system for high speed analysis of tape recorded data for ambulatory subjects has continued throughout the year. Since late 1971, 234 patients have been enrolled in the study of the precursors of sudden death. This study focuses on the analysis of arrhythmias recorded on Holter tapes from ambulatory patients with coronary artery disease. During the year the system for analyzing these tapes has steadily improved. Editors routinely review all computer scanned tapes, a detailed report is prepared and a panel of cardiologists review the results. Nearly 600 ten-hour ECG records have been completely processed and in these records moe than 300,000 beats were called PVCs by Argus/H; of these, more than 125,000 (42%) were edited as true PVCs. Several efforts have been launched to evaluate the performance of this system. Our results are incomplete but all available evidence indicates that the detection of couplets and runs is very good. This is true because the editor will see these events even if only one PVC is detected by Argus/H.

The development of MUMPS for the System/7 has been completed and is being utilized to assist in scheduling tape recording sessions and in managing the processing of tapes. The utilization of this system has greatly alleviated the time consuming chores of manual record keeping. The ease with which MUMPS data bases may be changed or expanded has been an important feature in the evolution of the information management functions associated with the Argus/H processing system.

An analysis of the demographic data on 393 patients with acute myocardial infarction has been carried out and reveals a number of interesting relationships between the demographic profile of the patient and complications or death. Data is incomplete to test the basic hypothesis that patients who die suddenly can be identified before they die through the analysis of arrhythmias. However, preliminary results should be available with the statistical analysis of the tapes already scanned. The use of Argus/H in studies of

antiarrhythmic drugs, of the relationship of arrhythmias to infarct size and of the effect of coronary bypass surgery on arrhythmias are underway. Argus/H is quite clearly useful in each of these studies and interesting results have begun to emerge.

B. Regional Tracer Kinetics. Work continues on mathematical models aimed at gaining fundamental understanding for use in future clinical applications of computers through regional tracer kinetics. This work has already yielded new results in the assessment of cerebral blood volume and in the study of brain capillary permeability.

With the maturation of the computer system in the Radiation Sciences Division, its use is being turned to an exciting new project in positron-emission transaxial tomography. This technique reconstructs the density of the radionuclide distribution in an imaginary cross-section through a subject and is obtained by an hexagonal array of 24 radiation detectors surrounding the subject. Accuracy, efficiency and other design criteria are being evaluated in preparation for the construction of a larger system to be applied to human subjects.

A new program in the quantification of myocardial infarct size from limited data obtained soon after infarction is effective under certain conditions and is useful in clinical intervention studies. This prediction has been particularly successful for certain well-defined conditions, but it is desirable to widen the area of applicability, to define its limitations and to calculate confidence intervals for the results. To this end, a mathematical model based on plausible physiological phenomena has been developed. Early results are promising and it is hoped that the techniques of estimation theory can be utilized to define the circumstances under which infarct size can be predicted.

C. Monitoring the Critically Ill. The digital computer system installed in the cardiothoracic Surgical Intensive Care Unit (SICU) has completed its first fifteen months of clinical trial, has performed well and has been effectively used by clinical personnel. The reliability has been good and all unintentional interruptions of patient monitoring have been documented with their sources identified. Since the computer system was installed, admissions to the SICU have increased by 20% without any increase in nurse staffing. The estimated cost of the computer system is $10.00 per patient day with an average length of stay of 2.6 days.

A major new development is the construction of a satellite system for clinical physiologic research. The system is based on a bedside mini-computer that can monitor eight analog and eight digital signals, preprocess the signals and with the aid of the SICU computer system, maintain alpha-numeric and closed circuit television displays.

D. Communications for Information Processing. The teleprocessing net-work for minicomputers continues to function for a small number of our applications of computers to medicine. Research on optical communications, effects of sample jitter on the reconstruction of physiological signals and some theoretical studies of a distributed digital communications network

have been carried out. The wide-band bus on which the design of the SICU was based continues to function well justifying the substantial development effort that we reported in previous years.

E. <u>Cardiac Catheterization Laboratory</u>. Refinement of the cardiac catheterization laboratory computer system is proceeding both in the Jewish Hospital and in the Washington University settings. The latter installation was brought up to date this year with a new computer, but changes in the laboratory facilities and procedure have brought to light a number of short-comings not apparent in the Jewish Hospital setting. The recognition of these short-comings underscores the importance of evaluating new computer systems in several trial situations before fielding the system on a large scale.

An experimental system to acquire digitized video images obtained during angiography is now in operation and will utilize macromodules to study several techniques for on time digital storage of images and automated calculation of ventricular volumes.

F. <u>Mass Spectrometry</u>. The PDP-12 system for the acquisition and analysis of data from a mass spectrometer continues to be used heavily in this institution and in a number of others around the world. Emphasis has been on multiple-ion detection techniques which provide for the measurement of two picogram samples with a signal-to-noise ratio of 3:1. This represents a tenfold improvement in sensitivity over the original multiple-ion detection system and makes possible a number of new clinical applications. Design of a new mass spectrometer system based on a Finnegan quadrupole system is proceeding with major emphasis on a full mass range multiple-ion detection capability.

With the increase in the library of mass spectra on file, new search programs have been developed which include the ability to compress the mass spectra data into a variety of formats for increased speed of search. Mass spectrum files are being exchanged with other workers through the medium of the standard Aldermastron Format and the University IBM System/360 Model 65. Clinical applications of the system have been to glucose utilization, anti-convulsive drugs, abnormal metabolytes in patients with in-grown errors of metabolism, the effects of plasticizers and the serum levels of vitamin D metabolytes.

G. <u>Speech and Hearing</u>. The computer system for speech and hearing research continues to mature and is now being applied to the synthesis of speech to experiments on real-time speech analysis and to the digital filtering of the speech. Of particular interest is a study of the linear-predictor method of speech analysis through the use of acoustic tubes with known cross-sectional areas approximating the shape of the human vocal tract. The tentative results indicate that the spectrum of the driving function (glottal waveform) can significantly alter the results of the analysis. If true, this may cast doubt on linear-predictor methods of speech analysis which rely exclusively on the radiated acoustic waveform.

H. <u>Health Care Technology</u>. Our Training Program in Health Care Technology continues at a steady level of activity with about ten new students each year.

This level has been maintained despite the interruption in funding announced by DHEW in January, 1973. Although funding has been temporarily restored, the future of this training grant as well as many others in the nation remains in doubt. Supporting activities for the training grant include the continued development of MUMPS, an enlarged summer internship program, the support of a small information system for Washington University's Medical Care Group and an IBM System/360 version of MUMPS.

A new program in this area is the establishment at BCL of the Office of the Executive Secretary of the MUMPS Users' Group (MUG). The primary activities of MUG have been the organization of an annual user's group meeting, publication of a newsletter and the organization and dissemination of information about existing MUMPS applications.

I. <u>Other Applications of Computers</u>. As in previous years, mathematical, equipment or program development supporting two or more of the major programs of the laboratory or computer applications for users not related to any of the major programs are grouped together in this section. This year for the first time, several reports on radiation therapy appear here instead of in a section of their own.

Individual Projects

A.   Electrocardiographic Rhythm Monitoring

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

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

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

        Data gathering activities have continued throughout the year toward
an investigation of the precursors of sudden death (see PR 9, B-3). We have
been testing the hypothesis that patients who die suddenly can be identified
before they die, and that they will manifest at some prior time arrhythmias
which can be detected by appropriate analysis of Holter monitor tapes. The
major population group studied has been patients who have been admitted to
the Jewish Hospital or Barnes Hospital Coronary Care Units with an acute
myocardial infarction, and who meet certain other criteria (e.g., all are
70 years old or less and agree to participate in the study). Sequential
Holter tape monitorings are made of each patient for as long as he partici-
pates. Since late 1971, 234 patients have been enrolled in the study, and
1593 tapes have been recorded, making the data base probably the largest on
myocardial infarction patients accumulated by any one institution in the
country.

        All tapes have been scanned manually when received, and a qualitative
interpretation is sent to the patient's physician. Analog tapes, records
of manual scan results, and participant diaries of individual recordings
are now stored at BCL to facilitate data analysis efforts. To reduce the
amount of manual labor involved in acquiring and processing Holter tapes, a
MUMPS data base called PLOG has been constructed (see A-11). It contains
information pertinent to each participant and each recording and is used for
the scheduling of future recordings. The Argus/H system for high speed
scanning is now processing these tapes for quantitative measures of PVC
activity (see A-4).

Demographic data continues to be collected on all patients entering the Coronary Care Units and added to the file on the IBM System/360 Model 65 (this file now contains approximately 800 demographic data forms). All patient charts are microfilmed for ready accessibility and future reference.

In addition to the above study, several other intimately related projects are underway. Collection of data for related studies on antiarrhythmic drug therapy (see A-12), coronary vein bypass surgery (see A-13), and influence of infarct size on arrhythmias (see A-14) have begun, and the ECG tape recordings are being analyzed using the Argus/H system.

A-2. Demographic Data Analysis of Acute Myocardial Infarction Patients

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The demographic data base which was constructed to provide a fuller understanding of post-hospitalization arrhythmias and sudden death continues to be a valuable data base for analysis in and of itself (see PR 9, B-4).

Mortality data on 393 patients has been extensively analyzed with respect to hospital mortality and its relationship to the demographic profile of the patient, type and location of the infarct, electrocardiographic records and complications arising during the hospitalization.[1] The complications associated with the highest increase in mortality were cardiogenic shock, pulmonary edema, pulmonary infarction, congestive heart failure, and cardiomegaly, in decreasing order of significance.

The cause of death was examined in each case and in almost all cases was related to pump failure. The complications, as well as death, occurred most frequently with age over 60, anterior myocardial infarction, atrioventricular and intraventricular conduction disturbances, sinus tachycardia, atrial fibrillation, history of previous myocardial infarction, and female sex. A negative correlation was found with a history of smoking and an inferior myocardial infarction.

Even in patients in whose demise an arrhythmia seems to play a major role (i.e., when the arrhythmia proves intractable to standard antiarrhythmic therapy), it is likely that a cardiac disaster such as myocardial rupture or massive new infarction is the primary cause. Thus, to prevent or reduce in-hospital mortality, attention must be directed to either emergency surgical or

medical therapies which limit the size of the infarct, and prevent the death of ischemic yet viable myocardium.

Additional analysis of the data base has been undertaken in order to understand particular phenomena of interest, such as the relationship of sinus tachycardia and atrioventricular dissociation to the subsequent courses of the patients.

[1]R. E. Kleiger, T. F. Martin, J. P. Miller, and G. C. Oliver, "Mortality of Myocardial Infarction Treated in the CCU," Heart and Lung, in press.

A-3.   Manual Tape Scanning of Post Myocardial Infarction Patients and Low-Risk Subjects

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All 1593 Holter tapes collected on the 234 study patients (see A-1) have been manually scanned and qualitatively analyzed. Comparison of a group of patients (70 years old or less) who survived myocardial infarction but did not enter the study showed that the groups were generally comparable; but the members of the non-study group were significantly older, and the study group had a somewhat increased incidence of arrhythmias. Ventricular and atrial arrhythmias were noted by the manual scan; each tape was then classi- fied by the Lown system for ventricular arrhythmias and by the K system for atrial arrhythmias. Tapes with no PVCs were accorded the Lown classification L-0; infrequent unifocal PVCs, L-1; frequent unifocal PVCs, L-2; multiform PVCs, L-3; couplets, L-4; ventricular tachycardia or accelerated idioven- tricular rhythm, L-5. Atrial arrhythmias were graded similarly, with K-5 representing atrial fibrillation, PAT, or atrial flutter, and K-6 denoting multifocal atrial tachycardia.

Some initial results from the tapes of 141 patients were recently reported.[1] The analysis of the results from 1417 tapes from 194 patients is being prepared for publication. Of the study patient tapes, 38% were

classified L-0, 19% L-1, 9% L-2, 24% L-3, 8% L-4, and 2% L-5. Only 10% of the tapes showed atrial arrhythmias (K-1 to K-6). Within the first three months of recordings, the distribution of highest Lown classifications in the patient group was as follows: 18% L-0, 20% L-1, 11% L-2, 30% L-3, 15% L-4, and 6% L-5. The best predictor noted thus far of the Lown class of any given tape was the Lown class of the preceding tape. Over extended periods of time, a patient's tape classifications tended to remain the same or in adjacent classes. High Lown classifications (L-3 to L-5) had a significant positive correlation with a history of previous myocardial infarction prior to the infarct of entry into the study, previous hypertension, and cardiomegaly; but this correlation was not as strong as that between the various tapes for each individual patient. From one recording session to another, the distribution of Lown frequencies remained approximately the same.

A group of 50 subjects without known coronary artery disease or risk factors was compared to this group of post-infarction patients. The distribution of Lown classifications for the group was significantly different, with a much higher proportion of lower L categories. The distribution is as follows: 56% L-0, 22% L-1, 10% L-2, 10% L-3, 2% L-4, and 0% L-5.

[1]R. E. Kleiger, T. F. Martin, J. P. Miller, and G. C. Oliver, "Ventricular Tachycardia and Ventricular Extrasystoles During the Late Recovery Phase of Myocardial Infarction," American Journal of Cardiology, vol. 33, p. 149, January 1974 (abstract).

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

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Processing of ECG tapes for the study of ventricular arrhythmias and sudden death using the Argus/H system (see PR 9, B-6) has taken place on a regular basis since August 1973. The October 1973 acquisition of a second

IBM System/7 computer to be devoted to Argus/H processing (see A-7) has partially freed the original System/7 for further development of Argus/H programs and hardware.

When a Holter tape is scheduled for processing, the present system configuration carries it through the following steps:

1. The ECG from the Holter tape is first digitized at high speed and written on industry compatible tape. An identification number is assigned to insure blind processing.

2. Argus/H algorithms on the System/7 process the digital ECG tape in three stages (Aztec, Primitive, and Cycle) which compress the data, delineate beats (QRS complexes), and identify premature ventricular contractions (PVCs). The Cycle output, which provides a beat-by-beat description of the ECG, is written on the tape. As this processing takes place, the decoded ECG waveform is displayed on a high speed, long-persistence oscilloscope to allow visual checking for obvious errors.

3. After Argus/H processing, a trained technician (occasionally, a cardiologist) performs computer-aided editing on the System/7, using a keyboard and the high speed display scope to affirm or deny all computer-identified PVCs (see A-6). Strip recordings are made of selected portions of the record. The edited Cycle data stream is written onto the tape behind the ECG data, a three-page summary printout is produced, and a more detailed statistical summary is written onto disc for optional printing or tape storage. In addition, the editor fills out a one-page log of observations.

4. The results from the editing pass (printout, editor's log, and mounted ECG strips) are reviewed by cardiologists. If there are obvious editing errors, the tape is reedited; otherwise, Argus/H summary data along with results from the cardiologists (a Lown classification and a classification of PVCs as "early," "middle," or "late") are keypunched and entered into the data base for statistical analysis.

The operations of Steps 1 and 2 are adequately described elsewhere in this Report (see A-8) or in PR 9, but the last two steps need further elaboration.

Editing process and summary output. The present protocol requires that the editor obtain a number of ECG strip chart examples which describe the PVC activity in the record, including: 1) the basic rhythm; 2) at least two strips of each different PVC shape; 3) the earliest PVCs; 4) couplets and runs; 5) false positive PVCs; 6) PVCs missed by Argus/H but seen by the editor; and 7) other episodes of interest.

After the tape has been edited, a summarizing program is run to print the following: 1) a plot of PVC activity for each 15 minutes with an overall peak hourly PVC rate and time of such rate; 2) a plot of heart rate based on the average interval between adjacent normal beats for each 15

minutes with an overall average heart rate; and 3) a gross summary showing totals and percentages of true, false, questionable, and unedited (if any) PVCs, PVC rate adjusted and unadjusted for data loss (relative amount of time PVC detection was inhibited because of artifact), length of record, total number of beats, and overall average height of normal beats.

Cardiologist review procedure. The printouts described above, along with the editor's log and mounted ECG strip charts, are submitted in a folder to a cardiologist who routinely acts as first reviewer. If obvious editing mistakes are found, the tapes are sent back for reediting. If no obvious mistakes are found, a Lown classification is assigned, a record is kept of "early," "middle," or "late" PVCs, and possible minor editing changes are noted. The editor's summary results are also submitted to one of several cardiologists who acts as second reviewer without the first reviewer's results. If the two reviews are in complete agreement with respect to the Lown classification and the early-middle-late classifications, the review is considered completed. If not, a third cardiologist review is made and if total agreement is reached with either of the first two reviewers, the major- ity opinion is chosen. Otherwise, a panel of the three reviewers is convened, and the discrepancies are adjusted to the agreement of all.

A final check on the quality of the records is then made to catch any which might need to be reedited or reprocessed. A summarizing sheet is filled out for keypunching and statistical analysis purposes, and the ECG folder is then filed with others which have gone through the complete pro- cessing procedure.

The vast majority of tapes processed to date have been the four tapes per patient which are numbered 2 through 5 and correspond to recordings at 2 weeks through 3 months post myocardial infarction. Some initial results on a small group of patients were reported recently.[1] While the summary data was initially confined to the SPSS data base (see PR 9, B-3) the summary results are now also available in one of three MUMPS data bases (see A-11) which have been developed for the study of ventricular arrhythmias and sudden death. Nearly 600 ECG records have been completely processed. In these records, more than 300,000 beats were called PVCs by Argus/H; of these, more than 125,000 (42%) were edited as true PVCs.

[1] G. C. Oliver, F. M. Nolle, A. J. Tiefenbrunn, R. E. Kleiger, T. F. Martin, R. J. Krone, J. P. Miller, and J. R. Cox, Jr., "Ventricular Arrhythmias Associated with Sudden Death in Survivors of Acute Myocardial Infarction," American Journal of Cardiology, vol. 33, p. 160, January 1974 (abstract).

A-5.   Outpatient Mortality of Post Myocardial Infarction Patients

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All patients enrolled into the study of ventricular arrhythmias and sudden death are followed for the occurrence of death. Because of the increasing frequency of surgical interventions, the patient who undergoes coronary bypass surgery, heart transplant or pacemaker implantation presents a particularly difficult methodological problem. Figure 1 presents the mortality experience for the 194 patients described in A-3. The solid line represents the mortality from 14 sudden deaths and 4 new fatal MIs. This line is the result of a traditional life table analysis and treats patients who had various other cardiac events as being withdrawn alive at the time of that event. These other cardiac events consist of 6 bypass surgeries, 5 new non-fatal MIs, 2 pacemaker insertions, and 1 cardiac transplant operation. If these 14 other cardiac events are added to the 14 sudden deaths and the 4 new fatal MIs and all are treated as endpoints, then the dotted line represents the experience of these 194 patients.

Preliminary analysis has been conducted exploring the relationship of the clinical features observed during the hospitalization in the acute phase of the MI and subsequent mortality. These features are noted for all patients entering the Barnes and Jewish CCUs (see A-1). A comparison between the patients studied and those eligible but not studied has been completed. The non-studied group were older, more apt to have suffered complications during the acute phase, and less likely to have demonstrated serious ventricular arrhythmias during the acute phase of their MI, but more likely to have had atrial arrhythmias. A preliminary analysis of the relationship of acute clinical features to subsequent death within the first year following the MI has revealed that those patients with multiple MIs, a history of hypertension, experiencing congestive heart failure, pulmonary edema or cardiomegaly during the acute phase or not having an inferior MI are at higher risk. Patients who demonstrated serious arrhythmias (Lown classes 3, 4 and 5) during the period 1 to 3 months post MI were also at higher risk. All of these factors resulted in a two- to three-fold increase in risk. Since many of these clinical features are also significantly related to the ventricular arrhythmias found during the post-acute phase, work has begun to determine whether the arrhythmias noted in ambulatory monitoring are expressions of independent risk or mere reflections of the increased risk noted from the clinical features alone. Several statistical models for this determination have been explored, and the integration of the quantitative results available from the Argus/H processing of the tapes (see A-4) will hopefully yield illuminating results.

- 29 -
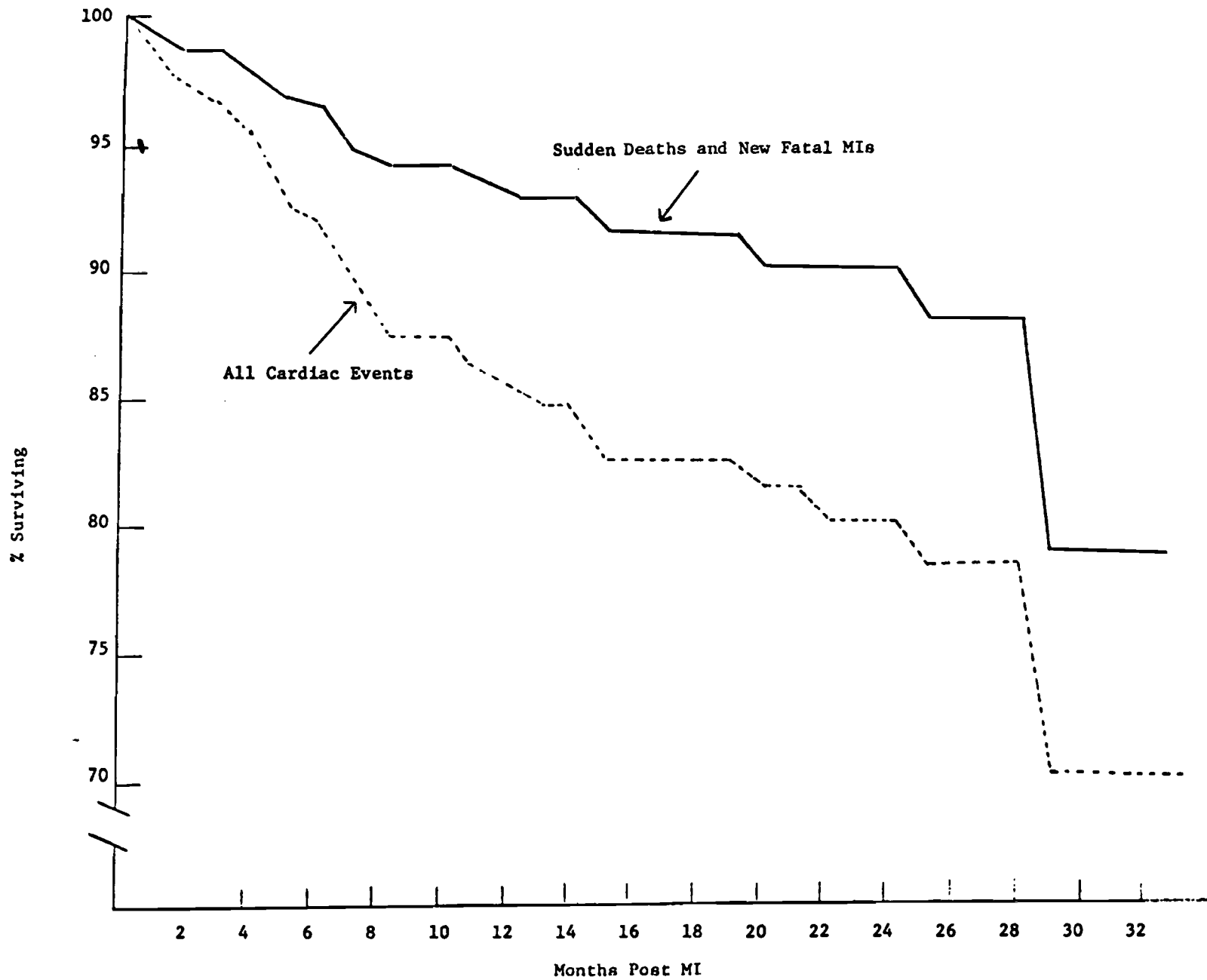
Figure 1. Mortality Experience for 194 Patients

A-6.   Argus/H: Program Development

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        The Argus/H system for rapid analysis of long ECG records consists
of three categories of programs (high speed scan, interactive data review
and edit, and generation of summary results). Individual programs, together
with several generalized utility programs, are accessible from an executive
routine called ARGEXEC; all reside in a System/7 Disc Support System data
set. Through ARGEXEC, an operator loads a program with the strike of a single
key; the program executes, then automatically reloads ARGEXEC, which returns
control to the operator. Progress in each of the three categories is reported
below.

        High speed scan. The core routines of sample decode and display,
Aztec, and Primitive (see PR 9, B-7) have undergone no significant changes.
The Cycle algorithm has been amended to inhibit PVC detection up to 300 ms
following the onset of a QRS complex when very large T waves are present.
The inhibition is optional and is keyed in by an operator prior to the high
speed scan if a previous scan has wrongly and consistently labeled those
large T waves PVCs.

        Interactive data review and editing. Of major import during the past
year has been the implementation, refinement, and operational use of an
editing program which permits (a) rapid access to any portion of the ECG
waveforms scanned by the Argus/H processors and (b) machine-readable records
of a human editor's choice of agreement or disagreement with computer-flagged
PVCs.

        Editing takes place on the System/7. The disc module contains the
original encoded sample data and the Argus/H generated Cycle data stream
describing each beat as to kind and exact occurrence time. The editing
program displays a 16-second segment of the waveform on a high speed oscil-
loscope together with Cycle annotation for the QRS complexes within that
segment. The display remains until an editor takes positive action by
depressing an appropriate button on a keyboard below the display scope. The
segment to be displayed and the computer action taken as a result of the
struck key depend upon the editor's choice of the many options which are
available for reviewing the waveform and evaluating computer-flagged PVCs.

        Any 16-second segment in the entire waveform may be displayed; the
editor merely specifies the time he desires. The program determines where
that segment of encoded sample waveform is located on disc and then decodes
to the original samples, filling a buffer with 16 seconds worth of sampled
data points (4K samples at 250 samples/s). The program then must access the
Cycle data stream on disc to fetch the appropriate labels for the QRS
complexes in the 16 seconds and insert these in a buffer. In addition, if
any PVCs occur in the segment, an edit status code (true, false, questionable,

or unedited) is also fetched from the Cycle data. When the buffers have been filled, the display presented shows waveform, beat annotation, PVC edit status, and beginning and ending times of the segment. From this time-requested display, the editor may a) make a hard copy of the displayed waveform on a conventional strip chart recorder; b) enter into a search mode of operation; c) enter into an edit mode of operation; d) request another time; or e) exit from the program entirely.

In the search mode, the editor may a) advance or retreat the wave-form 2 or 16 seconds; b) advance to the next PVC or retreat to the previous PVC—the PVC always appears at the 10th second of the 16 seconds displayed, providing ample prior and trailing waveform; or c) advance to the next true, false, or questionable PVC if the editor is reviewing a previously edited waveform. At any time the editor may generate a strip of the displayed waveform, enter into the edit mode of operation or exit to specify a new time.

The edit mode is the usual mode of operation. Typically, the editor locates to the first PVC in the record. The editor depresses a "true," "false," or "questionable" key to indicate his decision about that PVC. When the key is struck, the portion of the Cycle data stream pertaining to that PVC is updated to reflect the editor's decision; the display is auto-matically advanced to the next PVC. If many PVCs appear in a 16-second display and the editor decides that all are true or all false or all ques-tionable, he may enter a "page-edit" mode to hasten the editing; instead of striking the same key for each PVC on the page, the editor strikes the appropriate key once and all PVCs are updated. The program remains in page-edit mode, and the display is advanced to the next 16-second segment containing an unedited PVC. The first unedited PVC in that segment is positioned at 2 seconds in order to show waveform before that PVC and to accommodate as many PVCs as possible for page-editing. The page-edit mode may be exited at any time to return to straight edit mode. In the edit mode, typical operation is to edit one PVC at a time, but one may generate a strip at any time, enter the search mode of operation, or exit to specify a new time.

In order to acquaint trainees with the editing procedure as quickly as possible, a modified version of the edit program ("Teacher") is used as a training device. As the trainee is presented with a PVC and surrounding waveform for a record already edited, he makes a true, false, or questionable decision on that PVC. If his choice agrees with the previous edit, the dis-play is advanced to the next PVC. If not, the trainee's choice and the pre-vious edit decision are displayed side by side; the trainee is encouraged to generate a strip and resolve his error before advancing to the next PVC.

Generation of summary results. Summaries of the Argus/H scan and subsequent edit are printed out and inserted into a folder together with ECG strips produced by the editor. The computer-generated summaries include:

1. PVC plot. This includes the following data for each 15-minute period in the record: a) PVC frequency, in both bar graph and numerical form; b) the total number of PVCs in the current period plus those in the three previous periods; c) the percentage of time Argus/H was not looking

for PVCs because of artifact or loss of signal;   d) an indication of the presence of any couplets, runs, or both.

2. Heart rate plot. The following data are presented for each 15-minute period: a) heart rate, in both bar graph and numerical form, computed according to the average interval between successive normal beats for each 15-minute period;   b) data loss, or the percentage of time during which Argus/H did not find two consecutive normal beats. The overall heart rate, computed in the same manner as the rate for each period, is also printed.

3. Gross summary. The following data are printed: a) length of record in hours and minutes;   b) total beats, or number of QRS complexes identified and labeled by Argus/H;   c) average data loss, or the percentage of time Argus/H was not searching for PVCs because of artifact or signal loss;   d) raw PVC rate;   e) raw PVC rate adjusted for data loss;   f) average height of normal beats;   g) totals and percentages for true, false, questionable, and unedited PVCs.

Optional and generally not printed are 5-minute summaries detailing beat types, interval information, and QRS feature characteristcs. These 5-minute summaries may also be written on magnetic tape for higher-level statistical analysis.

A-7.   Argus/H: Hardware Development

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A second IBM System/7 computer, configured the same as the first Argus/H computer (see PR 9, B-8) and dedicated to the processing of ECG tapes, was obtained under lease and installed in November, 1973. It consists of an IBM 8K 5010 Processor Module with Cycle Steal, 5022 Disc Module, and 5013 Digital I/O Module. The peripherals connected to this system are: a Pertec 45-ips, 9-track, 800-bpi tape drive; a Hewlett-Packard Model 1310-A high speed, long-persistence oscilloscope; a single channel Mennen Greatbatch ECG paper recorder; dual 10-bit digital-to-analog converters with glitch suppression; and a Datapoint model 3000 terminal operating serially at 300 baud. The Data Products Model 2310 line printer and the 5028 Operator Station are shared with the first System/7 computer.

A System/7 channel interface, which provides communications between the processor module and assorted I/O modules, has been installed in the first Argus/H computer. A general-purpose interface is being designed and

constructed; when completed, this interface will replace the IBM 5012 I/O Module, which is not particularly well suited for our peripheral devices.

The interface being designed uses Schottky TTL logic and is based on a bus structure. The multiplexer, receivers, and transmitters for the common bus logic have been constructed and tested. General-purpose modules, with and without cycle-stealing operation, are being designed; each module will accommodate up to four individual device interfaces.

A second Pertec 45-ips, 9-track, 800-bpi tape drive was also installed on the first System/7. Both tape drives share a common buffered formatter. This installation now permits tape copying operations.

A-8.   Argus/H: Digitizing, Scanning, and Editing

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During the past year nearly 1000 Holter recorded ECGs have undergone the Argus/H processing steps of digitizing, scanning, and editing (see A-4). The Argus/H scan requires little human interaction; digitizing and editing are heavily dependent upon human-machine interaction, and some facets of those operations are discussed below.

Digitizing. The analog ECG tape is fed through an Avionics Model 650 Electrocardioscanner at 60 times real time (X60). The analog signal from the Electrocardioscanner passes through a notch filter to attenuate power line interference, and a low-pass filter (see PR 9, B-8). A three-channel, multiplexed, macromodule-compatible, analog-to-digital converter transforms the filtered signal into a digital data stream representing 15,000 samples per second (250 samples per real-time second). A macromodular system derives the second difference of the digitized data and encodes the result using an entropy coding technique (see PR 9, B-11). A macromodule-compatible tape controller writes the encoded data onto industry compatible tape.

During digitization, the analog signal from the Electrocardioscanner is visually monitored and its gain manually adjusted, if necessary, to ensure

optimal processing by Argus/H. Specifically, an attempt is made to maintain the normal QRS amplitude at a nominal level. As a check, the Argus/H scan computes an average normal height (ANH) for each record; any record with an ANH deviating by more than ±20% about a nominal value of 100 warrants re-examination at the digitizing level. Occasionally, the analog signal must be played back at higher than usual gain in order for Argus/H to detect nearly isoelectric PVCs, or at a lower gain to prevent huge PVCs from going off-scale.

The average time to digitize a ten-hour tape has been about 15 minutes. The time includes 10 minutes of X60 playback plus 5 minutes overhead for analog and digital magnetic tape setup and occasional equipment down time.

Earlier in the year, two types of problems had been encountered with the macromodules, causing about 18% down time. Most frequent were faulty mechanical connections caused by the restructurable nature of the macro-modules. The other type of problem was power supply failures. With a more stable system and an engineering change to the power supply, the macromodular encoder is now routinely used with less down time.

High Speed Automatic Scanning. The full scanning process, previously described (see PR 9, B-7), has reached a momentary steady state of develop-ment. A sample of 50 tapes from as many subjects was taken to measure the performance of the high speed scan.[1] The percentage times spent in the different stages were: decoding of sampled data, 47.5%; display of sampled waveform, 14.2%; Aztec, 11.8%; Primitive, 18.2%; and Cycle, 8.3%. Average processing runs at better than X40 with the display and at X50 without the display.

Editing. Since the end of July 1973, 785 Holter tapes from the study of ventricular arrhythmias and sudden death (the core project) have been digitized, scanned by Argus/H, and edited. Generally, these represent second through fifth recordings of patients enrolled in the study. Included in the 785 are the first tapes (CCU recordings) for 36 patients as well as a total of 86 tapes beyond the fifth recording for 18 patients. One tape from each of 33 low-risk subjects was also processed. Other projects proc-essing tapes were infarct size study (134 tapes), coronary bypass study (36), and drug study (44).

A MUMPS data base, called the EDIT LOG (see A-11), contains informa-tion pertinent to the digitizing, scanning, and editing phases of tape processing. The EDIT LOG has become an integral part of Argus/H operations and is used for scheduling, quality control, and generation of summary statistics relating to production. Since each digital ECG record from the core project is saved, the inventory of digital tapes is large and has ne-cessitated the packing of two digital records onto one tape. At present, only tapes belonging to the same patient are packed together; there are 128 tapes each containing two records. Coronary bypass and drug study tapes are not packed; digital tapes from the infarct size study are erased and used again.

Most records (88%) have been edited by trained personnel, including premedical, medical, and bioscience students. The remainder have been edited by professional personnel. Training of the editors requires familiarization with electrocardiograms and the operation of computer equipment. Trainees work closely with qualified personnel for about a month and independently thereafter, although expertise is generally available for records difficult to interpret and for equipment problems which arise.

[1] K. W. Clark, F. M. Nolle, J. R. Cox, Jr., and G. C. Oliver, "High Performance Computer Programs for Rapid Analysis of Long ECG Records," Proceedings of the San Diego Biomedical Symposium, vol. 13, San Diego, 1974 (in press).

A-9.   Argus/H: Evaluation

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To our knowledge, there are no existing standards of performance or documented test data for computer-aided processing of Holter tapes. This has also been true in the closely related area of rhythm monitoring in the coronary care unit; but plans are now underway to produce relatively short, annotated ECG test segments for use in this latter area (see A-16).

Evaluation of the present system for production analysis of Holter tapes with Argus/H (see A-4) must involve procedures for measuring both human and machine performance. The four processing steps of digitization, high speed scan, edit, and review must all be performed properly to obtain reliable and consistent results. Of these steps, all but the high speed scan rely mainly on the ability of the human. It should not be surprising, then, that several evaluation efforts have been under way to measure both the whole system's performance and the characteristics of the individual processing steps.

Validation. A set of 34 segments of ECG data with a total duration
of about 10 hours comprises the only validation data for the Argus algorithms
(see PR 7, B-1). The data is available in Aztec, Primitive, and Cycle form,
but not in either analog or sampled data form. Special techniques are con-
sequently required to use it. The Primitive and Cycle processors of Argus/H
were developed and informally tested with the use of this data, but a more
formal and complete validation effort using the data is now underway. This
work is being conducted in parallel with validation of a commercial version
of Argus (see VI-B).

Reprocessing. A project has been· undertaken to measure the stability
and reproducibility of the complete Holter tape processing system. The
current procedure involves complete reprocessing of 43 Holter tapes selected
from the set which have been processed to date in the core project study of
ventricular arrhythmias and sudden death. The sampling strategy selects
every twentieth tape processed or a tape from every seventh day of processing,
whichever comes first. It is expected that this work, which was only
recently instituted after several trial runs, will lead to a method for
routine quality control in the future.

Evaluation Data Bases. In addition to the reprocessing data base,
other data bases have been identified to investigate Argus/H processing
speeds (50 tapes from 50 subjects; see A-8), and to study the frequency of
false negative PVCs in survivors and patients dying suddenly (20 tapes from
20 subjects). In the latter study, an attempt is being made to devise a
sampling strategy for looking through portions of the tapes on a beat-by-beat
basis to detect missed PVCs.

Another data base has been chosen to evaluate more systematically
the various ECG processing steps. It consists of 97 tapes numbered 2 through
5 (corresponding to the 2 weeks through the 3 months recordings) which had
been analyzed using Argus/H and were from 29 patients in the core project
study chosen in numerical order starting with patient number one. The
following projects have been undertaken with this data base, with a qualified
electrocardiographer making the majority of the necessary judgments and
identifying numerous examples for compiling multiple opinions.

Manual scan comparison. A comparison of Argus/H results with those
obtained by manual scanning (see A-3) is being made to help determine if
there are any records in which significant ventricular arrhythmias are
missed completely by processing with Argus/H. To do this, the manual scan
records are first being subjected to a review process similar to that
given to the Argus/H-processed records.

Editor evaluation. Forty of the ninety-seven records have been
examined by a so-called "super editor" using the "Teacher" program (see A-6).
A judgment was made concerning the validity of the first editor's decision
on each and every computer-labeled PVC in which his decision conflicted with
that of the super editor. Illustrative ECG strips were also gathered to
produce a report on each record, and the quality of the first editor's report
was evaluated.

Couplets and runs. ECG paper records of all couplets and runs seen by the super editor were collected in the editor evaluation project. A subset consisting of 19 of the 40 records were then examined on a beat-by-beat basis to determine how many additional couplets and runs were missed. A few of these records had been selected to determine the number of missed PVCs due to the T-wave option. The remainder consisted of records classed as Lown 4 or 5, plus recordings following these but classed as Lown 3 or less. Records were also kept of the time of occurrence of all PVCs seen, including those missed by Argus/H.

New edit protocol. The 19 tapes which had been examined beat-by-beat were edited to evaluate a new protocol. The editor was required to obtain strips on all couplets and runs and on all missed PVCs that he saw, while otherwise editing in the normal fashion.

Reviewer comparison. While most differences among Argus/H reviewers are concerned with the classification of PVC coupling intervals as early, middle, or late, in 16 of the 97 records there was also dissension on Lown classification.

Most evaluation results are still being compiled. All available evidence indicates that the detection of couplets and runs is very good. This happens because the editor will see them even if only one PVC is detected by Argus/H. The new editing protocol also looks very promising, achieving substantial gains in overall percentage detection of PVCs in the records studied to date. It is hoped that the work on evaluation will lead to a set of documented data for future testing of alterations in the Argus/H processing system.

A-10.   Argus/H: Program Documentation

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              F. M. Nolle, BCL

Support: RR 00396
              HV 12481

The entire Argus/H high speed scanning package (see A-6) of sample decoding and display, Aztec, Primitive, and Cycle has been documented using the IBM System/360 Host Program Preparation Facilities for the System/7 (see PR 9 supp., #1); however, most portions still require some refinement and more profuse commentary, and testing is not yet completed. The editing and summary programs are still subject to occasional modification, and formal documentation of these programs has not yet begun.

A-11.   Argus/H: MUMPS Data Bases

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     With the steady increase in the number of tapes processed by Argus/H
in the core project study of ventricular arrhythmias and sudden death (see
A-4), the tasks of providing management information and easy access to a
wide variety of data being produced developed into major information storage
and retrieval problems.

     The MUMPS programming language for the System/7 (see A-19) was
developed primarily as a filing system to supplement existing manual files.
The global files, called "global logs," contain information pertaining to the
status of individual recordings involved in the Argus/H procedure. The data
contained within the global logs is used to generate various files, summaries
and cross-references which are useful for higher-level analyses of the summary
results obtained from the Argus/H scanning and editing process. There are
three global logs used on a daily basis: 1) a patient status and recording
log, PLOG; 2) an accounting log of digitizing and editing actions, EDIT
LOG; and 3) a log of the summary data and review actions, SUMMARY LOG.

     In PLOG, a file is created and updated periodically for each partici-
pant in the project. These files contain dates and manual scan information
for all tape recordings obtained for the study (see A-3). Both the L and K
classifications are included in the manual scan summary results. The PLOG
also indicates the status (active or inactive) of a particular patient. The
reason for a participant's change from an active to an inactive status is
also recorded. A MUMPS program is used for the task of scheduling recording
sessions for each participant in the core project. The program examines the
individual PLOG files and determines the week in which the next recording is
due. A recording schedule for the upcoming week is then generated.

     After a Holter tape has been digitized, scanned, and edited, perti-
nent information (see A-6 and A-8) is recorded in the EDIT LOG: the tape's
identification number, date of digitization, date of edit, editor's initials,
time required to edit, average normal QRS height, T-wave option interval (if
used), digital tape status or location, and digitizer and editor comments.
The EDIT LOG is updated and printed at periodic intervals.

When a tape has passed through the entire Argus/H procedure, the summary information is reviewed by a group of cardiologists and an Argus/H Summary Sheet is produced. The contents of the summary sheet are transferred into the MUMPS SUMMARY LOG. The data are filed by tape identification number within the log and contain the date of summarization, total numbers of Argus/H PVCs and true PVCs, peak hourly PVC rate, average percentage data loss, average heart rate, Lown classification for the tape, and coupling interval classifications (early, middle, late) of the earliest PVCs following non-PVCs and following PVCs.

A MUMPS program has been written to merge the three logs into a master status log. This log is printed periodically and indicates the status of each tape in the study. Summary information for each of the stages through which the tapes have been processed are listed, along with each analog tape status, by participant file identification number.

The utilization of the MUMPS filing system has greatly alleviated the time-consuming chores of manual record keeping. Desired information is easily retrieved from the MUMPS files and may be displayed or printed at the user's request. The relative ease with which MUMPS data bases may be changed or expanded has been an important feature in the evolution of the information management functions of the Argus/H processing system.

A-12. A Study of Antiarrhythmic Drug Therapy Using Argus/H

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The ability of Argus/H to quantitate premature ventricular contractions permits its use to evaluate the effectiveness of antiarrhythmic drug therapy. Accordingly, a protocol was devised to evaluate the results of treating patients with diphenylhydantoin, quinidine sulfate, procainamide, and placebo in a double-blind randomized study. Twenty-four-hour Holter recordings were obtained after one week on each drug. Initially the protocol required one week of abstinence between drugs; but the drugs are now given sequentially with no intervening period of abstinence. Dosages chosen were those in common clinical usage. Patients were selected from the population studied in the investigation of ventricular arrhythmias and sudden death (see A-1) and from the patients following bypass surgery (see A-13) who

- 40 -

demonstrated two or more recordings with 50-100 PVCs per hour and Lown classifications 3, 4, or 5. To date, 7 patients have completed the protocol, and data is available on 4. Tapes were analyzed using the Argus/H system with a modified editing and review protocol, so that examples of all couplets and runs were saved and analyzed by the cardiologists. Results to date are preliminary (Table 1). While as yet no definite statements about the efficacy of antiarrhythmic medications in this group of patients with coronary disease can be made, it is clear that some of the drugs in clinical use may be totally ineffective in certain individuals or even deleterious and other drugs formerly thought to be ineffective may be in fact quite effective (diphenylhydantoin). These data will be expanded by enrolling more patients in the study, but the feasibility of using the Argus/H system for drug evaluation has been proven.

Table 1: Effect of Antiarrhythmic Drugs on
Total PVCs for 12 Hour Monitoring

PATIENT

DRUG	#1	#2	#3	#4
Placebo	2861	135	425	1147
Procainamide	188	176	378	6250
Quinidine Sulfate	1216	3	38	4681
Diphenyl-hydantoin	9	132	247	2771

A-13.   A Study of the Effect of Coronary Bypass Surgery on Ventricular
         Arrhythmias Using Argus/H

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              Y. Hamuth, M.D., Jewish Hospital
              G. C. Kaiser, M.D., St. Louis University
              R. E. Kleiger, M.D., Jewish Hospital
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        An intervention currently being used to alleviate angina pectoris in
patients with severe coronary artery disease is coronary bypass surgery. The
present study is designed to evaluate the effect of this surgery on arrhyth-
mias. The protocol calls for up to three recordings prior to surgery and
then recordings every 2-3 months up to a year, with an exercise test at the
end of that time to evaluate work performance. To date, 24 patients have
been entered into this study, and recordings of 8 patients have been analyzed
on the Argus/H system. Results on these 8 patients are preliminary, but
none has shown improvement with surgery, and all patients have had either
the same or greater severity of ectopic beats. One patient died, presumably
of an arrhythmia, one month following successful surgery. The feasibility
of using the Argus/H system to evaluate the effectiveness of interventions
such as coronary bypass in reducing ventricular ectopic beats has been
demonstrated.

A-14.   Influence of Infarct Size on Electrical Instability of the Heart

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        During the first ten months of operation of this project, patients
admitted to the Barnes Hospital Coronary Care Unit have been studied to
determine whether a relationship exists between electrocardiographic abnor-

malities indicative of major dysrhythmia and infarct size estimated from serial changes in serum CPK activity (see B-2). Continuous electrocardiographic recordings have been obtained with the use of sequential ten-hour Holter tapes. Arrhythmia analysis has been performed by digitizing and analyzing the tapes with the Argus/H system. Results obtained include the total number of premature ventricular contractions (PVCs) during a selected interval, peak rate of PVCs, the number of episodes of couplets, and the number of episodes of ventricular tachycardia (defined for purposes of this study as three or more PVCs in succession).

During the past ten months 62 patients have been studied and 134 tapes analyzed. This group comprises 20 control patients in whom the diagnosis of acute myocardial infarction was excluded; 29 patients with definitely established acute myocardial infarction treated conventionally; and 13 patients with acute myocardial infarction treated with physiological or pharmacological interventions designed to modify infarct size.

Preliminary results. Patients were divided according to infarct size index (ISI) into Group I (ISI=1 to 24 CPK-g-eq); Group II (ISI=25 to 49); and Group III (ISI$\geq$50). The Norris prognostic index in the three groups averaged 4.9, 5.0, and 8.6. Thus, on the basis of demographic and hemodynamic information, Groups I and II were quite similar. Serum potassium and arterial oxygen tension were similar in all three groups. Premature ventricular contractions per 20 hours averaged 54±21 (SE), 99±33, and 635±258 in the three groups respectively. Episodes of couplets or ventricular tachycardia averaged 1.5±.6, 4.3±1.3, and 9.9±2.2. Differences between groups were significant at the $p<.01$ level. In some patients, an increase in the rate of PVCs presaged extension of infarction by several hours. These preliminary results indicate that the severity of ventricular dysrhythmia early after acute myocardial infarction is correlated with the extent of myocardial injury assessed by serial changes in serum CPK activity. The findings suggest that the efficacy in evaluation of antiarrhythmic agents in this setting may be influenced by the magnitude of injury sustained by the heart.

Studies in progress are concerned with improving the precision of estimation of infarct size by the use of CPK isoenzyme analyses in addition to assessment of total serum CPK activity, by the improvement of mathematical models used in analyzing serial serum CPK changes (see B-1), and by the extension of the observations longitudinally during follow-up periods after patients are discharged from the hospital to determine whether the extent of infarction is related to persistence of dysrhythmia in patients recovering from acute episodes.

A-15.   Construction of a Hardwired Aztec Processor

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Support: RR 00396
            HV 12481

        A hardwired Aztec processor (see PR 9, B-10) has been constructed of
Digital Equipment Corporation Register Transfer Modules (RTMs). A general-
purpose interface has been built and used to make the RTM Aztec compatible
with macromodules. Both the control and the data communications between the
RTM Aztec and the macromodules are conducted inside the interface. There
are 32 different types of Register Transfer Modules used in the RTM Aztec.
The total parts cost, including power supply, is about $2600.

        The validity of the RTM Aztec has been tested by comparing the Aztec
output data from the RTM Aztec with those from a software Aztec program
running concurrently in a μ-LINC. A set of 30 LINC tapes, each containing
about 4-1/2 minutes of ECG samples at 500 samples/s was used. The speed of
the RTM Aztec was also measured by using the μ-LINC. Waiting loops in a
μ-LINC program are used to measure different processing times.

        The shortest pathway for a single ECG sample is 9 μs, and the longest
pathway of a single sample to output of an Aztec datum is 54 μs, which is
longer than the 33.3 μs inter-sample arrival time at 60 times real time. The
testing program was then modified to determine the size of sampled data
buffer which would be necessary in order to process at a speed 60 times real
time. For the 30 ECG sample tapes it was found that a FIFO buffer memory
with a capacity of 16 samples would be sufficient to smooth the sample-to-
sample fluctuations in the RTM Aztec processing times.

A-16. Evaluation Group for Automated Arrhythmia Detectors

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            C. L. Feldman, Ph.D., Worcester Polytechnic Institute
            T. F. Martin, M.D., Medicine
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During the past year, meetings of the Evaluation Group for Automated
Arrhythmia Detectors (see PR 9, B-12) were held at Atlantic City in November
and at New York City in February. Arrangements to affiliate the group with
the American Heart Association have been completed through Dr. Hubert Pip-
berger. Plans were formulated to process a set of test ECG tapes through
a three-institute consortium consisting of Worcester Polytechnic Institute
(WPI), Washington University (WU) and Stanford University Medical Center
(SUMC). Financial support for the development of the test set is being
sought.

The arrangement would hold WPI responsible for the collection of
tapes at a number of cooperating sites around the country. About 400 half-
hour ECG segments would be collected and stored on industry compatible digi-
tal tapes. These tapes would be forwarded to WU, where they would be proc-
essed using Argus/H. Paper records would be generated containing the com-
plete ECG, along with the computer annotation indicating time of occurrence
and individual beat classifications. Two identical copies of these paper
records would be sent to SUMC, where arrangements would be made to have them
reviewed by one cardiologist at the recording site and independently by a
second cardiologist at SUMC. Reviewers would prepare correction sheets which
would be processed at WU to correct the digital tape records. A reannotated
paper record would be produced and sent to WPI for independent validation
against the correction sheets. All corrected industry compatible tapes would
be reproduced on microfilm, analog magnetic tape and industry compatible
digital tape for the American Heart Association. Distribution to interested
scientists and commercial firms would be carried out on a fee-for-service
basis.

A-17.   Episodic ECG Data Acquisition System

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            B. F. Spenner, BCL

Support: RR 00396

        Development has continued on a system to capture transient segments
of ECG data on multiple patients (see PR 9, B-13). Hardware development is
for the most part complete. Software development for the PC-1200 is still
in progress; the original algorithms which were initially tested on a single
patient are now being rewritten for eight patients.

A-18.   Heart Station Computer ECG Assessment

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        Consultation was provided during the installation of an in-house
computer ECG analysis system at Barnes Hospital. An initial evaluation of
the diagnostic accuracy of this system did not agree with published perfor-
mance figures, but it was subsequently shown that there were a number of
problems connected with the acquisition of the digitized ECG. An IBM System/360
program was written for plotting the digitized ECG data as an aid to checking
the computer measurements and the validity of the input data. The system
for digitizing the ECG using analog cassette carts had a number of problems,
and it was replaced with carts and equipment for on-line operation. A sub-
sequent evaluation has indicated that when the digitized ECG is properly
acquired, the ECG analysis program appears to conform to published
performance figures.

A-19. MUMPS/7 - A Programming Language for the System/7

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Support: RR 00396
            HS 00074
            HV 12481

     The MUMPS programming language has been implemented on the IBM
System/7.[1]   MUMPS/7 is a translation of the single-user PC MUMPS (see
PR 8, I-2). A few modifications and extensions of the language were made
during translation: the local symbol table management routines were rewrit-
ten for multi-level subscripting, global file operations were modified to
take advantage of the System/7 dual-platter disc module, and the program
directory was restructured to allow eight-character program names.

     Other modifications pertain to the operation of the various peripheral
devices available on the System/7, and to the change from a 12-bit to a 16-
bit word length. The input-output devices available to the MUMPS/7 user
are: a Teletype, an 80-column Data Products line printer, a Tektronix
graphics display terminal with hard-copy unit, two industry compatible tape
drives, and the System/7 disc module.

     Final modifications and testing of MUMPS/7 have been completed. The
MUMPS/7 system is now fully operational and is being used on a daily basis,
primarily for the management of information pertaining to and generated from
the processing of ECG tapes by Argus/H (see A-11).

[1] E. D. Scheifler and F. M. Nolle, "MUMPS for the System/7," Proceedings
of the 1973 MUMPS User's Group Meeting, St. Louis, September, 1973, in press.

B.   Tracer Kinetics

B-1.   Quantification of Myocardial Infarct Size with Serum CPK Enzymes:
        Computer Programming Activities

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It has been shown that the extent of myocardial damage during evolving myocardial infarction is reflected by serial serum creatine phosphokinase (CPK) activity and that, under certain conditions, CPK values can be projected on the basis of best-fit curves for data obtained soon after the onset of infarction. (1) A FORTRAN program was developed at the University of California (San Diego) which calculates "infarct size" from log-normal fits of serum CPK data. This program has been implemented on the Washington University IBM System/360 Model 65 digital computer.

Because of the delays in processing CPK data associated with the use of a remote terminal, we considered implementing the program on the LINC-8 located in the CCU. The algorithm used in the program for obtaining log-normal fits to the data entails lengthy nonlinear iterative calculations, which could not be implemented on the LINC-8 because of memory and speed limitations. An attempt was made to reduce both the program size and the execution time through use of a linearizing transformation of the log-normal fitting function. This transformation consisted of fitting the logarithm of the serum CPK data to the logarithm of the fitting function, resulting in a linear function of the three parameters whose unknown values could be estimated by standard noniterative linear least-squares techniques. Such a procedure gave results in good agreement with those obtained with the nonlinear iterative technique when data for an entire serum-CPK history were processed. However, attempts to use the linear transformation to project the serum-CPK time course on the basis of a few early data points produced results which failed to agree with those obtained with the nonlinear iterative procedure. The linearizing transformation approach was therefore abandoned.

The FORTRAN program which runs on the Model 65 digital computer produces plots of serial serum CPK data points and the corresponding best-fit curves. In addition, the plots display the computed values of "observed" or

"predicted infarct size." There is normally a delay in receiving these plots. In order to speed up and simplify the operation, the plotting of the output was transferred from the Calcomp plotter at the Model 65 to the Calcomp interfaced to the LINC-8 at the CCU. This required revision of the Model 65 PLOT subroutine to delete the writing of the plotting codes to tape. In the new version, the codes are translated to LINC-8 codes, sequences of identical codes are combined (with counters appended), and the transformed codes are written Onto the Model 65 disc. This disc file may be brought into the LINC-8 over the data lines using the LINC Utility program (D-4) and saved on LINC tape. The final step in the new plotting procedure involves the use of a LINC-8 program which reads the LINC tape and plots the data.

With the new plotting procedure, the turnaround time between sub-mitting the Model 65 job and receiving the plots has been reduced from about 1 to 2 days to about 30 minutes. To further streamline this system, the various LINC-8 functions have been combined in a single program into which data acquisition capability has been incorporated. The input data are now entered via the teletype in response to oscilloscope displays. The data are stored in the LAP6 manuscript area, from which they may be saved in a LAP6 file, brought back into the program for editing, or sent over the data lines to the Model 65 disc. Another option available in using the new program enables the required Job Control Language and the input data to be fed into the job stream for batch processing of the FORTRAN program. If this option is selected, the output may be received and plotted as des-cribed above. This LINC-8 program has been in operation since April, 1974.

To further localize the data-processing operations and to hold down costs, a LINC-8 program was written to calculate the "observed infarct size". Again, the input is from the teletype guided by oscilloscope displays; there is, however, no editing option. The calculations are done using double-precision floating-point arithmetic, and the results are typed on the teletype. Calculation of "observed infarct size" is thus separated from the more lengthy "prediction" calculations.

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[1] W. E. Shell, J. F. Lavelle, J.W. Covell, and B. E. Sobel, "Early Estimation of Myocardial Damage in Conscious Dogs and Patients with Evolving Acute Myocardial Infarction," Journal of Clinical Investigation, vol. 52, pp. 2579-2590, 1973.

B-2.　Model-Based Parameter Estimation of Myocardial Infarct Size

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Prediction of "infarct size" from serial changes in serum creatine phosphokinase (CPK) activity measured during the first seven hours after myocardial infarction has been accomplished through a nonlinear curve-fitting procedure developed by Sobel and co-workers.[1] This prediction has been particularly successful for certain well-defined conditions, requiring normal serum CPK activity at the time of admission and requiring that constraints be placed on parameter values during the fitting procedure (B-1). It is desirable, however, to widen the area of applicability of this technique, define its limitations, and calculate confidence intervals for the results.

The mathematical model presently employed for interpreting serum CPK data is largely empirical and therefore probably of lessened utility in situations not conforming to the above-mentioned criteria. In an attempt to broaden the applicability of the method, a preliminary model based on plausible physiological phenomena and anatomical considerations in myocardial infarction has been developed and tested. This model is based on passive diffusion of CPK in myocardial tissue. It fits the experimental data reasonably well in spite of assumptions involving quite simplified boundary and initial conditions. The assumption is made that at the onset of ischemia, CPK contained in a sphere at a uniform concentration begins to diffuse into a larger concentric sphere of tissue. At the boundary of the outer sphere, CPK is carried away by either the lymph or the venous system, eventually to appear in blood serum. Only two adjustable parameters enter into this model. The preliminary fits are good with improved performance, particularly in the tails of the serum CPK activity-time data.

[1]W. E. Shell, J. F. Lavelle, J. W. Covell, and B. E. Sobel, "Early Estimation of Myocardial Damage in Conscious Dogs and Patients with Evolving Acute Myocardial Infarction," Journal of Clinical Investigation, vol. 52, pp. 2579-2590, 1973.

B-3.   Solution of Maximum-Likelihood Function for Tracer Kinetic Data

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A comparison of the performance of several nonlinear optimization techniques for estimating parameters from radiotracer data has been completed (PR 9, C-7). The results of the application of these techniques to the maximum-likelihood function for Poisson-distributed tracer data with a multiexponential intensity indicate that a modified gradient method with a non-Euclidean norm is the preferred choice.[1] This method involves the use of the Fisher information matrix in conjunction with a technique due to Marquardt.[2]

The algorithm is now being implemented on the Interdata Computer in the Radiation Sciences Division of the Department of Radiology.

[1] J. Markham, D. L. Snyder, J. R. Cox, Jr., and P. B. Zwart, "Solution of Maximum Likelihood Equation for Multiexponential Poisson-Distributed Data," BCL Monograph No. 233, December 1973.

[2] D. W. Marquardt, "An Algorithm for Least-Squares Estimation of Nonlinear Parameters," SIAM Journal of Applied Mathematics, vol. 11, no. 2, pp. 431-441, 1963.

B-4.   Kinetics of Chronic Subdural Effusions

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A compartmental model has been developed to describe the kinetics of proteins present in subdural effusion fluid. This model leads to equations which adequately describe the most complete set of experimental data we have available (PR 8, J-1). The results indicate that the movement of proteins between blood and the effusion fluid involves at least two other compartments. These two compartments have not yet been identified, but their presence and possible identity are suggested by published reports on the distribution of albumin in the body.

The model is now being tested with data from previous studies. The results of these tests should clarify the role of all compartments, and perhaps will suggest other studies which can help describe the kinetics of proteins in the effusion fluid.

B-5.   Quantitation of Left-to-Right Cardiac Shunts

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Support: RR 00396
             GM 01747
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Left-to-right cardiac shunts are being quantitated by three methods. The simple count-ratio methods (e.g., the c_2/c_1 method of Braunwald) are being compared with the gamma-variate area-ratio method of Maltz and Treves[1] and the exponential-extrapolation area-ratio method reported by Anderson.[2] The latter two methods involve the analysis of counts recorded by a gamma camera over the right lung following intravenous injection of ^{99m}Tc-pertechnetate.

Early results comparing the utility of these methods in 30 patients with pure left-to-right shunts and in 20 patients who were normal or had valvular heart lesions without shunts suggest that each of these methods has deficiences. Since the major problems appear to be associated with the curve-fitting procedures, we are investigating these in depth, in terms of the best numerical algorithm for fitting the data and in terms of the type of curve which best represents the data.

[1] B. L. Maltz and S. Treves, "Quantitative Radionuclide Angiocardiography Determination of QP:QS in Children," Circulation, vol. 47, p. 1049, 1973.

[2] P. A. W. Anderson, R. H. Jones, and D. C. Sabiston, Jr., "Quantitation of Left-to-Right Cardiac Shunts with Radionuclide Angiography," Circulation, vol. 49, pp. 512-516, 1974.

B-6.   Renal Metabolism Of Parathyroid Hormone

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             AM 05248
             AM 09976
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This study was undertaken to describe the renal contribution to parathyroid hormone (PTH) metabolism. The determination of the total metabolic clearance rate (MCR) was performed by both single-injection and constant-infusion techniques. In the single-injection technique, the disappearance curves for bovine PTH and the synthetic 1-34 fragment were analyzed on the IBM System/360 Model 65 computer by the SAAM program of Berman and Weiss to determine total MCR. The results to date document a marked decrease in total MCR and a prolongation of the disappearance curve in dogs with chronic renal disease due to impaired renal degradation of the hormones. Work has also been initiated to devise a multicompartmental model for PTH metabolism.

B-7. Brain Capillary Permeability Studies in the Rhesus Monkey

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B. K. Hartman, M.D., Psychiatry
K. B. Larson, BCL
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Support: RR 00396
HL 13851
HS 11059
NS 06833

The diffusion of labeled water into tissue has always been assumed by investigators to be sufficiently rapid relative to convective capillary transport (blood flow) to allow complete equilibration during a single capillary transit. We have examined the validity of this assumption by measuring the equilibration of labeled water ($H_2^{15}O$) with the exchangeable water pool for a single transcapillary exchange in the brain of rhesus monkeys. The technique utilizes external scintillation detection (residue recording) of the time course of the labeled water in the injected hemisphere. The extraction fraction of the injected label is determined by extrapolating the relatively slow clearance of labeled tissue water back to the time of the perfusion peak and computing the ratio of extracted water to available water. The resultant water extraction is flow dependent, having the relationship $\ln$ (1 - extraction fraction) = $-(136/CBF) - 0.35$, with a correlation coefficient r = -0.95.

Thus, our findings[1,2] indicate that the diffusion of water is not flow-limited in the brain of rhesus monkeys for mean cerebral blood flows (CBF) greater than approximately 20 (ml/100g)/min. At normal CBF [$\approx$50(ml/100g)/min] only 93% of the injected label freely equilibrates with the brain, and this value progressively declines with increasing CBF.

Several investigators pursuing brain permeability studies have proposed the use of labeled ethanol as a reference diffusible tracer rather than water or antipyrine. Accordingly, we have synthesized and measured the brain capillary permeability of several ^{11}C-labeled alcohols, namely methanol, ethanol, and isopropanol, relative to that of water, employing the extraction fraction technique. Our results indicate that of the four diffusible tracers, the brain capillary permeability in rhesus monkeys is greatest for isopropanol, followed in order by ethanol, methanol, and water. For example, at normal CBF [$\approx$50(ml/100g)/min] the extraction fractions are: isopropanol, 99%; ethanol, 97%; methanol, 94%; water, 93%.

Anatomical studies employing the Falck-Hillarp histofluorescence technique for brain catecholamines as well as the immunofluorescent histochemical technique of Hartman and Udenfriend for brain dopamine beta-hydroxylase have demonstrated noradrenergic nerve fibers on small intra-parenchymal brain blood vessels, including capillaries, which arise in the brain stem and ascend within the neuraxis to vessels. This system appears distinct from the noradrenergic system innervating the large, extraparenchymal cerebral arteries and veins. To investigate the role of this central noradrenergic system in the regulation of the brain microcirculation, chronically sympathectomized rhesus monkeys were studied. Blood flow and the capillary transport of water were measured as noted above. The central noradrenergic system was manipulated by instilling the short-acting alpha-adrenergic blocker phentolamine in the lateral ventricles or placing carbachol, an acetylcholine analogue, in the locus caeruleus (in the brain stem). The results of these preliminary studies suggest that stimulation of this central noradrenergic system increases the capillary permeability to water and that blocking the system has the opposite effect.

[1]M. E. Raichle, J. O. Eichling, and R. L. Grubb, Jr., "Brain Permeability of Water," Archives of Neurology, vol. 30, pp. 319-321, 1974.

[2]J. O. Eichling, M. E. Raichle, R. L. Grubb, Jr., and M. M. Ter-Pogossian, "Evidence of the Limitations of Water as a Freely Diffusible Tracer in the Brain," Circulation Research, in press.

B-8.   In-Vivo Tracer Assessment of Cerebral Blood Volume

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              HS 11059
              NS 06833

A method developed for the in-vivo determination of cerebral blood volume (CBV) has been tested in rhesus monkeys.[1] The technique utilizes

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external residue detection and requires the serial measurement of two mean transit times, namely, that of an intravascular tracer, $C^{15}O$-hemoglobin, and that of a diffusible tracer, H_2O. In computing the mean transit time for the intravascular tracer, it was found that the conventional Hamilton extrapolation of the downslope of the recording obtained for the washout of the tracer from the brain subsequent to an intracarotid bolus injection was an inadequate correction for tracer recirculation, yielding a mean transit time that systematically underestimates that parameter. Alternatively, it was found that the use of a power-law extrapolation, as proposed by Huang,[2] allows a more accurate prediction of the vascular mean transit time.

The method has been employed in monkeys to evaluate the role of CBV in overall cerebral hemodynamics.[3] At a normocarbic $PaCO_2$ (≈ 37 torr), an average value of 3.5 ml/100 g was found. CBV responded linearly to changes in $PaCO_2$. For each one-torr change in $PaCO_2$, there was a change of 0.041 ml/ 100 g perfused brain tissue. The relationship between CBV and CBF is best represented by the equation $CBV = 0.80\ CBF^{0.83}$ ($r = 0.90$) where CBF is in the range of 16-134 (ml/100 g)/min.

The method has been employed in humans with selected disease processes to measure regional CBV.[4-8] Studies relating CBV to changes in CBF and regional oxygen metabolism have been completed in patients with presenile dementia[6] and pseudotumor cerebri.[7] Studies are currently in progress in patients with cerebral arterial vasospasm associated with subarachnoid hemorrhage, patients with focal cerebral infarction associated with arteriosclerotic vascular disease, and patients with diffuse head injury.

[1] J. O. Eichling, M. E. Raichle, R. L. Grubb, Jr., and K. B. Larson, "In-Vivo Determination of Cerebral Blood Volume Employing Radioactive Oxygen-15," submitted to Circulation Research.

[2] S. C. Huang, "Stochastic Analysis of Transit-Time Distributions of Intravascular Tracers," D. Sc. dissertation, Department of Electrical Engineering, Washington University, St. Louis, Missouri, 1973.

[3] R. L. Grubb, Jr., M. E. Raichle, J. O. Eichling, and M. M. Ter-Pogossian, "The Effects of Changes in $PaCO_2$ on Cerebral Blood Volume, Blood Flow, and Vascular Mean Transit Time," Stroke, in press.

[4] M. Gado, M. E. Raichle, J. O. Eichling, M. E. Phelps, R. L. Grubb, Jr., and M. M. Ter-Pogossian, "Appraisal of the Angiographic Circulation Time as an Index of Cerebral Blood Flow," submitted to Radiology.

[5] M. E. Raichle, J. O. Eichling, M. Gado, and R. L. Grubb, Jr., "Cerebral Blood Volume in Dementia," Neurology, vol. 24, p. 350, 1974.

[6] M. E. Raichle, R. L. Grubb, Jr., M. Gado, and J. O. Eichling, "Cerebral Hemodynamics and Metabolism in Dementia," presented at the Second International Symposium on Intracranial Pressure, Lund, Sweden, June 1974.

[7] M. E. Raichle, R. L. Grubb, Jr., J. O. Eichling, M. Gado, M. E. Phelps, E. J. Hoffman, J. J. Corona, and M. M. Ter-Pogossian, "Cerebral Hemodynamics and Metabolism in Pseudotumor Cerebri," Neurology, vol. 24, p. 397, 1974.

[8] J. O. Eichling, M. E. Raichle, and M. Gado, "Limitation of the Anger Camera for the Determination of Regional Cerebral Blood Volume," presented at the 59th Meeting of the Radiological Society of North America, Chicago, December 1973.

B-9.   Radiation Sciences Division Computer System

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

Support: RR 00396
             HL 13851
             HL 14147

Continuing work has been carried out to implement the Radiation Sciences Division Computer System (PR 9, C-15). Each computer has now been expanded to 32 Kbytes, and the I/O multiplexers have been built and installed. Each processor is now capable of sharing the discs, tape drive, line printer and LINC communications. A Ramtek video display system capable of showing 256 x 256 resolution elements and 64 gray levels or colors has been added to the system. In addition, a new chromatograph interface capable of monitoring multiple chromatographs has been designed.

Considerable software has been written to do data collection from the multi-probe system (PR 9, C-2), data printout, semilog plots, data correction and data analysis.

B-10.   A   Physical Flow System for Studying Mathematical Models in Tracer Kinetics

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Support: RR 00396
             HL 13851

        A physical flow system has been designed and constructed to study the performance of various mathematical models in tracer kinetic studies under well-controlled conditions. The model can be altered for producing either open or recirculating flow. Flow rates can be varied over a wide range, and as many as four cells of known geometrical volume can be interconnected with tubing to form series or parallel combinations. In this way, idealized models of such physiological flow systems as heart or brain circulation can be realized physically. These physical models can be used to study the applicability of tracer-kinetic theories under conditions of rigorous control not achievable in the physiology laboratory.

        The system is presently being used to study the effects of tracer recirculation on the measurement of mean-transit time by residue detection. Results from a tracer-recirculation model[1] are being compared to those from other approaches, such as compartmental modeling and Zierler's height/area method.[2] Radiotracer activities are used in amounts sufficient to produce count rates typically encountered in physiological flow studies. In this way, the performance of the various tracer-kinetic models can be examined under the low count-rate conditions often encountered in practice. The effects of other variables, such as radiotracer injection rates and degree of mixing in the flow cells, are also under investigation.

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

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

B-11. New PDP-12 Gamma-Camera Interface

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

Support: RR 00396

        Work has continued on construction and testing of the new Nuclear
Medicine Division PDP-12 gamma-camera interface described previously
(PR 9, C-16).

        Preliminary work has been done on development of an extension of the
higher-level language FOCAL-12 available on the PDP-12. This expanded version
of FOCAL-12 has been written specifically for the Nuclear Medicine PDP-12, to
permit control of the gamma camera PDP-12 system with FOCAL programs rather
than machine language programs. This modification greatly increases the
ability of noncomputer personnel to use the gamma camera system for patient
care and research, and should therefore enable the Nuclear Medicine Division
radiologists to play a more active role in the design and execution of programs
required for their studies.

        A survey has been made of existing nuclear medicine data acquisition
systems. A comparison of the new Nuclear Medicine Division gamma camera
system with these existing systems indicates that completion of the new
interface and implementation of control through FOCAL commands will provide
a system with capabilities comparable to all currently existing nuclear
medicine data acquisition systems.

B-12. Mathematical Modeling of Cerebral Glucose Transport and Metabolism

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Support: RR 00396
            GM 02016
            NS 11059

        The modeling efforts[1,2] employing carbon-11-labeled glucose to
study cerebral glucose transport and metabolism in vivo, which were described
in the previous Progress Report (PR 9, C-1, C-3, C-6), have continued. An
objective of the studies currently in progress is to further investigate the
validity of the model through processing of additional data collected from
animals and human patients. A second objective is to study the effectiveness
of the parameter-estimation procedures of the model for differing radioglucose

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injection time courses. For this purpose, computer simulations of detector responses to bolus stimuli have been employed. Three primary model parameters are estimated from the relationship between the blood glucose activity and total head activity: the ratio of forward-to-reverse fluxes across the blood-brain barrier, the extravascular free-glucose compartment exchange rate, and the metabolic utilization rate. The simulation studies revealed that these three parameters can be distinguished in the detector response to a bolus injection, but that a continuous infusion presents difficulties in parameter estimation for the present form of the model due to count-rate limitations and parameter inseparability.

Additional experiments are being conducted to investigate the transport properties of the blood-brain barrier over a range of blood-glucose levels by measuring the unidirectional flux following a carotid-artery bolus injection[3] of radioglucose. By fitting this data to the Michaelis-Menten equation[3] for carrier-mediated membrane transport, the kinetic constants K_m and V_{max} can be estimated. A computer program to solve the nonlinear parameter-estimation problem has been implemented on the Radiation Sciences minicomputer (B-9).

Future plans include an investigation of any necessary modifications in the present form of the glucose model to allow the use of positron-emission transaxial tomographic data collection (B-13). In this way, it is hoped that measures of glucose transport and metabolism can be determined on a _regional_ basis.

The methodology developed for the glucose studies is also being investigated for its potential usefulness in the study of transport and metabolism of other metabolic substrates in brain, such as acetoacetate and amino acids, for which cyclotron-produced isotopes are available and for which metabolic information in the physiological literature is presently lacking.

[1] M. E. Raichle, K. B. Larson, M. E. Phelps, R. L. Grubb, M. J. Welch, and M. M. Ter-Pogossian, "In-Vivo Measurement of Brain-Glucose Transport and Metabolism Employing ^{11}C-glucose," _American Journal of Physiology,_ in press. Also published as BCL Monograph No. 234, December 1973.

[2] K. B. Larson, M. E. Raichle, M. E. Phelps, R. L. Grubb, M. J. Welch, and M. M. Ter-Pogossian, "A Mathematical Model for In-Vivo Measurement of Metabolic Rates Using Externally Monitored Radiotracers," _Proceedings of the Third International Conference on Data Handling and Image Processing in Scintigraphy,_ U. S. Atomic Energy Commission, in press. Also published as BCL Monograph No. 235, April 1974, and submitted for publication in a future volume of _Computers in Biomedical Research,_ Stacy and Waxman, eds., Academic Press, New York.

[3] A. L. Betz, D. D. Gilboe, D. L. Yudilevich, and L. R. Drewes, "Kinetics of Unidirectional Glucose Transport into the Isolated Dog Brain," _American Journal of Physiology,_ vol. 225, pp. 586-592, 1973.

B-13. Positron-Emission Transaxial Tomography

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            S. C. Huang, BCL
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Support: RR 00396
            HL 13851

        A prototype detection system for performing transaxial emission
reconstruction tomography was designed, constructed, and tested. The
system consists basically of a hexagonal array of twenty-four 5- x 5-cm
NaI(TI) crystals which surround the cross-section of interest in the object
to be studied. Each directly opposing set of detectors is connected to in-
dividual preamplifiers, amplifiers, single-channel analyzers, and a single
coincidence circuit. The coincidence circuit establishes an "electronic
collimation" for the detection of the annihilation radiation (two 511 deV
photons emitted simultaneously at $180°$) from positron-emitting radionuclides
which lie in a well-defined region between the two detectors. The coincidence
detection of the annihilation radiation is performed in a transverse and
angular direction by rotating the object on a computer-controlled platform
in the plane of the hexagonal array. The data are collected, sorted, and
processed by an Interdata Model 70 minicomputer which is interfaced to the
tomograph, to reconstruct the radionuclide distribution in the cross section
examined.

        The accuracy, efficiency, and other design criteria were evaluated
with reconstruction studies of phantoms with known shapes and radionuclide
concentrations. The system was also evaluated in animal studies (mongrel
dogs) using the positron-emitting radiopharmaceuticals $^{13}NH_3$, ^{18}F, $C^{15}O-$
hemoglobin, and $H_2^{15}O$, which concentrate in the myocardium and liver, bone,
blood, and soft tissue, respectively.

        A larger system is presently being built which will be applied to
human subjects. In the new system, the subject will remain stationary and
the detection system will be rotated.

C.   Monitoring the Critically Ill

C-1.   SICU: Evaluation

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Support: RR 00396
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     In its first fifteen months of clinical trial, the cardiothoracic
surgical intensive care unit (SICU) system has performed well and has been
effectively used by the clinical personnel. The efforts described in the
following subsections have been directed toward the further development of
a cost-effective computer-based system for improving the care and study of
the critically ill. Over the past year considerable experience has been
gained in identifying and finding solutions for both technical and "human
factor" problems. The development of a remote cart for extending the SICU
data-gathering capabilities to other clinical settings has proceeded through
the design stage, and the cart is now under construction (see C-7); the necessary
programming has also been initiated (see C-8). Indications are that signi-
ficantly improved cost effectiveness can be achieved for the SICU by later
applying to it the more advanced computer and the emerging software now being
developed for the satellite cart. Planned research efforts in the SICU have
been initiated but hampered by the necessity to redesign the ultrasonic
spirometer (see C-13) and by technical difficulties in completing the thermo-
dilution system for cardiac output (see C-12). Both instruments are now
near completion and should yield useful information within a few months.

     An engineering evaluation of the SICU patient monitoring system has
continued since its installation, and the first six months' experience has
been reported. [1] Now, over fifteen months of continuous use, there have
been a total of twenty unintentional interruptions of patient monitoring
(hard failures) for periods ranging from three minutes to several hours. A
careful documentation and analysis procedure has yielded specific diagnoses
in most cases, as follows:

No.	Cause
4	intermittent short by solder flake on PC board
4	CPU timing drift
4	large line-transients, 2 during severe electrical storms
2	power-supply failures
1	software error on program change
1	console strobe line artifact
1	illegal drop through background level on interrupt
1	sample clock failure or disabled interrupt (not resolved)
2	documentation waived for clinical priorities

The mean time between these patient monitoring failures has been 540 hours, and the total "down time" has been less than 36 hours over fifteen months. A soft failure has been stringently defined by us as any failure of any system function, no matter how trivial, but not causing any interruption of patient monitoring. There were 31 such soft failures detected. Some were as inconsequential as a ten-second loss of a displayed waveform or a spurious chart-recorder turn-on; others were as serious as a disabling of the background functions, with continued patient monitoring. The mean time between soft failures has been 360 hours. The frequency of both types of failures has decreased markedly over the past seven months. There has been only one failure (soft) over the past 840 hours; it was apparently caused by a large line-transient during a severe electrical storm.

Since the computer system was installed, admissions to the SICU have increased by 20% without any increase in nurse staffing, according to the admission/discharge logs for the interval January 22 through June 24 for 1973 and 1974. Excluding four extremely ill patients who were in the SICU more than 10 days in both periods, the average length of stay in the unit has been 2.6 days over the past five months, compared to 3.2 days for the same period one year ago. The estimated saving in nurse staffing is approximately offset by other system support personnel including a part-time engineer, a part-time programmer, and part-time technical assistants responsible for maintenance and repair of the computer system, instruction of clinical personnel, maintenance and calibration of transducers, and interfacing the patient to the system on admission to the unit. Full 24-hour coverage is provided by a part-time technician and one medical student. Based on a 60-month amortization of the incremental hardware cost and assuming an occupancy of 75% of capacity (actually 77% over past five months), the cost of the computer system would be only $10 per patient-day or $26 for an average length of stay.

Not all functions of the monitoring system are used equally well. Fewer than half of the physicians use the trend display capability effectively. This is partly due to unfamiliarity with the displays, but inquiries indicate that it is mostly due to the necessity of altering traditional procedures by leaving the bedside to get the information. The necessary programming (see C-4) has been started to provide trend data at the bedside video display, which the recent addition of a disc to the system (see C-3, I-5 and I-6) renders practical. In contrast, the unique bed-select option, which allows any patient's data to be displayed at any bedside, is highly regarded in this four-bed unit, where nurse coverage averages 1.5 nurses per shift on weekdays and only one nurse per shift on weekends. During the time necessary to solve and correct spurious bed-select switching due to defibrillator discharge interference (see C-3), the staff elected to live with the problem by alerting all users to the hazard of failing to note the switched data during resuscitation efforts rather than permit temporary defeat of this feature, to eliminate possible confusion.

As experience has been gained with this system, a number of worthwhile improvements have been suggested by the clinicians. This confirms the necessity of flexibility as a design goal; and the relative ease with which such changes have been incorporated suggests that it was given adequate attention here.

[1] V. W. Gerth, R. W. Hagen, and L. J. Thomas, Jr., "Engineering Evaluation of a Computer-Based Surgical Intensive Care Monitoring System," Proceedings of the 26th Annual Conference on Engineering in Medicine and Biology, Minneapolis, Minnesota, p. 175, October 1973.

C-2. SICU: Personnel Training

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

Support: RR 00396

A detailed User's Manual[1] has been in routine use by the clinical personnel since it was completed and released last fall. Because of rapid personnel turnover, however, the most effective instruction continues to be by individual interaction with the staff. In addition, several formal sessions have been held to acquaint the users with option changes and to solicit suggested improvements. One freshman medical student has been thoroughly trained to assist a BCL technician in sharing off-hour coverage for routine patient interfacing to the system and for trouble-shooting.

Revision of the User's Manual to incorporate system changes, and the writing of a Technician's Manual for expediting the training of assistants, will be completed early next year.

[1] T. F. Schuessler and L. J. Thomas, Jr., "User Manual for Computer-Based Surgical Intensive-Care Monitoring System," BCL Monograph No. 220, October 1973.

C-3.   SICU: Hardware Modifications

Personnel :   J. M. Pexa, BCL
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Support: RR 00396

A number of minor changes have been made to the monitoring hardware during the past year to improve operating performance and also to expand the capabilities of the system. Circuit changes were made on the Display Parameter Select Buffer boards located in the bedside logic files, to make the circuitry immune to electromagnetic interference generated from the defibrillators located at the bedsides.

The bed-select panel on the display package has been redesigned to overcome the short lifetime characteristics of the incandescent lamps used in the original configuration. An LED array was employed in the new design.

The bedside logic files were modified to provide optical isolation in the signal lines to and from the bus terminals located at each bedside. This provides isolation between the patient ground and the communication ground. Previously, this isolation had been provided on the Patient Analog Interface board in the bedside logic file, but the change was made because the input amplifier on the board was not able to completely reject the common mode signals that were found to be present.

A disc controller and Pertec disc unit (PR 9, J-2) were added to the PC-1200 computer system.

C-4.   SICU: Software

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              J. J. Schier, BCL

Support: RR 00396

More extensive documentation of the SICU software has been in progress to facilitate its translation to TI 980 order code by a programmer not previously familiar with the system (see C-8). The Artronix OS/PC Programming System is used to generate highly readable assembly listings from the original LAP6-PC version.

Over the past year a number of additions and modifications of the SICU system have been made to honor requests of the clinical personnel and improve some of the algorithms.

1. The QRS detection subroutine was modified to improve detection reliability where pacemaker artifacts merge with the R wave. This was necessary since the previous pacemaker-artifact rejection scheme sometimes resulted in also rejecting the nearly coincident R wave, a condition all too often encountered with the use of demand pacemakers. In addition, the AGC sequence was altered to permit embedding it in the QRS detection subroutine and thus facilitate more expeditious synchronization with beat detection. The result is superior noise rejection.

2. The arterial-pressure processing subroutine was altered to improve pulse detection in the presence of atrial fibrillation. Multiple records of arterial pressure in the presence of atrial fibrillation were analyzed to re-evaluate pulse-pressure threshold criteria for satisfactory acceptance of small pulse-pressures during the intermittent sequences of rapid beats. A pulse pressure criterion of 16/27 times the exponential pulse-pressure average was found to be most satisfactory.

3. The capability to display and obtain hard copy of any two parameter trends simultaneously was requested by two of the physician users and was implemented.

4. Automatic date and time annotation of all strip chart recordings was requested and provided by means of a software routine to draw easily readable numeric characters with the recorder pens at the termination of each recording. The character generation and formatting will be relegated to hardware in the future. The date and time information is taken from the (100-year) software clock-calendar.

5. Multiple changes in various background routines were made to capitalize on the expanded capability resulting from the installation of a moving-head disc. The operating system was previously "tape-bound". Further improvements now in progress include extended storage of trend data and video formatting of this data for presentation at the bedside.

6. Programs have been written and are in use for manipulation and plotting of trend data off line using a Spear PC (see C-9). The data collected is used to study parameter correlations and interactions. Current attention is directed toward exploring the relation between metabolic demands and circulatory instability in the first twelve hours following open-heart surgery.

C-5.   SICU: Mechanical Systems

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

Support: RR 00396

During the past year a number of additions and refinements to the mechanical systems of the Barnes Hospital Surgical Intensive Care Unit have been proposed and implemented. These efforts have primarily centered upon installation of hardware to assist personnel of the SICU in the performance of various tasks. In addition, a program of monitoring-hardware maintenance has been initiated to repair damage resulting from continual use. The equipment has proven to be quite rugged in 15 months of use, except for the cabinetry surface-finish.

Within each patient room of the SICU, specially designed racks have been installed to provide efficient bedside mounting of patient transducers and other associated hardware. These racks neatly confine the apparatus they support, thereby eliminating an equipment tangle at the bedside.

At the doctors' discussion station, a desk and shelf area have been installed to more efficiently organize and utilize the available space. With the addition of more monitoring hardware, space in this area is at a premium.

C-6. <u>SICU: Catheter-Transducer System for Pressure Measurements</u>

Personnel: A. L. Bodicky, BCL
            T. F. Schuessler, BCL

Support: RR 00396

The empirical equation developed by Geddes[1] expresses frequency in terms of physical parameters specifically applied to monitoring systems such as ours. At the resonant peak:

$$f_R = \frac{1.4 \times 10^3 d}{\sqrt{V_d L p}}$$

.where d is the inside line diameter; V_d the volume modulus of the system; L the total length of the line from tip to transducer; and p the density of the liquid.

Tests show that our present system with a six-foot line (.070" ID, .024" wall, high-density polyethylene) peaks (normalized amplitude of 3.3), at 11.5 Hz, with amplitudes of 1.25 and 2.50 at 5 and 10 Hz respectively.

Experiments were also conducted on an eight-foot line (with an internal diameter of .093"; .036" wall of high-density Teflon) which was needed for clinical reasons. Improvement of the frequency characteristics was obtained by moving the resonant frequency up so that the approach ramp to the peak would not be more than several mm of Hg. With the stiffer and wider eight-foot Teflon line the resonant peak has been raised to 20 Hz. Even though the resonant peak is higher in amplitude (4.8), marked improvement in the mid-range response has resulted; normalized amplitudes are 1.10 and 1.35 at 5 and 10 Hz respectively.

The pressure transducers in clinical use were tested to establish the reason for excessive drift when used for low-pressure measurements such as central venous and left atrial pressures. It was established that 20 out of 26 transducers showed temperature drift greater than the manufacturer's specifications. Considerable interaction with the manufacturer has resolved the discrepancy between their testing procedure and ours, with the result that they have altered their procedure. The defective transducers have been replaced, and no further drift problems have been encountered. Drift of <0.1 cm H_2O per degree centigrade is quite satisfactory for clinical purposes.

[1] L. A. Geddes, <u>The Direct and Indirect Measurement of Blood Pressure</u>, Year Book Medical Publishers, Chicago, p. 52, 1970.

C-7. Design of a Satellite System for Clinical Physiologic Research

Personnel: L. S. Sandler, M.S., Electrical Engineering
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            L. J. Thomas, Jr., BCL

Support: RR 00396
            Washington University

The design objectives of the computer-based satellite system for Clinical Physiologic Research included a desire to have the system be flexible enough to meet various clinical research needs, be powered by one general hospital branch circuit and have the total hardware cost in the $15,000 range.[1]

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

Video information generation and mass storage of data are provided to the satellite system through serial communication with the SICU at a considerable cost saving. The serial link is capable of full duplex operation, and consists of two transmitter/receiver modules which plug into the TI 980A I/O chassis and the SICU bus, and a two-twisted-pair cable.[2] The principal mode of operation is to transmit data from the cart to the SICU disc on a scheduled basis. This is accomplished by slaving both systems to the same clock source, which is the vertical sync signal from the SICU video display system. The TI 980A can be loaded from the SICU system using the Teletype bootstrap loader available in the TI 980A.

The total 120-volt peak current required for the system is 11 amperes; the total hardware cost is $15,500.

[1]L. S. Sandler, "The Design of an Interactive Computer-Based System for Clinical Physiological Research," BCL Monograph No. 240, May 1974.

(2) J. Pexa, "A Serial Link for SICU/Satellite Computer Communications," BCL Monograph No. 241, June 1974.

C-8. SICU: Translation of PC-1200 Patient Monitoring Programs for the TI 980

Personnel: W. A. Lavender, BCL
           L. J. Thomas, Jr., BCL

Support: RR 00396

SICU software developed on the PC-1200 computer is being translated for use with a TI 980 satellite system: subroutines for QRS detection, heart rate calculation, and arterial pressure parameters have been recoded.

The faster execution times and larger instruction set of the TI 980 result in significant improvements in memory utilization and processing speed over the PC-1200 version of the SICU system programs. For example, the QRS detection subroutine for four beds requires 709 twelve-bit memory locations plus 21 index registers, and has a worst-case time of 1488 μs, in the PC-1200; equivalent figures for the TI 980 are 585 sixteen-bit words and 470 μs. Assuming that these differences can be extrapolated to the other system functions, eight patients could be comfortably monitored by the TI 980, compared with the four-patient capability of the PC-1200 system.

C-9. SICU: Modification of a Spear PC for Trend Plots

Personnel: B. F. Spenner, BCL
           J. L. Robinson, BCL

Support: RR 00396

In mid-1973 the Barnes Hospital Cardiac Catheterization system was updated with the replacement of the Spear PC (PR 8, F-1) by an Artronix PC-1200. This replacement provided a Spear PC which could be used to plot trend data gathered by the SICU system (PR 9, D-5). The machine also serves as an entry and edit system for LAP6 manuscripts.

Modifications to this PC included a complete refurbishment and calibration of the machine main-frame and peripherals. The plotter interface, originally constructed to operate a Calcomp plotter, was adapted to operate a Houston plotter.

C-10. Revision of LINC/TI 980A Interface

Personnel: G. Roa, BCL
             G. C. Johns, CSL

Support: RR 00396
             NS 07498

Both BCL and CSL have become interested in utilizing the TI 980A, a small general-purpose computer built by Texas Instruments, which currently appears to be flexible and cost-effective. The SICU project "Design of a Satellite System for Clinical Physiologic Research" (see C-7) provides an excellent opportunity to use and evaluate the TI 980A for physiologic data processing.

Translation of PC-1200 SICU programs and other programming (see C-8) is and will be done using TI 980 software designed to be used with a teletype with paper-tape capability. Within the past year, CSL designed a system that greatly speeds up programming by using a classic LINC computer programmed such that the TI 980A can operate as if it were communicating with a very fast teletype with paper tape, with the added advantages to the programmer of LINC tape, display console, keyboard and usually a fast printer.

The fast teletype simulator system includes a LINC program called TILINC[1] and the hardware serial-data communications interfaces, TI 980A/ LINC and LINC/TI 980A. The TILINC program is documented and available on LINC tape, and the TI 980A/LINC interface is documented and easily reproducible. The LINC/TI 980 interface is currently being redesigned for use in the SICU project and easy replication for other users. The current LINC/TI 980 interface design uses an LSI "Universal Asynchronous Receiver Transmitter" (UART) which has separate shift registers, each with its own holding register.

[1]S. M. Schuetze, "TILINC," CSL Technical Memorandum No. 203, September 1973.

C-11. Modelling of Peripheral Artery Properties

Personnel: R. J. Arnzen, BCL
            R. R. Auer, Jr., BCL
            F. Bekhrad, B.A., Biomedical Engineering
            L. J. Thomas, Jr., BCL, Physiology and Biophysics

Support: RR 00396
            Washington University

The fact that differences as large as 55 mm Hg. may be observed between direct systolic arterial blood pressure measurements (via indwelling radial artery catheter) and indirect measurements (via occlusive cuff) has been well documented by personnel working in the Barnes Hospital Surgical Intensive Care Unit. Presently, in the literature regarding this phenomena, no satisfactory explanation exists to completely describe the probable cause of these differences. In an attempt to more fully understand and explain the fundamental nature of this problem, a series of experiments has been conducted over the course of the past year. The data obtained from these experiments have led to conclusions which are felt to be a rational explanation of the cause of the observed differences.

The measurement sites of interest are the arterial branches of the arm. One of these branches, in addition to the left ventricle and aorta, was modelled through the employ of a cardiovascular simulator whose resistive, capacitive, and inductive (R-C-L) properties could be varied to study their influence on the problem. A Starling resistor element in the arterial branch modelled the occlusive cuff and collapsible arterial segment. The phenomena of interest were recreated with the simulator. More significantly, it was shown that the introduction of a cuff at the arterial site causes an alteration of the effective RCL properties of the branch, resulting in measurement of the pressure existing at the origin of the branch (the subclavian artery in this case). Removal of the cuff re-establishes the RCL characteristics of the artery, with a resultant alteration of the arterial source pressure at sites along the artery through wave propagation mechanisms (i.e. pulse steepening).

Explanation and model demonstration of this phenomenon should remove the "mystery" that some personnel of the SICU have expressed regarding the observed differences. Moreover, it should re-establish in these people a belief in the computer-generated arterial pressure parameters derived from direct measurement and their relation to the more traditional cuff technique.

These model studies have been limited for technical reasons to semi-quantitative parameter estimations, but have served well to establish the essential relations. A revised apparatus permitting more precise quantification in continuing studies is now being developed.

C-12. Cardiac Output Via Thermal Dilution

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

Support: RR 00396
            Washington University

        In-vitro testing of the bridge/amplifier instrumentation has been
completed using commercially available thermodilution catheters. Analysis
of this data revealed that the non-linear response curve of the thermistors
must be compensated for in order to achieve the required accuracy in
the calculation of cardiac output. A considerable time delay was experienced
due to inaccurate data published by the manufacturer of an operational amp-
lifier which is used in the instrumentation.

        The calibration of electromagnetic flow probes is being completed
in the surgical animal laboratory. Flow data will be used as the standard
in determining errors in the measurement of cardiac output via the thermo-
dilution method. When suitable linearization is achieved, in-vivo tests will
begin in the surgical animal laboratory.

C-13. Redesign of Ultrasonic Gas-Flow System

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

Support: RR 00396

        A Statham Instruments, Inc., Ultrasonic Spirometer was evaluated for
monitoring the respiratory gas flow of patients in the SICU. This evaluation
revealed serious performance limitations, the most troublesome being zero
flow instability. Investigation pointed to several problem areas in the
design which prompted the initiation of a redesign effort. The redesigned
instrument has been assembled and tested. The results of the testing show
a drift reduction by a factor of greater than 20 to 0.5% of full scale;
however, a further reduction to 0.1% of full scale is necessary to guarantee
long-term tidal volume errors of less than 5% on integration of the flow
signal. The redesigned version was favorably received when presented [1]
and demonstrated at a conference with Statham Instruments, Inc. and investi-
gators from five other institutions with similar interests and objectives.

The flow transducer, which is now the limiting component, is currently being redesigned to meet or exceed the specifications developed at the conference.

When the instrument is completed it will be used in the SICU to derive tidal volume, respiratory rate, and total thoracic compliance as well as to detect airway leaks, obstructions and respirator malfunction.

[1]R. W. Hagen, "A Redesigned Ultrasonic Spirometer", presented at the Ultrasonic Spirometer Conference sponsored by Statham Instruments, Inc., Los Angeles, California, April 1974.

C-14. A Color Non-Fade Display for Operating Room Monitoring

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

Support: RR 00396
            Barnes Hospital
            Washington University

A display system has been designed for use in patient monitoring during cariothoracic surgery; it provides eight multi-color traces in either a static or scroll mode. The system can be configured as two fully redundant four-channel systems or as an eight-channel system to provide high reliability and flexibility for different surgical procedures.

An analog signal conditioner is provided for each channel which includes independent gain and position controls to aid in setup and calibration. The conditioned analog signals are then converted into CCTV video format by two commercially available American Optical Display Processors. The video waveform for each channel is brought out prior to mixing for encoding as one of seven colors obtained from linear combinations of red, green, and blue.

The controls of the A-O processors are remoted to a control panel which includes selector switches for color of each individual trace and generation of five scale calibration lines. Two Conrac 19" RGB monitors are used in either a parallel or a split channel mode, depending upon the needs of the surgical procedure. The mode is selected for each monitor by a switch on the control panel.

The A-O processors have been tested, and the remainder of the system is in final construction.

D.   Communications for Information Processing

D-1.   Digital Communication Systems

Personnel: D. L. Snyder, BCL
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             K. A. Lewis, M.S., Electrical Engineering

Support: RR 00396
             GK 32239

         Work on the optical communication link described previously
(PR 9, E-2) has continued. During the year, the link has been improved
from a short-length path device that was capable of transmitting repeated
non-random data blocks, to a medium-length path system capable of trans-
mitting random data words. The system presently takes 30,000 samples per
second of an analog signal at the input, and outputs these samples in a
12-bit digital format with word and parity check flags suitable for inter-
facing with a digital computer. In addition to the design and construc-
tion of the units first to convert the analog signal to a format suitable
for the optical transmitter, and secondly to convert the output of the
optical receiver to computer-usable signals, there were major changes
made in the receiver itself. Specifically, there were changes in the
integrating part of the correlation-detector using different circuitry to
obtain true integration of the signals, and the integrated-circuit phase-lock
loop for timing was replaced by a circuit which generates a clock
synchronized to the zero crossings in the signal independently of the data
pattern. Presently, the bread-boarded version of this improved system is
being converted to a semi-finished form for testing with real data over an
optical path length of about 500 meters.

         Theoretical studies of optical communication systems were also
performed, and two papers describing this effort have appeared.[1,2]

[1] R. H. Forrester, Jr. and D. L. Snyder, "Phase Tracking Performance of
Direct-Detection Optical Receivers," IEEE Transactions on Communications,
vol. COM-21, no. 9, pp. 1037-1039, September 1973.

[2] E. V. Hoversten, D. L. Snyder, R. O. Harger, and K. Kurimoto, "Direct
Detection Optical Communication Receivers," IEEE Transactions on Communica-
tions, vol. COM-22, no. 1, pp. 17-27, January 1974.

D-2.   Sampling and Reconstruction of Physiological Signals - Analysis
        of Sample Jitter Error

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

Support: RR 00396

Processing of physiological signals by digital computer is preceded
by sampling and analog-to-digital conversion. The digitized data often
provides a convenient source for replication of the original waveshape
via strip chart recorder, plotter, or oscillographic display. Fidelity of
the reconstructed waveshape can be degraded by introduction of time jitter
into a normally periodic sample plan.

Sample clock instabilities, traffic-induced variation in delay through
a communications network, and asynchronous cascade sampling are example
mechanisms which introduce sample-time jitter.

A sampling and reconstruction model was formulated following the work
of Kahn and Liu.[1] The mean-square error criterion was used as a perfor-
mance measure for the comparison of optimal and sub-optimal reconstruction
of signals subjected to sampling with time jitter. Results were obtained
for a variety of input spectra, sampling rates, jitter distributions and
jitter amplitudes.[2]

Relevance of the mean-square error criterion was examined. The
Chebyshev Inequality was used to relate mean-square error to peak amplitude
error. Although clinical ECG's subjected to binary distributed sample jitter
exhibited distortion when reconstructed via strip chart recording, the cal-
culated probability bound of exceeding a given peak error was found to be
somewhat pessimistic. A tighter probability bound and/or a better stochastic
approximation of the signal may enhance the usefulness of the mean-square
error as a fidelity criterion for physiological signals.

[1] R. E. Kahn and B. Liu, "Sampling with Time Jitter," Princeton University
Communications Laboratory Technical Report No. 8, June 1964.

[2] G. J. Blaine, "High Speed Digital Communications--A Design Study Applied
to the Hospital Environment," D.Sc. Dissertation, Department of Electrical
Engineering, Washington University, St. Louis, Missouri, May 1974.

D-3.   Network Aspects of Periodic Acquisition and Distribution of Data

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

Support: RR 00396

The hospital environment argues for an information system approach based on a distributed computer network. A distributed network readily satisfies the requirements of autonomy, takes advantage of the natural clustering of activities and allows current technology to be applied as additional areas are encompassed by computer processing.

A communications structure composed of local and global components was postulated (PR 7, D-3). The intra-area component, the Local Bus (PR 7, D-3, PR 8, D-3 and PR 9, D-2), has been developed and successfully applied to a patient monitoring environment. Network concepts applicable to the global communications requirements have been considered.[1] Cost, contention and delay are defined as basic performance measures. The Washington University Medical Center was used as an example hospital facility for performing quantitative and qualitative comparisons of the canonic network structures.

The tree network structure was modeled to determine relationships between topology, traffic loading, channel rate and delay. The modeling assumed the input-output character of a Local Bus to define source/sink characteristics. An approach was developed to calculate bounds on peak variation in transmission delays as a function of traffic-induced conflicts in the network. The variation in delay is of particular importance to the acquisition and distribution of patient monitoring data, since recon-struction error is related to sample jitter (D-2).

In a design context, the delay bound can be utilized to determine the required channel transmission rate for a specific network topology, given a sample rate requirement and the allowed sample jitter.

[1]G. J. Blaine, "High Speed Digital Communications--A Design Study Applied to the Hospital Environment," D.Sc. Dissertation, Department of Electrical Engineering, Washington University, St. Louis, Missouri, 1974.

D-4.   Teleprocessing for the LINC-8

Personnel: E. Van Patten, BCL

Support: RR 00396

         The LINC utility program for maintenance of IBM System/360 Model
65 disc files (PR 9, E-5) as well as the LINC communications subroutine[1]
have been adapted for the LINC-8. They run in LINC mode.

         The timing loops within the teleprocessing routines were revised to
conform to the faster memory cycle time of the LINC-8. Also, the routine
which handles teletype output required revision. In all other details,
the LINC-8 routines are identical to the LINC programs.

[1]E. Van Patten, "360/LINC, LINC/360 Communications Subroutine," BCL
Monograph No. 112, May 1969.

E.   Cardiac Catheterization Laboratories

E-1.   Macromodular Video Digitizer

Personnel: R. J. Arnzen, BCL
             B. R. Hieb, M.D., Medicine

Support: RR 00396
             Jewish Hospital

`There are, presently, a number of extremely time-consuming data processing tasks associated with the analysis of photographically recorded fluoroscopic images of the heart obtained during routine cardiac catheterization procedures. It is anticipated that many of these hand processing tasks could be eliminated by storing away, in real time, digitized samples of video data generated at the time of the catheterization procedure. Presently a number of problems require resolution before design of such a system is feasible; these center on storing away in real time, on a digital disc, samples of the analog video signal. There are essentially two aspects of the problem being investigated: 1) determining the minimum number of samples required to reconstruct the digitized image with a resolution that will allow sufficient accuracy to be achieved by processing algorithms, and 2) application of data compression techniques to minimize the resultant data rate.

The success of this plan depends quite heavily on how well the video data being sampled can be characterized. In order to determine the properties of this kind of data, a macromodular system has been built and put into operation this past year at the cardiac catheterization laboratory of Jewish Hospital. The system is basically two 4K x 12-bit core memories with associated address incrementing, load, and compare modules. With 8K of 12-bit storage available, up to 16,000 samples of video data can be taken by packing two 6-bit samples into each 12-bit memory location.

To make the sampling process efficient and thereby more effectively utilize the limited storage available, provision has been built into the word assembler and synchronization hardware to allow selection of a displayed rectangular area within the video format from which samples are taken each odd video field. As its name suggests, the word assembler and synchronization system combines two 6-bit samples of video data into a 12-bit word in preparation for delivery to one of the two macromodular memories which alternately store the data. In addition, this sychronizer issues commands to a high-speed analog-to-digital converter from which the 6-bit digital samples are derived. Preceding each macromodule store command is a test to determine if the respective memory is full; if so, the sampling stops. Following each storage completion, an indexing of the memory address which will be used for the subsequent test and store is initiated.

Sampling of data commences when a switch is closed by means of either a hand-held or a foot-operated unit. At the beginning of the first even field following the "start" command, the thumbwheel switch settings defining the boundaries of the rectangular sampling region are stored in memory location 0. Like the data, the four boundary values are 6-bit numbers assembled into two 12-bit words. This information is later used for the temporal and spatial reconstruction of the digitized image. As the next odd video field comes up, samples begin to be stored and continue until all memory locations have been filled.

Presently, it is possible to sample up to 128 points per video scan line, the limiting factor being the 1-μs cycle time of the macro-modular core memories. However, two full frames or up to 31 partial frames (four lines each) may be sampled using the 8K of memory available. This will provide ample data for investigation of both the static and dynamic characteristics of the digitized signal. Programs are currently being developed to process data gathered by the video digitizer.

E-2. PC Catheterization Laboratory Revisions

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             B. R. Hieb, M.D., Medicine
             J. L. Robinson, BCL
             B. F. Spenner, BCL

Support: RR 00396
             Jewish Hospital

Both the Jewish Hospital Cardiac Catheterization Laboratory computer system (Cath Lab System) and the new Washington University Cath Lab System are undergoing improvements and refinements. Important hardware additions have simplified operation of the system, decreased time delays during data acquisition, and made possible more extensive future software development.

A Pertec disc, controller and interfaces (I-5, I-6) have been added to the system. Because of the "LINC simulator" feature of the disc interface, no program changes were required. The file management part of the program was rewritten, however, to simplify data management. Delays due to tape motion are no longer apparent to the system user. Software changes, taking advantage of the disc's speed, are being made to reduce the possibility of losing data as a result of user error. In addition, the capability of rapid swapping of overlays will permit addition of many new data analysis overlays to the existing program.

The capability of remote operation for both the Washington University and the Jewish Hospital Cath Lab systems has been added. Since March 1973, the computer at Jewish Hospital has successfully been operated remotely from

the lab by the technician who operates the amplifiers and recorder. A Cardiology Fellow is no longer required to operate the system at the computer console.

Software changes have been made; these consist of changes to correct programming errors and to improve the system operation. Numerous changes have been made to accommodate new equipment at the Washington University Cath Lab (E-4); as a result, two versions of the Cath Lab software are evolving, although their differences at this point are minor. Improvements in both versions include updated empirical constants used in valve area calculation, changes in the numeric characters to improve display legibility, and modification of the filing system for use with the new disc.

Further software corrections, improvements and additions are now being completed. Among these are additions to the Cath Lab program of data analysis overlays written in FORTRAN at the Jewish Hospital Cath Lab, and additions, corrections and improvements developed at the Washington University Cath Lab (E-4).

E-3.   Scope-Oriented Version of PC MUMPS

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             W. E. Long, BCL

Support: HS 00074
             Jewish Hospital

The single-user PC version of MUMPS was modified from an 8K, Beehive-oriented system to a 12K system oriented for keyboard, storage scope and hard copy unit. This new version of MUMPS is compatible with the existing Catheterization Laboratory Systems' standard input and output devices.

Several changes were made to MUMPS. These include addition of software scope drive routines and appropriate character buffers. Additional commands were implemented to improve text editing. A "produce hard copy" command was added to the language to facilitate output of results. Further language modifications permit a conditional criterion on all commands and a Boolean "not" prior to all relational operators.

Changes were also made to make the system more compatible with the Pertec disc system. These modifications include automatic presetting of disc blank selection and the ability to write-protect desired disc banks.

E-4. Washington University Cardiac Catheterization Laboratory System

Personnel: G. H. Brandenburger, BCL

Support: RR 00396

Work on the new Washington University Cardiac Catheterization Laboratory System (Cath Lab System) began with the acquisition of an Artronix PC-12/7 computer and associated hardware and software in September, 1973. Design errors in the Artronix instrumentation interface and analog multiplexer were discovered and corrected. The software supplied was essentially the same as that supplied to the Jewish Hospital Cath Lab System. Numerous software changes have been made by BCL as a result of differences between the Honeywell amplifiers and recorder at Washington University and the corresponding Electronics for Medicine equipment for which the software was written at the Jewish Hospital Cath Lab. Further software changes were made to compensate for differences in the manner in which the Honeywell equipment is operated at the Washington University Cath Lab.

Software refinements and error corrections have been made, and new changes and features will be added soon. Remote operation of the system from the lab is now possible, and a cart is being constructed to make remote operation more convenient.

Considerable time and effort have been devoted to evaluating the Cath Lab System, and deciding upon the direction of future changes. Much experience has been gained from the highly successful operation of the Jewish Hospital Cath Lab System (more than 200 cases have been analyzed since June 1972). Numerous cases have been analyzed with the Washington University Cath Lab System, and experience from both labs suggests changes to be made in the future. Particularly at the Washington University Cath Lab, it has become very apparent that different cardiologists have different approaches and philosophies and, hence, different requirements. To be generally acceptable, a Cath Lab System is needed that can be tailored to each individual cardiologist's requirements and which requires minimal human intervention, particularly during data acquisition.

A preliminary design of all new hardware for data acquisition has been developed, while the specifications for a completely new software system have been formulated. During the development period, the new system is being operated by BCL personnel at the Washington University unit.

F.   Mass Spectrometry

F-1.   Mass Spectrometer Computer System

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             B. L. Shore, BCL

Support: RR 00396
             AM 51159
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             NS 05159
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        The revised version of the PDP-12 mass spectrometry programs (see
PR 9, G-1, 3, and 4) has now been completed,[1,2] and is in general use here
and elsewhere. The original multiple-ion detection programs (PR 9, G-2)
have been extended considerably in scope.[3] Nine mass channels can now be
monitored, with selection of the relative time spent sampling each mass.
Thus peaks of very different intensity can be measured simultaneously with
considerable improvement in the precision of peak ratios, which lowers the
minimum detectible level of stable isotope tracer. Absolute sensitivity has
also increased. Levels of TMS-*myo*inositol as low as two picograms have been
measured with a signal-to-noise ratio of 3:1. This represents a ten-fold
improvement in sensitivity over the original system, partly due to the new
programs, and partly due to use of a higher gain pre-amplifier for the ion
current signal. The revised programs permit mass storage of the data so that
multiple analyses of compounds with different GC retention times are now
possible. The programs have been further adapted to work with a Finnigan
quadrupole mass spectrometer over the full mass range (see F-2). During the
past year, more than 50% of mass spectrometer time at Washington University
has been devoted to multiple-ion detection analyses. Examples include
measurements of stable isotope labelled alanine and glucose in humans
(F-4),plasma levels of anticonvulsive drugs in neonates (F-5), plasma
levels of anti-depressant drugs in hospitalized patients (F-7), and
concentrations of plasticizer in neonate heart tissue (F-8). Two other
laboratories are planning to add the multiple-ion detector circuit to their
mass spectrometer/PDP-12 systems. One laboratory has an LKB-9000; the other
a Perkin-Elmer Model 270-B.

        The plotting programs have been revised for increased flexibility.
The incremental plotter program will handle several sizes of plotter increment,
and has incorporated normalization, background subtraction, and multiple
spectrum plotting capabilities. The Versatec plotting program has an automatic
intensity scaling option, so that low-intensity, high-mass peaks can be
plotted on the same graph with high-intensity peaks, giving a complete
spectrum on one graph without requiring individual selection of scale factors.
This feature is a practical necessity for rapid plotting of GC runs with
many spectra.

Other developments include a spectrum comparison display, where two spectra can be overlayed with variable scaling for visual analysis of their resemblance to each other. This display incorporates the use of graphic data codes, which are interpreted and displayed with no reference to the program that generated the display. The graphic codes can be saved in a file and processed later by other graphic output devices. A Versatec plot program is under development. The codes result in a display with much less flicker. They are also intended to serve as the preliminary developmental stage for a hardware display processor that will free the computer from repetitive generation of displays.

The acceptance of the PDP-12 system in other laboratories, including the current adaption of the system to a quadrupole mass spectrometer at the Research Triangle Institute (F-2), has resulted in the decision to begin development of a new computer system for gas chromatograph/mass spectrometry, applicable to both quadrupole and magnetic scanning mass spectrometers. Since quadrupole instruments are becoming the dominant class of mass spectrometer for medical biochemical analyses, we have purchased a Finnigan quadrupole mass spectrometer for use in the Medical School, in the context of a program of computer system development. The mass spectrometer was badly needed to serve current mass spectrometry needs. The major users of the LKB-9000/PDP-12 system were able to contribute over forty per cent of funding, as well as purchase a Versatec printer/plotter. BCL funded the rest of the mass spectrometer as well as the computer. The computer selected is a Computer Automation Alpha LSI-2, a well-designed, compact, sixteen-bit computer intended primarily for incorporation into systems requiring a dedicated computer. The central processor and memory costs are very low, with a convenient electrical and mechanical bus system for interface design.

(1) W. F. Holmes, B. L. Shore, and R. I. Inselberg, "A General-Purpose Computer System for Gas Chromatograph/Mass Spectrometry," Proceedings of the 22nd Annual Conference on Mass Spectrometry, Philadelphia, Pa., May 1974.

(2) W. F. Holmes, B. L. Shore, W. H. Holland, R. I. Inselberg, and H. J. Weiss, "Washington University Mass Spectrometer Computer System," BCL Monograph No. 236, December 1973.

(3) W. F. Holmes, W. H. Holland, B. L. Shore, D. M. Bier, and W. R. Sherman, "A Versatile Computer-Generated Variable Accelerating Voltage Circuit for Magnetically Scanned Mass Spectrometers. Use for Assays in the Picogram Range and for Assays of Stable Isotope Tracers," Analytical Chemistry, vol. 45, pp. 2063-2071, 1973.

F-2. <u>PDP-12/Finnigan Quadrupole System</u>

Personnel: W. F. Holmes, BCL
            T. J. Odiorne, Ph.D., Research Triangle Institute, Durham, N.C.
            D. W. Rosenthal, Ph.D., Research Triangle Institute, Durham, N.C.
            B. L. Shore, BCL

Support: RR 00396
            State of North Carolina

        The PDP-12 mass spectrometry programs (F-1), originally designed
for the LKB-9000 magnetic scanning mass spectrometer, are being adapted for
use with the Finnigan quadrupole mass spectrometer. The total number of newly
written or modified program lines will represent less than ten percent of the
total lines in the system, due to the modular nature of the existing programs.
The impetus for this development came from Dr. David Rosenthal of the Research
Triangle Institute, who received funds from a Mass Spectrometry Resource Grant
for a new gas chromatograph/mass spectrometer and computer. After evaluation
of the alternatives, he selected a quadrupole mass spectrometer for its combi-
nation of price, high scanning rate, and potential for full mass range multiple-
ion detection. An evaluation of computer alternatives, including the manufac-
turer's system, led to a decision to use the Washington University PDP-12
System. The decision was strongly influenced by the accessibility of the
system to further program development, and the use of the Versatec printer/
plotter for high speed output.

        The multiple-ion detection programs (PR 9, G-2) have been adapted
for full mass range analyses, and are being tested at the Research Triangle
Institute along with the Finnigan/PDP-12 interface designed there. A system
of mass spectrum acquisition and calibration programs is nearing completion.
Two scan modes are being implemented, a continuous mass increment with peak
detection, and increments by integer mass values offset by a selectible mass
defect. Each method is used by one of the two major quadrupole manufacturers,
Finnigan and Hewlett-Packard.

F-3.   Mass Spectrometric File Searches

Personnel: R. I. Inselberg, BCL
             W. F. Holmes, BCL
             J. A. Paskowitz, BCL
             B. L. Shore, BCL

Support: RR 00396

The file search programs for identifying unknown mass spectra (see
PR 9, G-5) have been greatly expanded. The new programs include the ability
to compress the data into a variety of formats that require less storage
space while resulting in increased search speeds. A number of data-compression
formats have been proposed, which involve coding the peak intensities with a
limited number of bits, or selectively removing some of the peaks altogether.
Both methods may be combined. In order to test which data-compression procedure
works best in practice, a number of alternatives can be chosen using the new
programs. Peak intensities may be encoded as 1, 2, 3, 4, or 6 bits, allowing
1, 4, 8, 16, or 64 levels of intensity. Peaks may be removed altogether by
dividing the mass spectrum into a set of equally spaced mass intervals, and
allowing a maximum number of peaks for each interval. Both the size of the
mass interval, and the maximum number of peaks, can be chosen by the user.
If the maximum equals the mass interval, all of the peaks are retained. Thus
a wide range of data-compression formats is possible. The same reference
file can be kept in several compression formats, and the best method determined
in actual practice. Preliminary testing indicates that three bits of peak
intensity (8 levels) with one or two peaks per fourteen-mass-unit interval
is the most effective format for searching, more so than searching with
complete spectra. The reason seems to lie in the fact that high mass peaks
are more unique in identifying compounds, but are generally weak in intensity
and few in number compared with low mass peaks. Data compression tends to
emphasize the high mass peaks relative to the low mass ones. The above
format is also quite conservative of storage space, so that even the largest
reference files could fit on a Pertec dual disc (F-10).

The search procedure is simple. The user selects a reference file
of compressed spectra, and a sequence of one or more spectra for automatic
searching. Spectra from an entire GC run can be searched at once. The
unknown spectra are automatically compressed to the correct data format and
searched one by one. The best matches for each spectrum are displayed, or
printed on a Teletype or a Versatec printer/plotter. The user may specify
certain search parameters : a molecular weight range, the presence of one or
more elements, and elimination from the search procedure of selected masses
or all of those below a minimum mass. Another method of operation has proven
quite useful, where the spectra in a GC run are regarded as a reference file.
One or more known compounds are then used for the "unknown" spectra. The
resulting search detects and locates these compounds in the GC run, without
the time required for searching a large file. This procedure is beneficial
when the experimenter is looking for the presence of a few known compounds,
as when using a drug assay (F-5).

The spectrum interconversion programs between PDP-12 LINC-tape format
and IBM format (PR 8, G-3) were revised so as to allow spectra obtained
with the PDP-12 to be transmitted to the IBM System/360 Model 65 and
converted into standard Aldermaston format on punch cards. These programs
were used to produce punch cards of 87 spectra collected here, which were
contributed to a reference file assembled by Dr. S. Markey of the University
of Colorado Medical Center. We are obtaining this reference file, which
contains nearly 2000 compounds in derivatized form extracted from urine
and blood plasma.

F-4.   In-Vivo Measurement of Gluconeogenesis and Glucose Utilization with
        Stable Isotopically Labelled Alanine and Glucose

Personnel: K. J. Arnold, M.D., Surgery
             D. M. Bier, M.D., Medicine
             D. M. Kipnis, M.D., Medicine

Support: RR 00396
             AM 01921
             GM 00371

The techniques for the separation and detection of tracer amounts of
deuterium and carbon-13 labelled glucose and alanine have previously been
worked out in this program (PR 9, G-6). Validation of the use of these
tracers in determining glucose and alanine turnover rates by comparison to
results with radioactive tracers was accomplished in animals.[1]   By using
stable isotope tracers the hazards of radioactive tracers are avoided in the
patients studied, and patients in whom radioactive tracers are contraindicated
(children and pregnant women) can now be investigated. The speed and precision
of the multiple ion detection system (PR 9, G-2), has been the backbone
of this system.

Application of these techniques has now entered the clinical arena, and
several groups of patients with abnormal glucose and alanine metabolism are
being studied. The ultimate aim is a better understanding of gluconeogenesis
and proteolysis with improved management of patients with disorders in these
areas. Patient groups currently under study are: 1) children with ketotic
hypoglycemia; 2) children with cyanotic congenital heart disease; 3) normal
adults (relating alanine turnover to nitrogen balance). Shortly, postoperative
surgical patients and children with muscular dystrophy will be added to this
study.

[1]D. M. Bier, W. R. Sherman, W. H. Holland, and D. M. Kipnis, "The In-Vivo
Measurement of Alanine and Glucose Turnover with Deuterium-Labelled Metabolites,"
Proceedings of the First International Conference on Stable Isotopes in Chemistry,
Biology and Medicine, Argonne National Laboratory, pp. 397-403, 1973.

F-5.   Measurement of Anticonvulsive Drugs Using the Mass Spectrometer as a
        Specific Ultrasensitive Detector

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

Support: RR 00396
            Washington University

        Mass spectra have been obtained for frequently used anticonvulsants
and compounds used as internal standards. These include phenobarbital,
primidone, phenylethylmalonamide, carbamazepine, ethosuximide, ααdimethyl
βmethylsuccinimide, alphenol, diphenylhydantoin and methyldiphenylhydantoin.
The technique of mass chromatography (PR 9, G-3) has been applied to
rapidly identify anticonvulsants in crude serum extracts. Brain tissue
levels from surgical biopsy specimens are being determined for phenobarbital,
primidone, phenylethylmalonamide, and carbamazepine. A regional and subcellular
localization of ethosuximide in rat brain is underway. In addition, methods
have been developed to measure anticonvulsive drugs in micro samples of blood
obtained from newborn infants by heel stick.

F-6.   Identification of Abnormal Metabolites in Urine Derived from Patients
        with Inborn Errors of Metabolism

Personnel: R. E. Hillman, M.D., Pediatrics
            W. R. Sherman, Ph.D., Psychiatry

Support: RR 00396
            AM 15531
            Rankin-Jordan Trust Fund
            Washington University

        Since last year's report (PR 9, G-7), the use of gas liquid
chromatography (GLC) and GLC-linked mass spectrometry have become almost
routine techniques for the evaluation of complex metabolic problems in
patients. In the past year over 200 urine, serum, and spinal fluid
specimens have been examined by these techniques (1, 2, 3, 4). Two patients
with maple syrup urine disease have been identified and their therapy
monitored. In addition, a dominant pedigree with bone disease similar to
that seen in hypophosphotasia has been identified where the primary product
of altered metabolism excreted in the urine was phosphoserine rather than
phosphoethanolamine.[5]

        In the next year, major emphasis in this program will be toward the
study of protein tolerance in premature infants. The incidence of inborn
errors of metabolism is low, but the incidence of transient protein intolerance
in premature infants appears to be fairly high. This may be related to

immature liver function. Present plans call for the evaluation of serum organic acids in normal newborns, and in premature infants fed various protein loads as part of their usual care. It is hoped that this program will allow a more rational approach to the feeding of premature infants.

[1] R. E. Hillman and J. P. Keating, "β-Ketothiolase Deficiency as a Cause of the Ketotic Hyperglycinemia Syndrome," Pediatrics, vol. 53, p. 221, 1974.

[2] R. E. Hillman, L. H. Sowers, and J. L. Cohen, "Inhibition of Glycine Oxidation in Cultured Fibroblasts by Isoleucine," Pediatric Research, vol. 7, p. 945, 1973.

[3] R. E. Hillman and E. F. Otto, "Inhibition of Serine-Glycine Interconversion by Products of Isoleucine Metabolism," Pediatric Research, in press.

[4] R. E. Hillman and W. R. Sherman, "Rapid Identification of Long Chain Ketones in Patients with Ketotic Hyperglycinemia by GLC," submitted for publication.

[5] R. Lang, R. E. Hillman, and L. V. Avioli, "Familial Bone Disease Associated with the Excretion of Phosphoserine," submitted for publication.

F-7.   Tricyclic Antidepressant Studies

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

Support: MH 05804
            MH 13002
            NS 05159
            GM 21863

"Tricyclic" antidepressants are a class of structurally related compounds which have wide application in the treatment of depressions. Effectiveness is variable, partly because there is about a thirty-six-fold difference between the lowest and highest steady-state plasma level, in those drugs which have been studied, when patients were dosed with equal amounts of the drug. [1] This is apparently a reflection of genetic variation in metabolic capability. There has been a growing body of literature indicating that plasma levels of tricyclic antidepressants provide a rational approach to their use in the treatment of depression. The use of tricyclic blood levels to monitor dosage in clinical psychiatric practice has been limited in the past by the inability to assay the tertiary amines, imipramine, amitriptyline and doxepin, accurately; and in the case of the secondary amines, desipramine, nortriptyline and protriptyline, at a rate which is practical on large numbers of patients. Research in our laboratory this past year has

been directed toward the development of rapid and accurate gas chromatographic-mass spectrometric assays of imipramine, amitriptyline, doxepin, desipramine, nortriptyline and protriptyline, using the multiple ion detection system (PR 9, G-2).

Standard curves have been produced indicating that imipramine, amitriptyline, doxepin, desipramine, nortriptyline, monomethyl doxepin and protriptyline can be extracted from human plasma whenever the plasma drug concentration ranges from 10 to 300 ng/cc. Accuracy in the measurement of the tertiary amines has been enhanced by the use of deuterated internal standards added to the tissue sample prior to extraction and analyses. Comparison of blood levels and clinical response has not yet been made; however, preliminary results indicate that a large number of patients who fail to respond to tricyclic therapy fail to have adequate blood levels of the drug prescribed, often probably due to failure to ingest the medication. Other preliminary data suggests protriptyline produces a plasma blood level much greater than would be expected from the size of the prescribed dose (see Table 1). By way of comparison, in two studies run elsewhere, patients treated with 150 mg/day of nortriptyline had blood levels of 90 and 141 ng/cc. [2,3]

With the development of a rapid and accurate means to measure tricyclic antidepressants, large-population clinical trials can now be begun to determine the relationship between blood levels and therapeutic effect. Rapid assay of blood levels may also be of benefit in predicting impending toxicity.

TABLE 1

Protriptyline Steady-State Blood Levels

Patient	Mg Daily Dose	Ng/cc Plasma
SB	70	300
CB	30	70
MD	40	434
MH	60	221
KK	20	80
LK	30	158
SM	10	53
LM	20	148
FR	10	65

All samples were assayed in duplicate, and the difference between duplicates in all cases was less than ten percent.

[1] M. Asberg, B. Cronholm, F. Sjoqvist and D. Tuck, "Relationship Between Plasma Level and Therapeutic Effect of Nortriptyline," British Medical Journal, vol. 3, pp. 331-334, 1971.

[2] W. Hammer, C.M. Idestrom, and F. Sjoqvist, "Chemical Control of Antidepressant Drug Therapy," in Proceedings of the First International Symposium (on) Antidepressant Drugs, Excerpta Medica Foundation, Amsterdam, pp. 301-310, 1966.

[3] P. Kragh-Sorenson, M. Asberg, and C. Eggert-Hansen, "Plasma-nortriptyline Levels in Endogenous Depression," <u>Lancet</u>, vol. 1, pp. 113-115, 20 January 1973.

F-8. <u>Plasticizers in Tissues of Newborn Infants</u>

Personnel: W. R. Sherman, Ph.D., Psychiatry, Biochemistry
            L. S. Hillman, M.D., Pediatrics

Support: RR 00396
            GM 21863
            NS 05159
            Washington University

Using the multiple-ion detection system we have developed with the LKB-9000 GC/MS and PDP-12, we have continued the study (PR 9, G-8) on the measurement and identification of the plasticizer di-(2-ethylhexyl)phthalate (DEHP) in heart tissue of neonates that die after birth and in stillborns.[1] DEHP is widely used as a plasticizer in catheters and blood bags, and in tubing used for medical applications (e.g., heart-lung, blood dialysis, etc.). A common specific application is in umbilical artery catheters used to support ill prematures here at Children's Hospital. These children also often receive blood products which have been stored in plastic bags. To evaluate tissue uptake and storage, DEHP was measured in heart tissue from eight stillborn and seven liveborn controls and in seventeen neonates dying after umbilical catheterization alone or after also being given blood products. The heart tissue was prepared for study by passing it through a heart press which gives two fractions, a pressate which should reflect whole tissue on a wet weight basis, and a collagenous residue. The range of DEHP in the study group heart residue was 0.16 to 5.4 µg/gm, and in the heart pressate 0.2 to 2.94 µg/gm. Higher levels were associated with larger amounts of blood products, more extensive use of catheters, and early demise. The mean DEHP levels in heart tissue of study patients was 1.37 ± 1.73 µg/gm in residue and $.66 \pm .89$ in pressate. These were significantly higher than in controls, which were $.074 \pm .095$ and $.063 \pm .139$ respectively. The DEHP was mass spectrally identified from tissue in one subject. It is concluded that plasticizers from catheters and blood products do accumulate in tissue of newborn infants dying shortly thereafter. The ability to metabolize DEHP and any detrimental effects of DEHP remain unclear.

[1] L. S. Hillman, S. L. Goodwin, and W. R. Sherman, "Identification and Measurement of the Plasticizer Di-(2-ethylhexyl)phthalate in Neonatal Tissues," submitted for publication.

F-9. Chemical Studies on Carbohydrate Derivatives and Isotopically
      Labeled Inositols for Mass Spectrometric Applications

Personnel: W. R. Sherman, Ph.D., Psychiatry, Biochemistry
            S. L. Goodwin, B.S., Psychiatry
            J. Wiecko, Ph.D., Psychiatry

Support: NS 05159
            GM 21863

Studies have continued on derivatives of carbohydrates which give
prominent mass spectral ions retaining all skeletal carbon and hydrogen
atoms. The finding was made that when derivatives are prepared using
alkaneboronic acids ($RB[OH]_2$), and where, in addition, a phosphate ester is
present, a fortuitous interaction occurs. This interaction, of a phosphate
P-O with a boron, facilitates loss of the alkane group of the boronate and
results in an ion which is very stable (due to charge delocalization by
phosphate) and therefore abundant. This may be of general utility in electron
impact mass spectrometry and is being further studied.

Another study has involved the base-catalyzed deuterium exchange of
inososes in deuterium oxide. Inososes, which are pentahydroxycyclohexanones,
can be reduced to inositols, thus providing a route to stable isotope-labeled
inositols for human studies on inositol metabolism. The deuterium exchange
is complicated by the basic conditions required, conditions under which
inosose breakdown occurs. This, and the formation of inosose isomers, has
complicated the process. Deuterium uptake studies have been monitored
kinetically using the multiple-ion detector, and the products formed identified
by standard GC/MS.

F-10. PDP-12/Pertec Disc System

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

Support: RR 00396

The interface design reported in PR 9, J-3 has been implemented
and installed on the DEC PDP-12 computer in the Department of Biochemistry
for use in mass spectrometry and kinetic enzyme data analysis. The system
is compatible with the DEC RK-8E disc system, except for some small differ-
ences, and extends the storage capacity of the RK-8E by using two disc
platters instead of one. The disc interface provides additional capabil-
ities, such as storage of bytes as an alternative to twelve bit words, and
a more thorough set of maintenance-diagnostic instructions.

A second PDP-12/Pertec system has been completed and is to be installed shortly in the Nuclear Medicine area of the Department of Radiology.

A third system is under construction and will be installed late this summer (1974) in the Department of Psychiatry for use in mass spectrometry and programming.

DEC software has been adapted to drive the Pertec system and is presently being used in the Department of Biochemistry (see F-11).

F-11. PDP-12 Systems and Test Programs for the Pertec Disc

Personnel: R. W. Scheifler, BCL
            J. A. Paskowitz, BCL

Support: RR 00396

Virtually all major modifications to existing software for the PDP-12 to accomodate the new Pertec Model D3341 dual-platter disc drive and interface (F-10) are complete. The interface is designed to correspond to the DEC RK-8E disc instruction set, except for maintenance instructions.

Three standard DEC operating systems have been updated to utilize the disc as the system device and/or for mass storage: LAP6 DIAL-MS, AIPOS, and OS/8. Each system is designed to operate in the same manner as using a standard DEC RK-8E disc, so far as possible. The DEC disc contains only one disc platter, while the Pertec disc has two platters, a fixed and a removable one. The operating systems have been set up to use one platter or the other, but not both. These assignments are easily changed. The present configuration of LAP6 DIAL-MS allows access to 8 logical disc units, each 1000_8 blocks long, residing on the fixed platter. AIPOS, a data acquisition and manipulation system used with kinetic enzyme data analysis (PR 9, G-12), is currently implemented to utilize 7 logical units of 1600_8 blocks, each of which resides on the removable cartridge. These unit sizes are equivalent to LINC tapes in length, permitting convenient interchange of storage media. LINC tapes are used for primary data storage and backup. The OS/8 operating system, with a FORTRAN IV compiler, will also access a removable cartridge split in half to form two logical units of 6,496 pages (1 page = 128 words) each.

In addition, the Washington University Mass Spectrometry System (F-1) has been updated to use the fixed platter.

To aid in the pinpointing of hardware problems, a comprehensive test program has been written. Many of the testing features are duplications of those used in the Programmed Console Disc Test Programs (PR 9, J-2). All modes of reading and writing data are tested with those pattern words considered most likely to cause errors. Interrupt features are checked,

track seek times are displayed, an interference test is run, and all formatting options are extensively checked. Additional error checking is greatly benefited by maintenance instructions allowing access to major interface status registers. Complete status dumps to either the Teletype or the Versatec printer are performed after any disc error, as well as output of key software information. Total run time for this complete testing procedure is approximately 45 minutes for testing a single platter. Provisions are made for checking either platter or both.

A separate option of the test program provides an interactive mode for performing special operations on selected sectors, either in operate mode or in maintenance mode where actual input/output is inhibited. An additional option allows repeated looping of a specified operation to facilitate hardware checks with an oscilloscope.

Two utility programs are available to the general user, one providing formatting options, which is intended primarily for use on virgin cartridges, and a second which does a simple read of all sectors to check the integrity of the data.

F-12.   A Versatec Printer/Plotter Interface for The PDP-12 Computer

Personnel: P. S. Berger, BCL
            W. H. Holland, A.B., Psychiatry

Support: RR 00396

The Versatec 1110A Matrix printer/plotter was installed by the Department of Psychiatry for use as a high speed output device for mass spectrometry data. The hardware interface, which handles 8-bit data words in parallel, was constructed on a double height Digital Equipment Corp (DEC) interface board and is installed in an input-output extension card file. The hardware handles the Versatec/DEC software, and the device replaces the more expensive Versatec controller C-PDP12. Cost savings are a result of repackaging and some redesign.

F-13. Studies of the Transplacental Transport of Local Anesthetics

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

Support: RR 00396
            Rankin-Jordan Trust Fund
            Washington University

        Four infants with severe neonatal intoxication with mepivacaine
(Carbocaine) associated with maternal paracervical analgesia have been
identified. Blood levels of the drug were monitored and various therapeutic
measures evaluated by measuring mepivacaine levels in exchanged blood,
gastric lavage fluids, and urine.[1] In addition, in one infant who died,
local brain measurements of mepivacaine were made using multiple ion detection
mass spectrometry.[2] In progress is a prospective study of mothers receiving
paracervical analgesia and their offspring.

[1] L. S. Hillman, W. E. Dodson, and R. E. Hillman, "Fetal Mepivacaine
Intoxication Associated with Maternal Paracervical Analgesia -- A Report
of Four Cases," submitted for publication.

[2] W. E. Dodson, R. E. Hillman, and L. S. Hillman, "Measurement of Brain
Levels of Mepivacaine in an Infant Dying of Fetal Intoxication," submitted
for publication.

F-14. Measurement of Serum Levels of Vitamin D Metabolites Using Computer
       Controlled Multiple Ion Detection Mass Spectrometry

Personnel: R. E. Hillman, M.D., Pediatrics
            J. Haddad, M.D., Medicine, Jewish Hospital
            L. S. Hillman, M.D., Pediatrics
            P. S. Tchang, Ph.D., Pediatrics

Support: RR 00396
            GM 01511
            Rankin-Jordan Trust Fund
            Washington University

        Although suitable protein binding assays for the measurement of 25-OH
vitamin D in serum are available, no easily applicable assay for vitamin D
has been published. In addition, present assays do not distinguish between
vitamin D_2 and its metabolites and vitamin D_3 and its metabolites. Using the

mass spectrometer, we have now established assays based on specific mass fragmentation ions for vitamins D_2, D_3, 25-OH D_2, and 25-OH D_3. When we are satisfied that these assays are reproducible in serum samples, a wide variety of clinical studies will be undertaken. These studies will include investigations of absorption of orally administered vitamins D_2 and D_3 in adults and infants, the effects of intestinal disease on absorption of vitamin D, and studies of the relative levels of vitamins D_2 and D_3 in adult populations fed various diets.

G.   Speech and Hearing

G-1.   RAP-1 Peripheral Equipment and Dual Disc Installation

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

Support: RR 00396
             NS 03856

RAP (PR 9, H-1) (Random Access Programmer for Complex Sounds) has been used extensively at CID throughout the past year in experiments of the animal behavior laboratory and in a number of additional experiments involving the spectral analysis of various acoustic stimuli, for the preparation of randomized analog tapes of natural speech sounds, and for recording signals for use with the speech system. Several changes have been made to accommodate different experimental designs and to improve the reliability of the system.

The original disc drive has been replaced by a new disc drive that has twice the data capacity (50 M bits). The total storage capacity for audio sounds is therefore 203 seconds. The new disc was substituted not only to double the storage capacity but also to improve the reliability of the total system.

Improvements to the peripheral equipment (PR 9, H-7) included the addition of a pause/continue function to the paper tape controller and an external item memory control. The pause/continue function allows the paper tape to specify a stimulus sequence, play the sequence, and then pause. The paper tape is restarted by an external contact closure. This improvement provides synchronization of RAP to other laboratory timing devices.

A second improvement provides dynamic external stimulus selection. With this function enabled, the RAP interface appears to have two eight-item memories, rather than a single 16-item memory as described in PR 9, H-7. The eight-item memories can be interchanged during an experiment by asserting an external line to the RAP interface. In this way the stimulus set can be made contingent on partial results of an experiment.

Because of the demand for RAP this year, a second unit is under construction. This mini-RAP is an abbreviated version of RAP-1 that will be interfaced to existing laboratory computer systems at CID. The mini-RAP is being designed in a modular way so that subsystems can be reused as computer systems are updated and the needs of the laboratories change. The basic modular parts of mini-RAP include a buffer memory and 2-channel memory controller, a 50-megabit disc drive and disc controller, an analog-to-digital and digital-to-analog conversion module, and interface logic for the LINC and PDP-8S computers. Console functions of mini-RAP will be COPY and MARK. Other functions such as RECORD, PLAYBACK, EDIT, STORE, and LOAD will be controlled by appropriate programs written for the laboratory computers.

G-2.   A Mathematical Model of the Mechanics of the Cochlea

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

Support: RR 00396

        Results of the model reported last year (PR 9, H-2) agree with
experimental data extremely well and were presented to the Acoustical Society
in October, 1973.[1] In preparing computational results for presentation,
a simplification used by Lien[2] was reexamined. In evaluating the Green's
function for an impulse volume velocity source located on the basilar membrane,
Lien decomposed the Green's function expression into two parts: 1) a plane wave
part that is essentially identical to the results obtained from long-wave-
length approximations to the hydrodynamics of the cochlea, and 2) a local
response to the volume velocity impulse that can be viewed approximately as
a pressure impulse. In evaluating this pressure impulse, Lien integrated
the Green's function for a distance equivalent to 0.1 b (b = the half width
of the basilar membrane). Although these results fit theory well, justifica-
tion for the short interval of integration has been lacking. Recent work has
been to study the Green's function for a two-dimensional model in order to
understand more clearly the approximations involved in decomposing the
Green's function.

[1]M. D. Lien and J. R . Cox, Jr., "A Mathematical Model of the Mechanics of
the Cochlea," Journal of the Acoustical Society of America, vol. 55, no. 2,
February 1974.

[2]M. D. Lien, "A Mathematical Model of the Mechanics of the Cochlea,"
D.Sc. dissertation, Dept. of Electrical Engineering, Washington University,
St. Louis, Missouri, 1973. (Also published as BCL Monograph No. 212.)

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

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

Support: RR 00396
NS 03856

A number of ongoing activities have developed over this past year involving the speech and hearing system (PR 9, H-3). About 20% of the usage has been related to cochlear microphonic (CM) experiments in the physiology laboratory at Central Institute for the Deaf. These activities involve the generation of calibration-adjusted stimuli and the processing of CM data. About 60% of the work has been related to speech research at BCL and Central Institute for the Deaf. Much of this effort has been to develop programs and techniques for generating synthetic speech sounds (G-4) and for tailoring natural sounds that are recorded on RAP discs (G-7), and to study speech analysis (G-5, G-6) and digital filtering methods (G-8). About 20% has been associated with other activities at BCL. A library of general-purpose FORTRAN subroutines for use with the system has been started. Documentation and indexing of the subroutines is in the style of the Collected Algorithms from Communications of the Association for Computing Machinery. Subroutines in the library so far include I/O operations for the special peripheral devices, number conversion between FORTRAN variables and the format required by the floating-point processor, random number generation, and Discrete Fourier Transform routines. Other subroutines for assembly language programs have been written which include various Fast Fourier Transform routines, a subroutine for reproducing the oscillographic display on the digital plotter, and subroutines for converting between the non-standard RAP disc format and a standard FORTRAN disc file.

Several changes were made to the system this year. The disc controller and PC-1200 were modified (I-5, I-6) so that commercially available software systems can be used with the Pertec disc unit rather than the slower tape unit. Additional memory was added to increase the CPU memory size to 16K words of storage, and a high-speed line printer was installed. These changes, along with the recently released FORTRAN operating system, have significangly increased our programming effectiveness.

Plans next year include installing a sound booth and upgrading the analog to digital and digital to analog converters, and audio system.

G-4.   A Speech Synthesizer

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

Support: RR 00396
            NS 03856

        Testing and verification of SPEAKER (PR 9, H-5) is nearly complete.
Two new features have been added to the basic system: 1) The user may choose
between two alternative approximations to the glottal wave, linear (triangular)
or polynomial, and 2) Files of parameter values for driving SPEAKER may be
created by using a new FORTRAN program, PARGEN, allowing the user to specify
parameters algebraically instead of graphically.

        The first version of SPEAKER has been described in a monograph.[1]
A semi-tutorial paper covering the algorithms used in SPEAKER will be
presented at the 1974 annual meeting of the Association for Computational
Linguistics and submitted for publication in the American Journal of
Computational Linguistics.

[1]W. Fisher, "SPEAKER User's Manual," BCL Monograph No. 238, December
1973.

G-5.   An Interactive Speech Wave Examiner System

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

Support: RR 00396
            NS 03856

        A system of FORTRAN programs is under development with which the
user can visually examine a recorded speech wave displayed statically on a
scope. The scope display can be thought of as a camera or microscope viewing
the speech wave; the user can pass the camera left or right and zoom in or
out. Analysis in terms of selected features of the speech wave or its
short-time power spectrum can be performed at any point of the wave. It is
expected that this system will prove to be a valuable adjunct to the usual
sonogram.

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

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

Support: RR 00396
           NS 03856

Work is continuing on the study of the linear-predictor and related methods of speech analysis. Our interest is in the possible use of these methods to study the speech process, and in particular to study the motion of the articulators during speech production. Alternative methods for studying articulation (for example, X-ray studies) are both tedious and complex, and therefore have not yielded a large amount of data. The linear predictor method is attractive because of the possibility of obtaining a good estimate of the cross-sectional area of the vocal tract from the speech wave.

A real-time speech analysis system has been described (PR 9, H-6) that used a linear predictor algorithm implemented with macromodules. Use of this system raised several questions about the analysis method.

The first question concerns the validity of modelling the acoustics of the vocal tract as a plane wave in a nonuniform tube. This model is used in deriving the transformation between the linear-predictor parameters and the area function. The second question involves the accuracy of the transformation itself.

Acoustic tubes have been constructed with known cross-sectional areas. The physical size of the models is approximately the size of the male vocal tract both in length and cross-sectional area. Dimensions were taken from Fant's data.[1] Models have been built to correspond to the vocal-tract geometry for the vowels /i/, /a/, and /e/. Several other tubes were constructed with simpler area functions. The tubes are excited with either a sinusoid signal or an acoustic impulse. In the case of sinusoidal excitation, the volume velocity at the input to the horn is monitored and held constant while the frequency is changed. The resulting plot of the output pressure thus represents the transfer characteristic of the horn (the ratio of output pressure to input volume velocity). These measured transfer functions can then be compared with the corresponding curves obtained from the acoustic theory.

The impulse response is used to determine the accuracy of the linear-predictor method for estimating the area function. The acoustic models are excited with a high-impedance acoustic impulse, and the output pressure is recorded and analyzed with a partial-correlation method to determine the linear-predictor parameters. The transfer function and area function are then computed and compared with the measured transfer function and the known area function.

Tentative results indicate that the spectrum of the driving function (glottal waveform) can significantly alter the results of the analysis. To provide an accurate estimate of the vocal tract area, the model must include corrections for the glottal waveform and the radiation characteristics of the lips.

[1]G. Fant, Acoustic Theory of Speech Production, Mouton & Co., The Hague, p. 115, 1970.

G-7. Programs For Tailoring Natural Sounds For Use As Speech Stimuli In Speech Perception Studies

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
            C. K. Burdick, M.A., Central Institute for the Deaf
            S. A. Garfield, BCL
            P. K. Kuhl, Ph.D., Central Institute for the Deaf
            J. D. Miller, Ph.D., Central Institute for the Deaf

Support: RR 00396
            NS 03856

Numerous special programs have been written for "windowing" of RAP-recorded natural speech segments to reduce the on-off transients caused by abrupt sectioning. A cosine-pedestal window has been used most often with a 12.5-ms rise and fall time. A more recent program enables arbitrary rise and fall times and other types of windows to be used.

A program has also been completed for generating a family of speech stimuli consisting of an arbitrary speech signal and an arbitrary noise. The RMS signal-to-noise ratio is varied in fixed decibel steps, while the overall RMS energy of the composite signal is held constant.

A third program has been written for manipulating speech sounds recorded on RAP. The envelope of the original signal is computed and displayed. By using the graphic tablet the signal can be sectioned and the envelope of the original signal can be changed. The modified envelope is displayed simultaneously with the original envelope for comparison. Portions of the original signal can be replaced by arbitrary signals stored on the RAP disc pack, and the results can be listened to and saved on the disc for playback on RAP.

G-8.   System Simulation by Digital Filtering

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

Support: RR 00396
             NS 03856

Work has started recently in using digital filtering methods to
simulate various kinds of electrical and acoustical systems. A 1024-point
FFT has been used which gives a reasonably fine grain (20 Hz) for character-
izing the filter at a 20-kHz sampling rate.

Because the speech sounds are longer than one window of the FFT, the
speech sound must be segmented and the FFT filtering applied to each segment.
The resulting filtered speech is obtained by concatenating the filtered
segments.

To eliminate the Gibbs phenomenon discontinuity between segments, a
cosine-pedestal window is applied to each segment, and segments are
overlapped by 50%. Adding the overlapped portions, the rising edge of one
window to the falling edge of the previous window, results in a smooth
transition between segments. So far, simple filter characteristics with
abrupt or linear skirts and linear phase have been used.

H.   Health Care Technology

H-1.   Population and Utilization Data System for the Medical Care Group

Personnel: S. R. Holmes, BCL
              J. Kenner, B.S., Medical Care Group
              J. Zimmerman, BCL

Support: HS 00074
            HSM-110-72-267

        BCL has continued to provide a population and utilization data stor-
age system for the Medical Care Group (MCG). The many changes which have oc-
curred in both routine and special capabilities since the last report (PR 9,
I-1) are summarized below. Also given is an overview of special projects
and of resolved problems associated with the MCG work.

        During the last year, the population of prepaid patients has grown
from 1766 to 2504; the annual patient encounter rate (average number of
encounters by a patient in one year) was 4.4 for the prepaid patients. The
fee-for-service population has increased from about 1300 to about 2000. A
new patient group of so-called "registered" patients was added in January
1974. These patients are essentially fee-for-service patients, as they pay
for the services they receive; however, after a 6-month trial period they
must decide either to join MCG as prepaid patients or to leave MCG. Currently
there are fewer than 200 patients in this group, and their effective annual
encounter rate (calculated over the six months January to June 1974) is
about 0.6, significantly lower than the value of 4.4 for the prepaid
patients during the same time period. The total patient population growth
has been slower than planned, and MCG intends to generate a significant
population increase during the next months.

        Some population data items additional to those stored last year are
now routinely entered: these are the patient name, marital status for each
subscriber or household head, and entry/exit dates for the prepaid and
registered patients. With the addition of these items, an average of about
40 characters per patient are used for storage of such population data
(this includes 4 characters per patient for MUMPS global file overhead).

        The encounter form program has been partially modified to reflect
recent MCG changes in the paper encounter form. These changes include
additional MCG health care providers, additional specified procedures
ordered, and changes of allowed "purpose" of encounter.

        The stored data are used in the production of various periodic print-
outs, as were made last year. Some routinely used printout capabilities
have been added, including the production of the Densen Tables for utiliza-
tion totals and for quarterly, half-yearly and yearly time windows, as well
as for the original monthly time window used. [1]

        Various special projects have been performed during the last year.
These include:

1. Reducing errors in the patient data base, particularly by paying special attention to the dates of patient eligibility for prepaid care, to each patient's birthdate, and to family linkages.

2. Printout of data on all patients associated with a particular physician (the printout is alphabetic by patient).

3. Alphabetic printout of data on all patients in a certain age range and given sex.

4. Inspection of the data base to identify what X-rays were being ordered, for what purpose and by whom. (These data were required in order to answer the question "Why is MCG spending more money on X-rays than they had expected to?" The answer appeared to be primarily that more screening X-rays than necessary were being ordered, and the MCG policy for X-ray ordering has been appropriately modified as result of this investigation.)

5. A study of completed referral (i.e., non-MCG) encounter forms, compared with the requests by MCG health care providers for referral encounters. It turned out that during January through September 1973, approximately half of the requested encounters had no associated encounter form; subsequently the chief offenders were identified and approached, and an improvement in referral encounter form completion has since been observed.

6. An investigation of causes of error in source data on the paper encounter form (from which data is transcribed into the computer). It appeared that during July through October 1973, about 3% of the fee-for-service encounter forms had some error, while the encounter forms for the prepaid patients had the much higher error rate of about 12%; the difference arose because different personnel were completing the encounter form for the two types of patient. The major causes of error were 1) misunderstanding of the meanings of various encounter purposes and diagnoses, and 2) errors in the birthdate (either during transcription or on the record from which the birthdate was transcribed to the encounter form). After the identification of these problems, some effort was made to alleviate them. (Note: In this and the previous two studies, although the data were obtained by computer searches of the computer data base, the results were hand-tabulated.)

7. The capability to print out a summary of visits by patient (as yet only partially implemented).

Some of the hardware used in this project has been modified. Among the most important alterations are: 1) the change of the PC-1200 from its original octave-origin registers to the now standard twin-origin registers; 2) the replacement of the prototype PC-1200 disc interface by a more recent version (I-6); and 3) the modification of the disc controller to conform with the current revision (I-5). Such changes necessitated modifications in the MUMPS system, and produced the inevitable batches of fresh system bugs to be found and removed.

Minor system improvements include the addition of cooling fans to the Beehive terminals to alleviate overheating problems and the addition of a sound-proofing cover to the Centronics printer.

The Administrative position of MCG Data Supervisor has been established to coordinate all aspects of data entry, report generation and usage of the MCG data system.

[1] J. Zimmerman, "Users' Guide to the Densen Table Package in MUMPS-PC," BCL, Washington University, preliminary issue, 29 April 1974.

H-2.   Internship Program

Personnel: R. M. Arthur, BCL and Electrical Engineering
             J. R. Cox, Jr., BCL
             R. R. Pfeiffer, Ph.D., Electrical Engineering
             J. Zimmerman, BCL

Support: HS 00074

The internship is a 12-week program, now in its third year, which is designed to allow Technology in Health Care students to gain a familiarity with daily operations and the role of technology in a variety of health-care facilities (PR 9, I-2; PR 8, I-1). The program is divided into two 6-week segments. The Progress Report period ends in the middle of the program for a given summer. Thus, this report covers the second portion of the second year of the program and the first portion of the third-year offering.

In the in-depth (second) half of the program each student is engaged in a detailed study of the problems of a particular health-care setting, suggested by encounters which occurred during the first half of the summer. As was the case last year, most of the in-depth studies served as the basis for developing thesis projects. Topics included: 1) Electrical system and medical equipment preventive maintenance programs;   2) Automatic frequency analysis of electromyograms;   3) Emergency department design;   4) Monitoring bacterial growth and metabolism in a clinical laboratory;   5) Outpatient appointment systems;   6) Multichannel cell-size distribution analyzer; 7) Data acquisition, storage and distribution in a cardiovascular clinical research center;   8) Automated medical interviews; and   9) Computerized system for antibiotic sensitivity testing.

A highly-organized visit schedule was again developed for the first six-week segment of the summer. Eight master's-degree candidates in pairs, or occasionally larger groups, visited many facilities in the following institutions: Barnes Hospital, St. Mary's, Jewish Hospital, Christian Northwest, St. Vincent de Paul, St. John's, St. Louis City Hospital, Yeatman Clinic,

Homer G. Phillips, Firmin Desloge, Children's Hospital, Deaconess, St. Louis County Hospital, St. Luke's, and Cochran Hospital (VA). Companies visited included Artronix and McDonnell-Douglas Automation.

Several central topics were identified for each week to provide a basis for comparison and discussion. These included ECG and EEG analysis, operation of catheterization labs, exercise testing and heart stations, admitting procedures, emergency department procedures, radiation therapy, surgical and intensive care unit systems, diagnostic laboratories, pharmacies, medical records, data processing and information systems.

H-3.   MUMPS Development

Personnel: W. E. Long, BCL

Support: RR 00396
            HS 00074

During the year, a significant new single-user version of MUMPS-PC was released. This had expanded capabilities beyond previous versions (see PR 9, I-3; PR 8, I-2). The extended capabilities include:

1. The addition of (LAP6-like) buffered display and editing features which allow this MUMPS-PC to run with the standard peripherals of the PC (i.e., the Tektronix 611 storage scope and keyboard); this version may be run on any PC with 12K of core.

2. The conditional construct of all commands, excluding FOR, IF and ELSE.

3. The "binary not" operator in conjunction with any of the relational operators (for example, '>, which means "not greater than").

H-4.   Medical Information Systems Study Group

Personnel: J. R. Cox, BCL
             M. A. Franklin, Ph.D., Electrical Engineering
             J. W. Lewis, Ph.D., Pathology and BCL
             W. E. Long, BCL
             W. F. Pickard, Ph.D., Electrical Engineering

Support: RR 00396
             HS 00074

        A study group composed of workers with experience and interest
in the broad problems of medical information systems met weekly for
a seven-month period during the academic year 1973-1974. An attempt was
made initially to survey recent achievements and failures in medical infor-
mation system development. Particular emphasis was placed on two recurring
problems which seemed appropriate for innovative hardware solution: first,
the large overhead involved in executing programs interpretively when many
(up to several hundred) users are active in a data base management system;
and second, the throughput problems which have been encountered in some large
MUMPS systems due to the inefficiency of data storage and data retrieval
algorithms. (The underlying assumption in investigating these problems was
that the flexibility and ease of use of interpretive languages such as MUMPS,
and the power of a generalized data structure such as the MUMPS tree, are
highly desirable not only in small systems but even more so as system com-
plexity grows with increasing size.) Both problems clearly are fundamentally
hardware problems, in that increased CPU speed or lower access time on mass
storage devices would alleviate them.

        Hardware solutions investigated centered around a multi-micropro-
cessor system architecture for the first problem, and improvements in file
management indexing and directory techniques for the second. Briefly, the
system architecture envisaged was composed of a separate, dedicated pro-
cessor for each user. Each terminal processing unit (TPU) would have local
read-write memory for data and program segments and read-only memory for the
interpreter. A central processing unit (CPU) would coordinate requests from
the TPUs to one or more mass storage devices; not only cost but also system
reliability might well depend more on the interconnections than on the in-
dividual TPUs or CPUs.

        Hashing techniques were investigated as possible aids in the
design of a more efficient tree-structured data base management system.
Some consideration was given to the value of hardware hashing and of
pseudo-associative directory searches. In an attempt to gain more insight
into current software technology for data base management, the Codasyl
Data Base Management Task Group Report was studied and analyzed, as was
one commercial implementation of the Codasyl system.

        The hardware technology of large mass memory systems was investigated,
and an electron-beam storage system now in operation in prototype form at

Micro-Bit Corporation was used as a typical future memory device in performance calculations. Hardware aids for improving data base integrity and file security were studied.

The study group suspended meetings for the summer of 1974. A general consensus was reached that interconnection bus design, mass memory technology, and file structure techniques were not currently available to predict with confidence the success of a 250-terminal medical information system serving a large medical center of 2,000 inpatient beds and a correspondingly large outpatient load. Research into analytic modeling techniques for prediction of bus performance was directly motivated by this study group and is now in progress at Washington University.

H-5.   MUMPS Users' Group (MUG)

Personnel: J. Zimmerman, BCL
            J. R. Cox, Jr., BCL
            G. S. Lodwick, M.D., University of Missouri, Columbia, Mo.

Support: 4-35834
            HS 00074
            HS 01540

The MUMPS Users' Group is an informal organization of people interested in applications of the MUMPS programming system. During the last year, our primary activities for the MUMPS Users' Group have been oriented towards the dissemination of information about current work with MUMPS. This has been achieved through the international 1973 MUMPS Users' Group Meeting, held in St. Louis, on 24 September 1973,[1] through four quarterly newsletters,[2] and through various MUMPS Users' Group notes.[3] A library is being established of abstracts of MUMPS applications, in order to improve information exchange about existing MUMPS applications. The MUMPS Users' Group Ad Hoc Committee for the Identification and Evaluation of Computer Applications to Medicine has been formed; it is currently addressing the questions of application program exchange, and of problems associated with medical computing. The mailing list now contains about 830 individuals (a 40% increase during the last 12 months). This demonstrates the growing interest in and use of MUMPS.

[1] Proceedings of the 1973 MUMPS Users' Group Meeting, J. Zimmerman, ed., published by the MUMPS Users' Group, St. Louis, Mo.

[2] "MUMPS News," #6 (July 1973), #7 (November 1973), #8 (February 1974) and #9 (May 1974), published by the MUMPS Users' Group, St. Louis, Mo.

(3)MUG-1, "The MUMPS Users' Group", June 1974.
  MUG-2, "What is MUMPS?", June 1974.
  MUG-3, "Master Summary of MUMPS Applications and Institutions", February 1974.
  MUG-4, "The MUMPS Institution Notebook", June 1974.
These are all published by the MUMPS Users' Group, St. Louis, Mo.

H-6. MUMPS Programs for the MUMPS Users' Group

Personnel: J. Zimmerman, BCL
            A. G. Kegel, BCL

Support: 4-35834
            HS 00074
            HS 01540

The single-user MUMPS-PC (H-3; PR 9, I-3) has been used to set up a storage and retrieval system for information about MUMPS users (their name, affiliated institution, address, phone number and mailing code), their MUMPS hardware and dialect, and their MUMPS applications. This is in support of the MUMPS Users' Group activities reported in H-5. The data are stored in a three-level global, whose structure is described in a preliminary documentation manual. The primary uses of the stored data are:

1. To produce alphabetic listings by individual and by institution;

2. To produce mailing labels in alphabetic or in zip-code order (for mailing distributions to MUMPS users);

3. To print out institution profile data;

4. To generate a summary of known MUMPS applications.

All data may be entered, changed, removed or inspected upon demand. Plans for the immediate future include the storage and retrieval of more detailed information about the MUMPS applications.

H-7. MUMPS Development Committee (MDC)

Personnel: W. E. Long, BCL
            J. R. Cox, Jr., BCL
            J. Zimmerman, BCL

Support: RR 00396
            HS 00074
            4-35834
            HS 01540

During the year, BCL has been an institutional member of the national
MUMPS Development Committee (MDC). The primary goal of the MDC is to pro-
duce a MUMPS language standard by September, 1974. Additional goals include
the specification of standards for documenting MUMPS code and data, and the
discussion of MUMPS implementation techniques. BCL has a strong record of
MUMPS activity (A-19, H-3, H-11; PR 9, I-3; PR 9 supp., #15; PR 8, I-2), and
laboratory personnel have attended and contributed to all quarterly MDC meet-
ings and most meetings of the various MDC Task Groups concerned with each of
the specified goals. During the year, the MDC has made significant progress
toward a MUMPS language standard, and documentation standards have been
proposed.

H-8. Transferability of Computer Packages

Personnel: J. Zimmerman, BCL

Support: HS 01540
            4-35834
            HS 00074

Studies of alternate methodologies of transferring computer packages
are now in progress. This work is stimulated primarily by the interest
throughout the MUMPS community in the transfer of medical application pack-
ages.

Consider a computer package which has been designed with the intent
that it shall be readily transferable: key features in the design should
include not only good documentation of the package, but also sufficient
flexibility that the package can be molded to take on the characteristics
of a great variety of versions of the same environment (application area).
Such a package is called a "universal package," and it is discussed further
in a preliminary monograph.[1]

A concise mathematical model has been defined[1] which describes the
cost of alternate methods of package transfer. That model suggests not only
the obvious fact that it is worth increasing significant planning for appli-

cation transfer in approximate proportion to the number of differing institutions to which the package would be transferred, but also gives quantitative values for the effort it is worth expending on a package relative to that number of institutions.

[1] J. Zimmerman, "The Dissemination of Computer Applications via a Universal Package," BCL Monograph No. 249, to be published.

H-9.   Alternate Data-Processing Methods for the Medical Care Group

Personnel: J. Zimmerman, BCL
             P. J. Haas, M.A., Medical Care Group
             S. R. Holmes, BCL
             J. Kenner, B.S., Medical Care Group

Support: HS 00074
             HSM-110-72-267
             Robert Wood Johnson Foundation Grant #189

The current data-processing needs of the Medical Care Group (MCG) are the collection, retrieval and summary of basic population and utilization data concerning the MCG patients (see H-1); possible expansion of these needs calls for the collection and retrieval of more medical data than at present, and the establishment of a patient scheduling program. The total quantity of data currently stored for the MCG population is given approximately by the equation

$$C = 40P + 4.4m\bar{P},$$

where C is the total number of characters of storage for a current population of P patients when the encounter data are stored for an m-month period and the average population over the m-month period is $\bar{P}$. (P is almost 5000, $\bar{P}$ is about 3500, and m is 18, so that C is approximately 0.5 Mcharacters).

During the last two years, the MCG data processing has been performed using the single-user MUMPS-PC developed by W. E. Long (PR 9, I-3). Recently MCG and BCL realized that the initial research component of defining MCG's immediate data processing needs was almost complete. Therefore an inspection of possible services was made.

The major alternatives were: Meditech, Inc.; McDonnell-Douglas Automation; lease-purchase of an Artronix PC-1200 with disc; purchase of a DEC PDP-11/05 or PDP-11/40 with disc; use of a service bureau such as Service Bureau Corporation; or the use of the Washington University Computing Facilities. The approximate monthly cost for populations of 5000 patients (the approximate present load) and 30,000 patients (MCG's target patient

load) are given below for the first five alternatives.

Source of services	Monthly cost ($) to MCG, at a population of	
	5,000	30,000
Meditech (the "OMS" package); cost includes 1 man-month of custom programming per year plus estimated cost of data transcription; further programming costs extra.	1,600	3,800
McDonnell Automation (modified Bio-dynamics package); cost includes keypunching (data transcription), but excludes custom programming.	700	2,600
Lease-purchased 3-user PC-1200 with 200-Mbit (1234-type) disc from Artronix, at $1680/mo over a 3-year period ($51K purchase price); plus $1000/mo for programming and technical services and for overhead; estimated cost of data transcription is added.	2,900	3,400
Purchased 3-user PDP-11/05 for $36K, or a PDP-11/40 for $40K; each with a 19-Mbit RK05 disc; cost includes services, overhead, and estimated cost of data transcription.	2,400 for 11/05 2,500 for 11/40	2,900 for 11/05 3,000 for 11/40
Service Bureau Corporation (Assumes verifying as well as key-punching; note that possible extra significant charges for special programming might increase the prices stated.)	500	3,200

Each option is significantly more expensive than MCG wishes, especially at the 30,000-population level. Therefore MCG is currently looking to the Washington University Computing Facilities with the hope of running the MCG programs either in MUMPS on a computer operated by the Computer Facilities, or else perhaps in a version of Coaker's table-driven approach. [1]

[1] F. W. Coaker, "Table-Driven Input Editing for a Data Storage System," Information Storage and Retrieval, vol. 10, pp. 57-62, 1974.

H-10. Continuation of CAI (Computer-Aided Instruction) Programs

Personnel: R. H. Greenfield, BCL
            B. J. Halbrook, B.S., Medical Library

Support: RR 00396
            HS 00074
            Washington University

        The use of the CAI (Computer-Aided Instruction) Programs, sponsored
by the National Library of Medicine, has continued at the Medical School
Library along the lines reported last year (PR 9, I-8). About 20 sessions
a month have been held, primarily by second- and third-year medical students.
The Library is currently paying the $2.50/hour charge for connect time which
is now being made by the NLM.

        During this year, the MGH programs have been used approximately twice
as heavily as the Ohio State programs. The Illinois programs have been
discontinued.

H-11. MUMPS on the IBM System/360

Personnel: R. H. Greenfield, BCL

Support: RR 00396
            HS 00074

        Work has continued on the IBM System/360 implementation of MUMPS,
previously reported in PR 9 supp., #15, and elsewhere. This intermediate-
code generating system is being written primarily using the PL/I F-Level
Compiler, with small portions being written in Assembler Language where this
is more suitable.

        The employment of an intermediate code provides at least three
distinct advantages over the use of a pure interpretive system: first, the
input string need be parsed and checked for errors only once; second, all
errors are detected immediately upon entry of an erroneous statement into
the system; third, many different dialects of MUMPS may be mapped into one
common intermediate code string. This is because most dialects of MUMPS are,
in general, syntactically different rather than semantically different lan-
guages.

An initial working system is now over half-way completed. The translator from MUMPS to its syntax-free intermediate code is completed, and the intermediate code has been defined. The terminal input/output via EXCP is close to final working form. (The BTAM support provided by IBM was not felt to be appropriate for use with MUMPS.) Work on storage management is under way. Also, work on implementation of the interpreter for the intermediate code has begun. Most of this code is already hand- and machine-optimized for rapid performance. Some timing statistics on translation speed have been gathered.

[1] R. H. Greenfield, "MUMPS on the IBM System/360," Proceedings of the 1973 MUMPS Users' Group Meeting, 1974.

I.   Supporting Activities

I-1.   Radiation Therapy Machine Verification

Personnel: D. P. Ragan, Ph.D., Radiology

Support: RR 00396
          CA 13053

        Because delivery of radiation therapy has become very sophisticated
and complicated over the last decade, there is a great deal of concern that
human errors involved in the delivery of this radiation may have deleterious
effects on the outcome of treatment. In order to measure this and inhibit
treatment upon invalid setup, a therapy machine verification interface is
being built. By utilizing existing equipment, an attempt is being made to
develop a unit which will be cost-effective and generally exportable to
a large number of similarly equipped installations.

        Previous implementations of verification systems have all been compar-
atively expensive dedicated machine-language computer systems (for example,
the CART system by Varian). In contrast to this, a system is now being
developed which will include a standard ASCII interface such that the sys-
tem can be utilized conveniently with a large number of computer types. In
addition, software development and interfacing is being accomplished on a
multi-user PC-MUMPS computer system (see PR 9, A-4.) This system will have
the added advantage of interfacing directly to the Radiation Therapy Depart-
ment's already existing patient information system. The total cost of the
system should remain under $6,000, as contrasted to commercial quotes as
high as $80,000. It is felt that the combination of standard interfacing
and high-level language utilization will make this system significantly more
useful and flexible than previous systems.

I-2.   Densitometer Program Modifications

Personnel: E. Van Patten, BCL
            G. D. Oliver, Ph.D., Radiology
            J. A. Purdy, Ph.D., Radiology

Support: RR 00396
            CA 13053

        The densitometer program (PR 9, A-1) which is used to evaluate
dosimetry films has been expanded. The basic procedures for data acquisition
remain the same, but a number of options have been added, always with a
view to preserving simplicity of operation.

Plotting capability has been added. The matrix plot consists of labelled traces of specified percentages of either doses or densities. When there are areas of the same percentage, the trace describes the outer edge. The center of the 50% trace is marked, and the film identification is printed.

A single scan in either direction may now be read. It is printed or plotted as a graph with percentages marked on each side. A matrix may be renormalized to any data point for either printing or plotting. An entire data tape may be either printed or plotted without interruption, or a single set of data may be selected.

Densities are converted to doses by exposing film to known doses and measuring the optical densities. The values thus obtained may be typed into the program, which fits them to a third-order polynomial. The coefficients are stored on tape in a table which is ordered by film and radiation types. When requested, these coefficients are read in and used to convert the table, which was constructed by reading the test strip, from densities to doses.

The program runs as a stand-alone system on a PC-1200 with 8K of memory.

I-3.   PC-Rapid Program Additions

Personnel: E. Van Patten, BCL

Support: RR 00396

The program which calculates radiation intensities from needle implants and point sources, using the PC-1200 for input-output, is still in daily use (PR 9, A-2). The PC portion of the program, having been written for the flip-chip PC, has been revised to make better use of the expanded capabilities of the PC-1200. The program itself was removed from the IBM System/360 disc from which it was previously brought into the PC over the data line. It now resides on LINC tape as a stand-alone program, thus providing a tremendous saving in operating time. The overlay structure was also reduced by expanding the program to utilize the additional 4K of memory available. It now requires an 8K machine.

The plotter portion of the output has been completely rewritten (PR 6, A-1). Desired isodoses are selected during the scope output, and the function key 'P' initiates plotting with each plane drawn on a separate sheet. Patient identification is printed; the center and the needle intersections (if any) are marked. The contour of each isodose is traced using an algorithm which causes the pen to move in an uninterrupted clockwise sweep until it returns to its starting point. Contours are drawn full size using a standard 5-mm spacing between points. This standard may be overridden by using the function key, '0'.

The output portion has been further refined by providing repetitive requests for output from the IBM System/360 disc. A delay of about one minute spaces the requests and a scope display keeps the operator aware of what is going on. This display may be terminated to resume other program operation. Formerly, the request was sent just once, so that the operator had to type it in again when he hoped that the IBM System/360 program had completed execution.

I-4. A System for Automatic Drug Injection

Personnel: B. F. Spenner, BCL
J. L. Robinson, BCL
L. J. Tolmach, Ph.D., Radiology

Support: RR 00396
CA 04483

The Automatic Drug Injection system (PR 7, F-13) includes a collection of analog circuitry which positions selected Petri dishes under fluid injection nozzles. The original positioning circuitry proved to be unacceptable, since the dishes were occasionally incorrectly positioned. The positioning circuitry was therefore redesigned and replaced. The new circuitry provided a considerable improvement, although the positioner is still plagued with mechanical problems.

I-5. A General-Purpose Disc Controller

Personnel: B. F. Spenner, BCL
J. L. Robinson, BCL
R. W. Wodicker, BCL

Support: RR 00396

The general-purpose disc controller (PR 9, J-2) designed at BCL has proved to be a valuable computer peripheral, and it has fulfilled most mass storage needs of the laboratory community. The addition of this disc to various equipment has provided order-of-magnitude increases in system performance. Since disc systems are relatively new at the laboratory, they have come under close scrutiny by users. However, the reliability record compiled by these systems has provided reason for the users to become confident in disc operation.

Most of the recent disc controller project activity has centered around documentation, construction and checkout, and preventive main-

tenance. A rigid preventive maintenance schedule was established to insure continued reliability of the disc systems. There are at present ten operating controllers (Table 1); of these, five were completed this year.

TABLE 1

CONTROLLER	LOCATION	COMPUTER
1	BCL - Programming	PC-1200
2	Barnes Hospital - Radiation Sciences	Interdata 70/80
3	BCL - MUMPS	PC-1200
4	Biochemistry	PDP-12
5	BCL - Speech Processing	PC-1200
6	Jewish Hospital - Cath Lab	PC-1200
7	Barnes Hospital - SICU	PC-1200
8	Barnes Hospital - Cath Lab	PC-1200
9	Barnes Hospital - Nuclear Medicine	PDP-12
10	Mass Spectrometer	PDP-12

I-6. PC-1200 Disc Interface

Personnel: B. F. Spenner, BCL
            J. L. Robinson, BCL
            R. W. Wodicker, BCL

Support: RR 00396

The General-Purpose Disc Controller (I-5) has been connected to the PC-1200 through the PC-1200 disc interface. This interface allows the computer to transfer status information and data between itself and the controller. Besides the above capabilities, this interface provides a port which allows equipment other than the computer to access information located on the disc. Operations executed from the port do not require computer participation.

One device connected to the port is the LINC Simulator. This device intercepts LINC Tape commands (PR 7, F-14) before they reach the tape drives. The intercepted tape commands are then interpreted and redirected to the disc. The LINC Simulator therefore permits present software systems (i.e., PC FORTRAN) written for LINC Tape, to operate from disc without any software system changes. As part of the LINC Simulator System, a user software package was written. This software performs three essential functions: LINC Simulator set-up, tape-to-disc and disc-to-tape copying, and disc formatting.

Another device is the macromodular disc interface. This unit provides macromodules with direct access to a mass storage device. The macromodular

disc interface will be directly compatible with the present macromodules and will provide both read and write capabilities.

Any PC-1200 disc interface may have one or both of these devices connected to it.

I-7. Microprocessor-Based Multichannel Analyzer For Blood Cell Sizing

Personnel: J. W. Lewis, Ph.D., Pathology and BCL
T. J. Coleman, M.S., Biomedical Engineering

Support: RR 00396
HS 00074
Barnes Hospital

In pursuing studies of erythrocyte size distribution for clinical hematology, the need became evident for an inexpensive multichannel analyzer of very modest size (64-128 channels), channel capacity (10^4 counts per channel), and speed, but one which was capable of performing calculations of various statistical parameters of a distribution without requiring transfer of the data to another calculator or computer.

Using an Intel MCS-4 calculator chip set, an "intelligent" multi-channel analyzer was designed, programmed, constructed, and evaluated by a graduate student in the Program on Technology and Health Care. The device uses fewer than 35 integrated circuit chips, has 64 channels of 32,000 counts per channel capacity, displays a distribution on a CRT or chart recorder, prints the data on a teletype, and calculates the mean, skew (third moment) and kurtosis (fourth moment) of a distribution for display on seven-segment readout devices. Less than 35 seconds is required with the 4-bit chip set to calculate the three parameters, maintaining 60-bit accuracy in critical parts of the calculation. Three grant proposals have been submitted by other investigators at Washington University which request funds for construction of copies of this multichannel analyzer for use in their respective research projects. Publication of the design is anticipated in the near future.

I-8. <u>Physiology Teaching System, Blood Acid-Base Chemistry</u>

Personnel: L. J. Thomas, Jr., BCL, Physiology and Biophysics
            G. C. Johns, CSL

Support: RR 00396
            NS 07498
            Washington University

The algorithms for the student acid-base chemistry teaching system
(see PR 7, D-8) were revised to include updated estimates of the carbamino
reaction constants [1] as well as to improve output parameter ranges. The
revised algorithms were programmed in PC FORTRAN to generate intermediate
and final output values for validating assembly language programs written
for the new TI 980A teaching system (developed by the W.U. Computer Systems
Laboratory) and to examine the appropriateness of various titration ranges.

The TI 980A assembly language version has a running time of approx-
imately 1.5 sec. or less for each of the various titrations, which is more
than fast enough for practical use in the teaching situation. This version
is, of course, hardware specific and thus not exportable to most other po-
tential users. The earlier LINC version had been released to several other
institutions. The FORTRAN version is exportable; but since multiple iter-
ative calculations are necessary for each titration, the calculation time
on the PC-1200 using software arithmetic routines was too long (nearly one
minute, worst case) to be practical. After a hardware floating-point unit
was installed on the PC-1200, the running time was reexamined and found
to be improved by a factor of nearly eight. The FORTRAN version was then
reprogrammed for speed, using an extensively factored form to achieve a
PC FORTRAN version with a worst-case calculation time of less than 1.5 sec-
onds with the floating-point unit. All that remains is to add display rou-
tines to complete a version that could be used on any of the increasing
number of minicomputers provided with FORTRAN systems. Only minor modifi-
cations would be necessary to accomodate individual system peculiarities.

[1] C. Bauer and E. Schroder, "Carbamino Compounds of Haemoglobin in Human
Adult and Foetal Blood," <u>Journal of Physiology</u>, vol. 227, pp. 457-471,
1972.

I-9. Statistical Inference for Space-Time Point Processes

Personnel: D. L. Snyder, BCL
P. M. Fishman, D.Sc., Psychiatry

Support: RR 00396
GK 32239

A report [1] has been completed in which a theory of statistical inference for space-time point processes is developed. A space-time point process is a stochastic process whose realizations are point sets on $[0, \infty) \times R^n$, where $[0, \infty)$ corresponds to a time domain and R^n is a Euclidean n-space. Such processes occur naturally in many branches of science and engineering including optics, nuclear medicine, electron microscopy and neurophysiology.

A class of point processes, which are referred to as regular space-time point processes, is defined. This class includes many of the point process models which have been found useful in the applications. A number of important mathematical properties of regular processes are obtained. We consider in particular the class of doubly stochastic regular space-time point processes. These are regular space-time point processes influenced by an underlying and unobservable parameter; the parameter may, in general, be an element of a function space. The problem we consider is that of estimating the unobservable parameter given observations of the point process. A general solution to this problem is obtained in terms of a representation theorem which gives the measure transformation relating the posterior probability measure of the unobservable parameter to its prior probability measure. An important feature of this representation is that it relates prior and posterior measures rather than probability densities, though the latter relationship, when it exists, may be obtained from the measure representation in a straightforward manner. The representation theorem is used to obtain equations of filtering, smoothing, prediction and detection for a variety of point process models, including those which allow for feedback from the observed point process to the underlying parameter. These equations are used as a point of departure for developing suboptimal equations of filtering.

The theory presented here can be used to obtain estimation equations for a wide variety of models useful in applications, and may contribute to the solution of a number of problems such as: 1) estimating a random space-time field that influences the observed space-time point process; 2) imaging; 3) optical interferometry; 4) optical tracking; and 5) dynamic studies in nuclear medicine and radiation sciences.

[1] P. M. Fishman and D. L. Snyder, "Statistical Inference for Space-Time Point Processes," BCL Monograph No. 242, May 1974.

I-10. Random Point Processes

Personnel: D. L. Snyder, BCL

Support: RR 00396
          GK 32239

     Previously described efforts (PR 8, J-11 and PR 9, J-6) on the mathematical study of random point processes have continued. A set of notes for a graduate course on this topic has been written; Chapters I to VI are available.[1-4] These notes will be published in textbook form.

[1] D. L. Snyder, "Notes on the Theory and Application of Stochastic Point Processes and Their Generalizations: Chapters I-III," BCL Monograph No. 167, March 1972.

[2] D. L. Snyder, "Notes on the Theory and Application of Stochastic Point Processes and Their Generalizations: Chapter IV," BCL Monograph No. 175, August 1972.

[3] D. L. Snyder, "Notes on the Theory and Application of Stochastic Point Processes and Their Generalizations: Chapter V," BCL Monograph No. 208, March 1973.

[4] D. L. Snyder, "Notes on the Theory and Application of Stochastic Point Processes and Their Generalizations: Chapter VI," BCL Monograph No. 216, July 1973.

I-11. Inexpensive Computer-Controlled Flying Spot Scanner for Clinical Microbiology

Personnel: J. W. Lewis, Ph.D., Pathology and BCL
            R. S. Hertert, M.S., Biomedical Engineering
            R. E. Kumpf, B.S., Biomedical Engineering

Support: HS 00074
          Barnes Hospital
          Washington University

     Development continued during 1973-74 on a low-cost (under $3,000) flying spot scanner system intended for automation of reading of culture plates in the Kirby-Bauer antibiotic disc sensitivity test. The scanner was interfaced to a Texas Instruments 980A computer, optical alignment

performed and software written to locate and analyze zones of inhibition on a culture plate. Preliminary results indicate good agreement (to within ±1 mm) of zone size measurements made by the scanner system with those made by laboratory technologists. The design of the system has been presented at several conferences [1,2] and two theses have resulted.[3,4]

[1] J. W. Lewis and R. S. Hertert, "Design of an Inexpensive Flying-Spot Scanner System for the Kirby-Bauer Antibiotic Sensitivity Test," in Zarnstorff, Hendee, and Carson, eds., Application of Optical Instrumentation in Medicine II (in press).

[2] J. W. Lewis, R. S. Hertert, and R. Kumpf, "A Low-Cost Flying Spot Scanner System for Clinical Microbiology and Immunology," in Innovations in Biomedicine: Proceedings of the 1974 San Diego Biomedical Symposium (in press).

[3] R. S. Hertert, "A Flying-Spot Scanner for Automating in the Kirby-Bauer Antibiotic Disc Sensitivity Test," M.S. Thesis, Department of Electrical Engineering, Washington University, 1973.

[4] R. E. Kumpf, "An Image Processing System for Microbiology," M.S. Thesis, Department of Electrical Engineering, Washington University, 1974.

VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Several laboratory projects have now reached this stage, and the following new section of our annual report brings together the description of the progress being made in this important phase of the laboratory's activities.

A. <u>Radiation Treatment Planning</u>. In the four years since Artronix took over the production of the Programmed Console and distribution of the Radiation Treatment Planning system (PR 7, A-7), much progress has been made (PR 7-9, A). BCL now has turned over all activities in treatment planning to the Department of Radiology, Artronix, and their customers. Our pride in these recent accomplishments must be tempered by the realization that much hard work has been done by others. Soon the number of systems installed around the world will pass the one-hundred mark, a goal that we thought represented complete market saturation a few years ago. (BCL personnel: J. R. Cox, Jr., V. W. Gerth, E. Van Patten)

B. <u>Arrhythmia Monitoring</u>. Mennen-Greatbatch has developed the Argus/Sentinel computer system, a six patient monitoring system based on the Argus algorithm (see PR 8, B-7). Formal evaluation procedures for this system have been established and work has proceeded during the past year to improve these procedures and to compare the Argus/Sentinel results to those of the original Argus system.

A number of minor errors in the system have been detected and corrections suggested to Mennen-Greatbatch. Now an ECG waveform test-set originally used for the evaluation of Argus [1] and carefully annotated by a cardiologist has been processed by Argus/Sentinel. Each of the 50,000 annotated beats in this test-set is being checked for proper classification. Satisfactory completion of this analysis will complete the formal evaluation of the Argus/Sentinel system.

Several Argus/Sentinel systems are scheduled for installation in the latter part of 1974 and we will follow with keen interest their clinical performance in coronary care units quite different from that in which the system was developed. (BCL personnel: R. M. Arthur, J. R. Cox, Jr., F. M. Nolle, K. L. Ripley)

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[1] G. C. Oliver, F. M. Nolle, G. A. Wolff, J. R. Cox, Jr., and H. D. Ambos, "Detection of Premature Ventricular Contractions with a Clinical System for Monitoring Electrocardiographic Rhythms." <u>Computers and Biomedical Research</u>, vol. 4, pp. 523-541, 1971.

C. Small Information Systems. Beginning in the fall of 1971, translation of MUMPS to the Programmed Console was begun. MUMPS (MGH Utility MultiProgramming System) was developed at Massachusetts General Hospital by Neil Pappalardo in Dr. Octo Barnett's laboratory.[1] A successor version (MIIS) developed later at Medical Information Technology, Inc. (Meditech) was used as the basis for this translation. Less than a year later a single user version of MUMPS was operating on the Programmed Console. By the end of June of 1973 a reliable and substantially enlarged single user system was operating. Meanwhile Artronix had begun development of a multi-user system and had a preliminary version operating. In the past year this multi-user version has been installed at BCL and maintenance, documentation and further development of the program have been taken over completely by Artronix. (BCL Personnel: J. R. Cox, Jr., W. E. Long)

[1]R. A. Greenes, A. N. Pappalardo, C. W. Marble, and G. O. Barnett, "Design and Implementation of a Clinical Data Management System," Computers and Biomedical Research, vol. 2, pp. 469-485, 1969.

D. Reconstructive X-Ray Tomography. During the past year a collaborative effort with Picker Corporation has taken form within BCL. This work aims at the development of advanced techniques for reconstruction of cross-sectional images of x-ray absorption densities by means of computerized transaxial tomography. This technique, pioneered by Dr. G. N. Hounsfield,[1] has generated considerable interest in the radiological community. It uses a well-collimated, pencil-shaped beam of x-rays scanning a section of the head both transversely and axially. Measured values of attenuation are assembled in the computer and processed to yield a reconstruction of the absorption density throughout the scanned section of the head. Computer techniques that lead to improved speed of processing and reduced artifact in the reconstructed image are being investigated. (BCL Personnel: J. R. Cox, Jr. V. W. Gerth, R. E. Hitchens, S. C. Huang, D. L. Snyder)

[1]G. N. Hounsfield, "Computerized Transverse Axial Scanning (Tomography): Part I. Description of System." British Journal of Radiology, vol. 46, pp. 1016-1022, 1973.

VII. TRAINING ACTIVITIES

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

Programming for Medical Information Systems, Fall, 1973

This course was taught by Walter E. Long and covered MUMPS programming techniques. Programming examples from hospital and ambulatory care settings were included. Attending the course were:

Ferydoon Bekhrad, B.A.	Biomedical Engineering
James C. Boyd, M.D.	Laboratory Medicine
David E. Bruns, M.D.	Laboratory Medicine
Allen G. Gruber, B.S.	Health Care Administration
Leonard Jarett, M.D.	Laboratory Medicine
Margaret C. Jost, B.A.	EE/Biomedical Engineering
Mary F. Kenner, B.S.	Medical Care Group
J. Joseph Marr, M.D.	Internal Medicine-Microbiology Lab.
Thomas F. Martin, M.D.	Cardiology
Robert C. McDaniel, M.D.	Laboratory Medicine
John Mark Michael, M.D.	Laboratory Medicine
Mohamad Rahmanian, Ph.D.	Laboratory Medicine
Lii-Mei B. Tsai, M.D.	Laboratory Medicine-Pathology

Introduction to Assembly Language Programming, Spring, 1974

This course was taught by Walter E. Long and Elizabeth Van Patten and included the fundamental concepts of assembly language programming. The course was oriented toward the PC-1200; however, the concepts were general enough to apply to all digital computers. Attending the course were:

Ronald W. Hagen, MSEE	BCL
Kenneth L. Kunklemann	BCL
J. Lawrence Robinson	BCL
Paul E. Root, B.S.	Mallinckrodt
Steven A. Saltz, B.A.	Cardiothoracic Surgery
Joseph W. Sharp	CID

Fortran Programming on the PC-1200, Spring, 1974

This course was taught by Walter E. Long and Elizabeth Van Patten and was on Fortran programming with the major emphasis on details of the PC-1200 Fortran system. Attending the course were:

J. Lawrence Robinson	BCL
Paul E. Root, B.S.	Mallinckrodt
Joseph W. Sharp	CID
John Wetzel, B.S.	Mallinckrodt

VIII. SEMINARS

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

"The EMI Tomographic Scanner"

July 10, 1973

Dr. Saul Aronow
Department of Radiology
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

"Stochastic Analysis of Transit Time Distributions of Intravascular Tracers"

September 5, 1973

Mr. Sung-Cheng Huang
Department of Electrical Engineering
Washington University
St. Louis, Missouri

"The PC Fortran System"

October 11, 1973

Mr. David Bridger
Software Development Manager
Artronix Incorporated
St. Louis, Missouri

"The Facilitated Diffusion of Oxygen in Solutions of Hemoglobin and Myoglobin"

October 19, 1973

Dr. John A. Jacquez
Department of Physiology
School of Medicine
The University of Michigan
Ann Arbor, Michigan

"Microprogramming"

October 29, 1973

Mr. Frank Carallo
Interdata Corporation
Oceanside, New Jersey

"Design of a Flexible Interface System Using the Intel MCS4 Microprocessor"

November 16, 1973

Dr. John W. Lewis
Division of Laboratory Medicine
School of Medicine
Washington University
St. Louis, Missouri

"Exponential Fitting of Dynamic Tracer Data"

November 19, 1973

Ms. Joanne Markham
Department of Applied Mathematics
and Computer Science
Washington University
St. Louis, Missouri

"Microprogramming"

December 4, 1973

Mr. Norman Abbod
Microdata Corporation
Santa Ana, California

"Bit Synchronization"

December 5, 1973

Mr. Kenneth Lewis
Department of Electrical Engineering
Washington University
St. Louis, Missouri

"Equipment Changes and Plans for the
Washington University Computing
Facilities"

December 5, 1973

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

"Quantification of Myocardial Infarction"

December 11, 1973

Dr. Burton E. Sobel
Cardiovascular Division
Washington University Medical School
St. Louis, Missouri

"Computer Decision-Making in Glaucoma"

December 13, 1973

Dr. Aran Safir
Department of Computer Science
Rutgers University
New Brunswick, New Jersey

"Monte Carlo Simulation of Operating-
Room and Recovery-Room Usage"

February 21, 1974

Mr. Homer H. Schmitz
Management Systems
Deaconess Hospital
St. Louis, Missouri

"High Speed Digital Communications —
A Design Study Applied to the Hospital
Environment"

April 29, 1974

Mr. G. James Blaine
Department of Electrical Engineering
Washington University
St. Louis, Missouri

"Dynamic Imaging with Cyclotron-Produced
Nuclides"

June 17, 1974

Dr. Gordon L. Brownell
Physics Research Laboratory
Massachusetts General Hospital
Boston, Massachusetts

IX. PUBLICATIONS AND ORAL PRESENTATIONS

Alderson, P.O., Secker-Walker, R. H., Strominger, D. B., Markham, J., and Hill, R. L., "Pulmonary Deposition of Aerosols in Children with Cystic Fibrosis," Journal of Pediatrics, vol. 84, pp. 479-484, 1974.

Alderson, P. O., Secker-Walker, R. H., Strominger, D. B., McAlister, W. H., Hill, R. L., and Markham, J., "Quantitative Assessment of Regional Ventilation and Perfusion in Children with Cystic Fibrosis," Radiology, vol. 11, pp. 151-155, 1974.

Bier, D. M., Sherman, W. R., Holland, W. H., and Kipnis, D. M., "The In-Vivo Measurement of Alanine and Glucose Turnover with Deuterium-Labelled Metabolites," Proceedings of the First International Conference on Stable Isotopes in Chemistry, Biology, and Medicine, Argonne National Laboratory, pp. 397-403, 1973.

Blaine, G. J., "High Speed Digital Communications: A Design Study Applied to the Hospital Environment," Doctor of Science dissertation, Department of Electrical Engineering, Washington University, St. Louis, Missouri, May 1974.

Clark, K. W., Nolle, F. M., Cox, Jr., J. R., and Oliver, G. C., "High Performance Computer Programs for Rapid Analysis of Long ECG Records," Proceedings of the San Diego Biomedical Symposium, vol. 13, February 1974.

Eichling, J., Raichle, M., and Gado, M., "Limitation of the Anger Camera for the Determination of Regional Cerebral Blood Volume," presented at the 59th Meeting of the Radiological Society of North America, Chicago, December 1973.

Eichling, J. O., Raichle, M. E., Grubb, Jr., R. L., and Ter-Pogossian, M. M., "Evidence of the Limitations of Water as a Freely Diffusible Tracer in the Brain," Circulation Research, in press.

Evens, R. G., Falvey, N. J., Jost, R. G., and Hill, R. L., "The Applications of Computer Simulation Modeling to the Radiology Film Library," Radiology, in press.

Fishman, P. M., and Snyder, D. L., "Estimation of a Random Space-Time Field that Influences an Observed Space-Time Point Process," Proceedings of the Eleventh Annual Allerton Conference on Circuit and System Theory, University of Illinois, Urbana, Illinois, pp. 597-600, October 1973.

Forrester, Jr., R. H., and Snyder, D. L., "Phase Tracking Performance of Direct-Detection Optical Receivers," IEEE Transactions on Communications, vol. COM-21, pp. 1037-1039, September 1973.

Gerth, V. W., Hagen, R. W., and Thomas, L. J., "Engineering Evaluation of a Computer-Based Surgical Intensive Care Monitoring System," Proceedings of the 26th Annual Conference on Engineering in Medicine and Biology, Minneapolis, Minnesota, p. 175, October 1973.

Ghista, D. N., Huang, S. C., and Resnikoff, M., "A Method for Simultaneous Determination of (I) the Blood Flows to the Organs and (II) the Cardiac Output," Bulletin of Mathematical Biology, vol. 35, November 1973.

Greenfield, Robert H., "MUMPS on the IBM System/360," Proceedings of the 1973 MUMPS Users' Group Meeting, in press.

Grubb, Jr., R. L., Raichle, M. E., Eichling, J. O., and Ter-Pogossian, M. M., "The Effects of Changes in $PaCO_2$ on Cerebral Blood Volume, Blood Flow, and Vascular Mean Transit Time," Stroke, in press.

Hagen, R. W., "A Redesigned Ultrasonic Spirometer," presented at the Ultrasonic Spirometer Conference sponsored by Statham Instruments, Inc., Los Angeles, California, April 1974.

Hertert, R. S., "A Flying-Spot Scanner for Automating in the Kirby-Bauer Antibiotic Disc Sensitivity Test," Master of Science thesis, Department of Electrical Engineering, Washington University, 1973.

Hillman, R. E., and Keating, J. P., "β-Ketothiolase Deficiency as a Cause of the Ketotic Hyperglycinemia Syndrome," Pediatrics, vol. 53, p. 221, 1974.

Hillman, R. E., and Otto, E. F., "Inhibition of Serine-Glycine Interconversion by Products of Isoleucine Metabolism," Pediatric Research, in press.

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Holmes, W. F., Shore, B. L., and Inselberg, R. I., "A General-Purpose Computer System for Gas Chromatograph/Mass Spectrometry," Proceedings of the 22nd Annual Conference of the American Society for Mass Spectrometry, Philadelphia, May 1974.

Hoversten, E. V., Snyder, D. L., Harger, R. O., and Kurimoto, K., "Direct Detection Optical Communication Receivers," IEEE Transactions on Communications, vol. COM-22, pp. 17-27, January 1974.

Huang, S. C., "Stochastic Analysis of Transit-Time Distributions of Intravascular Tracers," Doctor of Science dissertation, Department of Electrical Engineering, Washington University, St. Louis, Missouri, 1973.

Huang, S. C., and Cox, Jr., J. R., "Stochastic Formulation for Transit Time Distributions of Non-Diffusible Tracers in Tracer Kinetics," in _Proceedings of the 26th Annual Conference on Engineering in Medicine and Biology_, October 1973.

Kleiger, R. E., Martin, T. F., Miller, J. P., and Oliver, G. C., "Mortality of Myocardial Infarction Treated in the CCU," _Heart and Lung_, in press.

Kleiger, R. E., Martin, T. F., Miller, J. P., and Oliver, G. C., "Ventricular Tachycardia and Ventricular Extrasystoles During the Late Recovery Phase of Myocardial Infarction," _American Journal of Cardiology_, vol. 33, p. 149, January 1974 (abstract).

Kleiger, R. E., and Senior, R. M., "Long-Term Electrocardiographic Monitoring of Patients with Chronic Pulmonary Disease," _Chest_, vol. 65, pp. 483-487, May 1974.

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Larson, K. B., Raichle, M. E., Phelps, M. E., Grubb, R. L., Welch, M. J., and Ter-Pogossian, M. M., "A Mathematical Model for In-Vivo Measurement of Metabolic Rates Using Externally Monitored Radiotracers," _Proceedings of the Third International Conference on Data Handling and Image Processing in Scintigraphy_, in press; submitted for publication in a future volume of _Computers in Biomedical Research_, Stacy and Waxman, eds., Academic Press, New York.

Larson, K. B., and Snyder, D. L., "A Mathematical Model for Measuring Blood Flow by Residue Detection When Radiotracer Recirculation Interferes," _Proceedings of the National Conference on Research Animals in Medicine_, U.S. Government Printing Office, in press.

Lewis, J. W., "On the Evolution of Clinical Laboratory Computer Systems," _Journal of Clinical Computing_, in press.

Lewis, J. W., and Hertert, R. S., "Design of an Inexpensive Flying-Spot Scanner System for the Kirby-Bauer Antibiotic Sensitivity Test," in Zarnstorff, Hendee, and Carson, eds., _Application of Optical Instrumentation in Medicine II_, in press.

Lewis, J. W., Hertert, R. S., and Kumpf, R., "A Low-Cost Flying Spot Scanner System for Clinical Microbiology and Immunology," in _Innovations in Biomedicine: Proceedings of the 1974 San Diego Biomedical Symposium_, in press.

Lien, M. D., and Cox, Jr., J. R., "A Mathematical Model of the Mechanics of the Cochlea," _Journal of the Acoustical Society of America_, vol. 55, no. 2, February 1974.

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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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216	Snyder, D. L.	Notes on - The Theory and Application of Stochastic Point Processes and Their Generalizations - Chapt. VI	7/73
217	Snyder, D. L.	Current Trends in Information Processing for Observed Point Processes	8/73
218	Huang, S. C.	Stochastic Analysis of Transit Time Distributions of Intravascular Tracers	9/73
219	Snyder, D. L. Fishman, P. M.	Estimation of a Random Space-Time Field That Influences an Observed Space-Time Point Process	9/73
220	Schuessler, T. Thomas, L. J.	User Manual for Computer-Based Surgical Intensive-Care Monitoring System	10/73
225	Secker-Walker, R. Alderson, P. O. Wilhelm, J. Hill, R. L. Markham, J. Baker, J. Potchen, E. J.	The Measurement of Regional Ventilation During Tidal Breathing -- A Comparison of Two Methods in Healthy Subjects, Patients with Pulmonary Embolism and Patients with Chronic Obstructive Lung Disease	10/73
226	Secker-Walker, R. Alderson, P. O. Wilhelm, J. Hill, R. L. Markham, J. Kinzie, J.	Ventilation-Perfusion Scanning in Carcinoma of the Bronchus	10/73
227	Parker, J. A. Secker-Walker, R. Hill, R. L. Potchen, E. J.	On the Continuous Measurement of Left Ventricular Ejection Fraction	10/73

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228	Alderson, P. O. Secker-Walker, R. Strominger, D. B. McAlister, W. H. Hill, R. L. Markham, J.	Quantitative Assessment of Regional Ventilation and Perfusion in Children with Cystic Fibrosis	10/73
229	Alderson, P. O. Secker-Walker, R. Strominger, D. B. Markham, J. Hill, R. L.	Pulmonary Deposition of Aerosols in Children with Cystic Fibrosis	10/73
230		Supplement to Progress Report #9	10/73
231	Oliver, G. C. Miller, J. P. Martin, T. F.	A Critical Review of Computer ECG Monitoring: Present Confusion and Future Promise	11/73
232	Holland, W. H. Holmes, W. F.	LKB-9000/PDP-12 Interface	11/73
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234	Raichle, M. E. Larson, K. B. Phelps, M. E. Grubb, R. L. Welch, M. J. Ter-Pogossian, M. M.	In-Vivo Measurement of Brain Glucose Transport and Metabolism Employing ^{11}C-GLUCOSE	12/73
235	Larson, K. B. Raichle, M. E. Phelps, M. E. Grubb, R. L. Welch, M. J. Ter-Pogossian, M. M.	A Mathematical Model for In-Vivo Measurement of Metabolic Rates Using Externally Monitored Radiotracers	4/74
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238	Fisher, W.	Speaker User's Manual	12/73
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