# PROPOSAL FOR

# STANFORD UNIVERSITY

# MEDICAL EXPERIMENTAL COMPUTING FACILITY

# (SUMEX)

Submitted to the

Biotechnology Resources Branch

of the

National Institutes of Health

June 1, 1972

School of Medicine
Stanford University

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FIGURES

STANFORD UNIVERSITY MEDICAL EXPERIMENTAL COMPUTER RESOURCE

S U M E X

Proposal for a research resource in extension of the ACME project.

## A. INTRODUCTION

### 1. Objectives and Long Term Goals

General purpose computer support of research at Stanford University Medical School has reached substantial maturity under the impetus of the ACME project (Advanced Computer for Medical Research) funded since 1966 by NIH. We have understood that our technical success would be coupled with the gradual withdrawal of centralized agency support for a proven utility. Hence, June 1973 represents the termination of the longstanding NIH subsidy for ACME, which will thenceforth be operated as a fee-based service.

The present application seeks to establish a resource for a new set of technical horizons, in keeping with the expending capability and applications of computers in biomedical research. SUMEX would be a resource (1) to support a set of ongoing biomedical research programs that exploit state-of-the-art computer techniques, and help to shape further advances, and (2) the computer-science research that is essential to expedite the creative uses of computers in the laboratory, in the clinical research wards, and eventually in patient care at every level.

The unifying theme of the SUMEX resource is the management of a set of peripheral minicomputers by a powerful central facility. The minicomputers in question are immediately situated in laboratory and clinical-research environments. They can perform some tasks free-standing, but the selected projects require further backup to sustain high-data-rate and closed-loop operations. These machines, together with others on less demanding projects, can be enhanced by sharing peripherals, mutual backup, and higher level language programming and debugging in the central processor. More far-reaching in concept, and central to this proposal, is central and "intelligent" management of the data-gathering process to meet problem-oriented needs for information. (This is no more than a feeble emulation of the processes that higher organisms must have evolved to modulate the flow of sensory data into the perceptual mechanism.)

In the ideal situation this might entail a realtime closed-loop control of a laboratory instrument or a patient-monitoring device. Prior and currently updated information, related to partial solutions of a problem, would then selectively orient further data-taking so as to expedite a complete solution. A related example would be a kind of triage--allocating the time-shared partitions of a large

computer resource to concentrate on the patient with the most problematical symptoms. Even where realtime processing is unrealistic, in the present state of the art, as in motion-picture processing, the magnitude of computing requirements could be vastly reduced by analyzing each frame to pose specific questions of the next one, rather than prepare a digital core image of the entire sequence. Similar problems arise in every branch of spectrometry, including mass-spectrometry, where costly instruments and samples may be needlessly expended in conventionally serial acquisition of the whole spectrum, followed by its analysis (which usually relies upon a small part of the entire data set.)

The initial list of collaborating investigators is presented in part C-1. Others who are not yet prepared to commit themselves to this enterprise will continue to be recruited as discussed in part D. The hardware requirements are detailed in part E and further details of the operation of the SUMEX resource, and its relationship to service-computing at SUMC* are detailed in subsequent sections.

*(Stanford University Medical Center)

## 2. Background: ACME Computer Facility Experience

On August 1, 1966, the Biotechnology Research Resources Branch of NIH (then known as the Research Resources Branch) awarded a grant to Stanford University Medical School to support the establishment of ACME (Advanced Computer for MEdical Research) facility. The initial proposal included the following paragraph concerning hardware selection and resource allocation:

> "The IBM/360-50 has been selected for the initial realization of ACME (1) as a machine technically appropriate to the immediate tasks in mind and (2) for its system compatibility with the 360-67 already selected for the eventual replacement of the 7090 by the Stanford Computation Center. The 360-50 will be installed in ACME May 1966 and will run on three shifts under Operating System/360, subject to review by the policy committee. These will be dedicated respectively:
>
> (A) A prompt access time-sharing mode - perhaps over most of the working day.
>
> (B) A scheduled, full-use, on line mode - to service development work on high data rate and on line control applications, and for similar systems development.
>
> (C) Job-shop, especially longer runs for which overnight turnaround is acceptable, and which cannot be serviced with comparable effectiveness by SCC."

The following aims were added to the ACME charter at the time of the Renewal Proposal in the Spring of 1969:

(a) To improve hardware and software reliability for the benefit of the medical users.

(b) To provide small machine assemblers in PL/ACME so that code for small machines can be written from an ACME terminal.

(c) To achieve over time a state where income from user charges will match operational costs for the ACME system. The target date for this has not yet been fixed by Stanford and NIH.

All of the original objectives have been achieved to varying degrees of satisfaction. Of special note is the development of PL/ACME as an interactive timesharing system which can be easily learned and used by medical staff. On the other hand, the realtime support offered is inadequate due to system instabilities and data rate limitations. Access to Campus facility is inconvenient for ACME users.

In terms of the items added at renewal time, hardware and software reliability have been markedly improved. Small machine assemblers have been added, but the user must write code in the assembly code for whatever satellite he intends to run. At present, assemblers of this type exist for PDP-11, PDP-8, and 1800. The income of the facility has been rising steadily. Economic overlaps with NIH direct support for ACME have blurred the transition to totally non-subsidized use. A major rate increase was initiated in April, 1972. With this change,

income in the near term is expected to reach roughly 60% of direct operating costs (exclusive of development efforts). From the vantage point of hindsight one could well ask whether the selection of the 360/50 hardware and the decision to promote a large central time-sharing and data collection resource were appropriate. Given the availability of new third generation hardware and the promises of IBM or expectations of its customers in 1966, the 360/50 hardware selection is defensible. However, the development of low cost, fast, well-supported minicomputers was not anticipated to proceed at the phenomenal pace that it has. This major technological shift has strongly influenced our present thinking for the future of computing in medicine and related research. The role of a large shared resource has by no means been obviated by the minicomputer revolution. We will continue to need powerful facilities beyond the scope of current mini architecture.

The advantages of dedicated satellite processors make them mandatory for many applications which require high reliability and availability. A marriage of of the two architectures is proposed. The resultant synergism is designed to solve identified problems in our research environment.

B. SUMMARY

The resource for which we are applying consists essentially of a Digital Equipment Corporation PDP-10 system, to be procured on a lease-purchase plan over the 5-year term of the grant. The configuration has been designed for flexibility in interfacing with numerous small machines )provided by the collaborating investigators). The rationale for this system, the associated peripherals, and for the technical support staff, are detailed herein below. The SUMEX machine will be scheduled for the sole use of the SUMEX collaborative group, under the leadership of the principal investigator. Other investigators will, however, be recruited into the group if they qualify by virtue of their interest in and competence for computer research relevant to the main themes outlined here, and insofar as their theoretical and technical contributions will enlarge our understanding of the application of computers for the management of high-data-rate biomedical studies. SUMEX will not be available for routine computing that can be effectively purchased from existing utilities. The initial group of coinvestigators includes all respondents at SUMC who qualified by the stated criteria; however, several others are expected to advance the sophistication of their computer applications so as to qualify within the term of the grant.

SUMEX is expected to develop a number of applications that may become routine once perfected. These results would be transferred as appropriate to a service utility which continues to meet the demand for conversational time-shared computing as a legacy of the ACME project. For example, a number of workers at SUMC have utility-level requirements for support of their minicomputers. We believe this cognate requirement can be most efficaciously met if SUMC establishes a twin service facility based on a PDP-10, perhaps coupled with a small IBM machine for fiscal data-processing with company-furnished software. (These decisions are outside the policy cognizance of the present applicants, and outside the funding hereby requested. However, we are in good communication with the SUMC computer service committee that is establishing those policies.)

These decisions need not be fixed at an early date; for example, the existing IBM/360-50 ACME system might be retained for some time to provide feepaid timesharing service, during a transition period at the establishment of SUMEX as a research resource. In any case, the existing ACME project, for the remainder of its term (Expires July 31, 1973) and to some extent the new SUMEX program will have the responsibility of easing that transition for the community of users who have made large commitments to the ACME service. Except during an interim transition period and later on an emergency basis, SUMEX obligations to the ACME community will be confined to providing technical advice for conversion, and developing software that can be used interchangeably on the SUMEX and on the SUMC service machines. However, SUMEX developmental efforts will be strongly biased by that requirement for compatibility, and indeed for ready exportability to other biomedical computer groups.

The application of SUMEX could be summarized in terms of the scientific objectives of specific projects -- which are, however, detailed in section G. These lend substance to the technical research on computers themselves which is the unifying theme of our proposal. The principal investigator's interest in the DENDRAL project was, from the outset, motivated by the aim of broadening the application of machine intelligence to science generally (He is, after all,a geneticist first, and entered into mass spectrometry only because the latter was more amenable at the present level of the art.). While few other fields of biomedical research are, at present, ready for the full-blown application

of the techniques developed for DENDRAL as a problem in artifical intelligence, there is a broader base of common concern for related problems in data management. Briefly, in as many ways as possible, we will be developing the means to support small machines by a large central facility acting as an executive manager for the minicomputers. In addition, we will develop the technology of programming the mini's in higher level languages compiled on the PDP-10; will simulate minicomputer configurations as a way of designing new installations; will provide buffering and communications among small machines, and between them and various peripherals, including secondary storage, displays, and (if the opportunity materializes) access to other nodes on national computer networks. Where control loops are to be closed back on the mini's, a great deal of processing of the experimental data will presumably be done in the PDP-10. We will also investigate the utility of small machines as auxiliary subroutine-processors to increase the efficiency of a time-shared central device in some long computations.

## C. JUSTIFICATION

### 1. Demonstration of Need

The recruitment of an initial group of collaborators has made clear the need for:

- dedicated large computing resources
- high data rate acquisition and control capabilities
- development of software and hardware techniques
- integration of host and satellite computing systems

The SUMEX Resource responds to needs identified by a number of research projects within the Medical Center. Individually, their projects are unable to avail themselves of resources as large as SUMEX. Collectively, their research objectives demand the capabilities designed into SUMEX in this proposal. The requested facility calls for a high degree of cooperation among a small number of collaborators for their mutual benefit.

Five collaborative projects are described as part of this proposal. They are:

a. Predictive modelling of cardiovascular function utilizing X-ray and ultrasonic imaging techniques, Dr. Donald C. Harrison, Cardiology.

b. Development of computer based characterizations of radiographs of ureter, Drs. Thomas Stamey and Chris Constantinou, Urology.

c. DENDRAL -- Computer automation of the interpretation of mass spectrum, Dr. Joshua Lederberg, Genetics; Dr. Carl Djerassi, Chemistry; and Dr. Edward Feigenbaum, Computer Science.

d. Cell separator automation, Drs. L. Herzenberg and E. Levinthal, Genetics.

e. Electroencephalogram Driven Stimulus/Response Studies of Drug Effects, Drs. B. Kopell, T. Roth, and Pfefferbaum, Psychiatry.

2. SUMEX Relationship to Institutional Plans.

Stanford University has relied extensively on IBM equipment; the decision to procure a PDP-10 for SUMEX inevitably hinders compatibility and economy in system effort. Unfortunately, the IBM lines offer no cost-effective equivalent to the PDP-10 for small machine interfacing. An oversized and costly IBM machine would offer few advantages of portability to other research programs interested in similar objectives. Furthermore, our experience with the ACME IBM/360-50 suggests that one could easily overestimate the ease of retaining compatibility, even within the IBM line, of programming systems that address distinctive objectives. (DOS systems differ from OS systems to a degree comparable to the barriers between machines from different manufacturers.) The best we can expect to do, in the face of conflicting objectives, is to strive for the most efficacious compatibility we can achieve in higher level languages, files systems, etc. We do have the benefit of Dr. John McCarthy's long experience with the PDP-line in the Artificial Intelligence Laboratory at the edge of the Stanford Campus.

These decisions have been reviewed by Dr. Gene Franklin in his role as University Associate Provost for Computing.

The SUMEX resource will divert its users from existing computer facilities only to a limited degree. Most of the uses intended for SUMEX require services simply not available otherwise. Some of the LISP programming of the DENDRAL project would otherwise be run on one of the larger IBM machines. This would be at great cost, and in any case could not permit an approach to closed loop management of the laboratory instruments. The entire ACME machine, scheduled with no shared users, lacks the computing power required for these applications.

We are recommending a twin PDP-10 for the SUMC service facility to optimize the overall advantages of the SUMEX option. IBM's performance in delivering time-sharing and realtime software for the 360 line has been disappointing -- indeed this was an important crimp in the projected transfer of routine time-sharing service from ACME to the SCC's 360-67 based service. On the other hand, DEC has done rather well with manufacturer-supplied software for these users of the PDP line.

An important advantage to the Medical Center of the dual PDP-10 system would be the availability of a back-up system. The lack of redundant hardware has precluded some applications; one user has opted to buy two mini-systems with identical configurations in order to obtain maximum reliability. The financial burden of this approach would be too great in most applications. The availability of redundant hardware facilities will be an important factor in the Hospital's consideration of how to solve its computing problems.

The impact on the Medical Center of having shared data files for research, service (research support), and administration can be significant. Faculty members in several disciplines are asking with increasing frequency for access to data bases outside of their own department. Of course, the file system design will provide file integrity, protection from catastrophic loss of data, and security. The availability of shared common files will (1) reduce the need for duplicate files, (2) improve the visibility and availability of information to faculty and staff, and (3) encourage placement of data on large, less expensive, rotating memories as opposed to smaller, more expensive hardware on satellite systems.

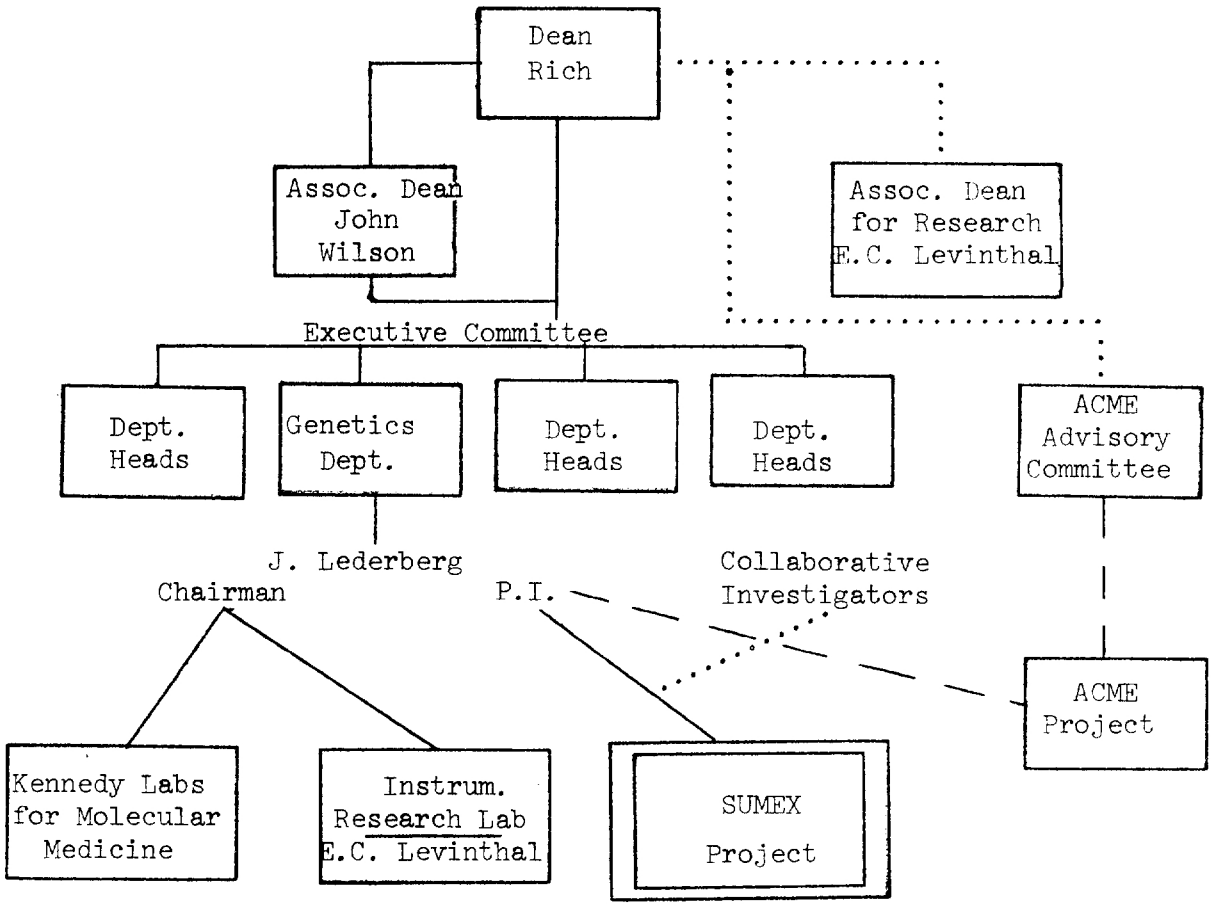
Common communications support for research service, and administrative computing systems is viewed as mandatory. The proliferation of terminal types, small machine types, etc. will breed a foul nest of communications hardware and software unless a sound, centralized, long-term plan is established. One can envision users with multiple terminals in each office, ward, or laboratory and multiple protocols needed by staff to use disparate systems unless the trends toward decentralization are encompassed under some umbrella of sound planning. The use of a shared communication system may permit redundancy and availability which would not be feasible in multiple independent systems. However, the hardware choices of the SUMC service operation are perhaps less important than the cooperative spirit that will be reinforced by the administrative arrangements for its coordination with SUMEX.

D. RESOURCE OPERATIONS

1. Administrative Structure

Line authority for SUMEX is vested in the P.I., Dr. Joshua Lederberg, who was also P.I. for the ACME system. He also functions as Chairman of the Department of Genetics, and, as a member of the Medical School's Executive Committee, is in good communications with the other department chairmen. In other roles (e.g., University Committees on Research and Computing Facilities, the Human Biology Program, etc.) he is also in frequent communication with general university activities. The Genetics Department includes the Instrumentation Research Laboratory directed by Dr. E. C. Levinthal.

Dr. Clayton Rich, as Dean, is the principal administrative officer for the Medical School, and Dr. Lederberg reports to him in several capacities.

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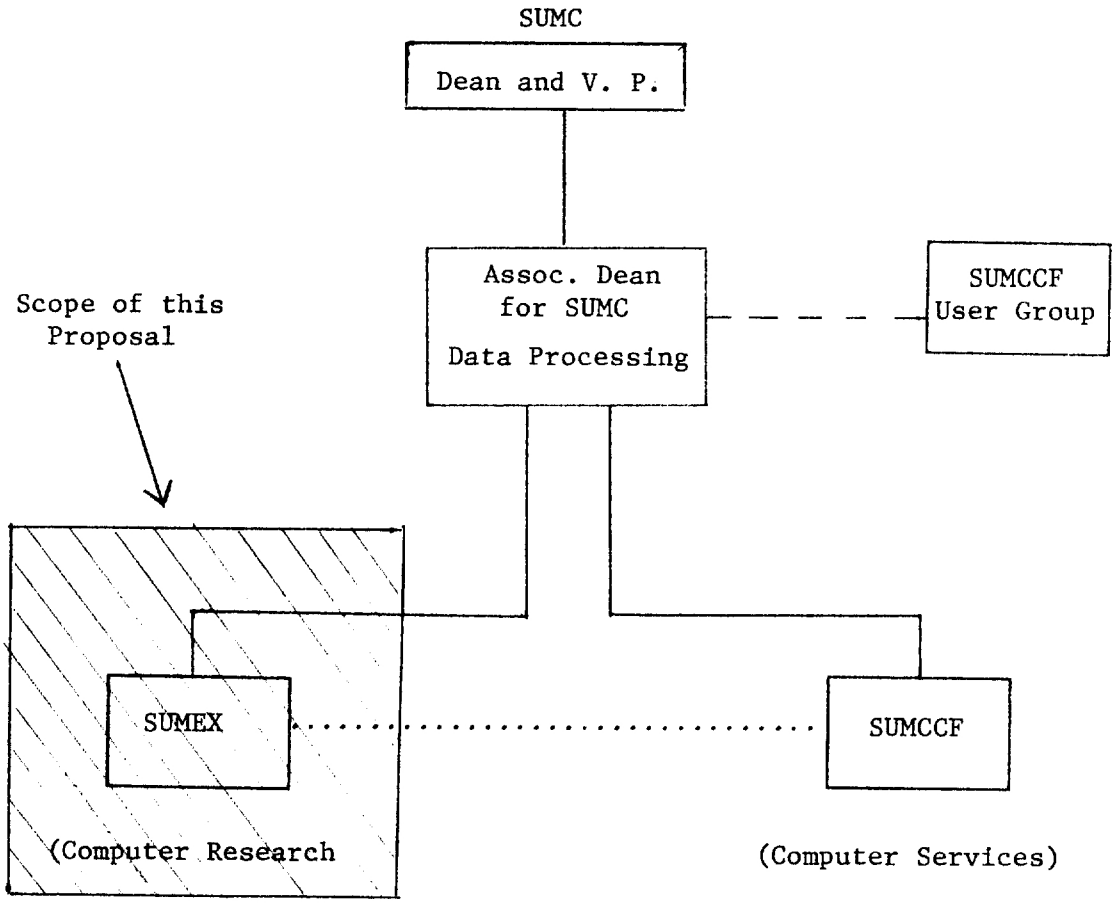
With the phasing out of ACME, its service responsibilities will be the responsibility of another organization reporting to the Dean independently of SUMEX. One proposed arrangement is:

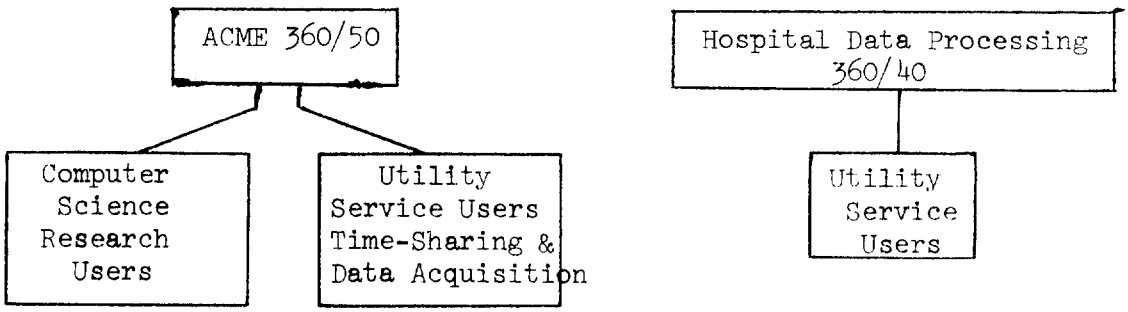



The Associate Dean will assure the optimum exchange of information and compatible policy development between computer research and computer services.

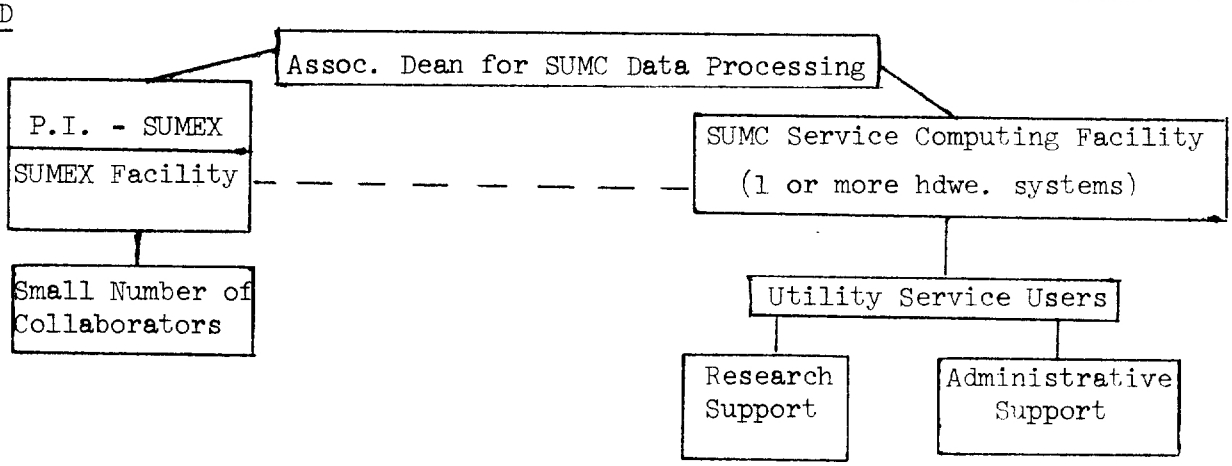
The hatched area signifies that this proposed grant will support (1) SUMEX operations and (2) liason with Stanford University Medical Center Computer Facility (SUMCCF). SUMEX will support development efforts on its PDP-10 machine of a kind that should be readily transferable to the SUMCCF as well. SUMEX will also assist the ACME community in the transition to SUMCCF services. However, operating expenses of the SUMCCF will be met from the SUMC budget including user fees, and not from the SUMEX

grant. SUMEX and SUMCCF may however, provide mutual back up, on mutually advantageous terms, with respect to downtime emergencies and experiments involving linked processors, on the basis of credits for demand availability and use. The functions of the existing ACME facility will then be partitioned between SUMEX, for a limited number of computer-research oriented collaborations, and a combined computer service facility for the S. U. Medical Center, which we will label SUMCCF.

CURRENT




PROPOSED




The SUMEX resource will operate under the direction of the Principal Investigator, who will be responsive to the research needs of the collaborators in terms of scheduling, use of the resources, and relative priorities for the programming staff. He will also establish liaison with SUMCCF to maximize the secondary gains of that relationship.

2. Operating Procedures and Policies

SUMEX is primarily responsive to a designated set of investigators interested in and competent to participate in major innovations in medical research applications of computers. They will have the opportunity to develop these applications in SUMEX prior to mounting them as new services on the Service Facility.

Authorized collaborators are limited and selected on the following grounds:

a. The Research Facility must remain capable of being dedicated to one experimenter's efforts if the total resource is needed for his work.

b. New hardware installation is likely to occur frequently on this facility. It should not have to be performed at odd hours in order to avoid normal service interruptions. The primary mission of this facility will be to service research users; routine service operations will be available only on the Service Facility.

c. Systems programmers will be testing new software concepts frequently. As a consequence, high system reliability and availability are not warranted.

d. Experience gained at ACME indicates that as time passes,more and more users come to expect (and demand) routine, stable, highly available service. Computer science related research cannot function efficiently in that environment.

e. Opening the Research Facility to routine use by many would inhibit the evolution of a fee-based Service Facility.

f. Management of the enterprise, including the selection of appropriate projects, will become increasingly difficult as the number of authorized users grows.

g. Their needs cannot be met on other local service facilities without undue disruption.

In the proposed grant period, no user service fees are contemplated for the Research Facility. As research concepts are developed and tested, it is expected that the Service Facility will be able to add services to meet user needs. Thus, the research objectives, once met, will be replaced with new research goals on the Research Facility.

Additional research collaborators will be recruited from the Stanford biomedical research community as indicated in paragraphs a. through g., above. We also contemplate cooperating with NIH grantees at other institutes via network facilities. During the interim period, prior to the settling down of reliable PDP-10 service on the SUMC facility, it may be desirable to coopt affiliated investigators who do not meet the full range of criteria but who are developing major projects in anticipation of the availability of the PDP-10 capabilities. Arrangements for servicing such users and for adding principal collaborators will be coordinated with the Biotechnology Research Resources Branch at regular intervals. The principal investigator will be responsible for applying these criteria for collaborating and affiliated projects, and for regular reporting to the Branch.

The Service Facility could provide routine services to SUMEX systems staff at times when the SUMEX was dedicated to a particular user's tasks. In addition, Service Facility usage would be needed to test newly transitioned packages from the Research Facility. The purchase of computer time on the SUMCCF would enhance the efficiency of SUMEX personnel. For these reasons, some funds are being requested to pay for services on the Service Facility.

## E. COMPUTER CONFIGURATION RATIONALE

### 1. Introduction

This section addresses the problems of system configuration design and computer selection based on projected requirements and available machines. To summarize the discussions of these topics which follow, we have arrived at the following conclusions and proposed course of action:

(a) Separate machines for computer research and utility service are required to provide simultaneously a continuous and reliable computing utility service like the current ACME system and support for new system developments.

(b) The two machines, including required communications and future data base interfaces, ideally should be as similar as possible and geographically contiguous to allow redundancy for reliability, ease of software transfer, and efficiency of operation.

(c) The two machines will have some level of coordinated management but with financing of the service machine derived from fee for service funds and of the research machine from the presently proposed grant funds.

(d) Based on evolving software requirements for time-shared and realtime support as well as the capabilities and economics of currently available systems, it is proposed that both machines be Digital Equipment Corporation PDP-10 computers.

(e) A phased transition (Figure E-5) from the present single IBM 360/50 configuration to the dual PDP-10 configuration including necessary PL/ACME modifications is planned so as to minimize the trauma of conversion.

### 2. Computing Environment

The design of a medical experimental computing resource for research on satellite machine interactions and extended realtime problems interacts strongly with the overall design of computing support within the Stanford Medical Center. Based on past ACME experience, hospital administration experience, and projected Medical Center needs, an overall facility must be able to accommodate three main types of computing simultaneously:

(a) Medical Service Computing - A stable and reliable computing utility service must be available which supports on-going medical research and clinical needs in the sense that ACME currently performs these functions. The users of this type of utility are presently largely within Stanford but can be expected to extend outside of Stanford as network facilities come more and more into use. Such a utility must include in its repertoire appropriate state-of-the-art services for time-sharing and batch operation as well as satellite machine programming and on-line data communications facilities.

(b) Hospital Administrative Computing - A stable and reliable computing support of hospital administrative computing must be available for processing data related to patient accountability, financial records, clinical laboratory records, pharmacy records, etc. This type of computing is based to a considerable extent on software packages which have been developed outside of Stanford for specific computing systems. In the future the system must be able to support some level of integrated hospital information system. A long term requirement exists for compatible file structures accessible from various machines and software packages over local and larger scale networks.

(c) Medical Computing Research - Computing service must be available to support the development of computer system software and hardware capabilities as well as research projects which require sporadic dedication of large amounts of computing resources or which endanger system reliability. Such a service must be tolerant of higher system volatility than the utility services in order to allow evolutions in system design and utilization without impacting essential on-going computing functions.

There are reliability, capability, and priority conflicts in the requirements which these three groups place on a computing facility. The evolution of the present ACME system, while successful in making powerful computing tools easily and broadly available to medical researchers and clinicians, has also provided examples of such conflicts between various users. The ideal facility design must embed support for these various computing functions in an overall configuration which optimizes the desirable interactions of information and technology while minimizing the fundamental conflicts. As needs for computing resources within the Stanford Medical Center and its affiliates grow, the computing facility must be capable of economical expansion based on these needs in ways which minimize conversion and transition trauma.

## 3. Technical Requirements

Estimates of requirements for future computing service in terms of capacity, response time, communications, etc. are based on past experience with existing systems as well as projected new requirements. In the following only the requirements related to this grant application are considered. The major non-administrative computing service offered in the Medical Center has been the interactive, time-shared PL/ACME system. This type of system will continue to be the basic environment for the proposed research in satellite machine support and realtime systems. Thus the evolution of the ACME system is an essential element of this plan.

ACME Background - The PL/ACME system currently runs on an IBM 360/50 computer system shown functionally in Figure E-1. The time-sharing aspects of the system, developed under the previous ACME grant, apportion memory resources to multiple users from a large fixed reservoir ($2.1 \times 10^6$ bytes). Realtime support for on-line experiments is provided by means of interfaces through either an IBM 1800 computer or an IBM 2701 data adapter. From a consideration of the loading history of this machine and related usage data a number of conclusions are drawn.

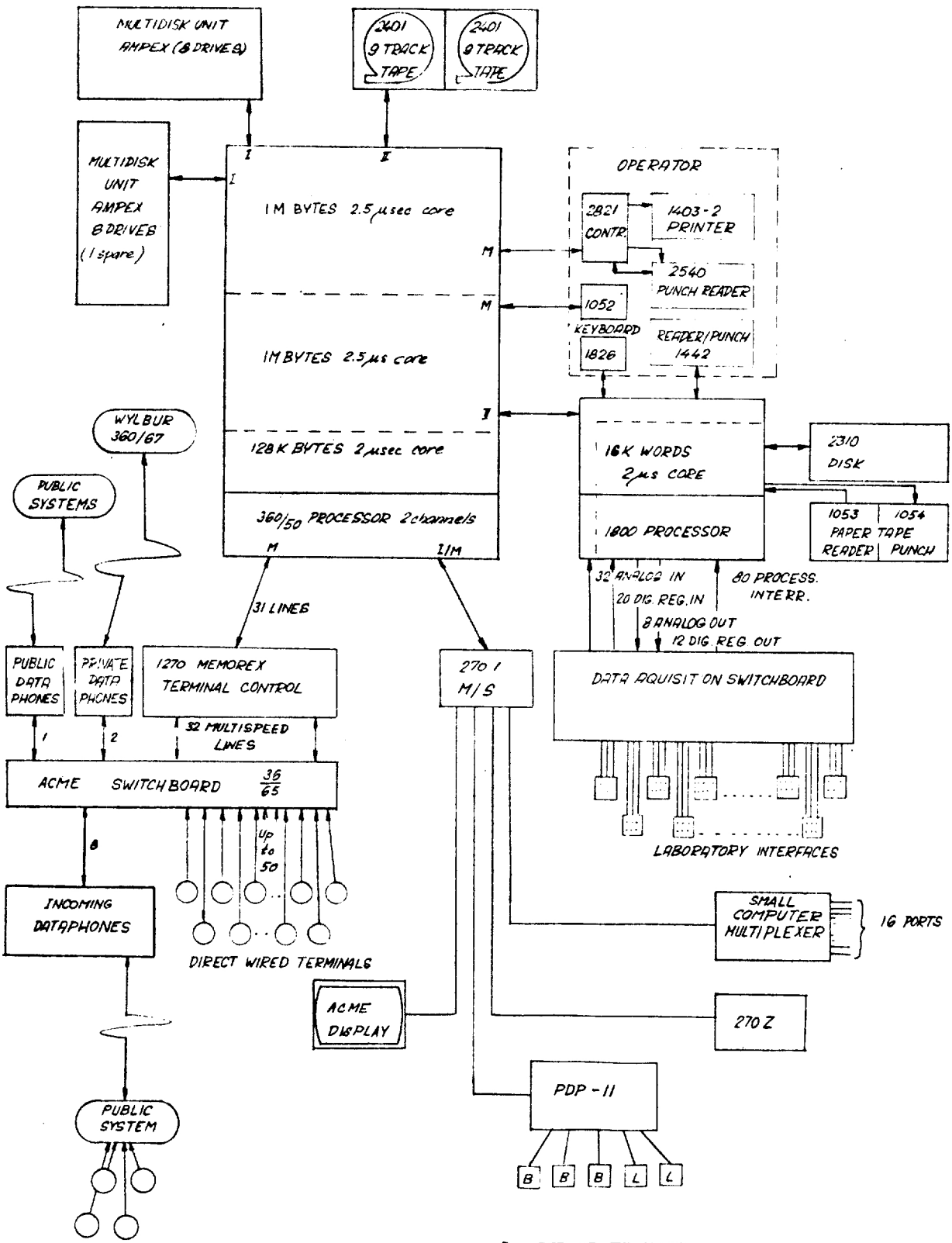
(a) The time-shared PL/ACME system has been of great benefit in fostering the medical use of computers at Stanford. It is expected that the needs for these services will increase in volume and sophistication.

(b) The 360/50 processor does not have the through-put capacity to provide adequate response service to existing heavy loads and is inadequate for closure of sophisticated realtime loops.

(c) Even with the large core memory available, core limitations impact performance and accessibility. A more sophisticated allocation of resources based on swapping and hardware relocation or on paging is required.

(d) The allocation of priorities to running tasks is too democratic with a resultant impact on applications with critical response timing requirements. Additional sophistication in the hardware and software priority hierarchy is necessary.

(e) Satellite machine programming and communication as well as real time needs will increase in terms of number of machines, complexity of application, aggregate data rates, and number of users. The system must integrate more flexible hardware and software satellite machine support into its repertoire.




B = BEEHIVE TERMINALS
L = LITTON PRINTERS

FIGURE E-1

ACME, May 1972

(f) More sophisticated usage of the system requires access to additional languages (such as list processing languages), more flexibility in organizing programs in terms of overlays, and more flexibility in overlapping task functions.

Future Needs - Based on these considerations, existing benchmarks for program through-put, and estimated new hardware and software requirements in support of research goals, the following gross summary of facility requirements is appropriate:

CPU: 2-4 times the through-put of the 360/50 with address relocation or paging and an interrupt hierarchy.

Memory: Approximately $10^6$ bytes of memory.

Bulk Storage: $4\text{-}8 \times 10^8$ bytes.

User Load: Research (this grant): 20-40 terminals (4 to 6 projects).
Service: 50 - 100 terminals.

Satellite Machine Interfaces: Satellite machines will be used both for remote instrument interfaces and for local multi-processing host support. Capabilities for direct memory sharing as well as normal satellite interfaces to the host as terminals are required.

System Software: The system software must allow effective scheduling and integration of conflicting time-sharing, batch and realtime computing loads.

## 4. Configuration Topologies

The requirements and priorities for computing services within the Medical Center place conflicting constraints on a computer facility. Some users require continuous, highly reliable service and others want access to develop system hardware and software capabilities which have an attendant risk of system crashes. Still others want sporadic dedication of sizable computing resources with response time constraints, and administrative elements of the computing load utilize software packages which require specific hardware and operating system characteristics (e.g. IBM developed business systems). One can consider a variety of facility configurations to attempt to meet these needs ranging from a large single processor to networks to completely distributed machines satisfying specific local needs.

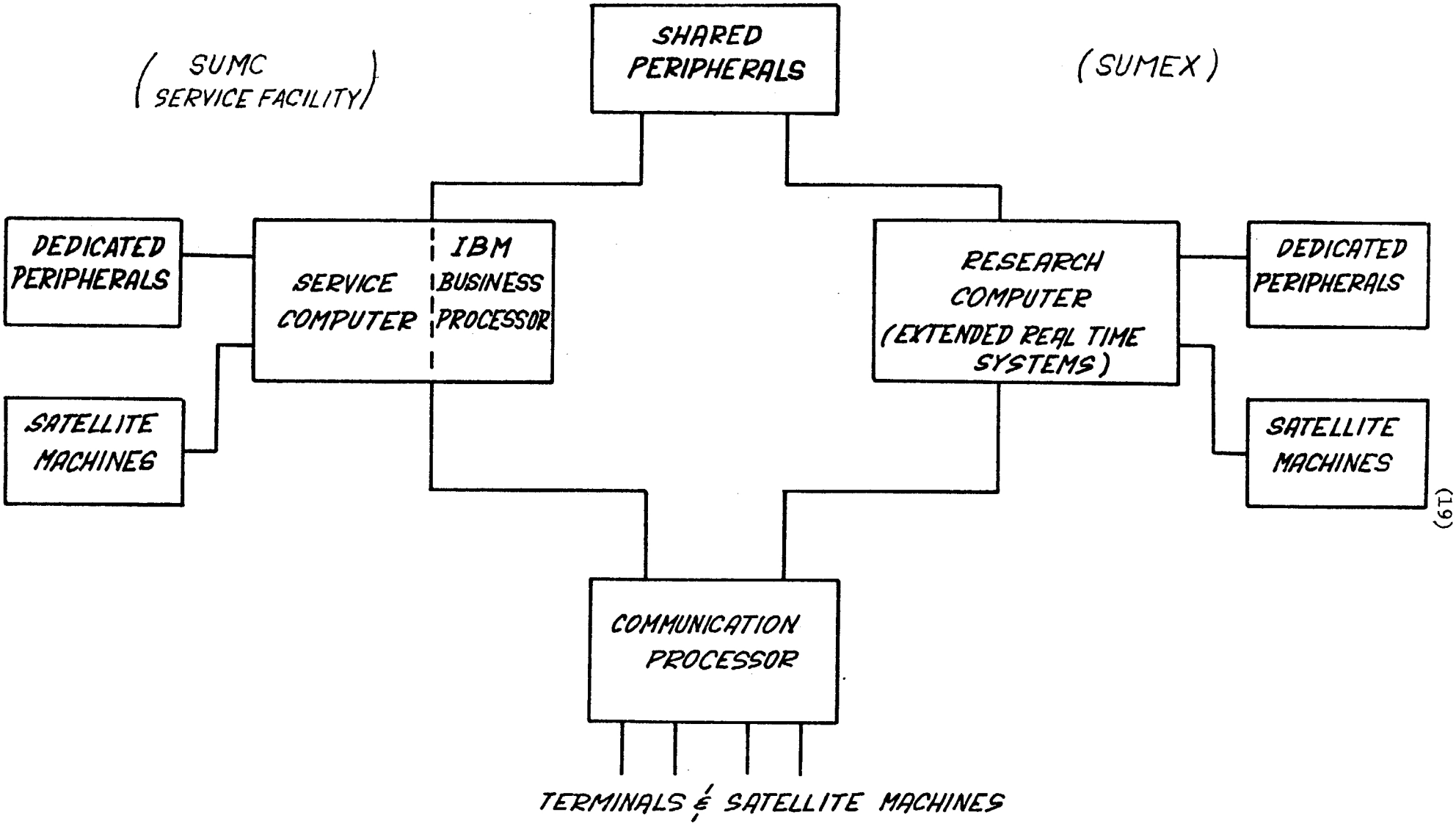
Single Central Machine - The single machine topology is not a satisfactory solution because the conflicting priorities and reliability requirements cannot be resolved simultaneously in an adequate fashion. Serial scheduling of the conflicting usage is not feasible either because of time constraints. The duty cycle for reliable service support for medical research, clinical service, and hospital administration can be expected to approach 24 hours per day. The requirement for reliability implies more than one machine to guarantee minimum interruption in service.

Network Facilities - Machines of adequate capacity and with applicable software system capabilities exist at a number of nodes on established networks such as the ARPANET. Currently, however, because of the developmental nature of specific facilities or operational constraints, no known node or set of nodes can commit the needed capacity with suitable response time and reliability to meet estimated Medical Center needs. These factors rule out network facilities in the near term for providing computing services.

Distributed Local Computers - The completely distributed system is equally unsatisfactory at present because of gross inefficiency. Rarely can individual users keep a machine fully utilized for most research work proceeds sporadically. Whereas the cost of processors is decreasing dramatically, the cost of peripherals and memory as well as small machine programming is still high. Thus either gross inefficiency results or the individual researcher must make do with a machine of less capability than required. It is not feasible in the near future to completely rely on distributed machines without the necessary ability to synergize and focus large processing capability on specific problems as required.

Dual Central Machine Compromise - This leads to a compromise dual machine topology for the Medical Center computer facility which meets the simultaneous needs of conflicting users. The general characteristics of such a system are shown in Figure E-2. This system allows the maintenance of reliable computing service by shifting system element commitments at the expense of lower priority uses in the event of some failure. Conflicting requirements are resolved through the scheduling of separate processors. The Research and Service subsystems should be of similar configuration allowing interchangeability to achieve reliability for service support. In addition the symmetry of this configuration provides for software interchange in the evolution of the fruits of computing research to a more routine service environment. Economy is advanced by geographic contiguity implying shared operations as well as peripheral and communications equipment.

The service computing subsystem has as its basic design goals the distribution of reliable computing support for PL/ACME time-share users, realtime computing as it develops, small machine support, and administrative computing. This system will be funded on a fee for service basis using the currently projected ACME customer base as well as anticipated network users.




GENERAL CHARACTERISTICS OF THE PROPOSED SYSTEM

FIGURE E-2

The research computing subsystem has as its basic design goals the support of work under this grant proposal. These needs include an evolving PL/ACME based system to develop satellite computing support (remote and local) and extended realtime systems in an environment tolerant of developmental system volatility. This system also provides back-up to the service machine in case of failure and allows service system modification without impacting on-going service. The research system will be funded out of this grant if approved and will include provision for documenting and passing developed capabilities into the service domain as they become available.

5. Hardware Selection

a. Main Frame

The selection of hardware elements to carry out the facility plan shown in Figure E-2 requires consideration of several issues:

(a) The current configuration and its suitability or adaptability for future goals.

(b) Alternative hardware systems including capability and reliability.

(c) Alternative software systems including capability and reliability.

(d) User community contributions to software developments.

Current System - As indicated previously, the ACME system is an interactive time-sharing concept implemented on a large memory IBM 360/50 computer. The system as it exists supplies a powerful service to the Stanford community and could supply that service to a broader community given expanded through-put capacity. Such expansion in capacity is possible by incorporating a faster processor with more memory or a faster processor with a swapping relocation core sharing scheme. IBM will eventually make such features available on the more reliable 370 computer line. The current 512K byte memory limitation on the 370/145, however, is not contemplated to be expanded. This would force an expanded implementation in the much more expensive 370/155 or in an old machine, the 360/65-67.

Future Needs - The proposed research in this grant application, based on the PL/ACME system, places several additional requirements on the future system. First, the system must allow interfacing other languages (such as LISP, Assembly language, etc.) in addition to PL-1 and permit a more sophisticated hierarchical structuring of programs and their interfaces to on-going realtime events. This implies a system which at one level is as easy to use as the present PL/ACME system but which affords, when desired, the opportunity for deeper control of computer functions without having to convert to an entirely new system environment. It is recognized that these levels of user control may endanger system reliability through user-caused software crashes.

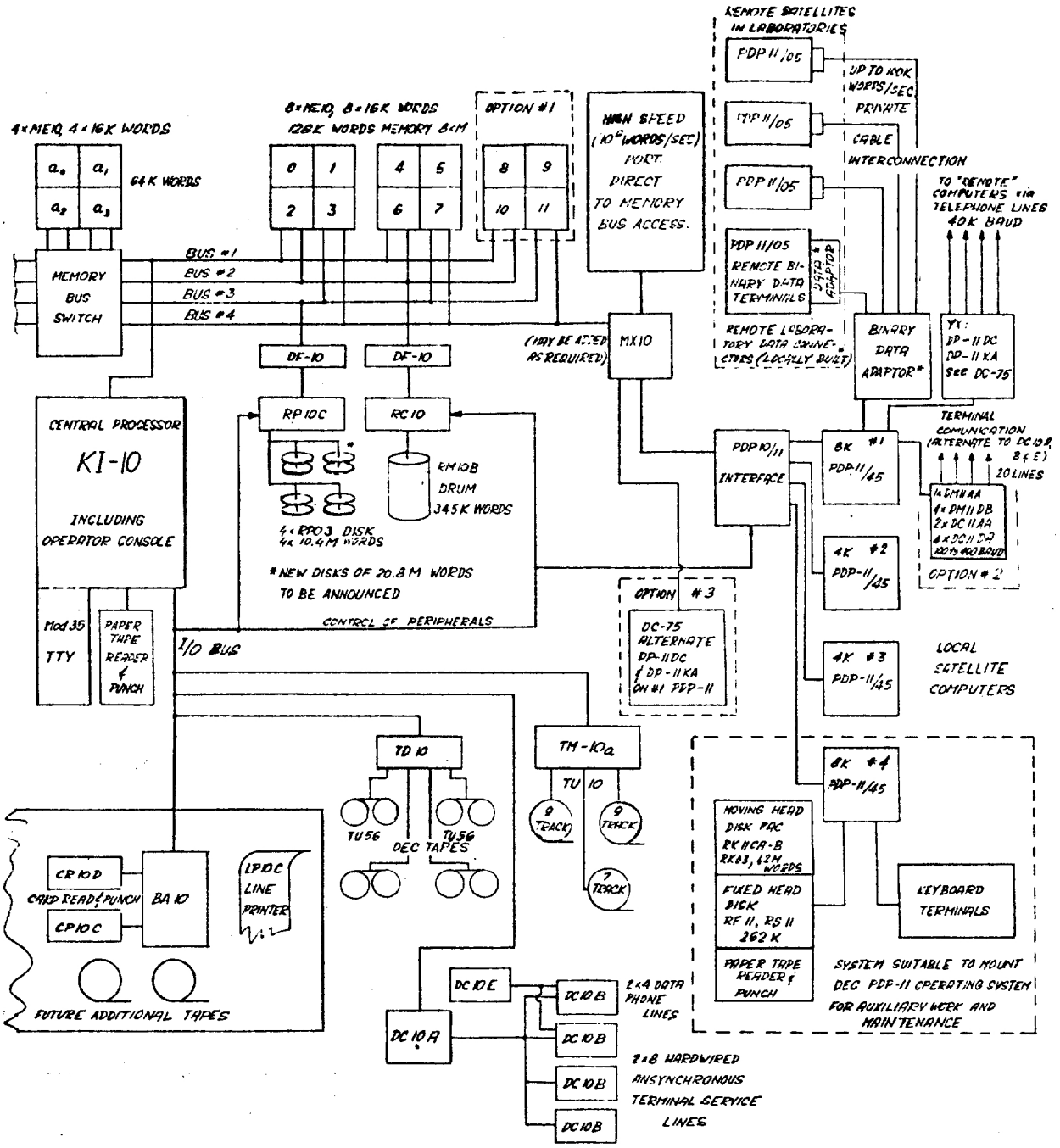
Secondly, the original system design did not foresee the proliferation of small machines which has occurred. Our research goals in the present plan include developing effective means for supporting and incorporating such systems in the distribution of computing services. This implies a requirement for more flexible ways of interfacing large and small machines in the form of memory to memory and CPU to external memory linkages. These go beyond the simple terminal or I/O device data forwarding roles currently in use.

Thirdly the design of realtime systems which allow "intelligent" loop closure commitments within time-sharing environments requires in addition to satellite machine interface flexibility, internal machine priority hierarchies, basically hardware implemented but with software control and extension.

Manufacturer Considerations - The size limitations of the 370/145, the high cost of the 370/155, the design age of the 360/65, and design goal considerations, suggest a reassessment of the selection of IBM hardware. This suggestion is enhanced by IBM's currently loose commitments to future time-sharing and realtime system support. The IBM systems provide a primitive priority and interrupt hierarchy and little flexibility in satellite processor interfaces.

From cost, hardware, and software points of view DEC equipment appears attractive. The PDP-10 hardware system (in particular the KI-10 processor) is of moderate capacity approximately comparable to the 360/65 and costs 30% less than the 370/155. The system is expandable to a multi-processor configuration to increase capacity at relatively low cost and has features comparable to those available on IBM hardware. These include soft fail machine check, hardware address relocation and paging (IBM will announce these shortly), and instruction look-ahead. In addition to these features, however, are a hierarchical interrupt structure and direct memory interfaces to satellite machines including other PDP-10's as well as PDP-11, and PDP-15 minicomputers. The software system is efficient and is designed around the integration of time-sharing, batch processing, and realtime computing taking advantage of appropriate hardware features. The PDP-10 community includes many research facilities working on aspects of machine architecture, system development, language support, artificial intelligence graphics, etc. These features of the PDP-10 and the computer science user community appear to be more in line with projected research and service requirements.

Other manufacturers offer hardware which incorporates many similar advantages but these systems lack the evolved software systems and applications packages as well as the large, actively working community of contributers which the DEC system has. Whereas IBM has a large community of users, the present impetus in the directions appropriate to this research are questionable. Thus, based on current information, it is felt that the PDP-10 offers a better technical and more




TENTATIVE INITIAL MACHINE CONFIGURATION

for

Stanford University Medical Center Experimental Computer Facility

"SUMEX"

*locally built

Figure E-3

economical long term posture for the experimental computing facility. This decision implies the judgment that the cost of converting the ACME software to run on a PDP-10 is offset by the longer term advantages expected to accrue from the more sophisticated system hardware and software support. The conversion effort is estimated to take 5.5 man years. A hardware change is painful but is less so the earlier it is made.

Hardware Configuration - The computer configuration as currently planned for the research subsystem is shown in Figure E-3. The service machine could appear as a symmetrical system.

b. Peripherals, Data Channels, and Satellite Computers

Attention is given here to the balance of the proposed hardware system. The RM10B drum is essential to DEC core swapping software. Certain other facilities are standard: The card reader and punch, line printer and operator's console need no explanation. The TD-10 controller and DEC tape units are necessary for maintenance of the PDP-10 system, hence a minimum configuration is included. 9 track tapes are selected for archive dumps, and some job entry or data interfaces with other computer facilities. A 7 track unit is included as experience has taught us that this tape format is still in use and a research facility must cope with this format from time-to-time.

Data Channels - This computer will quite literally exist for the processing of data from and to distant sites. Thus the remote data channels are of utmost interest. It is not intended to make a research project out of the communication aspects. On the contrary, it is proposed to have a set of solutions that can be implemented promptly and predictably in any laboratory, observing the due constraints of distance, cable, and rates. This service is to include diagnostic means for verification or troubleshooting.

Four classes of external communications are provided for:

1. Asynchronous character. 100 to approximately 400 baud. Suitable for TTY and other keyboard devices, many CRT terminals.

2. Synchronous character. Nominally up to 40,000 baud. Communication is suitable for telephone lines and will use nationally recognized standards. The modems used will be of standard commercial design, the proposed system uses exclusively DEC modems on the central computer end.

   The user may use commercial equipment of his choice on his end; however, there will be a unit available that incorporates a small remote satellite computer that is capable of running diagnostic programs to verify data communication to any

remote location. Also this unit will be a "preferred" design for standardization.

3. Binary data channels. Up to 100K words/second. This would be restricted to on-campus connections that have multi-pair cable connections. Probably there would be a 3 pair, 11 pair and 19 pair version with somewhat different maximum speeds.

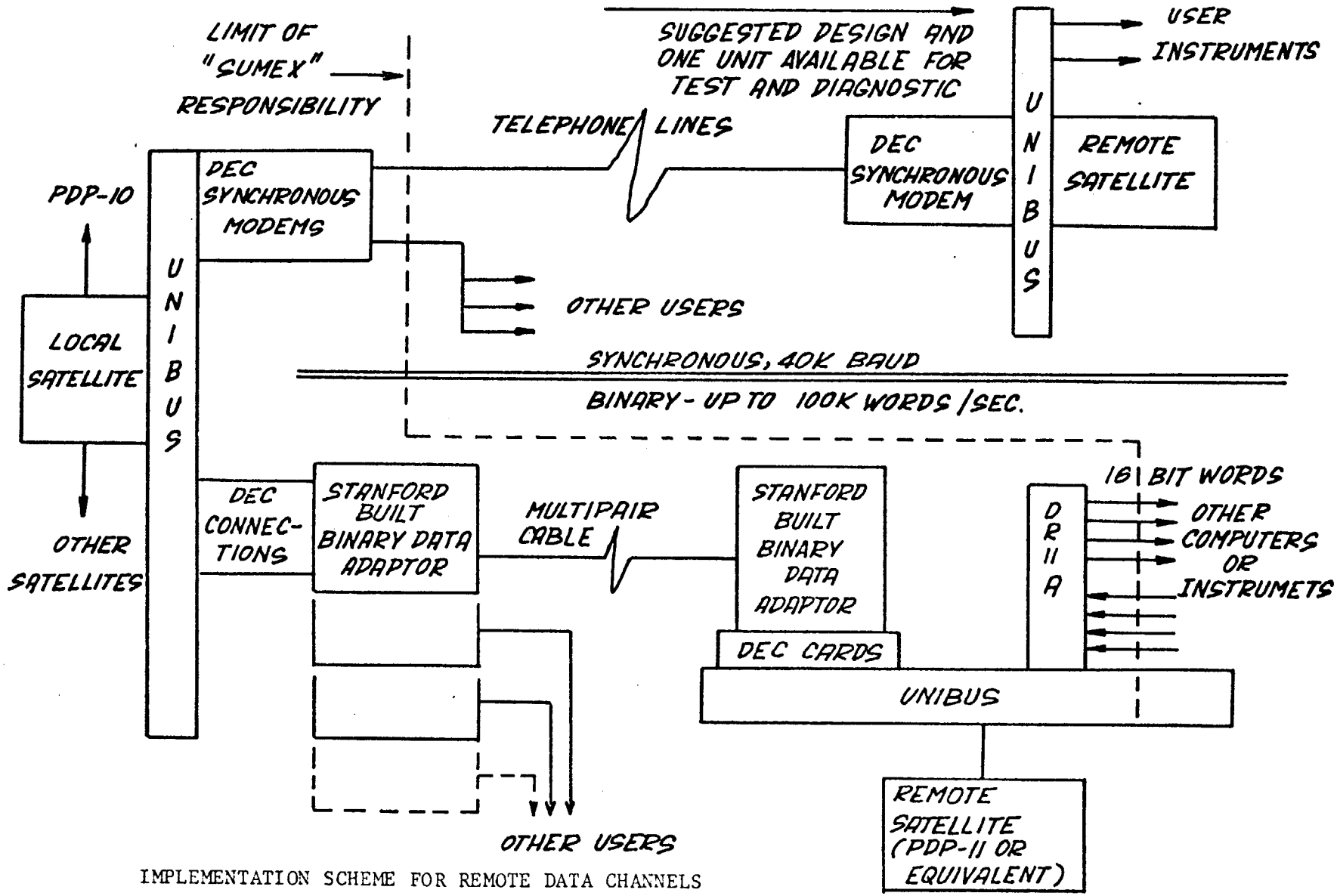
   The Binary Data Adaptors will be locally built. A characteristic is that both ends will plug into a PDP-11, or identical Unibus Models for this exist at Stanford in two versions, the IRL Chemistry-Medical Center connection, and the ACME small computer interface.

   Experience with many versions of these interfaces have taught the necessity of having standard service and connections to avoid the repetition of special engineering and resulting difficulty in maintaining service. The configuration of Figure E-4 provides standard service and is a configuration that may be checked by diagnostic software.

4. The need may arise for a superspeed data interface. None has been standardized for this purpose, but provision is being made to access Memory Bus #4 through the MX10 multiplexer for this purpose.

Alternate Ports for Types 1, 2, or 3 Channels - It is proposed currently to bring type 2 and type 3 channels into a local satellite computer. A trade-off exists here between hardware and software costs which will require further investigation. There is no commercial standard DEC service for type 2 to the memory bus or the I/O bus. For this and economy reasons the satellite PDP-11 is indicated. The hardware connection is to the PDP-11 bus, hence the configuration allows flexibility in moving any type 2 or type 3 channel to any of the local satellite computers.

Satellite Computers - To connect a PDP-11 to the PDP-10, the PDP-10/11 interface is indicated. This is a powerful but expensive device. It allows the PDP-11 to use segments of PDP-10 core. The segments allotted, and the interrupt service between computers, is enabled by the PDP-10. The PDP-10/11 interface also allows up to 8 PDP-11's; 4 are included in the present configuration. Incremental PDP-11's are economical and this allows exciting possibilities of small computer arrays for pipeline and parallel processing. This extra usefulness is thus a low priced expansion of the PDP-11/10 capability. The fourth PDP-11 has been configured as a DEC disc operating system. It can be used as a facility in a purely DEC fashion to assist other DEC users and the SUMEX staff in their software and interfacing efforts.




IMPLEMENTATION SCHEME FOR REMOTE DATA CHANNELS

FIGURE E-4

General Options - One of the most perplexing dilemmas confronting configuration planning today is the evolving technology and economy of memories. We have shown our planned configuration incorporating strictly DEC equipment including memory for simplicity. We are well aware, however, that DEC memory is not currently economically competitive and as indicated earlier in the small machine support proposal, the cost of large electronic memories in general is precarious and likely to drop significantly in the next few years. Whereas we must obtain sufficient memory immediately with our machine to allow initial developments, we will carefully consider a variety of manufacturers, incremental expansion, and leasing so as to optimize our posture for taking advantage of these new memory developments as they become available. A corollary problem exists in the peripheral equipment field such as disk drives.

In addition to these component problems several options exist in the design of terminal interfaces and synchronous data interfaces with the PDP-10. These trade-offs involve the relative cost and technical desirability of using a minicomputer interface which could require system software modification as opposed to standard DEC interface systems.

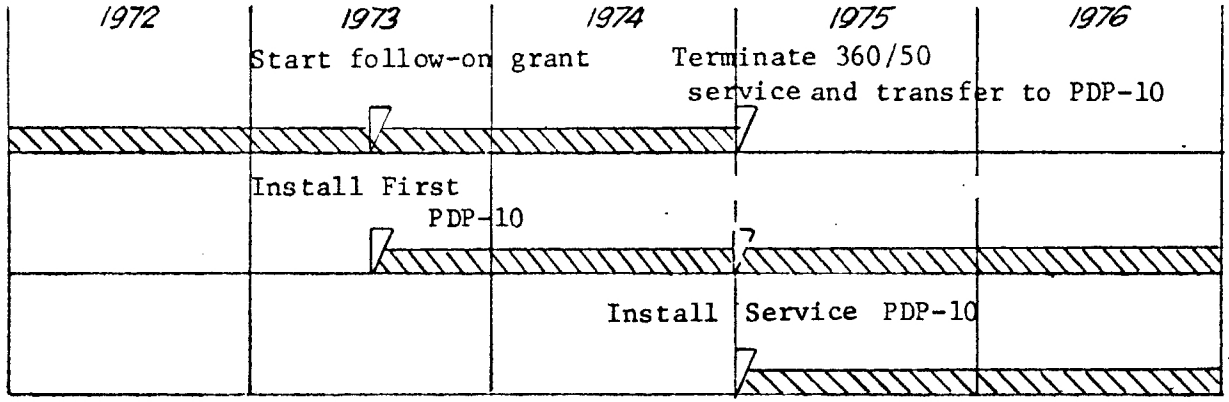
In general, the specification of a particular approach here does not preclude the lease or purchase of an alternate as long as system performance is optimized, the cost is attractive, and the agencies and regulations permit. In fact every effort will be made to search the market for the most effective and economical alternates, consistent with design goals.

## 6. Implementation Plan

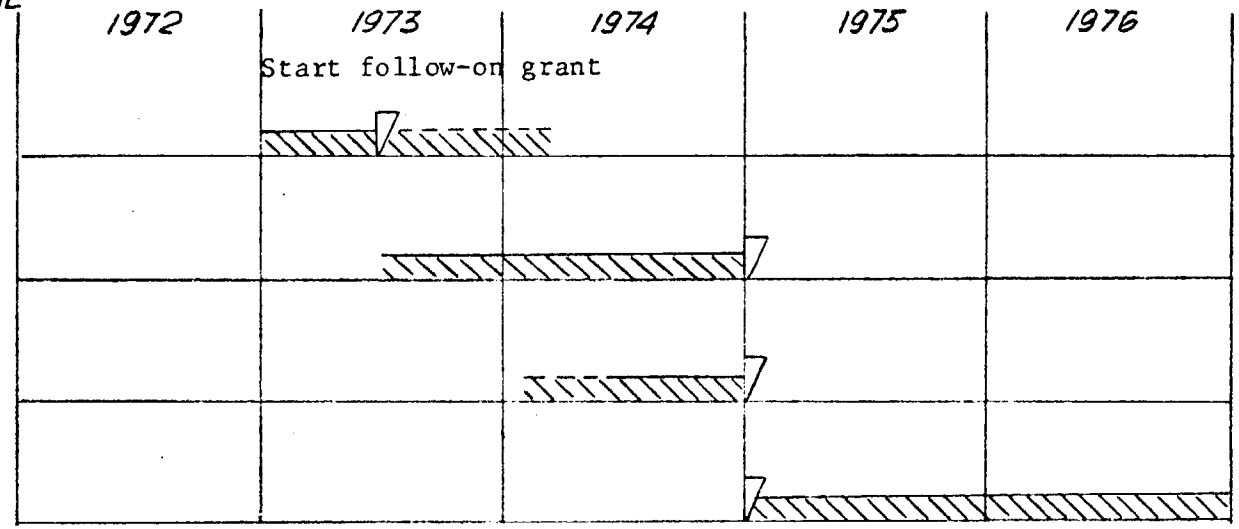
The implementation of the proposed dual machine facility must proceed so as to minimize the impact on on-going service computing. The phased conversion effort is shown schematically in Figure 5. Under this grant, the first PDP-10 machine will be procured and the PL/ACME software converted to run utilizing the PDP-10 time-share monitor functions and relocation features. When this system is checked out, the 360/50 will be removed with the service computing function wholely transferred to a second PDP-10 installed to take its place.

The facility accommodations for the two machines can be made within a straightforward modification of the current 360/50 facility. This modification is consistent with currently approved building plans for a corresponding arcade in the Medical Center; no formal commitment to these modifications has yet been requested from the University.

I. HARDWARE TIME LINE




II. SOFTWARE TIME LINE




*Assumes the selection of a PDP-10 as the service machine.

IMPLEMENTATION PHASING PLAN

FIGURE E-5

F. RESOURCE PERSONNEL

The senior personnel associated with this grant's core research activity will include Dr. Joshua Lederberg, Principal Investigator, Dr. Edward Feigenbaum Associate Investigator, and the technical staff with considerable experience in the development of computing techniques.

Among the technical staff currently employed in biomedical computing is Thomas Rindfleisch who supervised image processing development in an applications group in the Jet Propulsion Laboratory prior to coming to Stanford. He played a central role in developing the image processing for the Mariner Mars 1969 Space Photographic missions, which has also been extended to the realtime analysis of Mars photographs in the current (1971-72) Mariner program. These studies have also led to on-going advances at JPL in image enhancement of X-ray images, light microscope images, and other biomedical applications. At Stanford he has been engaged in the design of extended realtime systems for the DENDRAL Project and in planning activities for Medical Center computing in general. His nine years of experience in digital image processing at JPL provide a solid base of capability with which to undertake the imaging portions of the collaborator's projects.

Another member of the technical staff is Gio Wiederhold who led the design and implementation of the ACME time-sharing system. After directing the ACME facility for its initial five years, he participated in the design of a new computer architecture and consulted regularly with biomedical computer users. In the recent past he has assisted a number of new realtime users on the ACME system with their data acquisition problems.

Another senior member of the technical staff is Lee Hundley, who implemented much of the realtime data collection system under ACME. In addition, Lee Hundley has written the assemblers for PDP-8's and PDP-11's which are currently available to ACME users and has supervised the systems development group during the past three years.

Dr. Walter Reynolds has been working in the Instrumentation Research Laboratory for several years and has authored a number of publications on realtime connections of laboratory instruments to computers.

Other members of the ACME computing facility have significant experience in communications, file handling, compiler improvement, graphics, small machine assemblers and simulators, and related fields. Important contributions to the proposed goals can be made by a number of well-experienced staff members.

One member of the systems programming staff will serve as a point of contact on each collaborator's project. We would expect these programmers' loyalties to rest with the collaborator's objectives. It is felt that such an assignment would help to produce good communication and cooperation.

The collaborators who will perform the research for this proposed grant are a group of sophisticated, experienced computer users. Both the medical staff and the programming staff have achieved notable success in the past. The programming staff in the Division of Cardiology, led by William J. Sanders (formerly of the ACME staff), has achieved notable success in realtime monitoring of cardiac catheterization procedures and video image analysis. Chris Constantinou in Urology has spent the past three years studying the movement of the ureter using animal subjects connected in realtime to the ACME system. The Instrumentation Research Laboratory in the Department of Genetics has made major contributions to the DENDRAL and cell separation projects. Included in the IRL

engineering and programming staff are Dr. Walter Reynolds and Mark Stefik. Additional examples of accomplishments by current staff are briefly described in the collaborators' research statements and the lists of publications attached to the biographical sketches.

Another example of highly significant computer related research at Stanford is DENDRAL. This project has achieved acclaim as an artificial intelligence project performing automated interpretation of mass spectra. A number of publications authored by this group are cited in the collaborative project description and the individual biographical sketches. This research team adds considerable depth to the measure of technical talent affiliated with the proposed resource.

Over these past six years, ACME has had a number of outstanding successes. The initial implementation of a time-shared interactive complex in eighteen months was a feat of some magnitude. The accomplishment of a medium data rate, realtime data acquisition and control system in the framework of a time-shared system is impressive. ACME's major accomplishment, the education of the user community, can best be appreciated by noting that over 1000 people have attended ACME courses in the past five years. These accomplishments are attributable to the excellence, dedication and motivation of the ACME staff.

G. RESOURCE ACTIVITES

1. Services to be Provided

This proposal calls for the creations of a research resource called SUMEX. SUMEX will offer services of four types:

a. Central computing hardware (primarily in the form of a DEC PDP-10 system with KI-10 processor, 192K words of main memory and 4 satellite PDP-11's connected via a PDP10/11 interface. See figure E-3.) for use in computer science related research in biomedicine and development of new hardware interfaces to users' peripheral minicomputers.

b. Development of software support under a core research program and software support for collaborative research projects.

c. The resources will provide backup computing facilities for the Stanford University Medical Center Computer Facility.

d. The resource will include a group of people with strong technical skill to support computer-science type research in the biomedical community. Some additional personnel resources which can be shared among several collaborators are planned; the applied mathematician in the budget is one such position.

The SUMEX resource will support research on advanced computer applications. Specific examples of support anticipated are listed in the core research and collaborative projects described below.

2. Research

a. Core Research

(1) Satellite Machine Support

(a) Problem Statement

(1) Limitations of stand-alone small computers. The primary limitations of existing stand-alone systems are a) the economics of primary and secondary storage and b) the lack of highly sophisticated software. Secondary storage costs for small stand-alone systems tend to run twice the corresponding costs on large systems. Primary storage (core) costs approximately 2¢ per bit for Ampex bulk core memory (i.e., for the 360/50) capable of running at approximately 2.4 microseconds. DEC supplied 1.8 microsecond memory for the PDP-11 costs approximately $3,000 for 4K words or 4.5¢ per bit. The second major limitation of stand-alone small systems is the limited support for sophisticated programming languages and interactive capabilities. This implies that large amounts of effort are spent for software development even in rather simple applications. Some additional limitations are as follows:

(a) Because the hardware investment is low, users seem to have difficulty justifying significant programming effort. Only users with a large number of similar machines can justify a substantial software systems effort.

(b) The manufacturers tend to scale their system software to the smaller end of the line.

(c) Owners of small machines lack easy access to one another's data base because their planning has assumed dedicated use of the hardware.

(d) Finally, the software systems do not provide the ability to concurrently utilize a variety of system capabilities. For example, one cannot be performing realtime data acquisition and editing programs simultaneously.

(2) Attributes of large host systems.

(a) Needs not met by satellite systems. A large host computer can provide an array of services not available to stand-alone small machines in today's technology. Among such services are:

(1) access to large volumes of source programs,

(2) ability to edit them efficiently,

(3) ability to concurrently use multiple system capabilities,

(4) availability of highly sophisticated programming languages and interactive capabilities,

(5) availability of broader line of peripherals,

(6) shared access to common databases, and

(7) more extensive software support from the hardware manufacturer.

(b) Special attributes of larger systems. Larger systems such as the PDP-10 can directly address large quantities of memory (the PDP-10 can address directory up to 256K words). The large system has more input/output ports which can operate concurrently. Large machines provide a standard capability for handling scientific calculations (floating point hardware, etc.). Hardware and software systems are currently available for measuring performance on large systems; this cannot be said for most small systems.

(c) Impact on users. The objective of this part of the proposal is to provide to the small stand-alone user a link to a larger system. The link will make available to the satellite system services which can be obtained today on larger systems but cannot be obtained today on smaller systems. Thus, the satellite user will have available more sophisticated programming languages, access to cheaper primary and secondary storage, shared database, shared communications systems, backup support for large computational problems, and an overall significant degree of labor saving. In today's computer environment, most users can expect to spend two or more times their hardware investment for software development. The trend of this curve is to increase software costs relative to hardware (some say geometrically).

Small machine users have adopted patterns of thought which were appropriate to dedicated stand-alone systems. Part of the mission of this grant will be to demonstrate the feasibility of broader services which could be available in satellite mode and to expand their decision-making analysis to include more flexible and sophisticated computing services. If successful, the program should also enable the medical user community to save a considerable cost in hardware and software. Most satellites would no longer require an extensive collection of peripheral hardware.

(3) Anticipated direction of some technological innovations. Given the rapidly expanding market for computer-based applications and cost-effective hardware systems, major development effort is being expanded in the industry for the development of new techniques. Intelligent planning requires cognizance of the most likely near-term advances in relevant technology, involving the following:

(a) Primary storage. Very low cost primary storage will become available quite soon. The costs associated with integrated circuit memory can be expected to reach less than 1/10 the cost of the current MOS systems. The primary reason for this significant drop in cost is the removal of the high labor content of current core technologies. Currently, MOS costs are close to those of core memories, despite the fact that it is a very recent development and still heavily burdened with development costs.

(b) Secondary storage. Secondary storage systems are being developed which will have faster access times and transfer rates and higher density on the storage media. Current secondary storage technology involves physically rotating memories with inherent mechanical complexity and high costs of achieving the tolerances required and of maintaining the the system once installed. Major breakthroughs in the current technology bottleneck appear possible through development of magnetic bubble memories and charge coupled devices. In terms of information made public to date, Bell Telephone Laboratories seems to be spending the largest effort in both of these new non-mechanical approaches to large data storage devices. Corollary efforts on the parts of other manufacturers have a very low profile at this time.

(c) Low cost general purpose processors. The recent development of large scale integrated circuitry makes possible today the building of general purpose processors at very low costs. For example, ITEL Corporation now has an 8 bit central processor (designed with MOS technology) available on a single chip. The cost of such a component is expected to drop below $50 within the next year. It is of greater sophistication than a PDP-8, although 10 times slower. We anticipate that such developments will lead to new small computer organizations incorporating large numbers of such central processing units dedicated to a variety of applications. Of course this is but one element in a system, the balance of which includes significant cost components. The impact of this change cannot be postponement of solutions needed now. We can cite two recent examples of the development of special purpose processors which support applications on a general purpose computer. The Berkeley Computer Corporation, BCC-1, incorporated a number of micro-processors which were assigned tasks such as:

(1) file management,

(2) drum scheduling for a large swapping drum,

(3) terminal input/output and control of remote communication links.

In order to process large volumes of experimental data in realtime, Professor M. Schwartz of Stanford University (SLAC) is developing parallel processing hardware which can be attached to a PDP-11 processor via the unibus. This hardware allows multiple operations to be performed at a high speed. One can add two 16-element vectors together as one parallel operation. As well, one can compare 256 data points with one common value and determine which of these 256 entries is greater than this common value. This special purpose processor is extremely inexpensive and compact. Yet it provides high speed execution of many parallel operators such as those found in the APL language.

(d) Microprogramming techniques. Currently, several small computers permit the modification of their instruction set utilizing micro-programming techniques. For example, the Hewlett-Packard 2100 permits the extension of its instruction set by reloading alternate or modified versions of the basic micro-program. We visualize many applications in the area of data processing, communication control, and data compression which would gain substantially from new instructions specifically designed to improve the throughput of these operations. Previous studies of the implementation of microprogram techniques have indicated one to two orders of magnitude improvement in the handling of special problem areas such as communications control.

(e) Interactive graphics hardware. The development of low-cost interactive graphic hardware is anticipated in the near term. Today, a display scope, vector generator and keyboard costs on the order of $6,000. We would expect this cost level to be reduced to the $1,000 to $2,000 range in roughly three years. The primary reason for the price reduction is mass production coupled with lower component cost.

(f) High speed remote links. High speed remote links will become available as conventional communication industry services are extended. Current networks such as APRANET and TYMNET are initial entries into this general utility field. The Bell Telephone System is currently testing a 500,000 bit per second line and will offer experimental lines at this rate. We do not contemplate early connection to such networks, but are watching their evolution closely as a future option.

(g) Time multiplexed ring. The introduction of a commercial time multiplexed ring for digital communication started approximately three years ago in the form of the Collins C-System. This concept carries the potential of offering very high data rates at very low costs for inter-device communication. The data rates are sufficiently high that one could consider sharing memory among several satellite processors. It also provides a framework in which a number of satellite systems can be assigned selected portions of a common task. This concept may provide a redundant communications path among a large number of instruments and satellite machines throughout the Medical Center. A related development could well be a simple integrated circuit interface making it possible to inexpensively connect devices to the ring.

Perhaps, smaller subrings could be installed to individual laboratories. This ring would interconnect many experimental devices to one or several of the satellite computers. We believe that such a system would greatly reduce the problem inherent in interfacing large numbers of individual experiments to small satellite computers. The time division multiplexed ring may be compared to the PDP-11 unibus. The control features and inter-device communication paths are quite similar. The major difference is in the time division nature of the proposed ring which simplifies multiple

highspeed communication over a single path and also requires only one interconnecting wire rather than the number of wires in a PDP-11 unibus.

A time multiplexed ring on coaxial cable would have desirable characteristics for connecting satellite computers. This would provide a daisy chain in which very high data rates could be accepted. It would also provide a very reliable hardwire connection. In addition to the possibility of replacing fixed head disks with core on a ring, one can hope to replace small expensive fixed head disks with a few large moving head disks.

(h) Reliability. One general result of technological innovation will be substantial improvements in hardware reliability. This is a key point relating the use of satellite systems to the medical environment. Improved reliability can significantly impact the architecture of future medical systems.

(i) Satellite software. As the problems of inter-device communications approach solution, we could expect to see satellite processing units designed to handle higher level languages efficiently. There are several examples of powerful high level language processors currently available from computer manufacturers. The Burroughs B 1500 provides specialized micro-computer support for COBOL, ALGOL, and systems programming applications. The SYMBOL machine developed by Fairchild utilized many cooperating processors to provide a high level language environment. These processors were dedicated to the tasks of syntax analysis, storage management, garbage collection, and input/output handling. Also, commercially available is the Hewlett-Packard System 3000. It too provides a machine organization optimized to support a higher level language processor. A processor for APL is under development at the University of California at Berkeley. This system utilizes special microprogram techniques on a Digital Scientific Corporation META 4 computer.* Each of the systems we have mentioned attempts to reduce overall software costs by incorporating special features and language oriented architecture within a satellite computer.

(b) Background and Rationale

(1) Current environment for satellites in S. U. Medical Center. Stanford Medical Center today has approximately two dozen small stand-alone computing systems. They range in size from PDP-8's with 4K of core to a Sigma 3 with 32K of core. Some systems are being established to provide routine service. Examples of this include a Sigma 3 in the Clinical Laboratory, PDP-11's for Drug Interaction service in the Hospital Pharmacy, and an HP 2116 for physiological monitoring in the Catheterization Laboratory, and an HP 2100 being prepared for monitoring in the Cardiac Care Unit. Some of the research applications which currently use mini systems include PDP-11's for control of data acquisition and mass spectroscopy,

* "A Firmware APL Time-Sharing System", AFIPS-Spring 1971, R. Zaks, D. Stiengart and J. Moore, U. C. Berkeley.

two PDP-12's for realtime data acquisition research in Cardiovascular Surgery and Psychophysiology, a number of PDP-8's and an HP 2116 for research in Psychiatry and Cardiology, and an HP 2100 for realtime data acquisition from nuclear cameras for the Division of Nuclear Medicine. A number of these systems will be connected to the ACME system during the summer of 1972 via a new small machine multiplexor interfaced to the 360/50 by a 16 bit PDA port on the 2701. A few have been connected to ACME in the past via the IBM 2701 and 270X. Research groups in the Medical Center have hired approximately 20 scientific programmers (exclusive of the ACME facility staff) to work primarily on new applications. In addition the ACME Computing facility has a number of programmers well versed in small machines. ACME is used as a consulting source by a number of the small machine users in the Medical School.

(2) Initial approach in software. The small machine support development effort will initially be concerned with providing sophisticated software support for existing hardware in the Medical School. Specifically, it is our intention to provide a large number of new services for PDP-11 users and HP 2100 users. The new services will be software extensions to the systems currently provided by DEC and HP. For example, satellite machines will be given the ability to read and write files on the disk attached to the large host system, to communicate with other satellites in the network, and to prepare most of their software from a terminal connected to the host.

(3) Incorporation of new hardware techniques. In addition to the task of adding software to better serve existing satellite computers, it is our intent to integrate the new hardware technologies listed above within the Stanford medical environment. One possibility would be the modification of the HP 2100 system using micro-programming techniques.

Historically, the manufacturers of small computing systems have been slow to provide software support for new hardware technologies. Although DEC has announced its PDP-11/45 with memory segmentation hardware, no operating system has been announced to make use of this new feature.

One reason for selecting the PDP-11 as the primary small system to be supported under this program is the expectation that the PDP-11 family will continue to be the primary focus of DEC support over the next several years in the minicomputer market and that it will have broad acceptance. This market acceptance in turn will lead to new technological innovations being made compatible with this particular line of hardware. Two examples of hardware support needed for the PDP-11 are a) the ability to execute programs in PDP-10 core from a PDP-11 and b) the ability to utilize PDP-11's as links in a network.

C. G. Bell of Carnegie-Mellon is currently developing a computer network utilizing a large number of interconnected PDP-11's which share one common extremely large primary store.* This system is being

* "C.mmp: The Multiminiprocessor Computer", C. G. Bell, W. Brody, W. Wulf, and A. Newell, Dept. of Computer Science, Carnegie-Mellon University.

constructed in order to provide an appropriate computer system for the realtime processing and recognition of human speech. Their proposed system appears extremely economical and well thought out. It provides a highly reliable environment in which a large number of small processors can intercommunicate and cooperate in the processing of a realtime analysis. The results of their research may have a significant impact in understanding the benefits or problems in interconnecting large numbers of small satellite processors.

Finally, the overall goal of intelligently managing large volumes of source data in a realtime environment, and processing large bursts of data with highly variable content and significance, will require coordinated and sophisticated use of small computers operating as satellites to the large host machine. No major computer manufacturer appears to place the solution to this problem high among the list of software support goals. For example, much of the realtime support being developed in the computing industry today is designed to support industrial manufacturing processes which do not in general have high burst data rates and sophisticated computational requirements.

(4) Resolution of specific goals with collaborators. Early in the process of scheduling specific small machine support tasks, we will engage ourselves in extensive discussions with collaborators to determine which of their needs carry highest priorities and which of our proposed services should receive highest priority. A firm understanding of the user's environment is essential to the small machine support team. It is our intent to avoid the common pitfall of finding the solutions for which no known medical problem exists. This can only be done by close cooperation and collaboration with our prospective users. No large research tasks will be undertaken in the area of small machine support until a collaborator has been identified with a specific set of requirements to be met. This position does not prevent the development team from attempting to raise the horizons or expectations of the potential users.

(c) Methods and Procedures

(1) Satellite system software support

(a) Assemblers. The advantage of providing assemblers on the large host machine is that satellite users are permitted to flexibly save, edit, and assemble source programs for new applications. In addition, they have the advantage of better error diagnostics in far less time than is the case on their dedicated systems. At present the ACME system supports assemblers for the PDP-11, PDP-8 and the IBM 1800. (This will be extended to include the HP 2100.) The existing assemblers will be updated from time to time to take advantage of the extensions to the manufacturer-supplied operating systems as described below.

(b) High level language support.

(i) Machine dependent. We can simplify the code generation process while maintaining highly efficient execution on the satellite processors by introducing new languages modelled after PL/360 or BLISS. The applications programmer will be able to obtain optimal machine code without the need to be concerned with all details of architecture of the hardware upon which he will be running. The programmer is not prevented from inserting machine language where he feels he can improve upon the facilities provided. Over a five-year period, we would expect to spend roughly two man-years on this effort. Carnegie Mellon has produced a BLISS-11 and CERN Laboratory in Switzerland is producing a PL/11. We will select the best support from among several such development efforts and make them available at the Stanford Medical Center. We will not concern ourselves with the provision of standard language support in small machines as this is already being undertaken by manufacturers and others.

(ii) Machine transparent. The second class of non-machine-oriented language support deals with non-standard languages such as APL, SNOBOL, and LISP. Providing a subset of APL is highly appropriate for satellite machines. We intend to define new APL-like primitives and couple then with a subset of existing APL primitives to provide a high level language support for realtime medical computing. We want to make available an interactive language with user-oriented runtime diagnostics, simple language structure, and the ability to modify programs without complete recompilation or assembly, coupled with graphic output. Some examples of such primitives are:

a. Smoothing primitive. This primitive would employ a number of arguments such as window size, resolution, convolution function, or other user-supplied arguments. The second parameter would be the new data. The primitive would return smoothed data as its value.

b. Peak Extraction Primitive. This would return the coordinates of all peaks found above a threshold provided as a parameter by the user. If the data provided is a vector, the primitive would return the set of index values at which the function attains its peaks. If the data are paired coordinates (the first being the data point and the second being, for instance, time) then the primitive would return the peaks and times, possibly interpolated between two time values.

c. Curve Fitting Primitive. The parameters associated with this primitive would be data and name of a system or user function which would provide the shape of the curve to be fitted. The primitive would search for the parameters to the function which provide the best fit among the user supplied data points. The user function will automatically handle fitting of overlapping peaks as a natural outgrowth of the nature of the APL language.

Some of the current APL operators which would be very useful in a realtime environment include matrix manipulation, sorting, bit manipulation, and conversion of raw BCD data to binary by using the encode operator.

(c) Realtime applications module library. Some of the items expected to be provided are the following:

(i) Data collection routines. These would include automatic sampling of selected data channels at user specified breaks, interrupt driven data collection, and automatic scheduling of resources on the inter-computer communication network.

(ii) Data compression routines such as the Aztec procedure developed by Dr. Jerry Cox for compression of EEG data at Washington University in St. Louis.

(iii) Input/Output buffering routines. These routines would automate core management since, due to the great variability of data rates, a sophisticated scheme is necessary. Extensive effort will be needed in this area because manufacturer-supplied operating systems have not addressed themselves to the high data rate, burst mode, realtime data collection problem. The intelligent management of such data streams will require innovative techniques in core management.

(iv) Peripheral handlers. We wish to provide a standardized approach to unique peripherals similar to that currently provided by the manufacturers for standard peripherals. The newly developed peripheral handlers (for instruments such as mass spectrometers and gas chromatographs) can then utilize a standard interface to the operating system.

(v) Communications protocol with host computer. User programs would interface to the communications network via routines present in the applications library. The detailed operation of the communications system need be no more apparent to the user than the details of a disk or tape controller would be.

(vi) Debugging packages. Along with all the new facilities outlined above, we must provide the user with a complete set of debugging packages for realtime control systems. This function is essential in any realtime environment, where any one of several links in the total chain may prevent satisfactory operation. The ACME facility has consistently found it difficult to identify just which link in the chain is defective (despite the best efforts of good engineers and programming talent!).

(d) Extensions to manufacturers supplied operating systems. Handling realtime functions and using multiple processor configurations are two examples of activities contemplated here which are not covered by current operating systems but are needed in our labs. Our computing objectives cannot be met without extensions to what exists. For example, DEC permits several PDP-11's to be connected via Unibus links, but no multiprocessor software is provided for this (marketed) configuration. The particular problem areas where extensions are required have already been described above.

(2) Computer to computer communications.

(a) Data transfers.

(i) To share peripheral equipment. Software support should exist to make possible the sharing of peripheral devices on a host computer with all satellite processors. For example, high speed printers on the host should be accessible to data collections or data analysis programs on satellite systems. Similarly, results of data analysis on host machines should be available at printers connected to satellite systems. It is hoped that our commitment to software support for shared peripheral equipment will reduce the overall number of peripherals required in the Medical Center.

(ii) To move data to other systems. Data transfer software support will facilitate transfer of data collected on minicomputers to the host system and vice versa. In some cases, an intermediate system will serve as a store and forward device. In this way users will not be dependent upon the availability of the large host machine for long term data collection problems. A specific example of data transfer among satellite systems is the need for sharing of information between Clinical Laboratory and Pharmacy systems. The interpretation of a certain laboratory result could be influenced by the knowledge that a given drug had been administered prior to collecting the laboratory specimen.

(iii) Loading of Object Modules. Software support will be developed so that object modules can be loaded to satellite machines from the host machine. In this manner, satellite machines avoid the necessity of loading object modules from paper tape or other more expensive peripherals.

(b) Controlled interactions.

(i) Start satellite machine (IPL) remotely. Code will be developed to permit the startup of a satellite by a program in the host machine. The satellite in turn could be programmed to start up various laboratory instruments. The benefits of such a procedure are to permit control of experiments from one terminal and to enforce a common chain of events in the startup of each day's operation in the laboratory.

(ii) Detect failure of other systems. The host machine can be programmed to detect failure of satellite systems and satellite systems in turn can be instructed to detect failure of instrumentation. In the case of communications systems, failure detection is essential so that control of the communication system can be passed to an alternate source. The same will be true for some physiological monitoring systems.

(iii) Network management. Comtec, Honeywell, CDC, and Tymshare have devoted considerable effort to programming intelligent machines to handle network management tasks. It is not our intention to duplicate this effort. However, we may wish to supplement the existing network management programs by adding realtime support functions. One possible step in networking will entail the installation of a long-distance attachment for the ARPANET IMP. An IMP exists on the Stanford campus at the Artificial Intelligence Laboratory directed by Dr. John McCarthy. The long-distance attachment for an IMP is being designed at U. C. Santa Barbara. Assuming that the design will work, it may provide a relatively inexpensive connection to the ARPA Network. The Hardware costs exclusive of "lease" line will be approximately $15,000. At this time, we have elected to study the networking opportunities without further commitment.

(3) Data manipulation.

(a) Data collection

(i) Feedback to local controllers of realtime data flow. Intelligent management of large volumes of data implies an interaction between the initial data received, the long term goal, and feedback to the experimental apparatus. The closed loop situation is one in which special benefits should accrue as a result of the small machine support effort. Development of heuristic processors in models should permit increasing amounts of feedback to local controllers for instrument adjustment, calibration, and data management.

New predictive techniques could aid in image processing. In classical digital image processing, an image is first digitized to be in a machine readable form. This requires $10^5$ to $10^7$ bits, depending on the requirements for resolution and grey scale. At this point, data compression methods are often applied to reduce storage and computational requirements. This may result in compression factors of two to ten. These actions require additional computation and only serve to make the data manageable, rather than to extract information from it.

Another approach is to record only those elements of an image which differ from the previous image. This reduces the amount of data but still does not recognize the fact that for a large class of images (e.g., a beating heart) the position of the elements in a new image can be predicted with a high degree of accuracy, knowing the time between images, scale factor, and direction over the past few images. Since this is true, a significantly reduced number of data points need be taken to refine both the prediction and the model used to make the prediction. Gross deviation from a well established model might be used to indicate a pathological condition.

It is felt that this approach to image processing helps to reduce the gross data handling requirements to a manageable level. It concentrates required complex image analysis algorithms on that subset of the raw data worthy of attention. By using such methods, we feel that significant results can be drawn for a class of problems of biological interest.

(ii) Multiple paths to large files. We plan to provide multiple paths to large files from satellite computing systems. In this way, we can guarantee access to the large files for a 24 hour day, seven days a week period. Only by providing assurance on this point can satellite machine owners be convinced to assume the risk of minimizing their local dedicated configurations and depending upon shared use of larger resources.

(iii) Store and forward system. One satellite in the system may be dedicated to realtime communications management and interim storage of realtime data. The primary rationale for having such a facility is a) to guarantee better response time, b) to provide larger storage capacity than would be feasible for each of the experimenters connected to the system, and c) to assure continuous availability either from the host or from the store and forward processor.

(b) Data analysis.

(i) Multiple processor allocation. Optimal use of the resources available in a large system implies that repetitive tasks should be handed to less expensive processors dedicated to a more limited range of tasks. It is our intent to demonstrate that selected subroutines which are frequently used in a realtime environment can be passed to a satellite processor for execution, thus freeing the host machine for other tasks.

(ii) Software support for special hardware. Special purpose devices such as Fast Fourier Transform hardware, matrix multipliers, and graphics aids can be supported for satellite systems. One can make a specialized device available to more than one user's laboratory while at the same time limiting the software investment for its use.

(iii) Interactive graphics. Graphic interactions with realtime data streams is essential in the rapid interpretation by man of "what's going on". The objective of this effort will be to provide a smooth human interaction with graphics devices in both directions (man-to-machine and machine-to-man). The anticipated decrease in cost of graphics stations is likely to increase significantly the demand for this service. Common generalized software for support of such instruments can provide an important savings in programming manpower.

ACME currently supports a variety of graphics devices in a flexible manner. All graphics devices are treated as real-time output devices. Associated with the description of output devices on a realtime line are the programs that convert a graphic description into the detailed control sequences required for device operation. The user needs only to change the destination number parameter in his graphic output calls and the identical user program will drive any of the graphics devices available at ACME.

The devices currently supported are:

a) The ACME TV display (high precision, refreshed by an auxiliary core memory).

b) Tektronix 611 storage tube displays.

c) Calcomp and Houston incremental plotters.

d) General Purpose Graphics Terminals.

In addition to supporting other display types as they become available, ACME is planning to extend support for graphics activities in the following ways:

a) Development of interactive generation of display programs. The abstraction of a planned visual image into display-driving statements is not always obvious or easy for medical researchers. Computer languages such as PL/ACME, while providing all the required capabilities, do not express the two dimensional nature of graphs very clearly. A question and answer communication between computer and user is being prototyped which will generate the required instructions using decision trees which systematically reduce the alternatives of choice. The resulting protocols can be saved and subsequently modified as desired.

b) Current display support has been mainly oriented toward graphics. The General Purpose Graphics Terminal has the capability to handle text. This facility has been made available now to General Purpose Graphics Terminals users, but it should be made equally available on the other devices supported in graphics mode, which now have only limited text capability.

(4) Satellite performance measurement and evaluation. Very little has been done in the area of performance measurements for small computers. We feel that there is much to be gained from activity in this area. Both hardware and software monitors will be investigated.

It is known that most programs spend a large amount of time executing a small percentage of their total code. The classic approach to increasing a program's efficiency is to locate the most used code and

recode it in the most efficient manner available. If a program is to be written in a higher level language, the ability to "tune" with performance measurement tools may make code generated by a sub-optimal compiler (which many small-machine compilers are) acceptable.

Such monitors are also valuable debugging aides. The sorting out of a sequence of randomly occuring realtime events can be an almost impossible task without some monitoring ability. Excess time spent in error recovery can be located and corrected. Inadvertent loops may be detected by monitoring.

It is felt that this type of support for the satellite machine falls into that class of activity which needs very much to be done, but which the individual mini user cannot afford to do.

(d) Significance of satellite machine support.

(1) Remove the limitations in users' laboratories: Current satellite machine users continuously encounter physical limitations in their hardware, such as lack of core, lack of disk space, lack of registers, inadequate cycles, lack of generalized data acquisition, reduction and analysis subroutines, and problems associated with interfacing hardware to experimental apparatus. The proposed research program and satellite machine support will help to overcome most of these limitations.

(2) Reduce effort required of experimentalists: The application of standard interface hardware to the extent possible will reduce the amount of active involvement of the experimentalist in this problem. Furthermore, availability of tried and tested software for handling many of the problems frequently encountered in data acquisition situations will allow him to select from a library those elements which he needs. Additionally, the local satellite machine group will be aware of routines developed elsewhere in the country through DECUS and other user groups. As the relative investment in software becomes far greater than hardware, the impact on the user of extensive satellite machine support will be great.

(3) Effective easy access to shared data: Computers can truly be used as a means of sharing knowledge when the large volumes of machine readable data can be shared with trivial effort on the part of the user and at acceptable costs. Sharing of data among Clinical Pharmacology, Hospital Pharmacy, Infectious Disease Laboratory, other clinical laboratories, and physicians is currently being requested but has not been provided other than through manual transport of magnetic tape. In the research area it is felt that new algorithms, models, new graphics techniques, and other developments will be shared throughout the community more quickly with improved communications and file access systems.

(4) Integrate benefits of small and large systems: Both the small and the large systems offer unique benefits. The objective is to realize the synergism believed possible through the marriage of small and large systems.

(2) Extended Realtime Computing

(a) Problem Statement and Objectives

State-of-the-Art - Applications of computers have developed over the past ten years which involve the interaction of computer systems with various aspects of medical research. Computers are used in a broad spectrum of ways in support of the acquisition of raw instrument data, the reduction and standardization of data quality, the interpretation of experimental information and building of models, and finally the design of new experiments to test the models. Historically computers have performed simple supporting tasks such as prescribed data logging procedures and reduction computations with human investigators carrying out the higher level processes of adaptive system control as well as theory building and testing. In most cases errors arising from simplistic computer processing of the data are detected and corrected by human intervention. Typically the computer does not have access to a model of what it is doing to evaluate its success or failure. In applications involving relatively small amounts of data which can be collected simply and analyzed without severe time constraints, this division of labor is satisfactory and economical. Indeed this separation is to some extent necessary because computer programs are currently incapable of many of the complex reasoning and creative problem solving processes necessary for medical research.

Limitations and Future Needs - There is an increasing number of situations, however, for which this type of open loop or loosely closed loop solution is infeasible or unacceptable. The requirements for more automated loop closure may grow from a variety of circumstances such as:

(1) Human boredom with making large quantities of precise, detailed measurements.

(2) Experiment time constants allowing the collection of only a subset of possible types of available information requiring judicious on-line selection.

(3) Economy of extracting small sets of significant information from large quantities of raw data.

(4) Adaptive experiment optimization and control requirements too complex or rapid for human response.

(5) Large and complex information bases or models difficult for human manipulation and analysis.

A variety of examples can be listed of applications facing these problems today and most certainly increasing demands on computing capabilities of this kind will arise in the future. Such fields include image processing and perception (microscopy, radiology, ultrasonics, etc.);

stimulus/response experimentation (neurophysiology, anesthesiology, etc.); analytical instrumentation (gas chromatography/mass spectroscopy, x-ray diffractometry, etc.); and interactive system and data modelling.

Intelligence Requirements - Characteristic of these problem areas is a requirement for more and more "intelligent" handling of information within appropriate time constraints. The term "intelligent" is used to imply autonomous and adaptive performance of necessary operations. In becoming autonomous the computer must take advantage of the dynamic characteristics of the input data and extracted information as well as previous or evolving problem solutions to economically produce accurate and reliable results. In the simplest form, the computer has a model of its environment relative to the task it is performing and uses derived measures of success or failure to optimize performance. In the longer term more sophisticated reasoning and inductive processes are applied to an information base.

Difficult conceptual and implementation problems exist in designing intelligent information handling programs for computers. Beginnings have been made in developing such capabilities in a few applications. Much more work is necessary to improve program capabilities and reliability as well as to explore wider application areas in medicine.

Computing Requirements - As the sophistication of computer processing of information increases, so does the requirement for intensive usage of large computing resources. These requirements are typically applied over relatively short or sporadic periods of time. In effect each such application requires a large dedicated capability for high demand on-line work and a less responsive time-sharing or batch support for off-line or developmental work. Thus the extended realtime user is faced with the dilemma of needing to control for short periods of time a machine of a capacity that does his job but which he cannot afford or justify having totally dedicated to his work. Methods for providing this type of service economically must be developed.

Research Objectives - The overall objectives of this portion of the proposal are to develop a computer resource to investigate a range of problems associated with extended realtime computer applications in medicine including:

(1) The utilization of intelligent methods of information handling to increase system effectiveness and reliability and to allow the solution of problems which are unmanageable by brute force techniques.

(2) Methods for organizing and delivering large capacity computing power to extended realtime users within required time constraints and within the context of complementary time-sharing and batch machine utilization.

The short term objectives will be to fashion solutions to specific problems among a small set of collaborators. In the longer term more general methods for dealing with larger communities of users may become apparent. Experience has shown that progress with automated computer systems is difficult with success depending on the careful selection of problems as well as techniques. It is recognized that considerable differences exist and indeed must exist in hardware and software needed to solve specific problems. It is not our goal to attempt to force the solution to all problems within a rigid framework but rather to exploit the aspects of commonality between applications while explicitly allowing for necessary differences.

(b) Background

Realtime Experience - Many laboratories are working on developing on-line experiment support. At Stanford the ACME computing resource has had as one of its objectives the development of on-line, realtime instrument support capabilities in a time-shared environment (ref. 4,5). This system has had success in servicing laboratory instrumentation primarily as a store and forward data logging service followed by near realtime reduction processing. Experience has been gained in a variety of on-line applications including the measurement of heart function parameters (refs 6, 9-12), respiratory function parameters and interactions (refs 1,14), electroencephalogram correlations (refs 7-8), urinary function parameters (refs 2-3), and the design and application of gas chromatograph/mass spectrometer data systems (ref. 14).

Automated Systems - A number of application problems have arisen in the course of this work where significant autonomy in the computer handling of information is required. Specific examples include the quantitative analysis of cineradiograms (cardiology and urology), electroencephalograms, and mass spectograms (see the succeeding collaborative experiment descriptions). Without computers the quantitative utilization of these sources of information would be infeasible. Our experience in the design of automated mass spectrogram interpretation systems (see Section G.2.b.3. for Dendral references), and image processing systems (refs. 21-22, 31-32) indicate two types of problems will be important: First the design of algorithms to accomplish the required information extraction and second the design of algorithms to assess system performance to optimize information quality. Most such systems are complex and display highly abstracted versions of the source information as results. Unless models are available to check the quality of intermediate processing stages, subtle losses or distortions of the information may result leading to misinterpretations. Both types of problems are difficult, application specific, and require intensive computing resources.

Closed loop problems are under consideration in a variety of applications either with largely dedicated computer systems or with shared machines where loop closure time constants are flexible. Examples include image processing and pattern recognition systems, analytical instrumentation systems, robot systems, spacecraft operations, and military systems.

The DENDRAL programs at Stanford are able to infer the structures of complex biological molecules from mass spectra without human aid. Further work is under way to automate the computer extension of the domain of mass spectral problems it can solve. Highly autonomous robot systems such as SRI's SHAKEY (ref. 23) and the Stanford Artificial Intelligence Hand-Eye Project (ref. 24) are able to completely solve "simple" problems based on initial goal selection within geometrically structured environments (such as stocks of cubes). Pattern recognition systems dealing with more amorphous environments such as bubble chamber tracks (ref. 25), karyograms (refs. 26-28), or radiograms (refs. 29-30) must either carefully select samples for processing or rely on manual intervention. Much work remains to be done in automating computer applications to medical problems. We will draw upon related research as appropriate in our work.

Impact of Small Machines - Closed loop experiments on ACME have been limited to relatively low rate interactions or non-real time closure because of capacity constraints and usage priority conflicts. These difficulties with central machine support have led to an increased use of "mini" computers dedicated to each particular laboratory environment. For a variety of economic and technical reasons this experience is common as witness the tremendous market which has built up around small computers over the past few years. The trend of servicing laboratory instrumentation with local minicomputers is unmistakable and numerous self-contained instruments with supporting data systems are available commercially.

Small Machine Limitations - Small dedicated computer systems provide highly flexible data logging devices and perform straightforward data reduction tasks as well. A machine restricted in memory, peripherals, and instruction flexibility, however, must exercise many short-cuts to achieve results. These short-cuts restrict system adaptability and limit the domain of data-interpretation algorithms which can be employed.

Such limitations are offset by incrementally expanding "small" systems by adding special features such as floating point instructions or relatively expensive memory, disk, and other peripherals. The result is an increasingly expensive piece of general purpose equipment dedicated to a task, and inefficiently used.

Our experience has shown that such data systems, built around small machines, are adequate if limited realtime demands exist. The presence of a human being in the loop to make control decisions and adaptive adjustments is essential in many situations. More demanding applications, however, require the examination of more parallel system hardware and software configurations designed to balance the economy and capacity of central and distributed machines.

Related Efforts - Much effort has gone into designing fast computers by overlapping the micro-execution of program elements. Simultaneous operations on various elements of a computing load have been achieved through the design of special peripheral devices such as correlation processors and Fast Fourier Transform boxes. More flexible hardware devices may be designed using Clark's macromodules (ref. 15) or microprogrammed machines (ref. 16).

The coordinated use of clusters of small machines sharing memory and peripheral devices is being investigated by Bell (ref. 17, 18). This approach offers considerable long term potential when coupled to appropriate software capability. Software support must be available to effectively focus and manage such an array in a multi-user environment.

The proposed research in this grant does not have as its aim extensive research into computer architecture. Rather we will draw upon related developments in these areas (commercial and academic) as available for our specific medical applications.

Efforts are being made to provide support of remote computers by larger host systems. A number of manufacturers have available Assembly Language processors for minicomputers which run on larger hosts. IBM is developing a Distributed System Programming (DSP) system (ref. 19-20) which provides for communication of programs, data, and control information between a number of remote System 7 machines and a host. The announced capability of DSP is a 134 baud communication rate and no usable realtime priority structure in the host. The data rates of interest to this proposal are 3 to 4 orders of magnitudes higher.

(c) Rationale

The underlying rationale of our approach to extended realtime problems in medicine is based on the concepts:

1. For problems involving large volumes of data or complex instrumentation and analysis procedures, the computer becomes a more powerful tool the more reliably, adaptively, and accurately it can perform necessary tasks without need of human supervision.

2. The integration of coordinated satellite machine capabilities with time-shared host facilities offers an effective and economical method for providing required computing resources among intensive users.

Automation - Most laboratory instrumentation data systems consist of the elements shown in Figure G-1 or some subset of those elements. In many cases human beings perform some of these functions directly in order to introduce adaptability and reliability. Inherent in the human performance of these tasks is a feedback situation where the results of an operation are evaluated in terms of "reasonableness" to verify the degree of success with which the task is performed and to

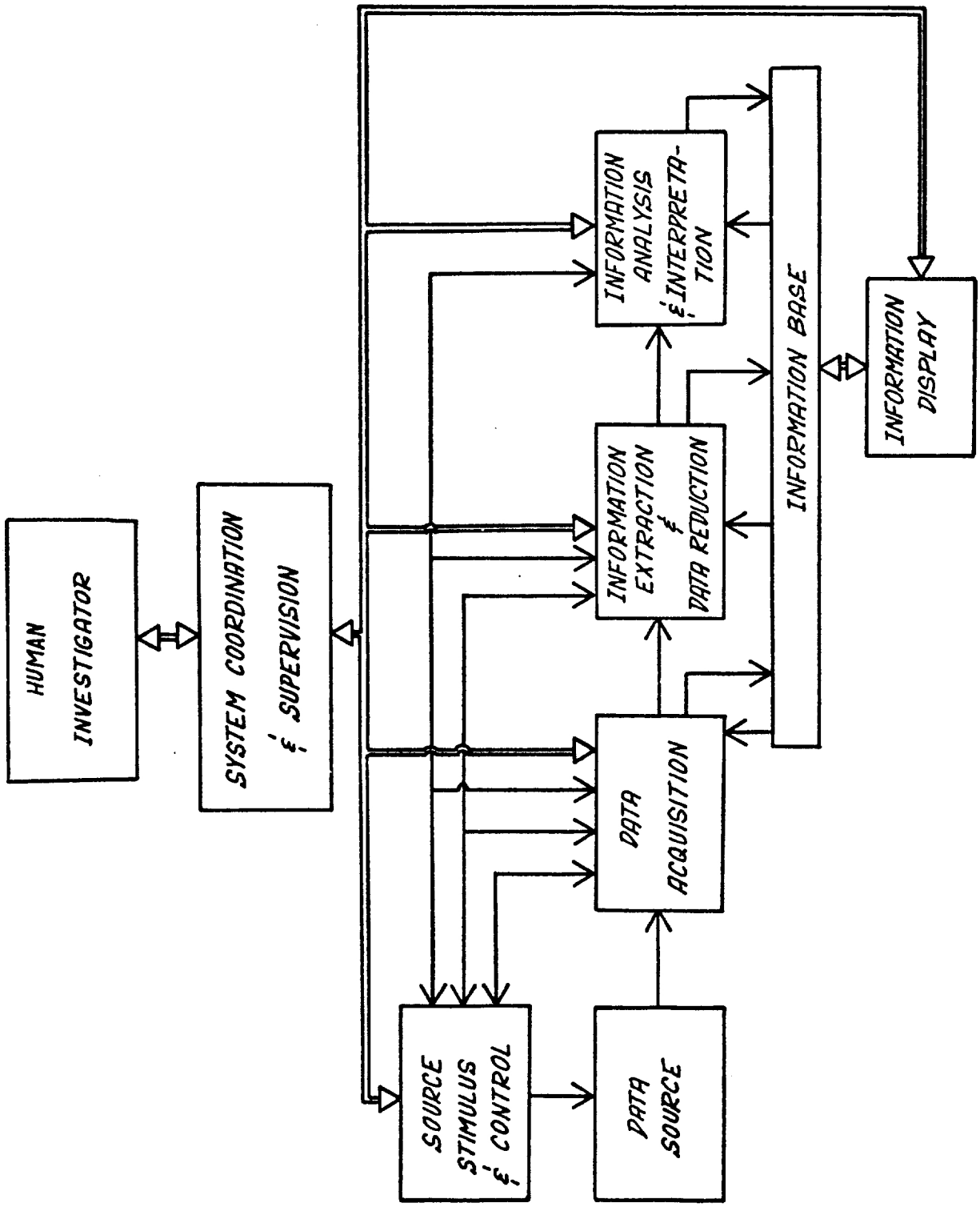

HUMAN INVESTIGATOR
SYSTEM COORDINATION & SUPERVISION
SOURCE STIMULUS & CONTROL
DATA SOURCE
DATA ACQUISITION
INFORMATION EXTRACTION & DATA REDUCTION
INFORMATION ANALYSIS & INTERPRETATION
INFORMATION BASE
INFORMATION DISPLAY

Figure G-1

modify the operation as required to optimize the result. Without this model for what constitutes an appropriate range for the process outcome, the human being would be no more reliable than the blind computer.

In situations where the human being cannot directly perform these functions, methods for automating the computer performance of such tasks must be developed. Such methods depend upon extending the underlying processing algorithms to include methods for adaptation, performance evaluation, and feedback optimization of processing parameters. Models by which the computer can judge and modify its performance can be based on physical models of the instrument or data source, heuristic models of the environment, or guidance from previously developed problem solutions. In the near term these models are defined by human control. In the longer term more autonomous computer organization of its problem domain will be required.

Computing Support - The use of remote and local satellite processors about a large host system with shared large core and peripheral equipment allows the economical expansion of parallel processing capacity and the efficiency benefit of sharing costly system resources. The general topology which we plan to use is shown in Figure G-2. This type of system can be constructed from available hardware and can take advantage of new developments underway at other locations. The satellite machines can be thought of as flexible building block processors which can be organized and programmed to support critical realtime projects while the main system acts to coordinate overall operation and provide less critical time-share, batch, and realtime service. These machines can be readily reconfigured by software to support various realtime tasks as needed and thereby are more efficiently shared among sporadic users. As necessary dedicated use of a satellite processor in a particular application such as a special instrument interface, is encouraged. Incompletely used and sharable resources are spread across a broader set of users.

(d) Methods and Procedures

Our approach to investigating extended realtime problems will be to set up a computing resource configured to meet anticipated extended realtime requirements and to select a set of problems in conjunction with a collaborator community with which to experiment with specific solutions. These problems will be selected to draw upon the expertise available in the Stanford medical and computing communities and to offer significant promise for application of these methods. It can be expected that the complement of problems under attack will evolve as successes and failures are encountered. In the longer term, attempts to generalize analogous solutions will be made. Significant progress remains to be made in the exposition of particular solutions ,

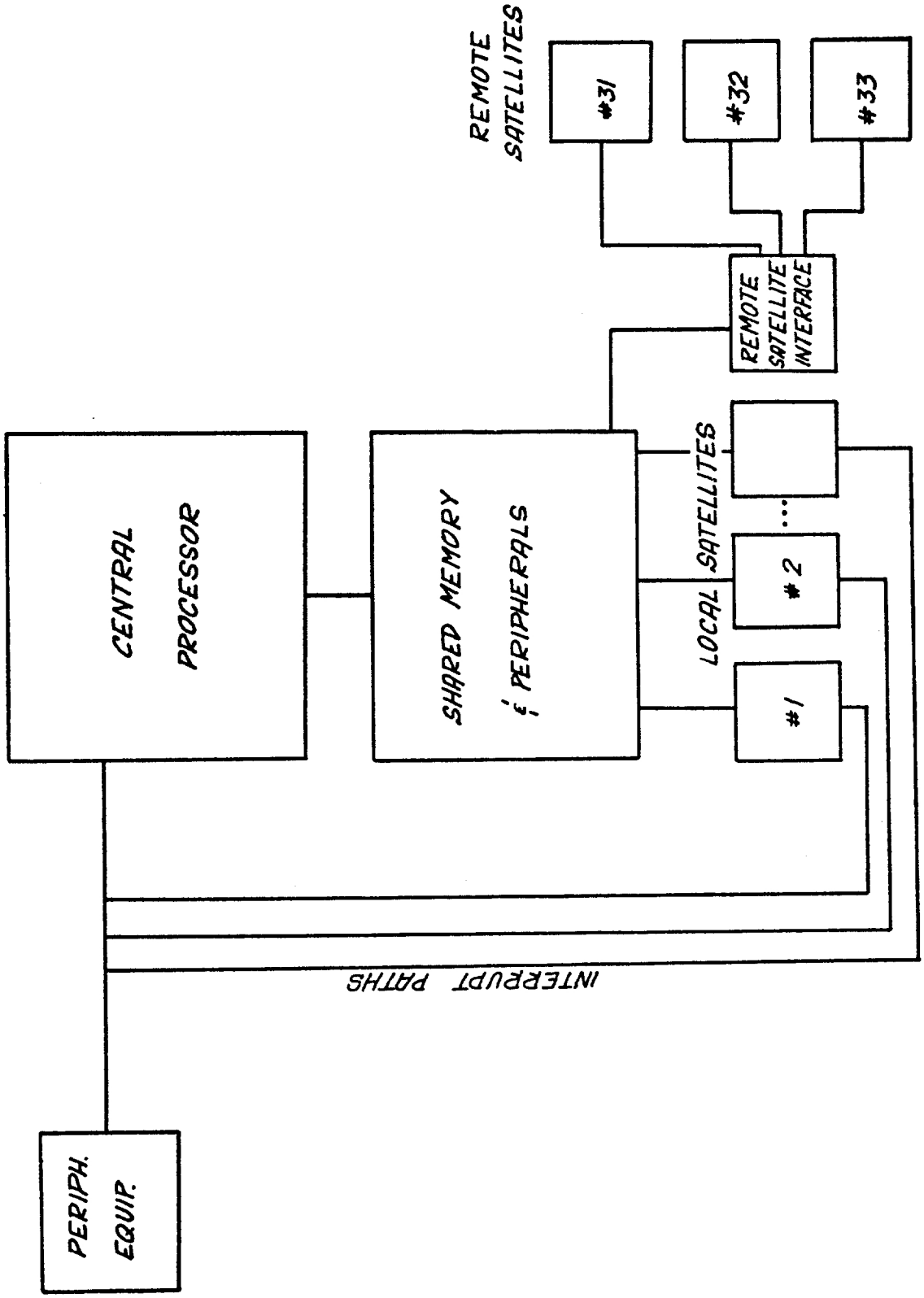

REMOTE SATELLITES
#31
#32
#33
REMOTE SATELLITE INTERFACE
CENTRAL PROCESSOR
SHARED MEMORY & PERIPHERALS
LOCAL SATELLITES
#2
#1
INTERRUPT PATHS
PERIPH. EQUIP.

Figure G-2

however, before this will be possible. The initial complement of collaborative problems includes:

1. Harrison, et al.: Cineangiogram Analysis Automation.
2. Constantinou: Cineradiogram Studies of the Ureter.
3. Lederberg, Feigenbaum, Djerassi, Buchanan, Duffield, Smith: DENDRAL - Automated Mass Spectrum Interpretation.
4. Herzenberg and Levinthal: Cell Separator Automation.
5. Kopell, Roth and Pfefferbaum: Electroencephalogram Driven Stimulus/Response Studies of Drug Effects.

The backgrounds and proposed approaches to these research applications are contained in corresponding succeeding sections of this proposal.

The computing resource will be built around a PDP-10 computer with a derivative of the PL/ACME time-share software system. The PDP-10 hardware configuration will be as shown in Figure G-3,* with the following significant features:

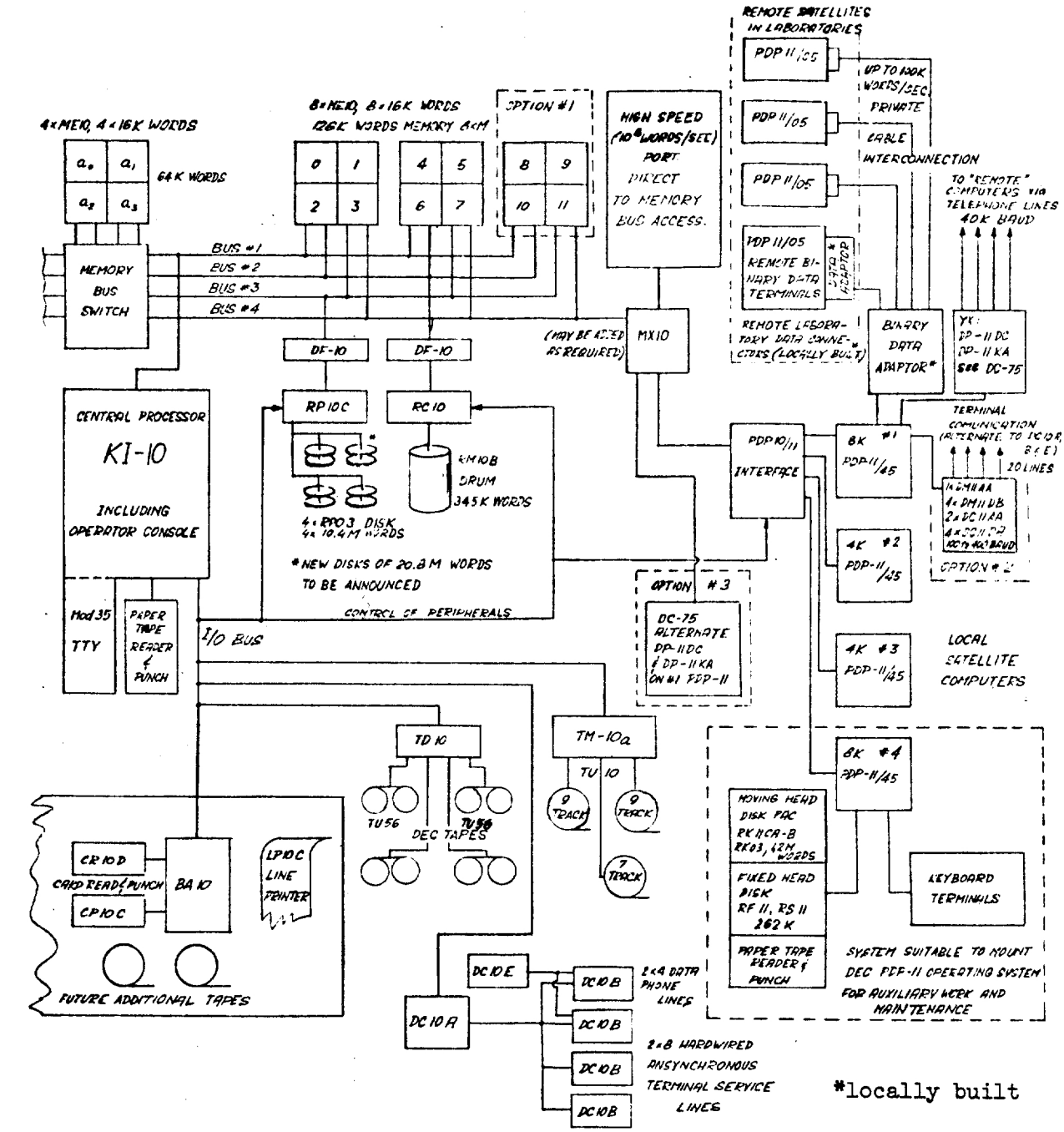
1. The host computer allows state-of-the-art time-shared computing for system and program development as well as dedicated application to developmental realtime problems as required.

2. The direct memory access of the array of satellite PDP-11/45 processors provides for the experimental parallel processing support of intensive realtime applications in the time-shared environment.

The system will utilize the converted PL/ACME system as a base together with the developed satellite machine programming and communication system described in an earlier section of this proposal. Additional system software will be developed for interfacing and coordinating the satellite PDP-11/45 machines. It is expected that this software will evolve as application requirements dictate (see Figure G-4).

The satellite computers are considered to be available on call for a class of realtime users. The machines contain supervisory software which formalizes the PDP-10/PDP-11 interface by providing interrupt handling, intermemory transfers, program loading, program termination, and intermachine status and control monitoring functions. The satellites are allocated when not busy on the basis of a task list accumulated in the host machine posting requested user activity by sequence, type and priority. Each user application with access to extended realtime service will have available a set of routines which allow communication with the host monitor for posting of satellite tasks, priority control, on-going processing control and interruption, error and exception handling, input/output processing, and debugging facilities based on host and satellite language capabilities. Remote laboratory satellite

*Identical to figure E-3. Repeated here for ease of reference.




TENTATIVE INITIAL MACHINE CONFIGURATION

for

Stanford University Medical Center Experimental Computer Facility

"SUMEX"

Figure G-3

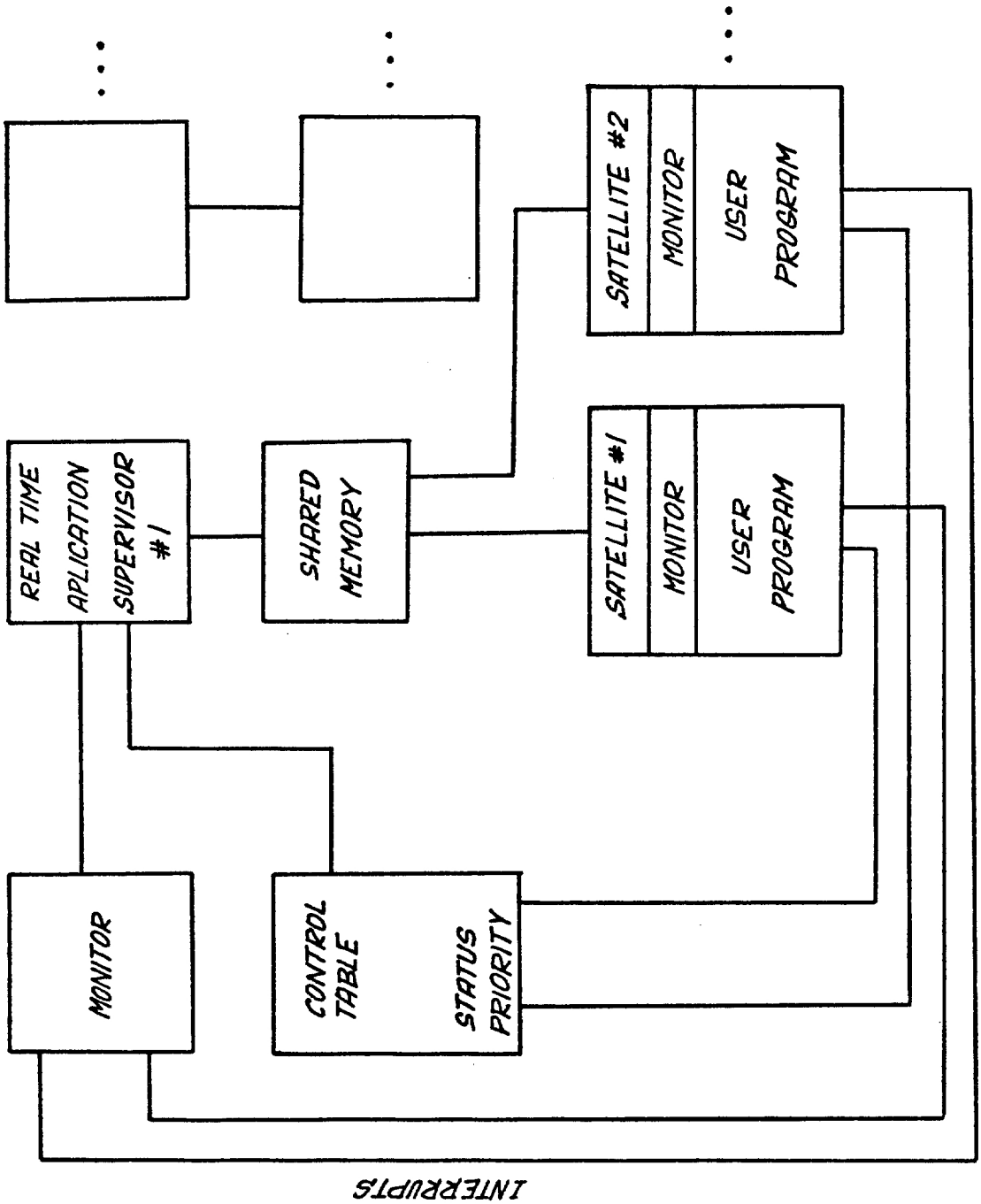

REAL TIME APLICATION SUPERVISOR #1
SHARED MEMORY
SATELLITE #1
MONITOR
USER PROGRAM
SATELLITE #2
MONITOR
USER PROGRAM
MONITOR
CONTROL TABLE
STATUS PRIORITY
INTERRUPTS

Figure G-4

computers will have similar support and responsibilities.

In general each realtime user has a supervisory driver which is responsible for job organization, synchronization, and coordination as well as outside user interactions. As each satellite performs specified tasks to completion it maintains updated status information on progress with the host system and upon completion of the task returns a completion status and frees itself for reallocation to the next highest priority task in the queue. The ability to service a community of users depends on providing enough satellites to accommodate scheduled loading within the adaptation constraints of each user.

(e) Significance

The development of reliable automated computer systems for dealing with complex and voluminous information in specific medical applications is important for a number of reasons:

1. Such tools augment capabilities for analysis and interpretation of increasingly complex measurements on biological systems.

2. Such tools provide a means for collecting quantitative data from large populations establishing statistically sound baselines for testing research hypotheses.

2. Such tools are an essential element to the routine delivery of preventative health care to large populations.

The significance of the associated research applications we have chosen speaks for itself. Clearly one must not expect the computer to replace human capabilities but to augment and extend them. Progress has been made on a few problems to date and progress must be made on many more fronts.

(f) Collaborative Arrangement

The essence of the proposed approach to extended realtime research is to select a specific set of significant problems to provide a basis for more general solutions. These specific applications draw upon the expertise of the collaborators named above.

References

1. Bellville, J., G. Fleischli, and G. Attura, "Servo Control of Inhaled Carbon Dioxide," J. APPL. PHYSIOL., vol. 24, pp 414-415, 1968.

2. Constantinou, C., E. Briggs, R. Dale, and D. Govan, "Real-Time Digital Computer System for Ureteral Physiology Investigation," URODYNAMICS, Chap. 33, Academic Press, New York, in press.

3. Constantinou, C., J. Sands, and D. Govan, "Computer Monitoring and Control Instrumentation in Urology Research," PROCEEDINGS OF THE 6TH ANNUAL BIOENGINEERING SYMPOSIUM, Fort Collins, Colorado, May 1971.

4. Crouse, L. and G. Wiederhold, "An Advanced Computer System for Real-Time Medical Applications," COMPUTERS AND BIOMEDICAL RESEARCH, vol. 2, no. 6, pp 582-598, Dec. 1969.

5. Crouse, L. and G. Wiederhold, "Interactive Use of Timesharing System for Medical Laboratory Support," presented at the San Diego Biomedical Symposium, San Diego, Calif., April 1970.

6. Dong, E., Jr. and B. A. Reitz, "Effect of Timing of Vagal Stimulation on Heart Rate in the Dog," CIRCULATION RES., Vol. 27, No. 5, Nov. 1970.

7. Gersch, W. and G. Goddard, "Epileptic Focus Location: Spectral Analysis Method," SCIENCE, vol. 169, pp 701-702, 1970.

8. Gersch, W., "Spectral Analysis of EEG's by Autoregressive Decomposition of Time Series," MATHEMATICAL BIOSCIENCES, vol. 7, pp 205-222, 1970.

9. Harrison, D., W. Henry, C. Ploeg, and S. Kountz, "An Improved Hydraulic Vascular Occluder for Chronic Electromagnetic Blood Flow Measurements," J. APPL. PHYSIOL., vol. 25, P. 790, 1968.

10. Harrison, D., R. Stenson, W. Henry, and L. Crouse, "Analysis of Hemodynamic Data from Cardiac Catheterization with a Digital Computer," OPTICS TECHN. REVIEW, 1969.

11. Henry, W., L. Crouse, R. Stenson, and D. Harrison, "Computer Analysis of Cardiac Catheterization Data," AM. J. OF CARDIOLOGY, vol. 22, no. 5, pp. 696-705, Nov. 1968.

12. Mesel, E. and M. J. Gelfand, "An Automated Data Analysis and Acquisition System for a Cardiac Catheterization Laboratory," COMPUTERS IN BIOLOGY AND MEDICINE, in press.

13. Reynolds, W., V. Bacon, J. Bridges, T. Coburn, B. Halpern, J. Lederberg, E. Levinthal, E. Steed, and R. Tucker, "A Computer Operated Mass Spectrometer System" submitted to ANALYTICAL CHEMISTRY, 1970.

14. Swanson, G., T. Carpenter, D. Snider, and J. Bellville, "An On-Line Hybrid Computing System for Dynamic Respiratory Response Studies," COMPUTERS AND BIOMEDICAL RESEARCH, vol. 4, pp 205-215, April 1971.

15. Clark, W. A., "Macromodular Computer Systems", Spring Joint Computer Conference Proceedings, vol. 30, p 335, 1967. (See also the succeeding 6 papers pp 337-401.)

16. Wu, Y. S., "Architectural Considerations of a Signal Processor under Microprogram Control", SPRING JOINT COMPUTER CONFERENCE PROCEEDINGS, vol. 40, p 675, 1972.

17. Bell, C. G. and Newell, A., "Possibilities for Computer Structure", FALL JOINT COMPUTER CONFERENCE PROCEEDINGS, vol. 39, p 387, 1971.

18. Bell, C. G., W. Broadley, W. Wult, and A. Newell, "C.mmp: The CMU Multi-miniprocessor Computer", CMU-CS-72-112, 1971.

19. IBM, "System/370 Distributed System Program (DSP)", Program Number 360A-TX-032, Brochure G520-2539.

20. IBM, "Real Time Monitor (RTM), Program Number 360A-SV-001, Program Description GH20-0876-0.

21. Quan, L.H., R. Tucker, S. Liebes, M. Hannah, and B. G. Eross, "Computer Interactive Picture Processing", Stanford Artificial Intelligence Project Memo AIM-166, STAN-CS-72-281, April 1972.

22. Rindfleisch, T. C., J. A. Dunne, H. J. Frieden, W. D. Stromberg, and R. M. Ruiz, "Digital Processing of the Mariner 6 and 7 Pictures", J. GEOPHYS. RES., vol. 76, no. 2, pp 394-417, January 1971.

23. Nilsson, N. J., "A Mobile Automaton: An Application of Artificial Intelligence Techniques", Proceedings of the International Joint Conference on Artificial Intelligence, pp 509-520, 1969.

24. Feldman, J. A., et al., "The Stanford Hand-Eye Project", Proceedings of the International Joint Conference on Artificial Intelligence, pp 521-526, 1969.

25. Strand, R. C., "Man-Machine Cooperation in Digital Pattern Recognition of Bubble Chamber Tracks", ANNALS OF NEW YORK ACADEMY OF SCIENCES, vol. 157, Art. 1, p 65, 1969.

26. Neurath, P.W., Gallus, G., Selles, W. D., "Interactive Computer Aided Chromosome Analysis", Lecture Notes, Engineering 871.S, UCLA Short Course, 1969.

27. Mendelsohn, M.L. et al., "Computer Oriented Analysis of Human Chromosomes II, Integrated Optical Density as a Single Parameter for Karyotype Analysis", ANNALS OF NEW YORK ACADEMY OF SCIENCES, vol. 157, Art. 1, p 376, 1969.

28. Castleman, K. R. and R. J. Wall, "The Analysis of Human Chromosomes", to be published.

29. Selzer, R. H., "Recent Advances in Computer Processing of X-ray and Radioisotope Scanner Images", Biomedical Sciences Instrumentation, vol. 6, p 225, 1969.

30. Brooks, S. H., Selzer, R. H., Crawford, D. H., and Blankenhorn, D. H., "Computer Image Processing of Peripheral Vascular Angiograms", to be published.

31. Levinthal, E. C., "Mariner 9 - Image Processing and Products", COSPAR Proceedings, May 1972 (to be published, ICARUS).

32. Green, W. B. and D. A. O'Handley, "Recent Developments in Digital Image Processing at the Jet Propulsion Laboratory", to be published, IEEE Special Issue, July 1972.

(3) PL/ACME on a PDP-10

The PDP-10 systems as provided by DEC contain an excellent timesharing system with its memory allocation, support a variety of languages and have an adequate file system.

A service that ACME has provided is a language and a support system that has a number of features not included in the DEC processors:

(a) A language that conveniently handles both numeric and string data.

(b) The capability to alter programs in terms of source statements at any time, including execution.

(c) The capability to carry out all debugging, including interruption, inquiry into state of variables or system change of variables, and continuation from such points, in source program formats.

These points have made ACME a useful tool for non-computer specialists in medical research.

Most of these features are part of the compiler and the execution time support provided through availability of symbol table, controlled linkages, etc.

We therefore would like to put a PL/ACME language processor on the PDP-10 if such a machine is obtained for Stanford. Before starting this project, we will look for other options to provide PL-type language support on the PDP-10. The language processor should be useable on other machines of similar type and configuration. We will seek other PDP-10 users of PL and form sharing efforts on language extension.

The work is simplified by the fact that major portions of PL/ACME are written in FORTRAN and that the compiler does not generate directly 360 machine language. It generates specification to a macro assembler which produces the detailed code.

It is DEC's impression that their new FORTRAN compiler will materially assist this conversion effort.

A number of decisions will have to be made regarding byte size and other parameters. ACME's byte size is 8 bits, determined by the IBM hardware; DEC hardware is flexible. Their software normally prefers 7, but their COBOL uses 6, as do their peripheral devices in standard mode.

The estimate of the required conversion effort that follows was made by the ACME staff members based on discussions with DEC to clarify PDP-10 system capabilities and services. DEC made no direct examination of ACME code in responding to our general queries.

The following assumptions were made in arriving at the estimate:

(a) Indicated man month requirements assume uniform concentration on the problems of conversion. Competing demands on personnel time will introduce inefficiencies and increase calendar time required.

(b) The staff will consist of qualified systems programmers familiar with the PL/ACME system augmented by member(s) previously familiar with the PDP-10 system.

(c) No attempt will be made to extend PL/ACME capabilities in the conversion effort. Reprogramming will include taking advantage of existing PDP-10 capabilities including monitor control of time-share allocations, core swapping/hardware relocation or paging, and a file system which on the surface is similar to that currently used by ACME (there may be differences in security and integrity provisions).

(d) The new FORTRAN compiler being designed by DEC will be efficient, compatible with language standards, and allow efficient provision for extended capabilities such as logical operators, byte manipulation, and binary shifting.

The following are the conversion estimates for a PDP-10:

| | System Function | Man-Months |
|---|---|---|
| 1. | Statistical programs | 2 mm |
| 2. | PL compiler | 12 |
| 3. | Error messages/processing | 1 |
| 4. | Execution time excluding I/O | 6 |
| 5. | File System | 6 |
| 6. | Run time I/O and text editing | 6 |
| 7. | LISP compiler | 0 |
| 8. | Miscellaneous | 1 |
| 9. | SYSI. FORTLIB (FORTRAN library) | 1 |
| 10. | Plotting routines | 2 |
| 11. | Core management | 1 |
| 12. | Realtime support (configuration dependent) | 3 |
| 13. | System control | 3 |
| 14. | Terminal handling | 1 |
| 15. | Assembly utility | 1 |
| | Sub Total | 46 mm |

In addition to converting program code, provision must be made for planning the conversion details, learning the new computer and monitor system, and assistance to users in file conversion:

| | | |
|---|---|---|
| 16. | System education (4-5 people @ 1.5 mo/person) | 7 mm |
| 17. | Conversion planning | 12 mm |
| 18. | User file conversion aids | 4 mm |
| | Sub Total: | 23 mm |
| | Grand Total | 69 mm |

In the above estimates no provision was made for project management, project service, or operations personnel time as well as hardware costs. Additional software effort will be involved in building accounting routines for a new machine/environment. More significant and user dependent will be some user effort to convert data files to a new word length system. For files of uniform format (numeric or alphameric (text)), conversion can be automated. For mixed files the user must be involved to define the formats of the data. Provision is made in the above estimate to generate file conversion program aids based on user format specifications.

The LISP conversion problem is in essence ignored above based on the following. No adequate LISP capability currently exists on ACME. The LISP 1.5 batch processor currently used on the 360/67 has a counterpart on the PDP-10 which requires minimal conversion of programs using conventional LISP functions. According to B. Buchanan, some DENDRAL LISP code includes special functions written in LAP (a LISP assembly language) which will require conversion. This code is not voluminous and some will benefit from conversion and/or redesign.

b. Collaborative Research and Development

(1) Predictive Modeling of Cardiovascular Function Utilizing X-Ray and Ultrasonic Imaging Techniques - prepared by Donald C. Harrison

(a) Problem Statement

Cardiovascular disease continues to be the leading cause of death in the United States and in most developed countries, even though significant research into the prevention, diagnosis, and treatment of cardiac conditions have provided much insight during the past several decades. Coronary artery disease (CAD) accounts for more than 50% of all deaths in the United States and between eight and ten million people are estimated to have symptomatic CAD at the present time. Untold more millions have latent CAD which has not yet been detected. CAD frequently does not involve the muscle of the heart wall symmetrically and in fact, typically, is segmental in nature leading to localized areas of dysfunction with areas which are dyskinetic, akinetic, or dyssynchronous in their contraction patterns. All of these abnormalities may occur in the same heart and in general, can be correlated with a decrease in coronary blood flow to the specific segment of myocardium. In order to determine which patient should receive medical or surgical therapy for CAD, and whether or not segments of wall should be removed in specific patients, it is important to define in quantitative terms the areas of abnormal contractility and their severity.

Patients with valvular heart disease also may have localized abnormalities of muscle contraction in their heart wall. In determining whether or not the valve damage is primary, thereby requiring surgical therapy, or whether it is secondary to the abnormal muscle function, sophisticated studies such as cardiac catheterization and specific angiographic procedures must be performed. Data which are obtained from these complex procedures are in many instances inadequate to make a precise assessment of muscle function. Thus, our overall desire is to develop techniques which will permit a better assessment of ventricular performance, first by using the invasive techniques of cardiac catheterization and angiography now available, but providing improvements for analyzing signals. Secondly, we wish to develop new techniques, primarily using ultrasound, which will not require cardiac catheterization and angiocardiographic procedures for defining precisely cardiac muscle function.

Computer technology has been applied successfully in order to permit more accurate assessment of cardiac function in recent years. Computer techniques for monitoring the electrical and mechanical performance of the heart in a number of disease states have been developed in the Cardiology Division at Stanford (1-4). Dedicated small computers have been used for these purposes and the programs for determining pressure and flow relationships in patients undergoing cardiac catheterization have been developed by the Cardiology Group at Stanford (1-3). These functions are now performed by a dedicated mini-computer operating in a real-time mode during much of the day. In addition, the software for monitoring electrical and pressure-flow relationships in patients following acute heart attacks is presently being developed by the Cardiology Group. The basic software package for this dedicated mini-computer has been developed, and validation of these computer programs is now in progress.

A technique for video image analysis obtained when patients are undergoing angiocardiographic procedures has also been developed by the Cardiology Group (4-6). Furthermore, techniques for monitoring the coronary blood flow as it is partitioned to various muscle segments in the heart has been developed using a gamma camera for counting radioisotopes after the injection of gamma emitting isotopes into the coronary arteries. Individual patients undergoing cardiac

evaluation or treatment at Stanford may well have tests or procedures which are analyzed by all three dedicated mini-computers now operative in Cardiology. Since all calculations are now being carried out by mini-computers which are not tied together in any network, the special calculation and integration of data from any specific given patient is not possible without the use of a larger computer system. The Cardiology Division desires to utilize the proposed research computer system in order to develop more sophisticated techniques for studying the function of the heart, and to develop techniques which can be applied widely for choosing the appropriate diagnosis or treatment of specific patients with cardiac disorders. The specific problems which we wish to solve are as follows:

1. To diagnose the presence of disease of the cardiovascular system and to quantitate its severity utilizing data being generated by the several dedicated mini-computers monitoring cardiovascular performance. The ability to perform multiple sophisticated calculations on these data which can be integrated from several dedicated mini-computers in Cardiology will provide a basis on which to define heart muscle and hydraulic pump function in a more precise manner.

2. Utilizing the X-ray image processing techniques to improve analysis of the hydraulic function of the heart, it should be possible to estimate and detect segmental abnormalities in function. Clearly, much can be learned from studying the geometric changes in the heart wall during contraction which can supplement the pressure-flow relationships which we are now using for analyzing function.

3. To integrate the pressure-flow-volume and geometric changes for the entire heart and for the small segments of the wall representing small areas of muscle dysfunction or necrosis which may be important for overall cardiac function.

4. To develop non-invasive methods utilizing ultrasound techniques as a substitute for angiography which will permit screening of patients with suspected cardiac function abnormalities without subjecting them to the considerable risk of cardiac catheterization and angiographic techniques. It is also possible that these ultrasonic techniques can be applied in non-hospitalized patients, thereby decreasing the cost of screening significantly.

5. To follow the course of cardiac disease by studying in quantitative fashion the changes in function in relationship to pressure flow, volume, and geometry as a natural history of a disease process unfolds.

(b) Background

During the past two decades, pressure measurements in the various chambers within the heart have been the primary method for determining dysfunction. Transducer systems for analyzing the cyclic changes in pressure have been available for several decades, and abnormalities of valve function and muscle function are reflected in changes in systolic pressures, diastolic pressures, and the rate at which pressures are developing. During the past two decades measures of total flow during the cardiac cycle have been developed and used together with pressure measurements to provide a more sophisticated technique to analyze the overall hydraulic pumping function of the heart. Recently techniques for measuring volume changes throughout the course of a cardiac

cycle have been developed at Stanford. Video images are stored on a video disc after the injection of radio-opaque media into the cardiovascular chambers. Then utilizing a light-pen for drawing the images on a video screen and transmitting the coordinants from the light-pen to a computer, has provided a basis upon which ventricular volumes could be determined throughout the cardiac cycle once geometric formulae for the changing ventricular shapes were developed. This technique is tedious, requires a human interface and does not provide high resolution. In an attempt to improve these methods of determining ventricular volume, techniques for videodensitometry which have been developed at the Mayo Clinic (7) and in Dr. Heintzen's laboratory in Germany (8) are now being planned for cardiology laboratories. Videodensitometry requires that computer processing techniques be developed to recognize borders and that the movement of these various borders be followed throughout several cardiac cycles while the ventricular chamber is filled with radio contrast material. These techniques offer great promise for studying the geometric changes which occur during cardiac contraction and for defining the changes which occur segmentally in patients with CAD. However, even these sophisticated techniques require cardiac catheterization and angiography.

Recently the use of reflected ultrasonic waves from the moving wall of the heart has been accomplished in a number of centers throughout the United States. These techniques offer promise for a non-invasive method to study heart function. Using these reflected ultrasound techniques, it is possible to determine specific patterns of wall motion for a given area of the heart. Unfortunately, it is difficult to locate precisely these areas and to make certain that one can focus the ultrasonic beams on a specific area throughout the course of a cardiac cycle or throughout several cardiac cycles. The development of new and multiple ultrasonic transducer systems may provide an opportunity to look at more than one area of movement in the heart wall. With multiple transducers, computer processing of ultrasonic data becomes essential. In the Cardiology Division at Stanford we have developed a rapid A-D conversion technique for computer processing these ultrasonic signals, and have developed tracking programs and pattern recognition techniques. At present our progress is limited without access to a large computer which can receive high data input, store it for later calculations and then display it graphically. Multiple transducers are now being developed and with them it should be possible to analyze more than one area of wall motion in a particular cardiac cycle. Such transducer systems are available now, but their use is delayed due to the general inability to process the accumulated data. Computer techniques for handling the large volume of data are now being considered and will require access to a large computer with extensive core, disc storage, and sophisticated graphic outputs.

(c) Rationale

The specific rationale for proposing the use of the large research computer facility at Stanford at this time is as follows:

1. The Cardiology Division has made a step-wise approach, utilizing dedicated small computers to measure cardiovascular functions and follow them in quantitative terms. Computer techniques for analyzing pressure and flow signals have already been developed and initial applications utilizing a human interface have also been made for video image processing.

2. Analysis of cardiac contraction patterns, segmentally, necessitates high video frame rates with video image processing of each frame. It appears that videodensitometric methods utilizing techniques for determining border movement for various segments of muscle throughout a cardiac chamber are essential to provide quantitative data.

3. Sequential analysis of discrete areas of ventricular wall motion so that disease which alters the function of a particular segmental area of the heart can be detected. The nature of coronary artery disease is that segmental wall damage is almost always the way in which ventricular function is altered.

4. Advanced technology in ultrasonic transducers is now being developed. Dr. Richard Popp of the Cardiology Division at Stanford and Dr. James Meindl of the Integrated Circuits Laboratories in the Stanford Electrical Engineering Department have been working on such multiple transducer systems. Clearly the ability to sense the signal from these transducers and to activate one transducer at a particular time during the cycle and analyze from that transducer will require large and sophisticated computer installations.

It is with these rationales in mind that the Cardiology Division desires to participate in the development of the research computer facility at Stanford.

(d) Methods and Procedures

Several specific procedures to improve definition and provide quantitation of cardiac function are planned.

1. X-ray Image Processing - New image processing techniques will be developed. The goals and methods for accomplishing this particular research project are:

   a. To outline the opacified heart chamber after the images are recorded on either X-ray film or on a video disc. Recording will generally be made at 30 frames/sec. for delayed analysis. Several techniques for border definition will be attempted. Gray Scale analysis techniques utilizing scan methods for digitizing data along lines on the film or video scan will be one of the methods attempted. A film scanner will be necessary and will need direct computer control.

   b. Since biplane opacified images will be processed, three dimensional geometric displays of ventricular contraction will be developed. A promising technique of cartooning video images in three dimension has been developed by the Cardiology Division in association with Dr. Harold Sandler at NASA Ames Research Center.

   c. Models of the normal contractile patterns for ventricles will be developed. Changes expected during various parts of the cardiac cycle can then be predicted by the computer and only those areas in which the contractile pattern differs significantly from normal will be studied in detail. This ability for the computer to focus the analysis on areas of abnormality by feed-back mechanism excludes extraneous data from being digitized and analyzed. This technique will permit a much more adequate use of the sophisticated computer technology and a great reduction in the volume of data handling necessary when high frame rates over many cardiac cycles are examined.

d. Segmental analysis of various portions of the heart wall motion will be possible using these computer techniques.

e. Data on pressure and flow accumulated simultaneously will allow precise calculation of muscle function in terms of force-load-velocity of contraction and will permit pressure-volume loop displays. Graphic display of the computed data will be essential for these calculations.

In the understanding of isolated muscle segment function it is important to ascertain the relationship between force developed and velocity of wall motion in a specific segment. This should provide a basis for understanding the hydraulic relationships developed in the pumping heart as a whole on the basis of individual segment analysis. Thus, it will be possible to develop pressure-volume loops for the analysis of overall cardiac function. The quantitative determinations of overall function can then be related to normal expected patterns. Predictions of change in cardiac performance, based on removal or alteration of contractility of a given segment, can then be made with precision. This will perhaps lead to a better understanding of the function of isolated segments of ventricular muscle and how these are affected by disease and the treatment of that disease by either medical or surgical means.

2. Ultrasonic Image Processing

It is the developmental plan of the Cardiology Division to utilize information concerning cardiac function obtained by contrast angiography to validate and provide a data base for the newer techniques of ultrasonic image generation and processing. Detailed measures of ventricular contraction utilizing ultrasonic image processing techniques appear possible in more than one dimension. Several transducers may be used to reflect the movement of the heart wall in three dimensions.

During the first year of the proposed grant we plan to develop better techniques for digitizing ultrasonic data and to improve our methods for tracking ultrasonic signals in real-time utilizing digital computer techniques. In addition, during this period of time the development of multiple transducers on a hemispherical array will be completed in collaboration with Dr. James Meindl in the Integrated Circuits Laboratory at Stanford. Computer software for activating one transducer and recording from it for a short period of time and then sequentially activating other transducers so that three dimensional ultrasonic display of ventricular wall motion can be made will be developed utilizing the PDP-10 computer system proposed.

Border definition recognition, and sequential motion analysis can be predicted for normal hearts and deviations from normal can be highlighted by activating the appropriate transducer in the hemispherical array for systematic data accumulation throughout cardiac cycles. This should permit the development of non-invasive techniques for studying wall motion in patients who have only latent heart disease and are not yet symptomatic. Mass screening techniques with physiological documentation will be required once these ultrasonic scanning techniques have been validated. It seems likely that ultrasonic techniques can replace the invasive radiographic methods now required to analyze wall motion in quantitative terms and relate this to pressure and flow data.

3. Small Computer Integration

The Cardiology Division wishes to transfer the data analyzed by the small dedicated computer systems in the cardiac catheterization laboratory, in the monitoring unit, from the gamma camera, from the electrocardiographic laboratory and from a gas chromatograph into the large research computer file automatically. Currently the integration of these data and performing calculations with interrelated data from the several systems can only be done manually. To this data pool for sophisticated analysis we plan to enter the X-ray image processed data, the clinical data, and the data from the operating rooms. Once these data can be analyzed in detail, highly sophisticated diagnoses, prognoses, and predictative estimates for specific patients with a variety of cardiovascular diseases can be made.

From the monitoring unit on the cardiology ward specific cardiac arrhythmias can be detected and their frequency quantitated. These arrhythmias are treated with drugs which can be measured precisely by gas chromatography. The level of the drug can be related to its effect in many patients. Control of its administration can be achieved by relating the frequency of arrhythmia to blood level of the drug used for treatment. We wish to experiment with computer control of drug administration in these specific circumstances.

e. Significance

The significance of the above proposed analyses of cardiac function is as follows:

1. To understand better the physiologic interrelationships between changes in coronary blood flow, segmental muscle dysfunction and overall hydraulic pumping abnormalities in the heart of patients with significant cardiac disease. It will be essential to study isolated muscle function in a segmental distribution and to integrate the pressure-flow-volume and geometric measures of ventricular performance.

2. To choose appropriate medical or surgical therapy for the large numbers of patients presenting with cardiac disease based on quantitative determinations of abnormalities in cardiac function.

3. To evaluate sequentially in quantitative terms the results to either medical or surgical therapy in these patients.

4. To develop and improve non-invasive techniques which will provide all of the information necessary to analyze heart function in quantitative terms. These approaches may later lead to mass screening techniques for latent disease.

Clearly, if the objectives outlined above are met successfully by the research computer facility, they will become daily operational activities for cardiologists. In this instance the programs developed could be moved to the utility machine or to small dedicated computers of this type now used by the Cardiology Division. Specifically, it is planned after each of these techniques are developed and validated they will be moved to the Medical Center utility machine.

f. Relationships

The Cardiology Division works with a number of other units within the Medical School and in the Undergraduate University. In order to utilize the proposed computer facility as has been described, it is essential that these relationships be maintained and increased. Presently the following interrelationships are maintained by the Cardiology Division as they are operative in relationship to this proposed computer grant.

1. Cardiology Division is directed by Dr. Donald C. Harrison, Professor of Medicine, Stanford University School of Medicine, who has during the last five years emphasized research for adapting computer techniques for cardiologic diagnosis and treatment. Dr. Robert Stenson will be joining the Cardiology Division as Assistant Professor of Medicine. He has an extensive background in computer sciences and in cardiology and will direct the computer research operations for the Division. Dr. Edwin Alderman and Dr. Richard Popp are both working with video image processing--Dr. Alderman with angiographic methods and Dr. Popp with ultrasonic techniques. They both are working with a number of collaborators and postdoctoral trainees on projects which will relate closely with this computer technique development. Mr. William Sanders, who has worked with the Cardiology Division for two and one-half years as the Chief Programmer, will direct the programming efforts and will work as a liaison man with the overall computer staff of the proposed central computer facility. During the past year two graduate students from Electrical Engineering, Mr. Michael Hirsh and Mr. Patrick McClure, have worked in association with Mr. Sanders. At the present time in Cardiology two Hewlett-Packard computer systems are operational on a day-to-day basis. The Cardiology Division has also been approved for an M.D. training program in computer sciences. This will be carried out in association with Dr. Edwin Parker of the Communications Department and the Computer Sciences Department in the Undergraduate School at Stanford. Furthermore, the Cardiology Division is presently negotiating with Hewlett-Packard for another 2100 computer system which would then give the Cardiology Division three small dedicated computer systems to be integrated into the larger proposed Research Computer network.

2. NASA Relationships - Dr. Harold Sandler, Head of the Biotechnology Group at NASA-Ames Research Center is one of the pioneers in angiographic methods in studying ventricular geometry and cardiac function. The Cardiology Division has worked closely with Dr. Sandler and at present all of his clinical work is performed in our cardiology laboratories at Stanford. NASA has also supported an ongoing project for the past five years at Stanford to develop better methods for analyzing ventricular performance.

3. Integrated Circuits Laboratory - Dr. Richard Popp is working closely with Dr. James Meindl in designing new arrays of ultrasonic transducers. This work is at an early phase at the present, but plans are being made for more than one transducer mounting so that several segments of wall motion may be studied in the same heart.

4. Communication Department - Dr. Edwin Parker of the Communication Department has agreed to work with the Cardiology Division in a training program for medical scientists in the application of computer techniques for data handling and analysis. Such a program has been approved by the Study Section of the National Library of Medicine and should be activated in the year 1972.

5. Artificial Intelligence Group - Numbers of individuals working in the Artificial Intelligence Group have worked with image processing techniques which will be complementary to the plans in Cardiology. Tom Rindfleisch, Dr. Elliott Levinthal, and Dr. Bruce Buchanan of this group have participated with the Cardiology Division in planning the image processing techniques to be utilized. Professor Lederberg and Dr. Levinthal are on the Mariner 9 TV Experimenter Team. In this capacity, Dr. Levinthal has headed the Data Processing Task Group which has had the team scientific and policy responsibility for the very large image processing computer requirements for this mission (ref. 34).

   Mr. Thomas Rindfleisch, when he was at the Jet Propulsion Laboratory had the responsibility for the implementation of this system. There is thus the opportunity to benefit from these space-related experiences in image-processing.

   In addition, Dr. Buchanan is closely related to the M.D. Computer Science training program of the Division of Cardiology. These interrelationships will provide high level computer consultation for the Division of Cardiology as the step-wise plan to utilize the proposed research computer facility above unfolds.

REFERENCES

1. Stenson, R.E., Crouse, L., Henry, W.L., and Harrison, D.C.: A time-shared digital computer system for on-line analysis of cardiac catheterization data. Comput. Biomed. Res. 1:605-614, 1968.

2. Henry, W.L., Crouse, L., Stenson, R., and Harrison, D.C.: Computer analysis of cardiac catheterization data. Amer. J. Cardiol. 22:696-705, 1968.

3. Harrison, D.C., Ridges, J.D., Sanders, W.J., Alderman, E.L., and Fanton, J.A.: Real-time analysis of cardiac catheterization data using a computer system. Circulation 44:709-718, 1971.

4. Sanders, W.J., Alderman, E.L. and Harrison, D.C: An interactive computer-based technique for left ventricular volume measurement. Jour. Assoc. Adv. of Med. Instr. 6:188, 1972.

5. Alderman, E.L., Sandler, H., Brooker, J.Z., Sanders, W.J., Simpson, C. and Harrison, D.C.: Light-pen computer processing of video image for the determination of LV volume. Submitted to Circulation.

6. Brooker, J.Z., Alderman, E.L. and Harrison, D.C.: Abstract. Angiographic documentation of changes in ventricular volumes during Valsalva maneuver. Accepted for presentation at the American College of Chest Physicians, October 1972.

7. Wood, E.H., Strum, R.E. and Sanders, J.J.: Data processing in cardiovascular physiology with particular reference to roentgen videodesitometry. Proc. Mayo Clin. 39:849, 1964.

8. Heintzen, P.H.: Roentgen-Cine-and Videodensitometry. Georg Thieme Verlag, Stuttgart, 1971.

2) Digital Computer Processing of Cineurographic Images of the Urinary Tract. - prepared by C. Constantinou and T. Stamey

(a) Problem Statement

Due to the expanding sophistication and specialization of the clinical urologist, the specific need for computer aided quantification and documentation of X-ray images is becoming increasingly urgent. Thus, with the routine introduction of cinefluoroscopy as a dynamic mode of visualization of the urinary tract, the quantity and quality of information available to every day diagnostic procedures has greatly increased. At the same time, the objective evaluation and quantification of this information remained in the cognitive mind of the radiologist who is asked to provide a larger volume, accurate measurements, and at the same time, maintain a consistent diagnosis. To this end, some information is available to the urologist from static X-ray films as measured by the radiologist. This information includes renal size, parenchymal thickness, calyceal geometry, pelvic and ureteral dimensions and can be reasonably abstracted and documented manually by measurement. But a living system is not static and therefore dynamic studies, using cinefluoroscopy, have been organized to view the kinetics of peristaltic flow, retrograde reflux, and dilation, in the ureter on film. This effort has proven very useful for first order visual evaluation by the urologist but has inherent limitations in terms of quantitative data that can be abstracted in a manner analogous to the static X-ray measurement.

The broader application and objective use of these dynamic studies is therefore limited due to the vast amount of work and calculations required for the determination of even the most basic parameterization of any of the kinematic constants. It is in this area of dynamic interpretation of extended cinefluoroscopic studies with its plethora of potentially valuable information that this program addresses itself now.

The overall objectives of this proposed program is the development of the computational capability to greatly increase the informational content of intravenous pyelographic film. It is expected in this way that an extensive determination of the dynamics of flow of the upper urinary tract under physiological and pathological conditions can be made. Specifically, the following parameters will, for the first time, become available in a simultaneous measurement from the computer processed film:

1. Volume, dimensions, and direction of propagation of the discrete urine bolus.
2. Speed of peristaltic transmission and frequency characteristics of a group of contractile waves.
3. Spatial separation of retrograde peristalsis and reflux under various conditions of flow.
4. Accurate documentation of time varying changes of above in disease situations where there is known progressive deterioration in the lower ureteral tract.

5. Correlation of these changes with the geometry of the upper tract and kidney.

The direct benefits of this integration and quantification of parameters would significantly enhance the informational content of pyelography for the urologist and radiologist. At the same time the underlying mechanisms of obstructive uropathy would be quantitatively evaluated and compared to normal physiological pressures.

(b) Background.

In clinical urology, the transport of urine from the kidney to the bladder is visualized radiographically by the injection of radiopaque contrast media into a vein and observing the outline of the calyceal walls and the excretion patterns of the ureter during peristalsis. This diagnostic procedure is termed intravenous pyelography and frequently performed in most hospitals. The dynamic nature of the transport of urine in the ureter is enhanced when observations are made continuously through a fluoroscope to visually trace the path of the contrast labelled urine along the entire length of urinary tract. Thus, the anatomical outline, from kidney to bladder, is illuminated and obstructive or restrictive pathways can be observed. The amount of information thus extracted is substantially increased when a permanent record of the flow patterns is documented on cine film or video tape, and subsequently examined at slower speeds. At that time, retrograde flows can be seen together with a host of other physical phenomena characteristic of a diseased kidney, ureter, or bladder. The informational content of this visual examination is presently limited to a qualitative description of size, shape, position, and primitive motion of the ureters. Films or tapes resulting from these studies are stored and subsequently used for comparison. Thus, it is possible to evaluate and correlate current visualization of a given patient with his previous cine fluoroscopic studies. The fact still remains that this form of evaluation remains a visualization and progressive anatomical changes are thus not easily documented. Some attempts have been made in grading the morphological appearance of these organs and following the changes of the grading as a function of time and disease. This has proven very unsatisfactory due to the variability of grading between different observers. In our earlier attempts in this area, a complex library of shapes of each anatomical landmark was constructed and stored on a computer. Thus, a review could be made on any patients by asking the computer graphics program to reconstruct a primitive image from the interpretive codes. This proved very unsatisfactory except in the simplest cases due to a lack of quantitative and dynamically obtained data. At that point, it becomes clear that other avenues approximating more closely the realities of the X-ray cine should be sought and coded.

(c) Rationale.

The capability and flexibility of a high data rate computer in the processing of urologically significant radiographic film would provide a medium for the application of sophisticated quantification

methods for the first time in the extraction of dynamic information from pyelograms. In this way, governing parameters determining the stability of a unidirectional flow towards the bladder and the prevention of ureteral reflux can be studied and properly evaluated. Furthermore, reliable quantitative documentation for developing disease states will be possible by the integration of the measurements of the outlines and significant features of radiographs with other archival medical records. In this way, it will be possible to document reliably the time dependent changes in the upper urinary tract dynamics of patients with spinal cord injuries, recurrent urinary tract infections, congenital abnormalities, stones, etc. The direct result of this classification is to reduce to a manageable level the amount of repetitive work and provide the urologist with a direct method of realizing the diagnostic information asked without having to handle massive loads of films and data.

(d) Methods and Procedures.

A great effort has been devoted during the last few years to image evaluation and enhancement. The group at the Jet Propulsion Laboratory has continued its work on image enhancement with application to space television and biomedical imagery. For the purposes of this study, it is not our desire to repeat any of this pioneering work. The field would obviously provide us with newer, better, and more efficient algorithms for picture encoding, computer processing, and pictorial pattern recognition. Philosophically, our approach will be in the domain of feature extraction algorithms which will outline the renal, ureteral, and bladder projections from each frame in the most economical way, avoiding brute force methods.

Additional features of interest will include video densitometry within outlined structures related to the concentration and thickness of radiopaque material. This information can be combined with peripheral boundary measurements to infer relative cross-section information.

The time evolution of pyelograms includes considerable redundancy and correlation from frame to frame. This information can be used to model local system dynamics (frame to frame variations) and hence direct the data processing. In this way the relatively sophisticated pattern analysis algorithms for edge detection, structure skeletonizing, and densitometry can concentrate on small important subsets of the large amount of raw data involved. We can minimize computing and time resources required by utilizing these solution guided processing schemes.

The initial orientation of the computer to an image sequence may require human interaction as well as to assist in processing difficult frames. We expect the application of these results to succeeding frames as described above to minimize the need for human interactions.

Algorithms which may be used for automated computer analysis of the images include dynamic threshold and maximum gradient techniques for edge detection. Continuity conditions can be imposed for sequential

edge following. Techniques similar to these are being successfully developed for karyo typing and arterioangiogram analysis. Relative video densitometric information can be used to determine ureter size by measuring variations in density about a local mean and relating these to cross sectional area. This is accomplished by correlating mean density to mean boundary separation and assuming vessel symmetries.

Time evolutions of extracted information will be studied through various on-line graphical presentations. Deviations from predicted local model behavior may be used to identify time dependent anomalies which could be of interest.

The pyelogram information is collected on 35 mm film and significant archives of patient histories exist and will be studied. Initially, to develop techniques, we will use existing video scanning equipment at Stanford (SLAC) to digitize the entire frame sequences of interest. In order to conveniently store this large volume of data for computer processing we may use data compression techniques which take into account intraframe as well as interframe correlations. A scheme requiring relatively little computational effort to encode and reconstruct the video information would be a Huffman code built around picture element difference statistics.

In the longer term we want to obtain resources to build a computer directed scanner so that only the pertinent information need be measured from the film.

(e) Collaborative Affiliations.

A continuing dialogue and exchange of ideas in both the experimental and theoretical aspects of image processing will be maintained with Dr. Harrison's group. Although the contrast and time constants of cardiac catheterization is very different from pyelography, it is hoped that this cooperation would prove economically and scientifically beneficial.

(f) Significance.

The development of computer based characterizations of radiographs would be of practical significance to the present and future need of urologists and radiologists. The information accrued from such a system would span a broad range of benefits in specific areas of quantification, standardization, and information storage of otherwise neglected parameters in pyelography.

The potential future development of pattern recognition methodologies which can be realized from these evaluations, can handle more variability and allow the consideration of biomedical applications. It is realized however, by other workers and us that instead of trying for completely automated systems, we would use an interactive man-machine system that would allow human intervention in questions and tasks not easily automated. Thus, a number of interesting and difficult applications for computer assisted analysis of radiographs can become technically feasible.

(3) Automated Gas Chromatography/Mass Spectrometry Analysis
Prepared by Tom Rindfleisch

(a) Introduction

This section of the proposal is concerned with the design and development of the computer hardware and software components necessary for a fully automated gas chromatography/mass spectrometry (GC/MS) system. This work represents an extension of a portion of the existing DENDRAL research grant (NIH grant RR-00612). Significant progress is being made in all phases of the DENDRAL research as summarized in the succeeding sections. We have gained a greater experience with the data system requirements for the automated collection and analysis of mass spectrometry data as well as the limitations of the existing ACME system for developing such system. Because of the critical requirements for information integrity throughout an automated GC/MS system for medical applications and because the DENDRAL project is a natural environment in which to explore "intelligent" information handling and instrument control problems, we are proposing this more extensive automation effort. This work complements the on-going DENDRAL artificial intelligence, chemistry, and instrumentation research as explained in subsequent paragraphs.

(b) Problem Statement

The combination of gas chromatography with mass spectrometry (GC/MS) has had a tremendous impact on analytical problems in organic chemistry and biochemistry over the past decade (1). Increasingly GC/MS is being used as a tool in clinical and medical research applications to identify metabolites and other materials contained in body fluids. For example, Biemann and collaborators (2) describe a dramatic series of events following the admission of an unconscious patient to a hospital following a drug overdose. GC/MS analysis provided an identification of the drug used in this suicide attempt. Fales and Milne have been active in the identification of abused drugs. They describe (3) the use of GC/MS for the analysis of drugs separated from the stomach contents of 45 would-be suicides, and the resulting aid to proper treatment of the patients involved.

Medical research applications of computerized GC/MS have included the detection of metabolic disorders of genetic origin from an analysis of the organic chemical constituents of a patient's body fluids (usually blood or urine). Jellum and his associates (4) in Norway have been active in this field and through largely manual methods have been able to identify four previously undescribed metabolic diseases of genetic origin based on urine analysis.

These examples serve to illustrate the potential of GC/MS analysis as a tool in medical research and clinical applications. The basic power of the techniques lies in the ability of the gas chromatograph to physically separate and pass the components of a complex mixture into a mass spectrometer. The spectrometer makes measurements leading to a "fingerprint" for identifying each component of the mixture. In urine samples such as studied by Jellum, et al., such a mixture may contain several hundred components and may be subjected to fractionation prior to GC/MS analysis. The amount of

data contained in the output of such a GC/MS experiment is very large and the procedures for extracting significant information including interpretation are complex. An experiment may last for 2 hours with a spectrum containing $10^5$ samples of data collected every 5 to 10 seconds. Out of the possible ensemble of $10^8$ data points must come an identification of all components with as little ambiguity as possible. Computer based data systems are essential for any effective utilization of this powerful technique.

Several computer-based approaches have been utilized to aid in the analysis of low resolution mass spectral data, whether or not collected by GC/MS (5) systems. For materials to be identified within a known class of possibilities, the potentials of library search routines have been explored (6). These procedures are frequently ambiguous as they use only a subset (low resolution spectra) of the information which a mass spectrometer can provide. Furthermore, in many medical research situations it is precisely the unexpected or previously unknown materials which are of greatest interest (4). Such problems cannot be solved within the domain of a library and currently fall back on human intervention to resolve ambiguities or synthesize new solutions. This limitation restricts considerably the utility of GC/MS systems because of the effort and time delays required to explore new situations.

The on-going DENDRAL work (7a-i) at Stanford (RR-00612) offers a far-reaching solution to this problem by designing into computer programs the ability to construct explanations for mass spectra in terms of chemical structure. Recently, these efforts in the context of high resolution mass spectra, have had considerable success in dealing with estrogenic steroids (7h). Future work will expand these capabilities to more classes of compounds as well as generalize the heuristic rule-forming processes to allow automatic computer extensions.

Manual, as well as automated interpretive procedures (7c,d,h) can utilize a variety of ancillary information (e.g., high resolution, low ionizing voltage, metastable data, and NMR data) to produce reliable and unambiguous results. Present low resolution GC/MS systems, because of limitations in system and/or instrument designs, are generally incapable of collecting all possible information on which to base an analysis during the finite interval of a gas chromatograph effluent peak. A realtime selection of instrument mode and information optimization type and quality is required.

Acquisition and reduction of mass spectral data in realtime have progressed to the stage where automation and closed-loop control are feasible and desirable. Closed loop automation of data extraction and instrument control processes places additional burdens for capability, integrity, and reliability on the overall data system. Because of the complexity of data reduction and interpretive processing, great care must be taken throughout the system to avoid the destruction of or artifactual invention of information.

The objectives of this portion of the proposal are to develop and demonstrate a fully automated gas chromatograph/mass spectrometer system in collaboration with on-going DENDRAL chemistry, artificial intelligence, and instrumentation research.

Specific objectives of the research include:

1. The development of autonomous and reliable instrument control and information extraction programs capable of reacting to a hierarchy of GC/MS response requirements within the context of a time-shared computer system.

2. The integration of evolving DENDRAL artificial intelligence programs to interpret extracted information and to provide feedback within the system specifying information requirements to insure optimal sample management.

3. The application of the developed system in cooperation with collaborating chemists and medical researchers to problems in the analysis of steroids and other metabolites found in biological fluids.

(c) Background

The elucidation of the systematics by which chemical compounds fragment under electron bombardment has a large literature with very significant contributions from the laboratory of Professor Carl Djerassi at Stanford. These systematics form the basis for computer automation of the interpretation of mass spectra - the DENDRAL project.

DENDRAL is a set of computer programs which have developed over a period of several years, initially for the interpretation of the low resolution mass spectra of specified classes (ketones, ethers, amines, alcohols, thiols, and thioethers) of alicyclic compounds (7b-7h). Subsequently, this theory was extended to include the high resolution mass spectra of the estrogen class (female sex hormones) of steroids (7i). This program has also demonstrated its ability to identify the components present in laboratory-made mixtures of estrogens. At the present time work is progressing with crude estrogenic mixtures obtained from biological sources. The successful completion of this project will represent a new, rapid approach for the identification of estrogenic steroids without the necessity of first derivatizing and then analysing the mixture by gas chromatography. Heuristic DENDRAL is also being enlarged to accommodate a theory of mass spectrometric fragmentation of other classes of steroids and alkaloids, utilizing high resolution mass spectra.

Metastable ions formed in the first field-free region of a double focussing mass spectrometer (so called defocussed metastable ions) have been used by mass spectroscopists for the identification of parent-daughter ion relationships. As part of its spectrometry theory, Heuristic DENDRAL will use this additional type of experimental data. A recent paper (8) described a new use of defocussed metastable ions for the unraveling of competing fragmentation pathways.

Meta-DENDRAL research efforts are aimed at the computer formulation of scientific theories based on the examination of related sets of data. Such

a capability will allow the automatic extension of computer capabilities for mass spectrum interpretation by the inference of new rules. To date these programs are capable of writing primitive rules about fragmentations and the influences of molecular parameters (e.g. substituent effects).

Work of others in the field. Data systems which can cope with the large accumulation of spectral information generated during a low resolution GC/MS run have been developed in a number of locations including Stanford (9). These systems run open loop in that they systematically collect data from sequential low resolution spectrometer scans, reduce the data based on instrument calibrations, and provide the chemist with the ability to retrieve particular spectra corresponding to gas chromatograph effluent activity. However, even when coupled with library search procedures (6), there systems make few, if any, intelligent decisions about the data, and provide the chemist with few clues about the validity of his results. Our approach will be to develop techniques to validate results under closed loop control based on instrument performance parameters and ancillary information such as the routine use of high resolution data. We will make use of the work by others in the development of suitable library search routines.

(d) Rationale

The power of the gas chromatograph/mass spectrometer data system as a medical research tool derives from the ability of the gas chromatograph to physically separate microgram quantities of complex mixtures followed by the mass spectrometer to identify each constituent from its "fingerprint" mass spectrum.

For each of the gas chromatographic peaks, the basic function of the mass spectrometer is to ionize sample molecules which then fragment and, through electromagnetic separation, to measure the abundance of fragments with different masses. At high resolution the elemental composition of the various fragments can be determined. These abundances are related to the molecular structure of the sample material and these relationships can be used by inference to derive the structures for unknown sample materials from their mass spectra. There are numerous modes of operation of a mass spectrometer which allow the measurement of ion abundances with varying time, mass, resolution, and ionization energy, as well as enable the observation of delayed or metastable ion fragmentation pathways. Not all information in all modes of operation can be collected during a gas chromatographic peak because of limitations in data rates, instrument sensitivity, and sample flow into the ion source. Conversely not all collectable information is necessary for the identification of an unknown. The optimum experimental conditions producing the most relevant information in the shortest time are not predictable a priori for an unknown material. Thus closed loop computer analysis of the spectrometer with subsequent feedback control of its operation could maximize collected data quality and ensure the collection of needed information for the interpretation of an unknown structure.

The essence of our proposal is to design the necessary information handling and system control intelligence to complement the DENDRAL spectrum interpre-

tation intelligence and to integrate these elements into a reliable, autonomous GC/MS system. The core of this work will be to design programs at the various processing stages shown in Figure 1 which allow the system to perform the required functions. The time constants and data rates involved in the various aspects of a typical GC/MS experiment range from ~1 msec to ~10 seconds. These requirements are based on the typical 5 - 30 second duration of sample uniformity in gas chromatographic peaks. The logical sequencing of the loop element operations of Figure 1 is dependent upon the sequence with which information becomes available and the degree of overlap possible between successive operations. Figure 2 shows conceptually how this sequence takes place.

The GC/MS data systems existing today run almost entirely open loop in that there is no attempt to modify experiment execution based on extracted results. The processes involved are implemented with inadaptive algorithms so that if instrument performance, or data quality do not fall within parameter specifications, information may be destroyed, ineffective filtering may occur, or catastrophic system failures may result. Specific examples of where added intelligence is required exist throughout the system:

(1) Failsafe data collection and management capabilities must be built into the system to accommodate the inherently variable data length and peak arrival rate statistics of the spectrometer output.

(2) Reliable and fast methods must be developed for detecting and resolving overlapping peaks in the gas chromatograph and mass spectrometer sensor outputs.

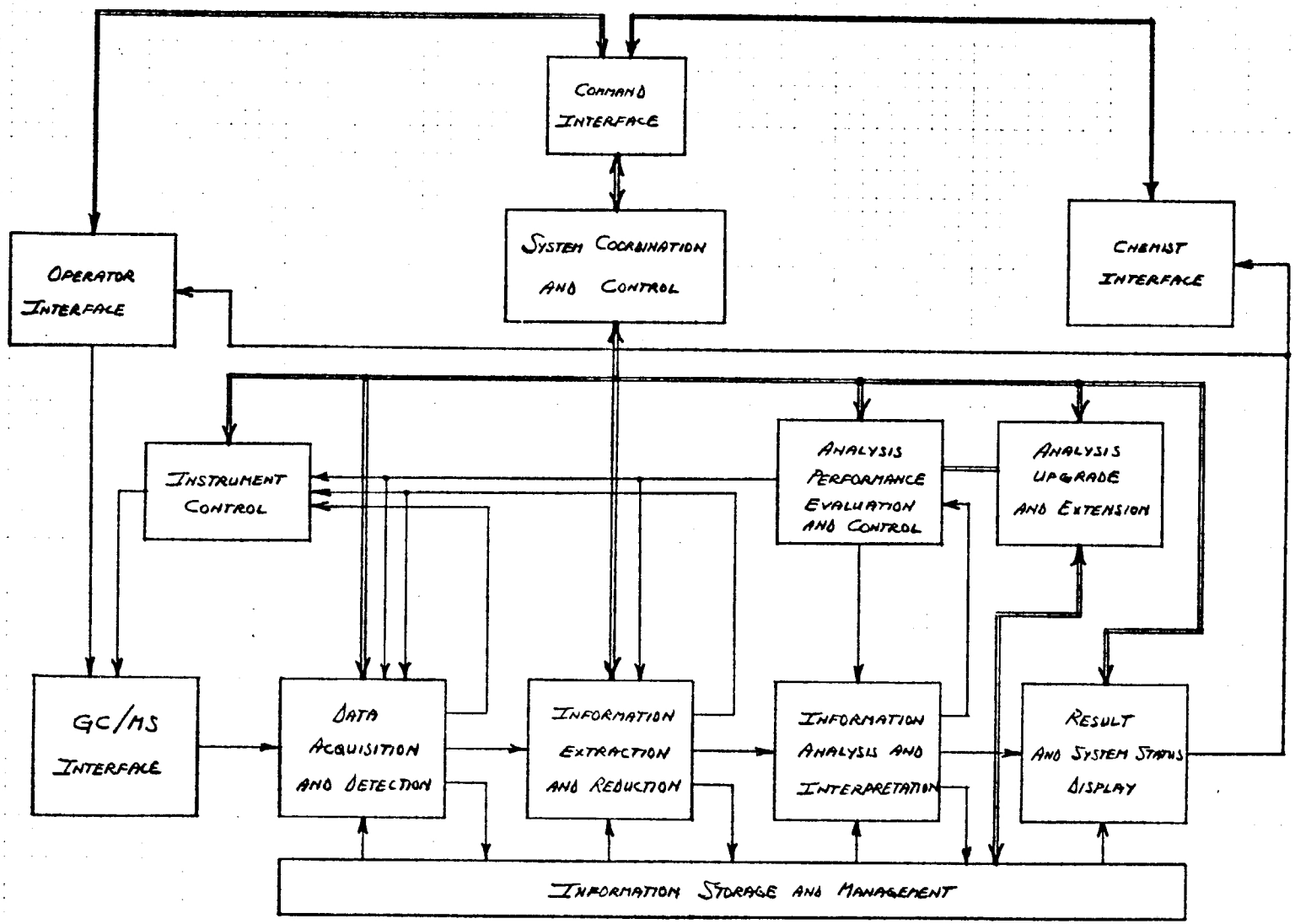
(3) The quality of extracted information must be evaluated based on instrument performance parameters and ion statistics.

(4) The characterization of instrument performance parameters must be continually updated and evaluated to allow optimum control of parameter settings for scan, focus, resolution, source and reference pressures, etc.

(5) The successive operations on extracted information must adapt their behavior based on the character and quality of their input information and must add their effect on uncertainties at their output.

(6) The overall management of resource allocation must be based on priorities derived from the on-going problem solving and interpretative processing to maximize the effectiveness of applied resources, to decrease processing time, and to minimize computing cycle consumption.

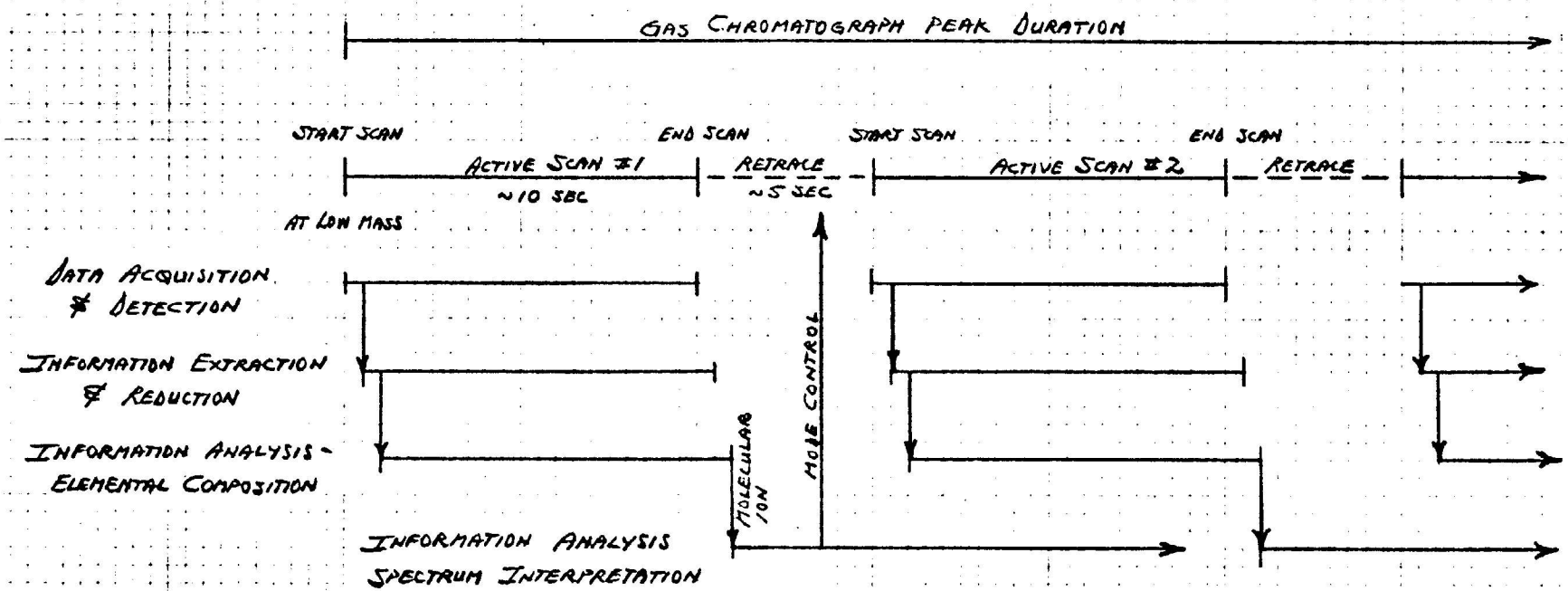
The evolution and collaborative application of this system will be complementary in nature. The conception, design, and implementation of the system benefit from experimenting with its applications. Conversely the power of the automated system allows the systematic exploration of new areas in medical and chemical research.




REAL TIME MASS SPECTRUM INTERPRETATION SYSTEM

Figure DENDRAL-1

TLR 2/17/72




PROCESSING TIME INTERDEPENDENCE

Figure DENDRAL-2

TCR 2/17/72

(e) Methods and Procedure

The implementation of the proposed automated gas chromatograph/mass spectrometer system will be a highly collaborative effort drawing as much as possible upon capabilities existing in laboratories at Stanford and elsewhere. Specifically we will use:

(1) The GC/MS-computer instrumentation and data system interfaces existing and being developed at Stanford under DENDRAL and NASA grants.

(2) Appropriate modifications of existing library search algorithms and data bases to effectively utilize (3) below.

(3) The artificial intelligence programs for mass spectrum interpretation being developed under the DENDRAL and ARPA grants.

In addition to these collaborative interactions, we will draw heavily on the satellite machine support capabilities, extended realtime system functions, and PDP-10/satellite hardware and software systems being developed under other sections of this grant application.

The various elements required in an automated GC/MS system are shown in Figure 1. These elements perform a variety of functions including:

(1) Data acquisition and detection. This element accepts the raw spectrometer output and detects peak information above a dynamic background threshold. Based on peak arrival statistics, control of the spectrometer scan may be used to increase ion collection efficiency (this would be based on similar work being done by McLafferty, private communication).

(2) Information extraction and reduction. This element extracts separated peak amplitude and position information from raw data. Instrument calibration data are used and resulting data quality is estimated. These quality measures can optimize instrument parameters.

(3) Information analysis and interpretation. This element computes elemental compositions as required and applies library search routine with appropriate verifications based on spectrum predictor routines. If no solution is found more basic DENDRAL theory construction routines are used to identify the unknown.

(4) Analysis performance evaluation and control. This element directs the search for an explanation of the sample spectrum using available a priori information. When ambiguities arise, control information is directed to obtain appropriate additional data.

(5) Analysis upgrade and extension. When new solutions outside of existing system capabilities are encountered this loop element incorporates these extensions into the system. Such extensions may come from META-DENDRAL analysis or from chemists.

(6) Result and system status display. This loop element provides the system user with rapid volatile plots and displays of on-going experiment results and status. Hard copy is available off-line.

(7) Instrument control. This loop element coordinates and implements control requests on instrument performance such as parameter adjustment or mode change by planning and issuing the appropriate electronic commands.

(8) System coordination and control. This loop element receives and maintains status and performance data relating to various system elements and guarantees the appropriate sequencing of interdependent operations. This element also coordinates system operation changes commanded from the outside.

(9) Command interface. This loop element decodes commands and control information received through the instrument operator or chemist user interface.

(10) Information storage and management. This element includes the organization and storage of spectral information and the ability to access this data on demand.

Models by which the computer can assess and optimize its performance will be developed based on physical principles for instrument performance and heuristic schemes for control and interpretation protocols.

Instrument control functions will be implemented as appropriate for parameters such as gas chromatograph temperature programming and mass spectrometer scan control, mode selection, resolution control, scan dwell, etc. The coordination of these parameters in terms of automated setting determination and sequences for control implementation will be developed heuristically from models of instrument performance and operator procedures.

Our concept of overall software organization follows the functional information flow shown in Figure 1 coupled with the timing interactions shown in Figure 2. The shortest term response requirements (~1 msec.) exist for the data acquisition functions and will be implemented in a dedicated machine interfaced to the GC/MS. This machine also allows open loop operation of the instruments in the existing modes during development of the integrated closed loop system. The other elements of the system will be implemented as subprocessors in the PDP-10/satellite extended realtime system affording required response without total commitment of the PDP-10 system.

(f) Significance. Low resolution GC/MS has become one of the most widely used and most powerful techniques available to the organic or biochemist (1). The potential applications of these techniques in medical research and practically in the clinic have just begun to be explored (4). Closed-loop control of this instrumentation would permit rapid exhaustive analysis of tissue extracts across large populations of individuals in various medical contexts and may provide new discoveries important to public health.

Extension of GC/MS to routine operation of the mass spectrometer at high resolving power would be an important breakthrough in terms of the specificity of information available per microgram of sample, compared to low resolution techniques.

The integration of library search techniques with the screening power of a spectrum predictor and the analytical capabilities of Heuristic DENDRAL would provide a powerful data analysis capability which would exploit the advantages of each approach.

These techniques are of unique importance to medical science since they alone of the current physical methods have sufficient sensitivity and analytical precision to study human biochemistry at the molecular level.

(g) Facilities Available. The research in this proposal will draw heavily upon the PDP-10/satellite computing resource we are proposing to establish. We have available two gas chromatograph/mass spectrometer systems which will be involved in this research including a Finnigan quadrupole instrument in the Department of Genetics and a Varian-MAT 711 instrument in the Department of Chemistry. Also available in the Department of Chemistry are MS-9 and Varian-MAT CH-4 instruments.

(h) Collaborative Arrangements. The proposed research project is a highly interdisciplinary effort involving collaboration between Professor J. Lederberg (Department of Genetics), Professor C. Djerassi (Department of Chemistry), Professor E. Feigenbaum (Department of Computer Science), Dr. B. Buchanan (Computer Science), Dr. A. Duffield (Genetics and Chemistry), Dr. D. Smith (Chemistry), and the Instrumentation Research Laboratory. The proximity of these people and facilities offers a highly unique opportunity for collaborative interaction.

REFERENCES

1. For pertinent reviews see: C. G. Hammar, B. Holmstedt, J. E. Lindgren and R. Tham, Advan. Pharma Col. Chemother., 7, 53, (1969); J. A. Vollmin and M. Muller, Enzymol. Biol. Clin., 10, 458 (1969)

2. J. R. Althans, K. Biemann, J. Biller, P. F. Donaghue, D. A. Evans, H. J. Forster, H. S. Hertz, C. E. Hignite, R. C. Murphy, G. Petrie and V. Reinhold, Experientia, 26, 714 (1970).

3. H. Fales, G. Milne and N. Law, reported in Medical World News, February 19, 1971.

4. E. Jellum, O. Stokke and L. Eldjarn, The Scandinavian Journal of Clinical and Laboratory Investigation, 27, 273 (1971).

5. A. L. Burlingame and G. A. Johanson, Anal. Chem., 44, 337R (1972).

6. H. S. Hertz, R. A. Hites and K. Biemann, Analytical Chemistry, 43, 681 (1971), S. L. Grotch, ibid., 43, 1362 (1971).

7a. Applications of Artificial Intelligence for Chemical Inference. I. The Number of Possible Organic Compounds: Acyclic Structures Containing C, H, O and N.
J. Am. Chem. Soc., 91, 2973 (1969)
By J. Lederberg, G. L. Sutherland, B. G. Buchanan, E. A. Feigenbaum, A. V. Robertson, A. M. Duffield and C. Djerassi.

7b. Applications of Artificial Intelligence for Chemical Inference. II. Interpretation of Low Resolution Mas Spectra of Ketones
J. Am. Chem. Soc., 91, 2977 (1969)
By A. M. Duffield, A.V. Robertson, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum and J. Lederberg

7c. Applications of ARtificial Intelligence for Chemical Inference. III. Aliphatic Ethers Diagnosed by Their Low Resolution Mass Spectra and NMR Data.
J. Am. Chem. Soc., 91, 7440 (1969)
By G. Schroll, A. M. Duffield, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum and J. Lederberg

7d. Applications of Artificial Intelligence for Chemical Inference. IV. Saturated Amines Diagnosed by Their Low Resolution Mass Spectra and Nuclear Magnetic Resonance Spectra.
J. Am. Chem. Soc., 92, 6831 (1970)
By A. Buchs, A. M. Duffield, G. Schroll, C. Djerassi, A. B. Delfino, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum and J. Lederberg

7e. Applications of Artificial Intelligence for Chemical Inference. V. An Approach to the Computer Generation of Cyclic Structures. Differentiation between all the Possible Isomeric Ketones of Composition $C_6H_{10}O$.

Org. Mass Spectr., 4, 493 (1970)
By Y. M. Sheikh, A. Buchs, A. B. Delfino, G. Schroll, A. M. Duffield, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum and J. Lederberg

7f. Applications of Artificial Intelligence for Chemical Inference. VI. An Approach to a General Method of Interpreting Low Resolution Mass Spectra with a Computer.
Helv. Chim. Acta., 53, 1394 (1970)
By A. Buchs, A. B. Delfino, A. M. Duffield, C. Djerassi, B. G. Buchanan, E. A. Feigenbaum and J. Lederberg

7g. The Application of Artificial Intelligence in the Interpretation of Low Resolution Mass Spectra.
Advances in Mass Spectrometry, 5, 314, (1970)
By A. Buchs, A. B. Delfino, C. Djerassi, A. M. Duffield, B. G. Buchanan, E. A. Feigenbaum, J. Lederberg, G. Schroll and G. L. Sutherland.

7h. Applications of Artificial Intelligence forChemical Inference. VIII. An Approach to the Computer Interpretation of the High Resolution Mass Spectra of Complex Molecules. Structure Elucidation of Estrogenic Steroids.
J. Amer. Chem. Soc.,
By D. H. Smith, B. G. Buchanan, R. S. Englemore, A. M. Duffield, A. Yeo, E. A. Feigenbaum, J. Lederberg and C. Djerassi

7i. An Application of Artificial Intelligence to the Interpretation of Mass Spectrometry.
By B. G. Buchanan, A. M. Duffield and A. V. Robertson,
Mass Spectrometry, B. W. G. Milne, Editor, John Wiley and Sons, New York, 1971. pp. 121-178.

8. D. H. Smith, A. M. Duffield - d C. Djerassi, Org. Mass Spectrom., Submitted for publication.

9. Anal. Chem., 42, 1122 (1970); W. E. Reynolds, V. A. Bacon, J. C. Bridges, T. C. Cobum, B. Halpern, J. Lederberg, E. Levinthal, E. C. Steed, and R. B. Tucker.

(4) Cell Separator Project. Prepared by L. A. Herzenberg and E. Levinthal.

The Cell Separator Project, currently in its third year, is developing the equipment and techniques for automated high speed sorting of functionally different human and other mammalian cells. This project involves an interdisciplinary group of biologists under the direction of Dr. Leonard Herzenberg, Professor of Genetics as well as a staff of engineers and supporting technicians located in the Instrumentation Research Laboratory under the direction of Dr. Elliott Levinthal, Senior Research Scientist. The biomedical objectives include:

(a) Separation of the various cells involved in the humoral (antibody) and cell mediated (hypersensitivity) immune response. Antigen binding cells, thymus derived cells, bone-marrow derived cells, cells with specific immunoglobulins on their surface will be detected and viably separated after appropriate immunofluorescent surface staining.

(b) Study the binding kinetics and affinities of cell surface molecular probes like Concanavalin A, other phytoagglutinins, and aniline napthalene sulfonate (ANS) with the aim of distinguishing and separating different cell types including perhaps malignant from normal cells.

(c) Select somatic cell intra or interspecific hybrids after Sendai virus fusion by nondestructive positive immunoselection.

(d) Detection of fetal red blood cells in maternal circulation.

(e) Differentiating leucocytes and other cell types in normal and pathological body fluids.

(f) Detection of tumors by reaction of circulating tumor cells with fluorescent labelled tumor specific antigens.

(g) Other related applications on an opportunistic basis, as it becomes apparent that such work is worthwhile.

The instrumentation effort involves the development of the optical flow system and separator components as well as the control electronics and software, for the cell separator. The instrument consists of a nozzle assembly designed to provide examination of single particles flowing in a narrow stream and a pulsing and deflection assembly designed to physically separate particles of interest from other constituents of the stream.

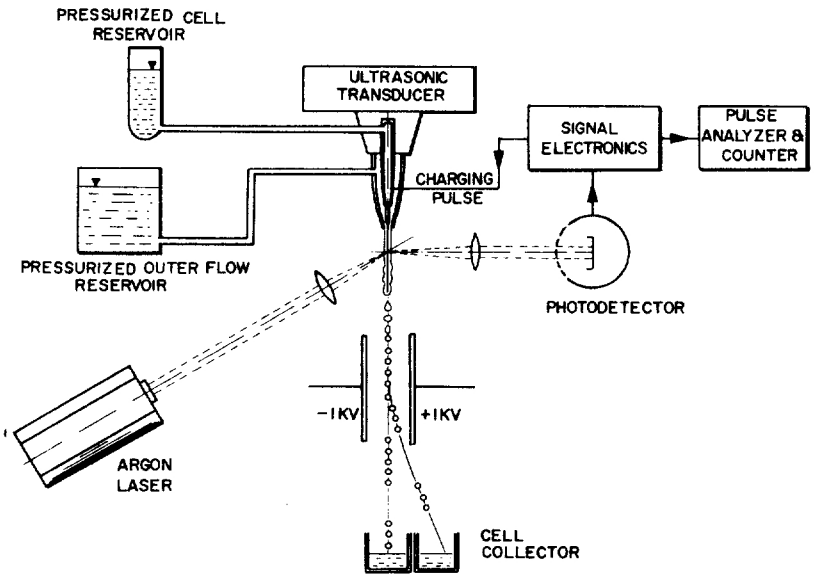



Figure Cell Separator-1

Simplified Block Diagram of
Cell Sorter

(a) Background

In the same way that many of the spectacular advances in molecular biology were impossible until it became possible to separate functionally different molecules by such techniques as electrophoresis and ultracentrifugation, advances in cell biology have awaited development of instrumentation able to separate large numbers of functionally different cell types. Many have attempted to do this by bulk methods, but the resolution of such methods is limited. It appeared to us that the best approach to the problem was to inspect the cells individually and sort them on the basis of these individually measured characteristics. We have found that a number of separations of biomedical interest could be accomplished using fluorescent markers on the desired cells and electronically deflecting drops containing the various types of cells into separate containers. The only other workers with a similar approach are Fulwyler, et al., who have demonstrated electronic cell sorters operating on volume (1) and are now building a unit able to operate on both volume and fluorescence (personal communication). Several workers have described cell analysis systems based on flow techniques similar to those used in our equipment (Van Dilla, et al. (2), and Kamentsky et al. (3).

Biophysics, Inc., ("Cytograph" and "Cytofluorograph") and Technicon Instruments Corp. ("Hemolab D") now market cell analysis instruments using flow techniques but these instruments do not have separation capability.

(1) Fulwyler, M. J., Glascock, R. B., and Hiebert, R. D. "Device Which Separates Minute Particles According to Electronically Sensed Volume". Rev. Sci. Inst. 40: 42, 1969.

(2) Van Dilla, M. A., Trujillo, T. T., Mullaney, P. F. and Coulter, J. R. "Cell Microfluorometry: A Method for Rapid Fluorescence Measurement". Science 163: 1213, 1969.

(3) Kamentsky, L. A., Melamed, M. R., and Derman, H. "Spectrophotometer: New Instrument for Ultrarapid Cell Analysis". Science 150: 630 (1965).

Since starting the major effort on this project in 1968 a number of significant successes have been achieved in both the technical development as well as the biological applications. The following bibliography provides a summary of these results:

(1) W. A. Bonner, H. R. Hulett, and L. A. Herzenberg. "Highspeed Sorting of Fluorescence Labeled Cells", Fed. Proc. 30, 699 Abs. 1971.

(2) L. A. Herzenberg. Chairman, Conference Session, "Fluid Transport Methods", Engineering Foundation Research Conference on Automatic Cytology, New England College, Henniker, New Hampshire, July 26-30, 1971.

(3) L. A. Herzenberg and R. G. Sweet. "Fluorescence Activated Cell Sorting", presented at Engineering Foundation Research Conference on Automatic Cytology, New England College, Henniker, New Hampshire, July 26-30, 1971.

(4) L. A. Herzenberg, T. Masuda, and M. Julius. Invited paper on Symposium on Thymus and Bone Marrow Cells in the Immune Response, Annual Meeting of the American Society for Hematology, San Francisco, Dec. 4, 1971.

(5) L. A. Herzenberg. Invited participant in symposium on Cell Purification by Use of Surface Antigens and Receptors, Midwinter Conference of Immunologists, Asilomar, California, Jan. 22, 1972.

(6) L. A. Herzenberg, R. G. Sweet, M. Julius, T. Masuda, and R. A. Merker. Invited paper, "Fluorescent Activated Electronic Cell Sorting in Immunology", to be presented at Biophysical Society Annual Meeting, Toronto, Canada, Feb. 19, 1972.

(7) W. A. Bonner, H. R. Hulett, R. G. Sweet, and L. A. Herzenberg. "Fluorescence Activated Cell Sorting", Rev. Sci. Inst. 43, 404, 1972.

(8) L. A. Herzenberg in "Immunological Intervention", Jonathan Uhr and Maurice Landy, eds. Academic Press. (In press, 1971).

(9) M. Julius, T. Masuda and L. A. Herzenberg. "Isolation of Functional Antibody Forming Cell Precursors Using a Fluorescence Activated Cell Sorter". (In preparation).

(b) Rationale

The rationale behind our approach was simply that separation of large numbers of functionally different cells would make it possible to conduct many important studies on specific cell functions. In order to acquire large numbers of cells in a reasonable time, rapid observation was necessary. This effectively eliminated scanning systems and limited us to use of only a few parameters. A flow system was a logical way to look at the cells rapidly and sequentially. Use of fluorescent techniques provided readily available means of differentiating between many funtionally different types of cells, but required incorporation of a laser light source in order to provide sufficient signal-to-noise ratio to detect the cells. Electronic sorting techniques originated by Sweet and adapted by Fulwyler (see Background) provided us with a basis for developing a rapid, accurate method of sorting desired cell types as a function of fluorescent information.

(c) Methods and Procedures

The procedure involved in the use of the cell separator presently involves three steps:

A. Preparation of cells occurs over a period of hours or days depending on the experiment. Cells of interest, immunologically sensitive cells for example, are collected and tagged with a fluorescent marker.

B. This single cell suspension is then brought to the instrument and analyzed and/or divided into fractions. This latter procedure involves a certain amount of subjective decision making by the experimentor and machine operator. Data on the cells, e.g. distribution of several fluorescent and low and wide angle light scattering amplitudes is acquired before separation for analysis and then thresholds and/or windows for the various parameters are set for separation. Data on the cells, usually the distribution of their fluorescent signal amplitudes, is acquired before or during separation. The resulting fractions are sometimes reexamined via the cell separator or by microscope. More frequently the fractions are tested by the Jerne plaqueing technique or reinjection into irradiated hosts.

C. Finally, the data collected from the cell separator (stored on the computer) and resulting biological procedures are correlated statistically.

The scientific gains to be made by collaboration with SUMEX are both improved operations under B by on-line coupling of the instrument to a computer to allow interactive decisions to be made during separations and under C by more sophisticated statistical analysis of the data.

(d) Significance

Separations of functionally different, viable cells permit their characterization and studies of their function and interactions. It is as crucial a step in cell biology as precise methods for protein and nucleic acid separations in molecular biology. Progress in understanding the immune system is being speeded by separation of functional cells of the lymphoid system.

Development of rapid machine assisted hematological, and cell pathological diagnostic methods will increase clinical laboratory capability and decrease the cost of current manual methods.

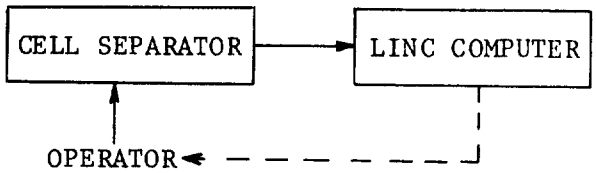
(e) Computer Interaction

As mentioned, in the background section, there are only one or two other groups successfully pursuing this approach to cell characterization and separation. This is due to the requirement for success of a juxtaposition of skilled biological and engineering personnel. Stanford is also especially fortunate in having a very active program in computer development.

The cell separator project is currently using a dedicated small computer on-line (LINC) as well as the ACME system on a less regular, off-line basis.

There are two levels of interaction between the cell separator(s) and general purpose computers.

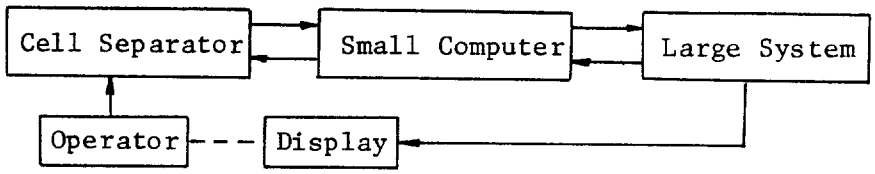
A. The on-line, hook-up of each instrument to a small computer provides a data collection and analyzer system for preliminary results. This is currently in use full time. It allows 4 to 8 hour experiments with assurance that the data is meaningful at each step of the experiment. The human operator is presently the primary link in the feedback loop from the data collection system and the experimental equipment.




Such interaction requires feedback times in the range of a few minutes. More rapid feedback between the small computer and cell separator is envisioned as the characteristics and uses of the instrument become better understood.

B. The second level of interaction, based on the capabilities of a larger computer system, will provide more sophisticated analysis of results.

C. A third level would use the larger computer to enhance the functioning and software developments necessary for the optimimum use of the small computer.




Multiparameter analysis of cell distributions is one of the features which would be of immediate benefit to the project.

Implicit in our need for multiparameter analysis, is a feedback time scale which allows modification of experimental procedures. For example, a three-dimensional display of 2 or 3 minutes of data offers the opportunity of more precise manual adjustment of separation parameters. Also, a numericalintegration of areas under three-dimensional curves could actually be used to automatically, and continuously readjust these separation controls. The result of such feedback will be more consistent and more precise definition of the cell populations separated and studied. The large system's language capability can dramatically increase the feasibility of "programming" the instrument to carry out various experimental regimes. At present, the effort involved in programming the small computer has forced the project to use a standard set of software routines and tailor the experiment to fit these. Increasing the coupling between the small computer and cell separator has received limited emphasis because of the software developments required.

After some years of experience with realtime use of computing facilities, we feel that the above uses are not only possible, but feasible without our taking on the role of a major computer development project ourselves.

## (5) Average Evoked Potentials and Perception - prepared by Bert S. Kopell and Walton T. Roth

### (a) Problem Statement

The Laboratory of Psychophysiology at the Palo Alto VAH has been studying human neurophysiology as related to psychiatric disturbance and the action of medications for about eight years. We have even been able to measure drug effects neurophysiologically at doses below the threshold for subjective effects in the cases of cortisol (Kopell et al., 1970a) and thyroid hormone (Kopell et al., 1970b). A major emphasis has been on finding neurophysiological measures of perceptual processes. Very little is known about the realtionship between subjective perception and its neurophysiological counterpart, but there is some indication that the average cortical evoked response afford an objective index of perceptual process and attention (Satterfield, 1965). Various perceptual processes are known to be disturbed or altered in psychiatric disorders and by psychoactive drugs. Objective neurophysiological measurements of subjective perceptual processes may have the potential for giving prognostic indicators regarding psychiatric decompensation or the predilection for alcohol or drug addiction.

### (b) Background and Rationale

Our primary interest is in the electrocortical activity in response to sensory stimulation. The averaged cortical evoked response has been shown to be affected by various physiological and psychological parameters including medications, alcohol, attention, and psychiatric disturbances. A small electrocortical response is generated with any sensory stimulation but this cannot be seen in the EEG as measured directly from the scalp. Computer averaging of the EEG over several stimulations, however, can be utilized to enhance the size of the signal and make it available for study. Recently various members of our laboratory have used the classic LINC and the PDP-12 for this purpose (Gips et al., 1972). While these computers are an advance on the technology of 10 years ago, they do have limitations. Just as these computers have provided for more sophisticated experimentation as compared to the special purpose computers, the proposed system will allow us to make a qualitative and quantitative advance in the complexity and sophistication of our investigations.

A particular problem in studying perception in this manner is presented by the fact that perception is an evanescent and continuous process and the evoked response is the stochastic result of an accumulation of this process over time. Very rapid on-line statistical manipulations of the EEG are needed if one is going to achieve a better understanding of the perceptual process utilizing this technique. With this proposed computation power, one can obtain a closer estimate of the perceptual process from second to second rather than only being able to talk about the "average" process over time. Indeed, further knowledge of the nature of the second to second variations is crucial in understanding the perceptual process.

(c) Methods and Procedures

The data acquisition methods that are needed in our experiments are in the order of 10 KHz and above sampling rate over a period of up to an hour. Though the PDP-12 can acquire data at this rate, it cannot either store or perform sufficient analytic operations on data at this rate. A solution to this problem is to use the PDP-12 as a peripheral to a larger computer (PDP-10) and perform the sampling and analog to digital conversion with the PDP-12 and the analysis and storage with the PDP-10.

An example would be the recording of the EEG from several locations on the scalp of a subject while he is viewing a given set of stimuli. By comparing successive responses to the cumulative response of previous experiments or a given segment of the current experiment, one can determine if he has been able to discriminate a change in stimulus intensity or if his attentional state with regard to the stimuli is changing. The comparison might require doing a statistical procedure such as the Pearson Product Moment Correlation or Fourier Analysis between the digitized EEG for the last second recorded and a previous similar sample for each of the six or eight electrode placements being used. The results of this on-line statistical analysis might then be used to determine certain qualities of the next stimulus to be presented. In this way we can have an on-line feedback controlled perceptual experiment based on a statistical analysis of the EEG. This is not possible with the PDP-12 alone because of the time and data storage requirements.

The major need for the PDP-10/12 configuration is to provide for adequate computer ability to perform on-line analytic procedures of high rate physiological samples and then use these results to alter the stimulus properties. This computer configuration will also allow us to produce complex visual stimuli (such as animated figures) on a computer driven cathode ray tube and simultaneously measure the neurophysiological responses.

The configuration needed includes a PDP-12 which we have from other funding sources. All interfacing with the PDP-10 must be provided for by this grant. This is to include an I/O capability of 10 KHz 12 bits wide (10,000 12 bit PDP-12 words per second) probably implemented via the PDP-12 accumulator and a single I/O command. In addition, a parallel remote graphic display terminal with CRT, keyboard, and hardcopy, which can be used to access the PDP-10 independent of the PDP-12 at least 110 baud is needed. Since our laboratory is physically about two miles from the proposed location of the PDP-10, adequate and reliable transmission facilities must also be provided.

These facilities will include 40K baud telephone lines and a remote PDP-11/05 data concentrator. If a 4:1 data compression is possible (a likely case), a single telephone line with synchronous modems will suffice. Otherwise one, up to an unlikely three, additional units will be needed. The CRT keyboard would be standard.

(d) Significance

The experiments that are being performed in our laboratory are designed to increase our knowledge of the action of drugs such as marihuana, alcohol, heroin, and methadone. Electrophysiological data correlates with central nervous system processes that are independent of language and other social response variables. Thus, such data can be generalized to drug users from different backgrounds. In addition, information obtained by physiological methods is appreciated by the general public as being objective and trustworthy, and can be used to reduce the credibility gaps between the scientific community and drug users.

In the case of marihuana little is known about its effects on attentional processes, which are of obvious relevance to such activities as driving an automobile. Many users claim that they can control their mental state while intoxicated with marihuana and perform normally if need be. With neurophysiologic measures of attention the claims can be objectively tested.

Addictive drugs such as heroin or alcohol raise other questions. For example, why do some persons become heavily dependent after experimenting with these drugs, while others do not, despite equivalent experimentation? Obviously socioeconomic and environmental factors play a role, but there also may be physiological differences in susceptibility. Another question is what is the most useful treatment program for a given individual? The individual differences we are looking for may allow rational decisions to be made as to whether a heroin addict should be put on a program of abstinence or methadone replacement, or whether neither of these alternatives is likely to succeed. Since there is a center for the treatment of heroin addicts here at Palo Alto Veterans Administration Hospital, we have a readily available source of experimental subjects that can be followed long enough to test prognostic predictions. Another ward specializes in the treatment of alcoholics, and it has provided a place for us to study an experimental cycle of intoxication and withdrawal under controlled conditions. In the case of alcoholics there are many pressing questions that may be approached neurophysiologically. As in the case of heroin addicts, there is the problem of differences of susceptibility with its implication for prognosis and the choice of treatment. Also there is the question of whether occult brain damage from chronic abuse of alcohol is present in a given patient. The determination of an alcoholic deficit has important medico-legal implications, as well as an implication as to how much rehabilitation is possible.

Thus, the investigations that we are undertaking are very important in view of the expanding use of drugs of all kinds. Aside from the obvious theoretical yield from studying the neurophysiological actions of psychoactive compounds, there are immediate social and treatment implications.

(e) Relationship to Other Work

Our work involving alcohol and heroin addicts is being performed in conjunction with Dr. Zarcone and Dr. Dement, members of the faculty of the Department of Psychiatry. They are especially interested in mechanisms of sleep dysfunction and hallucinosis in alcoholics in relation to serotonin metabolism. Our marihuana work has enjoyed the collaboration of Dr. Tinklenberg, also of the Department of Psychiatry, who is interested in measuring psychological changes simultaneously with neurophysiological ones. He has developed some special techniques for measuring memory and attention in drug states.

There are very few centers in the world which do work of a nature similar to ours. Dr. M. Buchsbaum at NIMH has been investigating evoked response correlates of perceptual process for several years, and has provided us with some valuable techniques. Dr. C. Shagass of the University of Pennsylvania Medical School has been a leader in studying aspects of the evoked responses that are relatively independent of attention and memory in patients with mental disease and patients under the influence of drugs. The design of some of our studies on alcoholism is based on work being done at St. Elizabeth's Hospital in Washington, D.C., by Dr. N. Mello under the direction of Dr. Morris Chavetz.

H. BUDGET

1. Detailed Budget for First 12-Month Period

2. Budget Estimates for All Years of Support

3. Explanation

SECTION II – PRIVILEGED COMMUNICATION

## DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

FROM: 8 - 1 - 73 THROUGH: 7 - 31 - 74

| DESCRIPTION (Itemize) PERSONNEL | | TIME OR EFFORT %/HRS. | AMOUNT REQUESTED (Omit cents) | | |
|---|---|---|---|---|---|
| NAME | TITLE OF POSITION | | SALARY | FRINGE BENEFITS | TOTAL |
| Joshua Lederberg | PRINCIPAL INVESTIGATOR | 10 | 0 | 0 | 0 |
| Edward Feigenbaum | Associate Investigator | 10 | 0 | 0 | 0 |
| Thomas Rindfleisch | SUMEX Facility Head | 100 | | | |
| Ron Jamtgaard | | 50 | (Details of Salary Budget | | |
| Gio Wiederhold | | 90 | are submitted in a separate | | |
| Lee Hundley | | 100 | letter) | | |
| 9 - Systems Programmers | | 900 | | | |
| 1 - Applied Mathematician | | 100 | | | |
| 2 - Engineers | | 200 | | | |
| 3 - Technicians | | 300 | | | |
| 3 - Operations Staff | | 300 | | | |
| 1 - Secretary | | 100 | | | |
| 1 - Administrative Aide | | 100 | | | |
| 2 - Grad. Student R.A.'s plus summer help | | 100 | | | |
| Total (24.6FTE) | | | 375,000 | 63,750 | 438,750 |

CONSULTANT COSTS 2,500

EQUIPMENT Lease of PDP-10 System (Purchase Price--$1,744,750 less 10% assumed Educational discount plus 5% Calif. Use Tax times DEC lease factor of 2.2% per month=$36,275/month plus miscellaneous features on hardware to be leased. 435,300*

Purchase graphics station--$8,000; small machine equipment peripherals $26,000; communications hardware--$6,000. 700

40,000*

SUPPLIES

| | | | | |
|---|---|---|---|---|
| Office Supplies | 4,000 | Computer Supplies | 6,000 | 10,000 |
| Books & Publications | 200 | Office Telephone | 7,000 | 7,200 |
| Reproduction Expense | 2,500 | Technical Services | 2,000 | 4,500 |
| Engineering Supplies | 15,000 | | | 15,000 |
| Postage & Freight | 2,500 | | | 2,500 |

TRAVEL

DOMESTIC 5 East, 5 Midwest, 6 West Coast 4,400

FOREIGN

PATIENT COSTS (See instructions)

ALTERATIONS AND RENOVATIONS

Air conditioning, false flooring, etc., needed for hardware installation. 45,000

OTHER EXPENSES (Itemize) Computer service from SUMCCF 24,000

Maintenance: For PDP-10 System--$84,600; for service contracts on graphics, peripherals, and communications hardware--$9,400. 94,000

Communications Costs (Transmission lines and modems) 12,000

Staff Training 2,000

TOTAL DIRECT COST (Enter on Page 1, Item 5) 1,137,850

INDIRECT COST (See Instructions)

DATE OF DHEW AGREEMENT:

_____ % S&W*

46 %TDC* pending

☐ WAIVED

☐ UNDER NEGOTIATION WITH:

*IF THIS IS A SPECIAL RATE (e.g. off-site), SO INDICATE.

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SECTION II – PRIVILEGED COMMUNICATION

**BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE**
**DIRECT COSTS ONLY (Omit Cents)**

| DESCRIPTION | 1ST PERIOD (SAME AS DETAILED BUDGET) | ADDITIONAL YEARS SUPPORT REQUESTED *(This application only)* | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2ND YEAR | 3RD YEAR | 4TH YEAR | 5TH YEAR | 6TH YEAR | 7TH YEAR |
| PERSONNEL COSTS | 438,750 | 464,630 | 491,990 | 520,930 | 551,530 | | |
| CONSULTANT COSTS *(Include fees, travel, etc.)* | 2,500 | 2,500 | 2,500 | 2,500 | 2,500 | | |
| EQUIPMENT Lease | 436,000 | 436,000 | 436,000 | 436,000 | 436,000 | | |
| EQUIPMENT Maint. | 94,000 | 94,000 | 160,000 | 160,000 | 160,000 | | |
| EQUIPMENT Purchase | 40,000 | 40,000 | 54,000 | 64,000 | 64,000 | | |
| SUPPLIES Communications | 12,000 | 16,000 | 16,000 | 18,000 | 18,000 | | |
| SUPPLIES Supplies | 39,200 | 40,000 | 41,000 | 42,000 | 43,000 | | |
| TRAVEL DOMESTIC | 4,400 | 4,400 | 4,000 | 4,200 | 4,200 | | |
| TRAVEL FOREIGN | | | | | | | |
| PATIENT COSTS | | | | | | | |
| ALTERATIONS AND RENOVATIONS | 45,000 | --- | --- | --- | --- | | |
| OTHER EXPENSES Computer Services | 24,000 | 24,000 | 24,000 | 24,000 | 24,000 | | |
| OTHER EXPENSES Training | 2,000 | 1,000 | 1,000 | 1,000 | 1,000 | | |
| TOTAL DIRECT COSTS | 1,137,850 | 1,122,530 | 1,230,490 | 1,272,630 | 1,304,230 | | |

**TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD** *(Enter on Page 1, Item 4)* → $ 6,0Ø7,730

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

1. Lease of equipment covers a PDP-10 Computer System.
2. Personnel salaries are increased at 5% per year. Staff benefits are 17% in Year 1 and 1% per year greater in each subsequent year.
3. Alteration and renovation funds of $45,000 are requested for air conditioning and false floors needed for hardware installation.
4. The PDP-10 maintenance contract will be changed from 12 hours, 5 days per week to 24 hours, 7 days per week in Year 3. This will provide the backup capability needed by the Service System, and -versa.

BUDGET ESTIMATES FOR PDP-10 SYSTEM:

| | Purchase Price | Monthly Maint. (12 hrs 5 days) |
|---|---|---|
| Central Processor<br>KI-10 incl. Operator's Console | $ 380,000 | $ 555 |
| Memory System<br>8 x ME10, 8 x 16k words | 400,000 | 1,336 |
| Auxillary Memory System<br>4 x ME10 and DT04C | 225,000 | 748* |
| Keyboard Terminals(16)<br>Hardcopy & CET, to be selected (16 x 3K) | 48,000 | 320 |
| Memory Bus Swapping Drum System<br>RM10 B & Controller | 83,000 | 265 |
| Memory Bus Disc System<br>4 x RP03 Disc & Controller | 150,000 | 826 |
| Input/Output Bus Peripheral System<br>Tape Systems, 3 x TU10, (9x7 track)<br>& 1 DEC TU56 & Controllers | 64,850 | 338 |
| Asynchronous Communication System<br>DC10 System for Keyboard Terminals | 37,500 | 110 (A) |
| SATELLITE COMPUTERS: Includes intercomputer communications and --<br>Multiplexed Memory System | | |
| PDP 11/45 #1: 8K | 74,050* | 547* (B) |
| #2: 4K | 16,450 | 195 |
| #3: 4K | 16,450 | 195 |
| #4: 8K (incl. RK11 and RF11 Disc, & PC11 Punch and tape) | 56,450 | 484* |
| 10/11 Interface | 70,000 | 500* |
| MX10 Memory Multiplexor | 4,500 | 15* |
| Peripherals<br>LP10C Line Printer, CP10A, CR10D Card Punch & Reader | 118,000 | 462* |
| Sub Totals | 1,744,250 | 6,896 |
| Assume 10% Educational Discount | - 174,425 | |
| Net | 1,569,825 (Not including sales tax) | |

Options:

| | | |
|---|---|---|
| 1) Memory System(4 x ME10) | 200,000 | 668 |
| 2) Terminal Communications(DP11DA's & DP11DC's) | 7,900 | 115 a) |
| 3) Sync Communications System(DC-75) | 50,000 | 250* b) |
| | 257,900 | 1,033 |
| (Incl. Option 1) TOTAL | $ 1,769,325 (Not incl. sales tax) | |

a) Added to A above.
b) Deletes $7,400 of B above.

3. Explanation

a. Major Assumptions

The five-year budget request has been prepared with the following major assumptions:

(1) SUMEX will include a PDP-10 KI-10 Processor with 192K words of core plus four PDP-11 satellite processors. Additional "user owned" remote satellites will be attached by collaborators.

(2) It is assumed that the Medical Center will opt to replace the 360/50 with a PDP-10 for the Service Facility. SUMEX personnel will mount a PL-type language on the PDP-10 in order to provide a transition from the 360/50 for current software.

(3) A 10% education discount from list price on the PDP-10 has been assumed. A higher discount may be negotiable.

(4) The staff of SUMEX will evolve from the existing groups which have demonstrated competence in tackling and solving biomedical computing problems.

(5) University authorization and funding of modifications to existing machine room space are assumed. Detailed and formal proposals will not be available for consideration by the University prior to submission of this proposal.

(6) We expect that the full lease costs associated with the SUMEX PDP-10 System will be covered by the proposed grant. A full pay-out, 5-year lease is proposed.

(7) In general, collaborators will provide their own laboratory hardware and applications programming. SUMEX will provide host computer services, system software support, and some assistance in interfacing to the host.

(8) A beginning date of August 1, 1973, is proposed. This coincides with the end of the current ACME grant.

b. Notes on Budget Elements -- Year 1

The explanation of each budget element requested for Year 1 is presented below.

Salaries: The salaries included in the budget are based upon the following manpower assumptions:

(1) SUMEX will have a Facility Director, a senior technical project leader, and a one-half time administrative manager on its management team. It is assumed that one project leader might be given the small machine support task while the other would handle the extended realtime support tasks. A total of 10 systems programming personnel are included in the budget. This will make a tight fit in Year 1 when an estimated 5.5 man-years will be devoted to the transition of a PL-type language

to the PDP-10. The number of programmers covered by the budget reflects our concern with becoming "too large" to be manageable as a research team, as well as recognition of the large effort required to achieve our goals.

Five man-years of engineering and technician effort are budgeted. Their primary efforts will involve design, fabrication, installation, and maintenance of special interfaces and communications lines. Much of the collaborators' work described in the proposal will be dependent upon interfacing new hardware to computing systems. For example, two scanning devices are to be acquired by collaborative projects and will be interfaced to machines in the Resource. Detailed planning for this group will be dependent upon future decisions in the participating projects.

The Operations staff will operate, by assumption, both the SUMEX and SUMCCF systems. Since the SUMEX operation will involve only a few research groups, the operations tasks should be relatively light during most hours of operation. If the SUMCCF budgets four full time equivalents and the SUMEX budgets three, then it is feasible to cover all 21 shifts per week. The operations staff figure includes an Operations Manager who would be shared by the two facilities. All of these estimates are based upon the assumptions that SUMEX and SUMCCF will be situated in a common area and that shared operating staffs are desired by computing coordinators in the Center.

The balance of the staff will be comprised of an applied mathematician, one administrative aide, one secretary, plus occasional part time help, including graduate student research assistants. The applied mathematician is requested in order to assist collaborators and core research efforts. Such assistance should prove especially valuable in developing new algorithms, appraising new techniques for image processing, etc.

(2) Staff Benefits: The standard rate for the University's FY1974 is 17%.

(3) Training, Consulting, Travel, and Publications: The training budget of $2,000 will be used to make the staff better acquainted with PDP-10's, various satellite processors, and new software techniques. The consulting item of $2,500 is an estimate of the first year's needs. It is double the current year budget for ACME outside consulting due to the complexity of tasks to be undertaken. The travel time should provide eight trips to the east coast, 3 to the midwest, and 6 on the west coase ($3,200 + 900 + 400 = $4,400). The travel funds will be used to exchange information with other research centers, attend training sessions, disseminate information, and investigate possible network participation.

(4) Materials and Supplies: These estimates are based entirely upon the experience gained in the ACME Grant. The items are as follows:

| Item | Est. Cost |
|---|---|
| Office Supplies | $ 4,000 |
| Computer Operations Supplies | 6,000 |
| Publications | 2,500 |
| Postage and Freight | 2,500 |
| Books and Periodicals | 200 |
| Office Telephone | 7,000 |
| Technical Services | 2,000 |
| Engineering Supplies | 15,000 |
| Total | $ 39,200 |

(5) Communications Costs: Collaborators in this proposal are situated from 100 feet to 2.5 miles from the existing machine room. This budget element will be used to provide high data rate communications lines as required by each research project. Dr. Kopell's group is located in the Palo Alto Veterans Hospital which is about 2.5 miles distant. The mass spectrometer used by the DENDRAL group is situated in the Chemistry Building which is more than 1,000 feet from the machine room. Communications will be handled by a combination of Telephone Company lines and local hardwire connections. Specific transmission requirements must precede detailed estimates. A 40kb telephone line connecting VA Hospital and the machine room has been priced at $596 per month plus an installation fee of $950. This budget element will also include some modem rentals. We anticipate the announcement of a number of commercially available modems which will accommodate bandwidths and data rates of interest.

(6) Equipment Lease: The hardware described in Section E of the proposal is a KI-10 System with a list purchase price of $1,744,750. A full payout lease has been offered by DEC at 2.2% of the purchase price per month. A 10% educational discount has been assumed; no negotiation has been held with DEC on this point. To this net price, the 5% California Use Tax must be added. The lease rate is calculated as $1,744,750 less 10% plus 5% tax at 2.2% per month giving a monthly rate of $36,274. At the end of five years, the equipment will be owned. The lease rate does not include maintenance. Additional equipment was presented in Section E as "options". The options included additional core, terminal communications add-ons, and a synchronous communications system. In view of the competing demands for funding, these items have been excluded from the budget. If future arrangements with DEC permit the acquisition of more equipment within the budgeted dollars, then optional items will be added to the configuration. The optional items were initially part of the required configuration but were set aside in order to obtain a balance between hardware and personnel within an overall budget which was deemed feasible.

(7) Maintenance of Equipment: The primary hardware maintenance contract will be with DEC. Using DEC's standard 5-day 12-hour maintenance contract for all items in the budgeted configuration results in monthly charges of $7,053. This figure includes estimates for six hardware items on which standard maintenance charges have not been announced. This level of maintenance may be adequate for the research activity of SUMEX. If more hours are needed in order to provide better backup support for the SUMCCF, the 5-day 12-hour assumption will be re-evaluated. In addition to the $84,600 for PDP-10 system maintenance, the budget includes $9,400 for maintenance contracts covering graphics stations, additional small machine peripherals, communications hardware, etc.

(8) Other Equipment: In addition to the items identified in the PDP-10 system, SUMEX will require equipment for its engineering group, communications hardware, and graphics support. In a research and development program of the type proposed, equipment needs will arise which cannot be specified today. A few examples of the types of hardware which are likely to be required include: complete graphics stations for $8,000; special hardware interfaces for small machines for $10,000; expansions to the small machine equipment pool for $16,000; and communications hardware for $6,000.

(9) Alterations and Renovations: $45,000 are included in the budget in order to provide adequate facilities in which to house the SUMEX hardware. Extension of the existing space occupied by the ACME Machine Room will be needed. The University is being asked to provide structural modifications. This proposal includes the funds to provide necessary air conditioning, false floors, cable tray access, and some special electrical provision for the computing facilities. The cost estimate is rough at this time. Efforts will be made in the near term to obtain requisite approvals from the University plus the funding for the building modifications. Also, more detailed estimates of special facilities associated with the hardware will be prepared.

## I. FUTURE PLANS

Our plans beyond the requested five-year period of support call for hardware dedicated to the types of user projects listed in our proposal. We expect that the central hardware will continue to be available as a research resource for a limited number of users. New projects presumably will emerge calling for development of new computing techniques. The current talents of the staff will be deepened and new skills will be developed which we assume will prove highly useful in solution of some of tomorrow's problems.

A lesson from the ACME experience is that technological change, as evidenced by the minicomputer revolution, must be carefully monitored. We hope to anticipate major changes more accurately so that new developments will integrate well with local research efforts. We would expect, based upon current trends, to involve ourselves with computer architectures other than the initial selection for this research resource.

J. APPENDICES

1. ACME User Publications

2. Biographical Sketches

ACME Note

Papers Written By ACME Users

APUB-9
Erica Baxter
February 23, 1972

This list contains papers voluntarily reported to ACME.


Balikian, H., A. Brodie, S. Willoughby, A. Dowdy, G. Nokes, M. Weinberger, and J. Luetscher, "Response of Plasma Aldosterone Concentration in Hypertensive Patients to Changes in Posture and Sodium Intake," CLIN. RES., vol. 17, p. 141, Jan. 1969, (abstract).

Barnett, C., J. Jackson, and H. Cann, "Child Spacing and Its Implications for Population Control in Highland Guatemala Community," presented at the 28th Annual Meeting of the Society for Applied Anthropology, Mexico City, Mexico, Apr. 1969.

Beatrice, E., I. Harding-Barlow, and D. Glick, "Electric Spark Cross-Excitation in Laser Microprobe-Emmission Spectroscopy for Samples of 10-25 Micron Diameter," APPLIED SPECTROSCOPY, vol. 23, pp. 257-259, 1969.

Beatrice, E. and D. Glick, "A Direct Reading Polychromator for Emission Spectroscopy," APPLIED SPECTROSCOPY, vol. 23, pp. 260-263, 1969.

Beatrice, E., D. Glick, E. Scribner, L. Alterton, R. Honey, I. Harding-Barlow, N. Peppers, and R. Rosan, "Q-Switched Ruby Laser for Emission Microspectroscopic Elemental Analysis," ANAL. CHEM., vol. 40, pp. 1178-1182, 1968.

Becker, J., Y.T. Thathachari, P.G. Simpson, "Molecular Conformation of L-DOPA," BIOCHEM. BIOPHYS. RES. COMM., Vol. 41, pp. 444-449, 1970.

Bellville, J., J. Green, and W. Forrest, Jr., "Respiratory Effects of Etomide and Codeine," CLIN. PHARM. THERAP., vol. 9, pp. 142-151, 1968.

Bellville, J. and W. Forrest Jr., "Respiratory and Subjective Effects of d and l Pentazocine," CLIN. PHARM. THERAP., vol. 9, pp. 142-151, 1968.

Bellville, J. and J. Seed, "A Comparison of the Respiratory Effects of Dextropropoxyphene and Codeine in Man," CLIN. PHARM. THERAP., vol. 9, pp. 428-434, 1968.

Bellville, J., W. Forrest, Jr., J. Stevens, and E. Beer, "The Hypnotic Effects of Ethchlorvynol and Secobarbital in Man," CLIN. PHARM. THERAP., vol. 9, pp. 625-530, 1968.

Bellville, J., L. Escarraga, S. Wallenstein, and R. Houd, "The Respiratory Effects of Codeine and Morphine in Man," CLIN. PHARM. THERAP., vol. 9, pp. 435-441, 1968.

Bellville, J., G. Fleischli, and J. Defares, "A New Method of Study Regulation of Respiration--The Response to Sinusoidally Varying CO2 Inhalation," COMPUTERS FOR BIOMEDICAL RESEARCH, vol. 2, no. 4, pp. 329-349, June 1969.

Bellville, J., G. Fleischli, and G. Attura, "Servo Control of Inhaled Carbon Dioxide," J. APPL. PHYSIOL., vol. 24, pp. 414-415, 1968.

Bernfield, M. and P. Maenpaa, "Quantitative Variation in Serine Transfer Ribonucleic Acid during Estrogen-Induced Phosphoprotein Synthesis in Rooster Liver," BIOCHEMISTRY, vol. 8, pp. 4926-4935, 1969.

Bernfield, M., "Chromatographic Properties of Pyrrolidone Carboxylate-tRNA," submitted to J BIOLOGICAL CHEM.

Bernfield, M., "Characterization of Pyrrolidone Carboxylate-RNA from Rat Liver," in preparation.

Bodmer, W. and L. Cavalli-Sforza, "A Migration Matrix Model for the Study of Random Genetic Drift," GENETICS, vol. 59, pp. 565-592, 1968.

Bodmer, W., M. Feldman, and M. Nabholz, "The Evolution of the Rh Polymorphism: A Model for the Interaction of Incompatibility, Reproductive Compensation, and Heterozygote Advantage," AMER. J. HUMAN GENETICS, vol. 21, no. 2, pp. 171-193, Mar. 1969.

Bodmer, W., J. Bodmer, D. Ihde, and S. Adler, "Genetic and Serological Association Analysis of the HL-A Leukocyte System," COMPUTER APPLICATIONS IN GENETICS (ed. N. Morton), Univ. Hawaii Press, pp. 117-127, 1969.

Bodmer, W., V. Miggiano, and M. Nabholz, "Hybrids between Human Leukocytes and a Mouse Cell Line: Production and Characterization," WISTAR INSTITUTE SYMPOSIUM, monograph no. 9, "Heterospecific Genome Interaction," (ed. V. Defendi), THE WISTAR INSTITUTE PRESS, 1969.

Bodmer, W., M. Nabholz, V. Miggiano, "Genetic Analysis Using Human-Mouse Somatic Cell Hybrids," NATURE, vol. 223, pp. 348-363, 1969.

Bodmer, W. and L. Cavalli-Sforza, "The Genetics of Human Populations," FREEMAN AND COMPANY, in press.

Bodmer, W. and J. Bodmer, "Studies on African Pygmies IV: A Comparative Study of the HL-A Polymorphism in the Babinga Pygmies and Other African and Caucasian Populations," AM. JOUR. HUM. GENET., July 1970.

Bodmer, W. and B. Gabb, "A Micro Complement Fixation Test for Platelet Antibodies," HISTOCOMPATIBILITY TESTING, July 1970

Bodmer, W., J. Bodmer, A. Coukell, R. Payne, and E. Shanbrom, "A New Allele for the LA Series of HL-A Antigens: The Analysis of a Complex Serum," HISTOCOMPATIBILITY TESTING, July 1970.

Bodmer, W., J. Bodmer, and M. Tripp, "Recombination between the LA and 4 Loci of the HL-A System," HISTOCOMPATIBILITY TESTING, July 1970.

Bodmer, W., P. Mattiuz, D. Ihde, A. Piazza, and R. Ceppellini, "New Approaches to the Population Genetic and Segregation Analysis of the HL-A System," HISTOCOMPATIBILITY TESTING, July 1970.

Breitbard, G. and G. Wiederhold, "PL/ACME: An Incremental Compiler for a Subset of PL/1," IFIP68 CONGRESS PROCEEDINGS, Edinburgh, Scotland, Aug. 1968.

Brown, B. and L. Soyka, "Survey of Drugs Administered to Nine-Hundred Hospitalized Children: I. Relation to Age, Sex, and Diagnostic Category," submitted to JAMA, Mar. 1970.

Bussien, R, "L'informatique medicale aux Etats-Unis, MEDECINE et HYGIENE, Nov 1970

*Calvert, J. Lee and John H. Frenster, "Economics of Effectiveness and Efficiency in Patient Care," CLINICAL RESEARCH, vol. 19 , p. 501 , 1971 (abstract).

*Calvert, J. Lee and John H. Frenster, "Economics of Investment in Biomedical Research and Current Patient Care," CLINICAL RESEARCH, vol. 19, p. 499, 1971 (abstract).

Cann, H., B. Van West, and C. Barnett, "Genetics of Diego Blood Groups in Guatemalan Indians: Use of Antiserums to Diego a and Diego b Antigens," SCIENCE, vol. 162, pp. 1391-1392, Dec. 1968.

Clayton, R., "Methods in Enzymology," STEROIDS AND TERPENOIDS, vol. 15, Academic Press, 1969.

Cohen, S. and J. Hurwitz, "Genetic Transcription in Bacteriophage : Studies of mRNA Synthesis in vivo," J. MOL. BIOL., vol. 37, pp. 387-406, 1968.

Cohen, S. and C. Miller, "Multiple Molecular Species of Circular R-Factor DNA Isolated from Escherichia coli," NATURE, vol. 224, pp. 1273-1277, 1969.

Cohen, S. and C. Miller, "Non-Chromosomal Antibiotic Resistance in Bacteria: II. Molecular Nature of R-Factors Isolated from Proteus mirabilis and Escherichia coli," J. MOL. BIOL., vol. 50, No. 3, pp.671-687, June 1970.

Cohen, S. and A. Chang, "Genetic Expression in Bacteriophage : III. Inhibition of E. coli Nucleic Acid and Protein Synthesis during Development," J. MOL. BIOL., Vol. 49, No. 3, pp. 557-575, May 1970.

Collins, K. and G. Stark, "Aspartate Transcarbamylase: Studies of the Catalytic Subumt by Ultraviolet Difference Spectroscopy," J. BIOL. CHEM., vol. 244, pp. 1869-1877, Apr. 1969.

Collins, R., M. Weinberger, C. Gonzales, G. Nokes, and J. Luetscher, "Catecholamine Excretion in Low Renin Hypertension," CLIN. RES., vol. 18, p. 167, 1970, (abstract).

Constantinou, C., and E. Butler, "Medical Application of Computer Displays in the Rapid Examination of Developing Abnormality Patterns in the Kidney," PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM OF THE SOCIETY OF INFORMATION DISPLAY, Philadelphia, May 1971.

Constantinou, C., E. Briggs, R. Dale, and D. Govan, "Real-Time Digital Computer System for Ureteral Physiology Investigation," URODYNAMICS, Chap. 33, Academic Press, New York, in press.

Constantinou, C., J. Sands, and D. Govan, "Computer Monitoring and Control Instrumentation in Urology Research," PROCEEDINGS OF THE 6TH ANNUAL BIOENGINEERING SYMPOSIUM, Fort Collins, Colo., May 1971.

Crouse, L. and G. Wiederhold, "An Advanced Computer System for Real-Time Medical Applications," COMPUTERS AND BIOMEDICAL RESEARCH, vol. 2, no. 6, pp. 582-598, Dec. 1969.

Crouse, L. and G. Wiederhold, "Interactive Use of Timesharing System for Medical Laboratory Support," presented at the San Diego Biomedical Symposium, San Diego, Calif., Apr. 1970.

Crouse, L., R. Stenson, W. Henry, and D. Harrison, "A Time Shared Digital Computer System for On-Line Analysis of Cardiac Catheterization Data," COMPUTERS AND BIOMEDICAL RESEARCH, vol. 1, no. 6, p. 605, Academic Press, Inc., June 1968.

Doering, C., "Cholesterol Side Chain Cleavage Activity in the Adrenal Gland of the Young Rat: Development and Responsiveness to Adrenocorticotropic Hormone," ENDOCRINOLOGY, vol. 85, pp. 500-511, 1969.

Doering, C., "A Microassay for the Enzymatic Cleavage of the Cholesterol Side Chain," METHODS IN ENZYMOLOGY, (ed. R. Clayton), vol. 15, pp. 591-596, Academic Press, 1969.

Dong, E., Jr. and B.A. Reitz , "Effect of Timing of Vagal Stimulation on Heart Rate in the Dog," CIRCULATION RES., Vol. 27, No. 5, Nov. 1970.

Englund, P., J. Huberman, T. Jovin, and A. Kornberg, "Enzymatic Synthesis of Deoxyribonucleic Acid, XXX. Binding of Triphosphates to DNA Polymerase," submitted to J. BIOL. CHEM., vol. 244, pp. 3038-3044, 1969.

Farber, E. and R. McClintock, Jr., "A Current Review of Psoriasis," MEDICAL PROGRESS, vol. 108, pp. 440-457, June 1968.

Farber, E. and A. Cox, "The Biology of Psoriasis," J. OF INVESTIGATIVE DERMATOLOGY, vol. 49, no. 4, pp. 348-357, 1967.

Farber, E., R. Bright, and M. Nall, "Psoriasis - A Questionnaire Survey of 2,144 Patients," ARCH. DERM., vol. 98, pp. 248-259, Sept. 1968.

Forrest, W., Jr. and J. Bellville, "The Use of Computers in Clinical Trials," BRIT. J. ANESTH., vol. 39, pp. 311-319, 1967.

Forrest, W., Jr. and J. Bellville, "Respiratory Effects of Alphaprodine in Man," OBST. AND GYN., vol. 31, pp. 61-68, 1968.

Forrest, W., Jr., B. Brown, and J. Peters, "Management of Cooperative Clinical Trials," Paper presented at the Annual Meeting of the American Statistical Association in Pittsburgh, Pa., Aug. 1968.

Fried, M. and K. Vosti, "The Importance of Underlying Disease in Patients with Gram-Negative Bacteremia," ARCH. INT. MED., vol. 121, pp. 418-423, 1968.

Fries, J., "Experience Counting in Sequential Computer Diagnosis," ARCHIVES OF INTERNAL MEDICINE, Vol. 126, Oct. 1970.

* Fries, J., "The Effect of Ice Water on Esophageal Rewarming in Connective Tissue Diseases (CTD)," abstract submitted to GASTROENTEROLOGY.

Gersch, W. and G. Goddard, "Epileptic Focus Location: Spectral Analysis Method," SCIENCE, Vol. 169, pp.701-702, 1970.

Gersch, W. and E. Dong, Jr., "A Note on Warner's Vagus Heart Rate Control Model," CIRCULATION RESEARCH, 1970.

Gersch, W., D. Eddy, and E. Dong, Jr., "Cardiac Arrhythmia Classification: A Heart Beat Interval-Markov Chain Approach," COMPUTERS AND BIOMEDICAL RESEARCH, Aug. 1970.

Gersch, W., "Spectral Analysis of EEG's by Autoregressive Decomposition of Time Series," MATHEMATICAL BIOSCIENCES, Vol. 7, pp.205-222, 1970.

Gersch, W., "Estimation of the Autoregressive Parameters of a Mixed Autoregressive-Moving Average Time Series," IEEE TRANS. AUTOMATIC CONTROL, Aug. 1970.

Glick, D. "Cytochemical Analysis by Laser Microprobe-Emission Spectroscopy," ANNALS N. Y. ACAD. SCI., vol. 157, pp. 265-274, 1969.

* Glick, D., "Cytochemical Analysis by Laser Microprobe - Emission Spectroscopy," RECENT ADVANCES IN QUANTITATIVE HISTO- AND CYTOCHEMISTRY, pp. 192-193, 1971.

* Glick, D., K. Marich, J. Orenberg, P. Carr, and D. Miller, "Effect of Atmosphere on Spectral Emission from Plasmas Generated by the Laser Microprobe," ANALYTICAL CHEMISTRY, vol. 43, pp. 1452-1456, September 1971.

Glick, D., K. Marich, P. Carr, and E. Beatrice, "Laser Microprobe-Emission Spectroscopy," ANNALS N. Y. ACAD. SCI., vol. 168, pp. 507-509, 1970.

Halpern, B., V. Close, A. Wegmann, and J. Westley, "Gas Chromatography of Amino Acids as N-Thiocarbonyl Ester Derivatives," TETRAHEDRON LETTERS, vol. 27, p. 3119, 1968.

Harman, C.E. and C.S. Raymond, "Computer Prediction of Chronic Psychiatric Patients," J. NERV. and MENTAL DIS., Vol. 150, pp. 490-503, 1970.

Harman, C.E. and K. Meinhardt, "A Computer System for Treatment Evaluation at the Community Mental Health Center," presented at the 2nd Bay Area Regional Conference on Program Evaluation in San Francisco, Calif., January 7, 1971.

Harrison, D., R. Goldman, M. Klughaupt, T. Metcalf, and A. Spivack, "Central Venous Oxygen Saturation Measurements in Patients with Myocardial Infarction," CIRCULATION, vol. 28, Nov. 1968.

Harrison, D., M. Flamm, and E. Hancock, "Muscular Subaortic Stenosis: Prevention of Outflow Obstruction with Propranolol," CIRCULATION, vol. 28, p. 846, 1968.

Harrison, D., R. Gianelly, W. Angell, E. Stinson, and N. Shumway, "Homograft Replacement of the Mitral Valve," CIRCULATION, vol. 28, p. 664, 1968.

Harrison, D., E. Stinson, E. Dong, Jr., and J. Schroeder, "Initial Clinical Experience with Heart Transplantation," AMER. J. OF CARDIOL., vol. 22, p. 791, 1968.

Harrison, D., M. Robinson, and R. Kleiger, "The Role of Hypoxia in Digitalis Toxicity," AMER. J. MED. SCI., vol. 256, p. 352, 1968.

Harrison, D. and R. Gianelly, "Studies on the Antiarrhythmic and Circulatory Actions of Lidocaine (Xylocaine(R))," ALA. J. MED. SCI., vol. 6, p. 74, 1969.

Harrison, D., W. Henry, C. Ploeg, and S. Kountz, "An Improved Hydraulic Vascular Occluder for Chronic Electromagnetic Blood Flow Measurements," J. APPL. PHYSIOL., vol. 25, p. 790, 1968.

Harrison, D. and R. Gianelly, "Drugs Used in the Treatment of Cardiac Arrhythmias," DISEASE-A-MONTH, Jan. 1969.

Harrison, D., M. Klughaupt, M. Flamm, and E. Hancock, "Non-Rheumatic Mitral Insufficiency: Determination of Operability and Prognosis," CIRCULATION, vol. 39, p. 307, 1969.

Harrison, D., W. Henry, S. Kountz, R. Cohn, and S. Robison, "Changes in Pulsatile Blood Flow in Autograft and Homograft Kidneys during Rejection," TRANSPLANTATION, vol. 7, p. 545, 1969.

Harrison, D., B. Treister, R. Gianelly, and R. Cohn, "The Circulatory Effects of Isoproterenol, Acetylstrophanthidin and Volume Loading in Acute Pericardial Tamponade," CARDIOVASC. RES., vol. 3, p. 299, 1969.

Harrison, D. and M. Perlroth, "Cardiogenic Shock: A Review," CLIN. PHARMACOL. AND THERAPEUT., vol. 10, p. 449, 1969.

Harrison, D., R. Gianelly, and B. Treister, "The Effect of Propranolol on Exercise-Induced Ischemic ST Segment Depression," AMER. J. CARDIOL., vol. 24, p. 161, 1969.

Harrison, D., J. Schroeder, R. Popp, E. Stinson, E. Dong, Jr., and N. Shumway, "Acute Rejection Following Cardiac Transplantation: Phonocardiographic and Ultrasound Observations," CIRCULATION, vol. 40, p. 155, 1969.

Harrison, D., B. Wintroub, J. Schroeder, M. Schroll, and S. Robison, "The Hemodynamic Response to Dopamine in Experimental Myocardial Infarction," AMER. J. PHYSIOL., vol. 217, pp. 1716-1720, Dec. 1969.

Harrison, D., B. Wintroub, S. Robison, and S. Pirages, "The Pulmonary and Systemic Circulatory Response to Dopamine Infusion," BRIT. J. PHARMACOL., Vol. 37, p. 618, 1969.

Harrison, D., S. Robison, and M. Schroll, "The Circulatory Response to Lidocaine in Experimental Myocardial Infarction," AM. J. MED. SCI., Vol. 258, p. 260, 1969.

Harrison, D. and J. Ridges, "Nomograms for Determination of Mixed Venous O2 Content and O2 Stepup in Atrial Septal Defect," AMER. HEART J., Vol. 80, p.575, 1970.

Harrison, D., R. Stenson, W. Henry, and L. Crouse, "Analysis of Hemodynamic Data from Cardiac Catheterization with a Digital Computer," OPTICS TECHN. REVIEW, 1969.

Henry, W., L. Crouse, R. Stenson, and D. Harrison, "Computer Analysis of Cardiac Catheterization Data," AM. J. OF CARDIOLOGY, vol. 22, no. 5, pp. 696-705, Nov. 1968.

Hillman, R., "The Teaching of Psychotherapy Problems by Computer," to be presented at the American Psychiatric Association Convention, San Francisco, Calif., May 1970.

Hillman, R., "The Teaching of Psychotherapy Problems by Computer," ARCHIVES OF GENERAL PSYCHIATRY, in press.

Hodgson, G., E. Petterson, K. Kvenvolden, E. Bunnenberg, B. Halpern, and C. Ponnamperuma, "Search for Porphyrins in Lunar Dust," SCIENCE, vol. 167, pp. 763-765, Jan. 1970.

Huberman, J. and A. Kornberg, "Enzymatic Synthesis of Deoxyribonucleic Acid, XXXV. A 3'-Hydroxylribonucleotide Binding Site of Escherichia coli Deoxyribonucleic Acid Polymerase," J. BIOL. CHEM., Vol. 245, p. 5326, 1970.

Ingels, N., S. Rush, and N. Thompson, "Analytic Stop Motion Stereo Photogrammetry," THE REVIEW OF SCIENTIFIC INSTRUMENTS, vol. 40, no. 3, pp. 487-492, Mar. 1969.

Kakihana, R., J. Butte, and E. Noble, "Effects of Goldthioglucose on Alcohol Consumption in C57BL Mice," LIFE SCIENCES, vol. 7, p. 825, 1968.

Kakihana, R., E. Noble, and J. Butte, "Corticosterone Response to Ethanol in Inbred Strains of Mice," NATURE, vol. 218, p. 360, 1968.

Kessler, S., "Speed of Mating and Sexual Isolation in Drosophila," NATURE, vol. 220, pp. 1044-1045, 1968.

Kessler, S., "The Genetics of Drosophila Mating Behavior I - Organizations of Mating Speed in Drosophila pseudoobscura," AN. BEHAV., vol. 16, pp. 485-491, 1968.

Kessler, S., "The Genetics of Drosophila Mating Behavior II - The Genetic Architecture of Mating Speed in Drosophila pseudoobscura," GENETICS, vol. 62, pp. 421-433, 1969.

Kessler, S. and R.H. Moos, "The XYY Karyotype and Criminality: A Review," J. PSYCHIATRIC RES., Vol. 7, pp. 153-170, 1970.

Kountz, S., K. Cochrum, H. Perkins, K. Douglas, and F. Belzer, "Selection of Allograft Recipients by Leukocyte and Kidney Cell Phenotyping," presented at the 31st Annual Meeting of the Society of University Surgeons, Pittsburgh, Pennsylvania, Feb. 1970.

Kriss, J., S. Kountz, S. Yeh, J. Wood, and R. Cohn, "99m Tc (V)-Citrate Complex for Estimation of Glomerular Filtration Rate," NATURE, vol. 215, p. 1937, 1967.

Kriss, J., "The Nature and Significance of the Long-Acting Thyroid Stimulator," ADVANCES IN METABOLIC DISORDERS, (eds. K. Levine and R. Luft), vol. 3, pp. 209-230, 1968.

Kriss, J., "The Long-Acting Thyroid Stimulator," CALIF. MED., vol. 109, p. 202, 1968.

Kriss, J., "The Long-Acting Thyroid Stimulator and Thyroid Disease," ADVANCES IN INTERNAL MEDICINE, 1970.

Kriss, J., T. Mori, and J. Fisher, "Studies of an in vitro Binding Reaction between Thyroid Microsomes and Long-Acting Thyroid Stimulator Globulin (LATS): I. Development of Solid-State Competitive Binding Radioassay Methods for Measurement of Anti-Microsomal and Anti-Thyroglobulin Antibodies," J. CLIN. ENDOCR. AND METAB., 1970.

Kriss, J. and S. McHardy-Young, "Simplified Technique for the Radioimmunoassay of Human TSH," J. NUCLEAR MED., vol. 10, p. 356, 1969, (abstract).

Kriss, J., S. McHardy-Young, and H. Kaplan, "Serum Tsh Levels Following Megavoltage Radiotherapy for Hodgkin's Disease," PROGRAM, 45TH AMERICAN THYROID ASSOCIATION, p. 83, July 1969, (abstract).

Kriss, J. and T. Mori, "Studies of a Rapid, in vitro, Binding Reaction between Human Thyroid Microsomes and Radioiodinated Long-Acting Thyroid Stimulator (LATS) IgG Globulin," PROGRAM, 45TH AMERICAN THYROID ASSOCIATION, p. 28, July 1969, (abstract).

Kriss, J., E. Glatstein, and J. Eltringham, "Serum TSH and Thyroid Function Following X-Ray Therapy in Patients with Malignant Lymphoma," CLINICAL RESEARCH, vol. 18, p. 168, 1970, (abstract).

Kriss, J. and T. Mori, "Rapid Competitive Binding Radioassay of Serum Anti-Microsomal and Anti-Thyroglobulin Antibodies: Measurements in Graves' Disease," CLINICAL RESEARCH, vol. 18, p. 170, 1970, (abstract).

Kriss, J. and T. Mori, "Rapid Competitive Binding Radioassay of Serum Anti-Microsomal and Anti-Thyroglobulin Antibodies: Measurements in Graves' Disease," submitted to 6TH INTERNATIONAL THYROID CONFERENCE, June 1970, (abstract).

Laipis, P., B. Olivera, and A. Ganesan, "Enzymatic Cleavage and Repair of Transforming DNA," P.N.A.S., vol. 62, p. 289, 1969.

Levine, R. and N. Kretchmer, "Conversion of Carbamyl Phosphate to Hydroxyurea: An Assay for Carbamyl Phosphate Synthetase, " ANALYTICAL BIOCHEMISTRY, vol. 42, no. 2, pp. 324-337, August 1971.

* Levine, R., N. Hoogenroad, and N. Kretchmer, "Copurification of Carbamoyl Phosphate Synthetase and Aspartate Transcarbamoylase from Mouse Spleen," BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 44, pp. 981-988, 1971.

* Levine, R., N. Hoogenroad, and N. Kretchmer, "Regulation of Activity of Carbamoyl Phosphate Synthetase from Mouse Spleen," BIOCHEMISTRY, vol. 10, no. 20, pp. 3694-3699, 1971.

Luetscher, J., M. Weinberger, and R. Collins, "Oral Contraceptives and Hypertension: Clinical and Laboratory Observations," METABOLIC EFFECTS OF GONADAL HORMONES AND CONTRACEPTIVE STEROIDS, edited by D. Kipnis, et al, Plenum Publishing Corp., 1969.

Luetscher, J., M. Weinberger, A. Dowdy, and G. Nokes, "Effects of Sodium Loading, Sodium Depletion and Posture on Plasma Aldosterone Concentration and Renin Activity in Hypertensive Patients," J. CLIN. ENDOCR., vol. 29, p. 1310, 1969.

Luzzatti, L., R. Greenstein, D. Harris, and H. Cann, "Cytogenetic Analysis of a Boy with the XXXY Syndrome: Origin of the X-Chromosomes," PEDIATRICS, Apr. 1970.

Luzzatti, L. and H. Pryor, "Body Proportions and Dermatoglyphic Patterns in Children with Cleft Lip and/or Palate," submitted to PEDIATRICS.

Luzzatti, L. and L. Knight, "Synchronization of Human Lymphocyte Cultures with FuDR," in preparation.

Luzzatti, L. and L. Knight, "Morphologic and Labeling Characteristics of the Late Replicating X Chromosome in Man," in preparation.

Luzzatti, L. and L. Knight, "Intrapair and Interpair Chromosome Distance at Metaphase in Human Lymphocytes," in preparation.

McIntosh, S., Jr., T. Weisshaar, and H. Ashley, "Progress in Aeroelastic Optimization - Analytical Versus Numerical Approaches," SUDAAR, no. 383, July 1969.

McIntosh, S., Jr., T. Weisshaar, and H. Ashley, "Progress in Aeroelastic Optimization - Analytical Versus Numerical Approaches," presented at the AIAA Structural Dynamics and Aeroelasticity Specialist Conference, New Orleans, Louisiana, Apr. 1969.

Marich, K., Carr, P., Treytl, W., and D. Glick, "Effect of Matrix Material on Laser-Induced Elemental Spectral Emission," ANALYTICAL CHEMISTRY, Vol. 42 Dec. 1970.

Melges, F.T., Tinklenberg, J.R., Hollister, L.E., and H.K. Gillespie, "Marihuana and Temporal Disintegration," SCIENCE, Vol. 168, pp. 1118-1120, 1970.

Melges, F.T., Tinklenberg, J.R., Hollister, L.E., and H.K. Gillespie, "Temporal Disintegration and Depersonalization During Marihuana Intoxication," ARCH GEN PSYCHIAT., Vol. 23, pp. 204-210, 1970.

Melges, F.T., Anderson, R.E., Kraemer, H.C., Tinklenberg, J.R., and Weisz, A.E., THE PERSONAL FUTURE AND SELF-ESTEEM, in press.

Mesel, E., "Direct Measurement of Intracardiac Blood Flow in Dogs with Experimental Ventricular Septal Defects," CIRCULATION RES., Vol. 27, Dec. 1970.

Mesel, E., "Transducer for Direct Measurement of Shunts in Experimental Ventricular Septal Defects," J. APPLIED PHYSIOL., Vol. 28, No. 3, March 1970.

Mesel, E. and M.J. Gelfand, "An Automated Data Analysis and Acquisition System for a Cardiac Catheterization Laboratory," COMPUTERS IN BIOLOGY AND MEDICINE, in press.

Morrell, F., "Neural Coding," NEUROSCIENCES RESEARCH PROGRAM BULLETIN, 1969.

Morris, S., "Metabolism of Mouse Brain Synaptosome Proteins," Ph.D. Dissertation, Stanford University, 1969.

Morris, S. and L. Shooter, "Half-Lives of Mouse Brain Synaptosomes," J. NEUROCHEM., in press.

Murray, G., F. Offensend, D. Silva, E. Sondik, and L. Klainer, "A Medical Service Requirements Model for Health System Design," special issue of the PROCEEDINGS OF THE IEEE ON HEALTH SYSTEMS, vol. 57, pp. 1880-1887, Nov. 1969.

Noble, E., S. Silbergeld, B. Kopell, W. McKinney, W. Wittner, and J. Butte, "The Effects of Physiologic Doses of Corticosteroid on Catecholamine Metabolism in Man," J. PSYCHIAT. RES., vol. 6, p. 159, 1968.

Oliver, I., O. Koskimies, R. Hurwitz, and N. Kretchmer, "Macromolecular Forms of Aspartate Transcarbamylase in Rat Liver," BIOCHEM. BIOPHYS. RSCH. COMMUN., vol. 37, pp. 505-511, 1969.

Peters, J., W. Forrest, Jr., and B. Brown, "Use of Computers in Management of a Cooperative Study," presented at the 31st Annual meeting of the Committee on Problems of Drug Dependence, Palo Alto, Calif., Feb. 1969.

Peters, J., "Using a Time-Shared Computer to Manage a Cooperative Study," Stanford University, May , 1969.

Petralli, J., S. Wallis, and T. Merigan, "A Computer Method for Improvement of Antibiotic Sensitivity Data and Guidance in Therapy," CLINICAL RESEARCH JOURNAL, 1968.

Petralli, J., Russell, E., Katooka, A., and T.C. Merigan, "On-Line Computer Quality Control of Antibiotic Sensitivity Testing," NEW ENGLAND J. OF MEDICINE, Vol. 283, pp. 735-738, Oct. 1970.

Porter, R., M. Modebe, and G. Stark, "Aspartate Transcarbamylase: Kinetic Studies of the Catalytic Subunit," J. OF BIOL. CHEM., vol. 244, pp. 1046-1057, April 1969.

Reynolds, W., "Computer Control of Mass Analyzers," PROCEEDINGS OF THE SIXTEENTH ANNUAL CONFERENCE ON MASS SPECTROMETRY AND APPLIED TOPICS, (ASTM Committee E-14), Pittsburgh, Pa., May 1968.

Reynolds, W., "A Small Computer Approach to Low Resolution Mass Spectrometry," presented at the Pacific Conference on Chemistry and Spectroscopy, Anaheim, Calif., Nov. 1967.

Reynolds, W., "Instrumentation in a Time Shared Computer Environment," RESEARCH AND DEVELOPMENT, Vol. 21, No. 4, pp. 20-26, Apr. 1970.

Reynolds, W., V. Bacon, J. Bridges, T. Coburn, B. Halpern, J. Lederberg, E. Levinthal, E. Steed, and R. Tucker, "A Computer Operated Mass Spectrometer System," submitted to ANALYTICAL CHEMISTRY, 1970.

Reynolds, W., "Biochemical Applications of Mass Spectrometry," Chapter III, (ed. by Waller), to be published by John Wiley & Sons, New York.

Rousseau, W., "A Method for Computing Probabilities in Complex Situations," Doctoral Dissertation, Stanford University, 1968.

Sachs, D., E. Jellum, and B. Halpern, "Determination of the Stereospecific Hydrolytic Action of Pepsin by Nuclear Magnetic Resonance Spectroscopy," BIOCHEM. BIOPHYS. ACTA., vol. 198, pp. 88-92, 1970.

Sanders, W., G. Breitbard, D. Cummins, J. Flexer, K. Holtz, J. Miller, and G. Wiederhold, "An Advanced Computer System for Medical Research," AFIPS CONFERENCE PROCEEDINGS, vol. 31, 1967.

Sanders, W.J. and A. Silvers, "Digital On-Line Computer Display to Investigate the Structure of Metabolic Systems," COMPUTERS AND BIOMED. RES., Vol. 3, pp. 133-145, April 1970.

Schneiderman, L., W. Sampson, W. Schoene, and G. Haydon, "Genetic Studies of a Family with Two Autosocial Dominant Conditions," AM. J. MED., vol. 46, p. 380, 1969.

Schneiderman, L., L. DeSalvo, S. Baylor, and P. Wolf, "The 'Abnormal' Screening Laboratory Result: Its Effect on Physician and Patient," AM. FED. CLIN. RES., 1970, (abstract).

Sibergeld, S., N. Brast, and E. Noble, "The Menstrual Cycle: A Double-Blind Study with Enovid and Placebo," PSYCHOSOMATIC MEDICINE, in press.

Smallwood, R., E. Sondik, and F. Offensend, "Toward an Integrated Methodology for the Analysis of Health Care Systems," in preparation, to be presented at the 37th National Meeting of the Operation Research Society of America, Washington, D. C., Apr. 1970.

Smith, R., "Discussion Tasks as a Measure of Family Role Structure: Implications for the Study of Pathological Families," submitted for publication in J. PSYCHIAT. RESEARCH.

Smith, R., "Discussion Versus Communication Network Tasks in the Study of Family Role Structure," submitted for publication in J. NERV. MENTAL DISEASES.

Solomon, G., S. Levine, and J. Kraft, "Early Experience and Immunity," NATURE, vol. 220, p. 821, Nov. 1968.

Solomon, G., "Stress and Antibody Response in Rats," INT. ARCH. ALLERGY AND APPLIED IMMUNOLOGY, vol. 35, pp. 97-104, 1969.

Starr, A. and J. Wernick, "Olivocochlear Bundle Stimulation: Effects on Spontaneous and Tone-Evoked Activities of Single Units in Cat Cochlear Nucleus," J. NEUROPHYSIOL., vol. 31, pp. 549-564, 1968.

Stenson, R., W. Henry, L. Crouse, and D. Harrison, "Computer Analysis of Cardiac Catheterization Data," AM. J. CARDIOLOGY, vol. 22, no. 5, pp. 696-705, Nov. 1968.

Stillman, R., W. Roth, K. Colby, and P. Rosenbaum, "An On-Line Computer System for Initial Psychiatric Inventory," AMER. J. PSYCHIAT., vol. 125, p. 7, Jan. 1969.

Stillman, R., R. Costell, and D. Cummins, "Computer Administered Psychiatric Inventory," presented at the Annual Meeting of the American Psychiatric Association, Miami, Florida, May, 1969.

Strickland, R., "The Effect of Prednisolone on Gastric Function and Structure in Man," GASTROENTEROLOGY, vol. 56, pp. 675-686, 1969.

Swanson, G., D. Snider, T. Carpenter, and J. Bellville, "A Hybrid Computing System for On-Line Respiratory Studies," published in the PROCEEDINGS OF THE SEVENTH ANNUAL ROCKY MOUNTAIN BIOENGINEERING SYMPOSIUM AND EIGHTH INTERNATIONAL ISA BIOMEDICAL SCIENCES INSTRUMENTATION SYMPOSIUM, Denver, Colorado, May 1970.

Swanson, G., T. Carpenter, D. Snider, and J. Bellville, "An On-Line Hybrid Computing System for Dynamic Respiratory Response Studies", COMPUTERS AND BIOMEDICAL RESEARCH, Vol. 4, pp. pp. 205-215, April 1971.

Thathachari, Y., "X-Ray Diffraction Studies on Melanins," PROCEEDINGS OF THE VII INTERNATIONAL PIGMENT CELL CONFERENCE, Seattle, Wash., 1969.

Thathachari, Y. and M. Blois, "Physical Studies on Melanins: X-Ray Diffraction," BIOPHYSICAL JOURNAL, vol. 9, no. 1, pp. 77-89, 1969.

Thathachari, Y., "X-Ray Diffraction Studies on Melanins," presented at the Annual Conference of the Biophysical Society, Los Angeles, Calif., Feb. 1969.

Thathachari, Y., "Radial Distribution Studies on Melanins," PROCEEDINGS OF THE THIRD INTERNATIONAL BIOPHYSICS CONGRESS, Cambridge, Mass., Aug.-Sept. 1969.

Thoman, E. and S. Levine, "Hormonal and Behavioral Responsiveness to Foster Pups as a Function of Prior Maternal Experience," presented at the Symposium of Maternal Behavior in Mammals, sponsored by the International Union of Biological Science, July 1969.

Thoman, E., S. Levine, and R. Conner, "Lactation Suppresses Adrenal Conticosteroid Activity and Aggressiveness in Rats," J. COMP. PHYSIOL. PSYCHOL., Vol. 3, pp. 364-369, 1970.

Thoman, E., A. Turner, P. Leiderman, and C. Barnett, "Neonate-Mother Interaction: Effects of Parity on Feeding Behavior," CHILD DEVELOPMENT, Vol. 40, pp. 1103-1111, 1970.

Thoman, E., and S. Levine, "Effects of Adrenalectomy on Maternal Behavior in Rats," DEVELOPMENTAL PSYCHOLOGY, in press.

Thoman, E., C. Barnett, and P. Leiderman, "Neonate-Mother Interaction: Development of Earliest Feeding Patterns as a Function of Parity," CHILD DEVELOPMENT.

Thoman, E., J. Olson, and P. Leiderman, "Behavior Patterns of Breast-Feeding Mothers and Neonates as a Function of Parity of the Mother and Sex of the Infant," in preparation.

Thoman, E. and A. Korner, "Effects of Vestibular Stimulation on Behavior and Development in Infant Rats," DEVELOPMENTAL PSYCHOLOGY, in press.

Tinklenberg, J.R., Melges, F.T., Hollister, L.E., and H.K. Gillespie, "Marihuana and Immediate Memory," NATURE, Vol. 226, pp. 1171-1172, 1970.

Weinberger, M., R. Collins, A. Dowdy, G. Nokes, and J. Luetscher, "Hypertension Induced by Oral Contraceptive Containing Estrogen and Gestagen - Effects on Plasma Renin Activity and Aldosterone Excretion," ANN. INTERN. MED., vol. 71, p. 891, 1969.

Weinberger, M., A. Dowdy, G. Nokes, and J. Luetscher, "Stimulation of Plasmas Renin Activity without Increased Aldosterone Production after Administration of Chlorothiazide to Hypertensive Patients," J. CLIN. INVEST., vol. 46, p. 1130, 1967.

Weinberger, M., A. Dowdy, G. Nokes, and J. Luetscher, "Plasma Renin Activity and Aldosterone Secretion in Hypertensive Patients during High and Low Sodium Intake and Administration of Diuretic," J. CLIN. ENDOCR., vol. 28, p. 359, 1968.

Weinberger, M., A. Dowdy, G. Nokes, and J. Luetscher, "Reversible Increases in Plasma Renin Activity, Aldosterone Secretion and Blood Pressure in Women Taking Oral Contraceptive Preparations," CLIN. RES., vol. 16, p. 150, 1968.

Westley, J. and B. Halpern, "The Use of (-)Menthyl Chloroformate in the Optical Analysis of Asymmetric Amino and Hydroxyl Compounds by Gas Chromatography," J. ORG. CHEM., vol. 33, p. 3978, 1968.

Westley, J., V. Close, D. Nitecki, and B. Halpern, "Determination of Steric Purity and Configuration of Diketopiperazines by Gas-Liquid Chromatography, Thin-Layer Chromatography and Nuclear Magnetic Resonance Spectrometry," ANAL. CHEM., vol. 40, p. 1888, 1968.

Wiederhold, G., "A Summary of the ACME System," PROCEEDINGS OF THE ONR COMPUTER AND PSYCHOBIOLOGY CONFERENCE, Monterey, Calif., May 1966.

Wiederhold, G., "A Summary of the ACME System," PROCEEDINGS OF THE CONVERSATION WITH A 50 CONFERENCE, Argonne National Laboratory, Chicago, Illinois, Oct.-Nov. 1966.

Wiederhold, G., "Setting up a General Purpose Data-Acquisition System," PROCEEDINGS OF THE IBM SCIENTIFIC COMPUTING SYMPOSIUM ON COMPUTERS IN CHEMISTRY, Yorktown Heights, New York, pp. 249-264, Oct. 1968.

Wiederhold, G. and L. Hundley, "A Timeshared Data-Acquisition System," published in the PROCEEDINGS OF THE IEEE COMPUTER GROUP CONFERENCE ON REAL-TIME SYSTEMS, Minneapolis, Minnesota, June 1969.

Wiederhold, G., "An Advanced Computer System for Medical Research," PROCEEDINGS OF THE IBM JAPAN COMPUTER SCIENCE SYMPOSIUM -- RESEARCH AND DEVELOPMENT AND COMPUTER SYSTEMS, Tokyo, Japan, pp. B1-B15, Nov. 1969.

Wiederhold, G., "Setting Up a General-Purpose Data-Acquisition System," PROCEEDINGS OF THE IBM SCIENTIFIC COMPUTING SYMPOSIUM ON COMPUTERS IN CHEMISTRY, Data Processing Division, White Plains, New York, pp. 249-264, Aug. 1969.

Wiederhold, G., R. Frey, and S. Girardi, "A Filing System for Medical Research," presented at Journees Internationales d'Informatique Medicale de Toulouse, France, Mar. 1970.

Wiederhold, G., R. Frey, and S. Girardi, "A Filing System for Medical Research," presented at the Eighth Annual Symposium on Biomathematics and Computer Science in the Life Sciences, Houston, Texas, Mar. 1970.

Wiederhold, G. and G. Breitbard, "A Method for Increasing the Modularity of of Large Systems," IEEE COMPUTER GROUP NEWS, vol. 3, no. 2, p. 30, Mar./Apr. 1970.

Wiederhold, V., "How to Use PL/ACME," Document No. 80-50-00, Stanford Computation Center, Stanford University, July 1967 (1st ed.), Sept. 1968 (2nd ed.).

Wolf, P., T. Durbridge, and D. Enlander, "An Evaluation of SNOP Coding of Pathologic Data for Computer Retrieval," LABORATORY MEDICINE - THE BULLETIN OF PATHOLOGY, pp. 400-401, Dec. 1969.

* New Entry Since Last APUB.

# BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| LEDERBERG, JOSHUA | Professor and Executive Head, Department of Genetics | 5-23-25 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Montclair, New Jersey | U.S.A. | ☒ Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Columbia College, New York | B.A. | 1944 | |
| College of Physicians & Surgeons, Columbia University, New York (1944-46) | | | |
| Yale University | Ph.D. | 1947 | Microbiology |

**HONORS**

1957 - National Academy of Sciences
1958 - Nobel Prize in Medicine

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Molecular Genetics; Artificial Intelligence | PRINCIPAL INVESTIGATOR |

**RESEARCH SUPPORT** *(See instructions)*

SEE ATTACHMENTS:

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

| | |
|---|---|
| 1961- | Stanford University<br>Director, Kennedy Laboratories for Molecular Medicine |
| 1959- | Professor, Genetics and Biology, and Executive Head, Department of Genetics, Stanford University |
| 1957-1959 | University of Wisconsin<br>Chairman, Department of Medical Genetics |
| 1957 | Melbourne University, Australia<br>Fullbright Visiting Professor of Bacteriology |
| 1950 | University of California, Berkeley<br>Visiting Professor of Bacteriology |
| 1947-1959 | University of Wisconsin<br>Professor of Genetics |
| 1946-1947 | Yale University. Research Fellow of the Jane Coffin Childs Fund for Medical Research |
| 1945-1946 | Columbia University. Research Assistant in Zoology |

Professional Activities:

| | |
|---|---|
| 1967- | NIMH: National Mental Health Advisory Council |
| 1961-1962 | President (Kennedy)'s Panel on Mental Retardation |
| 1960- | NASA Committees: Lunar and Planetary Missions Board |
| 1958- | National Academy of Sciences: Committees on Space Biology |
| 1950- | President's Science Advisory Committee panels. National Institutes of Health, National Science Foundation study sections (genetics) |

## LIST OF PUBLICATIONS

81. Lederberg, J., 1959
A View of Genetics.
Les Prix Nobel en 1958: 170-89.

182. Buchs, A., A.B. Delfino, A.M. Duffield, C. Djerassi, B.G. Buchanan, E.A. Feigenbaum, and J. Lederberg, 1970.
Applications of Artificial Intelligence for Chemical Inference. VI. Approach to a general method of interpreting low resolution mass spectra with a computer.
Helvitia Chimica Acta 53 (6): 1394-1417.

186. Feigenbaum, E. A., B. G. Buchanan, J. Lederberg, 1971
On generality and problem solving: a case study using the DENDRAL program in Machine Intelligence 6, (B. Meltzer and D. Michie, eds.), Edinburgh University Press, P. 165-190.

192. Reynolds, W.E., V.A. Bacon, J.C. Bridges, T.C. Coburn, B. Halpern, J. Lederberg, E.C. Levinthal, E. Steed, R.B. Tucker, 1970
A computer operated mass spectrometer system.
Analytical Chem. 42:1122-1129, September 1970.

194. Lederberg, J.
"Use of Computer to Identify Unknown Compounds: The Automation of Scientific Inference" in Biochemical Applications of Mass Spectrometry (G.R. Waller, ed.). John Wiley & Sons, New York (in press)

RESEARCH SUPPORT:

| Grant | Project Title | Dates | Amt. | Budgeted Amt. of Salary |
|---|---|---|---|---|
| **Research Projects:** | | | | |
| JPL Contract 952489 | Extended Mission of Mariner Mars | 9/1/69 - 6/30/72 | $185,000 | 16% |
| NASA NAS-19692 | Viking Biology Team | -6/30/72 | $ 9,608 | |
| NIH RR0311 | Advanced Computer for Med. Research | 1966 - 7/31/73 | $ | 25% |
| NIH A1 05160-14 | Genetics of Bacteria | 9/1/71 - 8/31/72 | $ 58,000 | |
| **Managerial:** | | | | |
| NIH GM 295-13 | Training Program in Genetics | 7/1/71 - 6/30/72 | $130,609 | |
| NSF GB 29094 | Exchange Program in Genetics and Molecular Biology between Universities of Stanford and Pavia (Italy) | 5/1/72 - 4/30/73 | $ 60,000 | (Applied for) |
| NASA NGR 05-020-004 | Cytochemical Studies of Planetary Micro-organisms | 9/1/71 - 8/30/72 | $240,000 | 05% |

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Edward A. Feigenbaum | Professor of Computer Science | 1-20-36 |

| PLACE OF BIRTH *(City, State, Country)* | PRESENT NATIONALITY *(If non-U.S. citizen, indicate kind of visa and expiration date)* | SEX |
|---|---|---|
| Weehawken, New Jersey | U. S. A. | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Carnegie Institute of Technology | B. S. | 1956 | Electrical Engineering |
| Carnegie Institute of Technology | Ph.D. | 1959 | Industrial Administration |

**HONORS**

Fulbright Research Scholar, Great Britain, National Physics Laboratory, Teddington, England, 1959-60.

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Artificial Intelligence Research<br>Heuristic Programming | Associate Investigator |

**RESEARCH SUPPORT** *(See instructions)*

| Contract/Grant No. | Title | Current Year | Total, Proj. Period | % Effort | Source of Support |
|---|---|---|---|---|---|
| ARPA SD-183 | The Heuristic Programming Project of the Stanford Artificial Intelligence Project | $200,000 | $700,548 | 42% | ARPA |
| 5 R24 RR00612-02 SSS | Resource-Related Research; Computers and Chemistry | 214,093 | 722,062 | 27% | NIH |

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1965- Stanford University, Computer Science Department Faculty
1965-68 Stanford University, Director, Computation Center
1968-72 National Institutes of Health, Member, Computer and Biomathematical Sciences Study Section
1965- Editor, Computer Science Series, McGraw-Hill Book Company, New York
1960-64 University of California, Berkeley
Research-Center for Research in Management Science, 1960-64
Research-Center for Human Learning, 1961-64
Assistant and Associate Professor, School of Business Administration, 1960-64
1963 National Science Foundation. Summer Research Training Institute in Computer Simulation of Cognitive Processes. Faculty member.
1962 Carnegie Corporation. Summer Research Training Institute in Heuristic Programming. Faculty member.
1956 IBM Scientific Computing Center, New York

Recent Publications

Smith, D. H., Buchanan, B. G., Engelmore, R. S., Duffield, A. M., Yeo, A., Feigenbaum, E. A., Lederberg, J., and Djerassi, Carl, "Applications of Artificial Intelligence for Chemical Inference VIII. An Approach to the Computer Interpretation of the High Resolution Mass Spectra of Complex Molecules. Structure Elucidation of Estrogenic Steroids," December, 1971.

Buchanan, B. G., Feigenbaum, E. A., and Lederberg, J., "A Heuristic Programming Study of Theory Formation in Science." In proceedings of the Second International Joint Conference on Artificial Intelligence, Imperial College, London (September 1971). (Also Stanford Artificial Intelligence Project Memo No. 145.)

Buchs, Armand, Delfino, Allan B., Djerassi, Carl, Duffield, A. M., Buchanan, B. G., Feigenbaum, E. A., Lederberg, J., Schroll, Gustav, and Sutherland, G. L., "The Application of Artificial Intelligence in the Interpretation of Low-Resolution Mass Spectra", Advances in Mass Spectrometry Volume 5, 314-318.

Feigenbaum, E. A., Buchanan, B. G., and Lederberg, J., "On Generality and Problem Solving: A Case Study Using the DENDRAL Program", Machine Intelligence 6, B. Meltzer and D. Michie, eds., Edinburgh University Press, 1971.

Lederberg, J., Sutherland, G. L., Buchanan, B. G., Feigenbaum, E. A., Robertson, A. V., Duffield, A. M. and Djerassi, C., "Applications of Artificial Intelligence for Chemical Inference I. The Number of Possible Organic Compounds. Acyclic Structures Containing C, H, O and N", Journal of the American Chemical Society, 91, 2973, 1969.

Duffield, A. M., Robertson, A. V., Djerassi, C., Buchanan, B. G., Sutherland, G. L., Feigenbaum, E. A. and Lederberg, J., "Applications of Artificial Intelligence for Chemical Inference II. Interpretation of Low Resolution Mass Spectra of Ketones", Journal of the American Chemical Society, 91, 2977, 1969.

Schroll, G., Duffield, A. M., Djerassi, C., Buchanan, B. G., Sutherland, G. L., Feigenbaum, E. A. and Lederberg, J., "Applications of Artificial Intelligence for Chemical Inference III. Aliphatic Ethers Diagnosed by Their Low Resolution Mass Spectra and Nuclear Magnetic Resonance", Journal of the American Chemical Society, 91, 7440, 1969.

Lederberg, J., Sutherland, G. L., Buchanan, B. G. and Feigenbaum, E. A., "A Heuristic Program for Solving a Scientific Inference Problem: Summary of Motivation and Implementation", Stanford Artificial Intelligence Project Memo No. 104, November 1969.

Buchanan, B. G., Sutherland, G. L. and Feigenbaum, E. A., "Toward an Understanding of Information Processes of Scientific Inference in the Context of Organic Chemistry", in Machine Intelligence 5, B. Meltzer and D. Michie, eds., Edinburgh University Press, 1970. (Also Stanford Artificial Intelligence Project Memo No. 99, September 1969)

Publications
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Buchanan, B. G., Sutherland, G. L., and Feigenbaum, E. A., "Heuristic DENDRAL: A Program for Generating Explanatory Hypotheses in Organic Chemistry", in Machine Intelligence 4, B. Meltzer and D. Michie, eds., Edinburgh University Press, 1969. (Also Stanford Artificial Intelligence Project Memo No. 62, July 1968.)

Feigenbaum, E. A., "Artificial Intelligence: Themes in the Second Decade", in Final Supplement to Proceedings of the IFIP68 International Congress, Edinburgh, August 1968. (Also Stanford Artificial Intelligence Project Memo No. 67, August 1967)

Lederberg, J. and Feigenbaum, E. A., "Mechanization of Inductive Inference in Organic Chemistry", in Formal Representations for Human Judgment, B. Kleinmuntz, ed., Wiley, 1968. (Also Stanford Artificial Intelligence Project Memo No. 54, August 1967.)

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Thomas C. Rindfleisch | Research Associate | 12-10-41 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Oshkosh, Wisconsin, USA | USA | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Purdue University, Lafayette, Ind. | B.S | 1962 | Physics |
| California Institute of Technology, Pasadena, CA | M.S | 1965 | Physics |
| | Ph.D | Thesis to be completed. All course work and examinations completed. | |

HONORS

Purdue University, Graduated with Highest Honors, Sigma Xi.

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Space sciences, computer science and image processing | Technical Support |

RESEARCH SUPPORT *(See instructions)*

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1971-Present Stanford University Medical School, Department of Genetics, Stanford, CA.
Research Associate - Mass Spectrometry, Instrumentation research.

1962-1971 Jet Propulsion Laboratory, California Institute of Technology, Pasadena, CA.
Relevant Experience:
1969-1971: Supervisor of Image Processing Development and Applications Group.
1968-1969: Mariner Mars 1969 Cognizant Engineer for Image Processing
1962-1968: Engineer - design and implement image processing computer software.

1. Rindfleisch, T. and Willingham, D., "A Figure of Merit Measuring Picture Resolution," JPL Technical Report 32-666, September 1, 1965.

2. Rindfleisch, T. and Willingham, D., "A Figure of Merit Measuring Picture Resolution," Advances in Electronics and Electron Physics, Volume 22A, Photo-Electronic Image Devices, Academic Press, 1966.

Thomas C. Rindfleisch
PUBLICATIONS (cont'd)

3. Rindfleisch, T., "A Photometric Method for Deriving Lunar Topographic Information," JPL Technical Report 32-786, September 15, 1965.

4. Rindfleisch, T., "Photometric Method for Lunar Topography," Photogrammetric Engineering, March 1966.

5. Rindfleisch, T., "Generalizations and Limitations of Photoclinometry," JPL Space Science Summary Volume III, 1967.

6. Rindfleisch, T., "The Digital Removal of Noise from Imagery," JPL Space Science Summary 37-62 Volume III, 1970.

7. Rindfleisch, T., "Digital Image Processing for the Rectification of Television Camera Distortions," Astronomical Use of Television-Type Image Sensors, NASA Special Publication SP-256, 1971.

8. Rindfleisch, T., Dunne, J., Frieden, H., Stromberg, W., and Ruiz, R., "Digital Processing of the Mariner 6 and 7 Pictures," Journal of Geophysical Research, Volume 76, Number 2, January 1971.

9. Rindfleisch, T., "Digital Image Processing," To be published, IEEE Special Issue, July 1972.

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Donald C. Harrison | Professor of Medicine | 2/24/34 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Blount County, Alabama | U.S. | X Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Birmingham Southern College, Ala. | B.S. | 1954 | Chemistry |
| Medical College of Alabama | M.D. | 1958 | Medicine |

**HONORS**

Omicron Delta Kappa, Phi Beta Kappa, Alpha Omega Alpha

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Computer applications in Cardiology | Collaborator |

**RESEARCH SUPPORT** *(See instructions)* Medical Cardiology, HE-5866, NIH, 7/70-6/71, $50,149 15% effort. Evaluation of Cardiovascular System During Various Circulatory Stresses, NGR-05-020-305, NASA, 9/70-8/71, $66,431, 6% effort. Undergraduate-Clinical, HE-5107, NIH, 3/71-2/72, $25,000, 5% effort. Investigative Cardiovascular Physiology & Pharmacology, HE-5709, NIH, 7/68-6/73, $497,835, 17.5% effort. Cardiovascular Adrenergic Receptors-Effects of Drugs, HE-9058, NIH, 9/67-8/72, $174,080, 17.5% effort.

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1972– Professor of Medicine, Stanford Univ. School of Med., Stanford, Ca.
1968-72 Associate Prof. of Medicine, Stanford Univ, School of Med.
1967– Chief, Division of Cardiology, Stanford Univ. School of Med.
1965-68 Asst. Prof. of Medicine, Stanford Univ. School of Med.
1964-69 Asst. Program Director, Clinical Research Center, Stanford Univ.
1963-64 Instructor in Medicine and Chief Resident in Medicine, Stanford Univ. School of Med.
1961-63 Clinical Research Associate, National Heart Institute, NIH, Bethesda, Md.
1960-61 Research Fellow, Harvard Medical School, Boston, Mass.
1958-60 Intern and Asst. Resident in Medicine, Peter Bent Brigham Hospital, Boston, Mass.

Donald C. Harrison, M.D.

Bibliography

1. Stenson, R.E., Crouse, L., Henry, W.L., and Harrison, D.C.: A time-shared digital computer system for on-line analysis of cardiac catheterization data. Comput. Biomed. Res. 1: 605-614, 1968.

2. Henry, W.L., Crouse, L., Stenson, R., and Harrison, D.C.: Computer analysis of cardiac catheterization data. Amer. J. Cardiol. 22:696-705, 1968.

3. Harrison, D.C., and Miller, H.A.: The expansion of a conventional cardiac catheterization laboratory to a computer-assisted laboratory. Measurements for Medicine (Hewlett-Packard). 1971 (Booklet)

4. Harrison, D.C., Ridges, J.D., Sanders, W.J., Alderman, E.L., and Fanton, J.A.: Real-time analysis of cardiac catheterization data using a computer system. Circulation 44: 709-718, 1971.

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Stenson, Robert E. | Asst. Prof. of Medicine | 6/1/38 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Pennsylvania | U.S. | ☒ Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Massachusetts Institute of Tech.<br>Harvard School of Medicine | M.S.<br>M.D. | 1960<br>1965 | Elec. Engr. |

**HONORS**

Eta Kappu Nu-Honorary Society of Electrical Engineers
Tau Beta Pi-Honorary Society of Engineers
Sigma Xi-Honorary Scientific Society

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Computer Applications in Cardiology | Collaborator |

**RESEARCH SUPPORT** *(See instructions)*

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1972- Assistant Professor of Medicine, Stanford University School of Medicine, Stanford, Cal.
1971- Clinical Instructor of Medicine, University of California, Davis, Cal.
1970-72 Major USAF, MC, Staff Cardiologist, Travis AFB, Cal.
1969-70 Sr. Resident, Stanford University Hospital, Stanford, Cal.
1967-69 Postdoctoral Fellow, Cardiology Division, Stanford University School of Medicine, Stanford, Cal.
1966-67 Resident, Beth Israel Hospital, Boston, Mass.
1965-66 Intern, Beth Israel Hospital, Boston, Mass.

Robert E. Stenson, M.D. Bibliography

1. Stenson, R.E., Crouse, L., Henry, W.L., Harrison, D.C.: A Time-Shared Digital Computer System for on-Line Analysis of Cardiac Catheterization Data: Computers and Biomedical Research 1:605, June 1968.

2. Henry, W.L., Crouse, L., Stenson, R.E., Harrison, D.C.: Computer Analysis of Cardiac Catheterization Data: Am. J. Cardiology, 22:696, Nov. 1968.

3. Stenson, R.E., Constantino, R., Harrison, D.C.: Interrelationships of Hepatic Blood Flow, Cardiac Output and Blood Levels of Lidocaine in Man: Circulation 43:205, Feb. 1971.

4. Stenson, R.E., Harrison, D.C.: Cardiac Output: Computer, Dow and Fick. (In press) Cardiovasc. Res., 1972.

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Thomas A. Stamey, M. D. | Professor of Surgery<br>Chairman, Division of Urology | April 26, 1928 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Rutherfordton, N.C. | USA | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Vanderbilt University, Nashville, Tenn. | A.B. | 1948 | |
| Johns Hopkins University School of Medicine | M.D. | 1952 | Medicine |
| Johns Hopkins University School of Medicine, Brady Urological House Staff Residency | | 1952-1956 | Urology |

**HONORS** Chairman, Comm. Renal Disease and Urology Training Grants, NIAMD, NIH; Member, Advisory Board, USPHS/Coop Study on Renal Disease and Pyelonephritis; Member, National Scientific Advisory Board, National Kidney Foundation; Member, Scientific Advisory Council, No. Calif. Kidney Foundation; Member, Research Comm., No. Calif. Kidney Fndtn; Editor, Urology Digest; Member, Editorial Board, Invest. Urol.; Member, Editorial Board, KIDNEY

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Renal Physiology. Infectious Diseases. | Collaborator |

**RESEARCH SUPPORT** *(See instructions)*

2 TO1 AM 05513 -- Training Grant in Urology
Period 7/1/71-6/30/76

5 RO1 AI 09366 -- Urinary Infection Grant
Period 1/1/70-12/31/72

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

| | |
|---|---|
| Professor of Surgery, Chairman, Division of Urology<br>Stanford University School of Medicine | 1964-present |
| Sabbatical year with Prof. Paul Beeson,<br>Nuffield Dept. of Medicine<br>Radcliffe Infirmary, Oxford, England | 1967-1968 |
| Assoc. Professor of Surgery, Chairman, Division of Urology<br>Stanford University School of Medicine | 1961-1964 |
| Assoc. Professor of Urology<br>Johns Hopkins University School of Medicine | 1960-1961 |
| Asst. Professor of Urology<br>Johns Hopkins University School of Medicine | 1958-1960 |
| U. S. Armed Forces, United Kingdom-Urological Consultant | 1956-1958 |

PUBLICATIONS:

See list attached

THOMAS A. STAMEY, M.D.

## PUBLICATIONS

### Books

Renovascular Hypertension. Baltimore: Williams & Wilkins Co., 1963. 1st reprinting, Mar. 1967.

Urinary Infections. Baltimore: Williams & Wilkins Co. (in press).

### Chapters in Books

Stamey, T.A. and Good, P.H.: Diagnostic tools in the evaluation of renal vascular disease. In: Hypertension, Recent Advances. Philadelphia: Lea & Febiger, 1961, pp. 189-203.

Stamey, T.A.: Differential renal function studies. In: Diagnostic Urology: A Handbook of Urologic Diagnostic Technique. Edited by J. Glenn. New York: Harper & Row, Chapt. 9, 1964.

Stamey, T.A.: Some observations on the filtration fraction, on the transport of sodium and water in the ischemic kidney, and on the prognostic importance of R.P.F. to the contralateral kidney in renovascular hypertension. In: Ciba Foundation Symposium on Antihypertensive Therapy. Edited by F. Gross. Heidelberg, Germany: Springer-Verlag, 1966, pp. 555-579.

Stamey, T.A.: The diagnosis of urinary tract disease in the patient with gastrointestinal symptoms. In: Gastroenterologic Medicine. Edited by M. Paulson, Philadelphia: Lea & Febiger, Chapt. 49, 1969.

Palmer, J.M. and Stamey, T.A.: History of differential renal function studies. In: History of Urology. Baltimore: Williams & Wilkins Co. (in press).

Meares, E.M. and Stamey, T.A.: Bacterial prostatitis and recurrent urinary tract infection. In: Infectious Diseases. Edited by P.D. Hoeprich. New York: Harper & Row (in press).

Stamey, T.A.: Renal vein renins or differential renal function studies in the diagnosis of curable, renovascular hypertension? W.W. Scott - Festschrift, Baltimore: Williams & Wilkins Co. (in press).

### Scientific Papers

Stamey, T.A.: The pathogenesis and implications of the electrolyte imbalance in ureterosigmoidostomy. S.G. & O., 103:736-758, 1956.

Stamey, T.A. and Scott, W.W.: Ureteroileal anastomosis. S.G. & O. 104:11-24, 1957.

Stamey, T.A., Nudelman, I.J., Good, P.H., Schwentker, F.N. and Hendricks, F.: Functional characteristics of renovascular hypertension. Medicine. 40:347-394, 1961.

Stamey, T.A.: The diagnosis of curable unilateral renal hypertension by ureteral catheterization. Postgraduate Medicine, 29:496-504, 1961.

Spencer, F.C., Stamey, T.A., Bahnson, H.T. and Cohen, A.: The diagnosis and treatment of hypertension due to occlusive disease of the renal artery. Ann. Surg., 154:674-697, 1961.

Stamey, T.A.: Functional characteristics of renovascular hypertension with emphasis on the relationship of renal blood flow to hypertension. Circ. Res., 11:209-219, 1962.

Stamey, T.A. and Pfau, A.: Some functional, pathological, bacteriological, and chemotherapeutic characteristics of unilateral pyelonephritis in man. (two articles: PartI and II). Invest. Urol. 1:134-172, 1963.

Pfau, A. and Stamey, T.A.: Some functional characteristics of polycystic renal disease. Invest. Urol., 1:593-603, 1964.

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Constantinou, Christos E. | Research Associate | July 21, 1939 |

| PLACE OF BIRTH *(City, State, Country)* | PRESENT NATIONALITY *(If non-U.S. citizen, indicate kind of visa and expiration date)* | SEX |
|---|---|---|
| Limassol, Cyprus | United Kingdom (TI) | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Borough Polytechnic, London, England | HNC | 1964 | Elect. Engineering |
| Stanford University, Stanford, Calif. | M.Sc. | 1968 | Biomedical Engineering |
| | Ph.D. | Expected 1972 | Biomechanics |

HONORS

Member, Institute of Electrical and Electronic Engineers

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Electrophysiology and biomechanics of the upper urinary tract. | Collaborator |

RESEARCH SUPPORT *(See instructions)*

NIH Training Grant in Urology - 2 T01 AM 05513
July 1, 1971 - June 30, 1973

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1969- Research Associate, Department of Surgery (Urology), Stanford University
1966-1969 Research Assistant, Department of Surgery (Urology), Stanford University

Development of computer based system for the real time collection and analysis of experimental data from the surgical laboratory. Integration and construction of physiological monitoring devices in the study of the dynamics of transport in the ureter. Incorporation of new electrophysiological techniques with bio-mechanical transducers to evaluate static and dynamic parameters of the peristaltis.

Cooperation with the Radiology Department in the assessment of contrast media and other methods of visualizing the ureter, *in vivo*, using the technique described in the list of publications enclosed.

Participate in the training of research residents in the quantification of experimental data and teaching in biophysical and biostatistical techniques using the time shared computer.

Ph.D. candidate. Biomedical Engineering.

1965-1966 Research Assistant, Microwave Laboratory, Department of Radiotherapy, Laser research on parametric oscillators.

Christos Constantinou
Research Associate



## Bibliography

### Chapters in Books

Constantinou, C.E., Dale, R.L., Briggs, E.M., and Govan, D.E.: Electrophysiological methods in the study of ureteral dynamics. In URODYNAMICS, ed. Boyarsky, S., Chapter 12, Academic Press, New York, 1971.

Constantinou, C.E., Briggs, E.M., Dale, R.L., and Govan, D.E.: Real time digital computer system for ureteral physiology investigation. In URODYNAMICS, ed. Boyarsky, S., Chapter 33, Academic Press, New York, 1971.

### Scientific Papers

Constantinou, C.E. and Briggs, E.M.: Precision electrostatic urine flowmeter. J. Appl. Physiol., 29:396-397, 1970.

Constantinou, C.E., Dale, R.L., Briggs, E.M., Perkash, I., Engelsgjerd, G.L., and Govan, D.E.: Dynamics of the upper urinary tract: I. System for data collection and evaluation. Invest. Urol., 8:645-654, 1971.

Dale, R.L., Constantinou, C.E., Briggs, E.M., and Govan, D.E.: Dynamics of the upper urinary tract: II. The effects of an indwelling ureteral catheter on ureteral peristalsis. Invest. Urol., 8:655-672, 1971.

Constantinou, C.E., Sands, J.P., and Govan, D.E.: Computer monitoring and control instrumentation in urology research. Proceedings of the 8th Annual Rocky Mountain Bioengineering Symposium. pp. 147-151, 1971.

Constantinou, C.E. and Butler, E.D.: Medical application of computer displays in the rapid examination of developing abnormality patterns in the kidney. Digest of Society of Information Display International Symposium, pp. 72-74, 1971.

Rosen, D.I., Constantinou, C.E., Sands, J.P., and Govan, D.E.: Dynamics of the upper urinary tract: III. The effects of changes in bladder pressure and volume on ureteral peristalsis. J. Urol., 106:209-213, 1971.

Sands, J.P., Constantinou, C.E., and Govan, D.E.: Bladder pressure and its effect on mean arterial blood pressure. Invest. Urol., 10:6-17, 1972.

Briggs, E.M., Constantinou, C.E., and Govan, D.E.: Dynamics of the upper urinary tract: IV. The relationship of urine flow rate and rate of ureteral peristalsis. Invest. Urol., 10:18-23, 1972.

### Abstracts and Demonstrations

Butler, E.D. and Constantinou, C.E.: The application of computers to urology. 64th Annual Meeting of the A.U.A., San Francisco, May 1969.

Constantinou, C.E., Butler, E.D., and Govan, D.E.: Computer graphic techniques in urologic follow-up of myelodysplasia in children. 39th Annual Meeting of American Academy of Pediatrics, San Francisco, Oct. 1970.

Friedland, G.W., Kohatsu, S., and Constantinou, C.E.: Relationship between motility of gastric sling fibers and distal esophagus. Proc. of 18th AUR Symposium. Invest. Radiol., p. 272 5(4)1970.

Dale, R.L., Constantinou, C.E., and Govan, D.E.: Dynamics of the upper urinary tract: The effects of acute and chronic obstruction on peristalsis. Presented at the Society of University Urologists - Residents Meeting, New Haven, Conn., May 6-9, 1970.

Granato, J.J., Constantinou, C.E., and Govan, D.E.: The effect of radiopaque contrast media on the ureter. Western Section, American Urological Association, Inc. July 2-7, 1972.

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Elliott C. Levinthal | Assoc. Dean for Research, SU Med School, Director of IRL | April 13, 1922 |
| **PLACE OF BIRTH (City, State, Country)** | **PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)** | **SEX** |
| Brooklyn, New York | USA | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Columbia College | B.A. | 1942 | Physics |
| Massachusetts Institute of Technology | M.S. | 1943 | Physics and Math |
| Stanford University | Ph.D. | 1949 | Physics and Math |

**HONORS**

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Medical Instrumentaion Research | Collaborator |

**RESEARCH SUPPORT** *(See instructions)*

Contract 952489 Mariner 71 Photo Interpretation, Current Year $71,000 Total $445,000
Jet Propulsion Lab, 25% time
Contract NAS-1-9687 Viking 75 Imaging, Current Year $31,658 Total $297,805
Langley Res. Center, 20% time
Grant NGR 05-020-064-513 Cytochemical Studies in Planetary Microorganisms,
Current Year $240,000 Total to date $3,800,000, 25% time
NIH Contract Proposed, Cell Separator Construction, Total $240,000 10% time, no salary
Grant GM17367-03 Automatic Cell Separation - Clinical and Biological Uses,
Current Year $132,000 Total $364,455, 10% time, no salary (cont'd below)

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

| | |
|---|---|
| 1970-present | Associate Dean for Research Affairs, Stanford University School of Medicine |
| 1961-present | Senior Scientist, Director of Instrumentation Research Laboratory, Dept. of Genetics, Stanford University School of Medicine |
| 1953-1961 | President, Levinthal Electronic Products |
| 1952-1953 | Chief Engineer, Century Electronics |
| 1950-1952 | Research Director, Member of Board of Directors, Varian Associates |
| 1949-1950 | Research Physicist, Varian Associates |
| 1946-1948 | Research Associate, Nuclear Physics, Stanford University |
| 1943-1946 | Project Engineer, Sperry Gyroscope Co., New York |
| 1943 | Teaching Fellow in Physics, Massachusetts Institute of Technology |

Research Support (cont'd)
Stanford Medical School Associate Dean for Research 25% time

**Relevant Publications and Papers:**

E. C. Levinthal,"Detection of Extraterrestrial Life", Professional and Technical Group of Instrumentation and Measurements of I.E.E.E., April, 1963.

E. C. Levinthal,"The Detection of Life Within Our Planetary System", Presented at WESCON, August, 1963.

E. C. Levinthal, "The Biological Exploration of Mars", Presented at the Space Technology Laboratory's Invited Lecture Series, November 6, 1963.

E. C. Levinthal, "The Biological Exploration of Mars", Presented at Moffet Field, Fullerton, Los Angles and San Diego, April 27-30, 1964, as part of the University of California Extension Series Lectures - Horizons in Space Biosciences: Exobiology.

E. C. Levinthal, J. Lederberg and L. Hundley, "Multivator - A Biochemical Laboratory for Martian Experiments", Life Sciences and Space Research II, COSPAR (Committee on Space Research) 1964.

B. Halpern, J. W. Westley, E. C. Levinthal, J. Lederberg, "The Pasteur Probe: An Assay for Molecular Asymmetry", Life Sciences and Space Research, COSPAR (Committee on Space Research) 1966.

E. C. Levinthal, "Space Vehicles for Planetary Missions", in: Biology and the Exploration of Mars, Nat. Acad. Sci., National Research Council.

E. C. Levinthal, "Prospects for Manned Mars Missions", in: Biology and the Exploration of Mars, Nat. Acad. Sci., National Research Council.

O. Reynolds, E. Levinthal, G. Soffen, "The Role of the Scientist in Automated Laboratory Systems", AIAA Paper No. 67-632, (1967).

E. C. Levinthal, J. Lederberg and C. Sagan, "Relationship of Planetary Quarantine to Biological Search Strategy", Presented at COSPAR Meeting (Committee on Space Research), London, (1967)

C. Sagan, E. C. Levinthal and J. Lederberg, "Contamination of Mars", Science, 159: 1191-1196 (1968)

E. C. Levinthal, "The Role of Molecular Asymmetry in Planetary Biological Exploration", Gordon Research Conferences, Nuclear Chemistry Section, 1968. (Paper)

**Relevant Publications (continued)**

J. P. Kriss, W. A. Bonner, E. C. Levinthal. "Variable Time-Lapse Videoscintiscope: A Modification of the Scintillation Camera Designed for Rapid Flow Studies." J. Nuclear Med. 10, 249 (1969).

W. E. Reynolds, V. A. Bacon, J. C. Bridges, T. C. Coburn, B. Halpern, J. Lederberg, E. C. Levinthal and E. Steed, "A Computer Operated Mass Spectrometer System" Anal. Chem. 42, 1122 (1970).

H. Masursky, R. Batson, W. Borgeson, M. Carr, J. McCauley, D. Milton, R. Wildey, and D. Wilhelms, B. Murray, N. Horowitz, R. Leighton, and R. Sharp, W. Thompson, G. Briggs, P. Chandeysson, and E. Shipley, C. Sagan and J. Pollack, J. Lederberg, E. Levinthal, W. Hartmann, T. McCord, B. Smith, M. Davies, G. DeVaucouleurs, C. Leovy. "Television Experiment for Mariner Mars 1971" Icarus 12, 10-45 (1970).

H. Masursky, R. M. Batson, J. F. McCauley, L. A. Soderblom R. L. Wildey, M. H. Carr, D. J. Milton, D. E. Wilhelms B. A. Smith, T. B. Kirby, J. C. Robinson, C. B. Leovy G. A. Briggs, T. C. Duxbury, C. H. Acton, Jr., B. C. Murray, J. A. Cutts, R. P. Sharp, Susan Smith, R. B. Leighton, C. Sagan, J. Veverka, M. Noland, J. Lederberg, E. Levinthal, J. B. Pollack, J. T. Moore, Jr., W. K. Hartmann, E. N. Shipley, G. de Vaucouleurs M. E. Davies. "Mariner 9 Television Reconnaissance of Mars and Its Satellites: Preliminary Results" Science, 175 (4019) 294 (1972).

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Leonard A. Herzenberg | Professor of Genetics | Nov. 5, 1931 |
| **PLACE OF BIRTH (City, State, Country)** | **PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)** | **SEX** |
| Brooklyn, New York | U.S. | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Brooklyn College, Brooklyn, New York | A.B. | 1952 | Biology, Chemistry |
| California Institute of Technology, Pasadena | Ph.D. | 1955 | Biochemistry, Immunology |
| Pasteur Institute, Paris, Postdoctoral fellow | | | |

HONORS

Phi Beta Kappa, Sigma Xi,
Distinguished Alumnus Award, Brooklyn College, 1970
Genetics Study Section, National Institutes of Health

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Immunogenetics, somatic cell genetics | Collaborator |

RESEARCH SUPPORT *(See instructions)*

N.I.H. GM-17367, Automated Cell Sorting-Clinical and Biological Uses, $115,072 current year, total funds for project $364,355.
N.I.H. AI-08917, Genetics of Immunoglobulins, $44,044 current year, $240,893 total funds for project period

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1969: present Stanford University School of Medicine, Stanford, California, Professor of Genetics
1964-1969: Stanford University School of Medicine, Stanford, California, Associate Professor of Genetics
1959-1964: Stanford University School of Medicine, Stanford, California, Assistant Professor of Genetics
1957-1959: National Institutes of Health, Bethesda, Maryland. Officer, USPHS (Dr. Harry Eagle)
1955-1957: Pasteur Institute, Paris, France (Prof. Jacques Monod, American Cancer Society Postdoctoral Fellow)
1952-1955: Ph.D. California Institute of Technology, Pasadena, California. (Major: Biochemistry, Prof. H. K. Mitchell; Minor: Immunology, Prof. R. D. Owen)
1948-1952: A.B. Brooklyn College, New York

Publications since 1967:

1. Herzenberg, L. A. and N. L. Warner. 1967. Genetic control of mouse immunoglobulins, p. In B. Cinader (Ed.), Regulation of the antibody response, Chapter XV. C. C. Thomas, Springfield, Illinois.
2. Tyan, M. L., L. J. Cole and L. A. Herzenberg. 1967. Fetal liver cells: a source of thymus-dependent specific immunoglobulin production in radiation chimeras. Proc. of Sec. of Exp. Biol. & Med. 1161-1163.

3. Klein, J., J. Martinkova & L. A. Herzenberg. 1967. Analysis of the histocompatibility-2 (H-2) locus of NZB mice. Transplantation 5: 1335-1337.
4. Klein, J. & L. A. Herzenberg. 1967. Congenic mouse strains with different immunoglobulins allotypes. I. Breeding scheme, histocompatibility tests and kinetics of $\gamma G_{2a}$ globulin production by transferred cells for C3H. S.W. and its congenic partner CWB/5. Transpl. 5:1484-1495.
5. Welton, J., S. R. Walker, G. C. Sharp, L. A. Herzenberg, R. Wistar and W. P. Creger. 1968. Macroglobulinemia with bone destruction. Difficulty of distinguishing between macroglobulinemia and myeloma. Amer. J. of Med. 44:280-288.
6. Warner, Noel L. and L. A. Herzenberg. 1967. Immunoglobulin isoantigens (allotypes) in the mouse. IV. Allotypic specificities common to two distinct immunoglobulin classes. J of Immunol. 99:675-678.
7. Minna, J. D., G. M. Iverson & L. A. Herzenberg. 1967. Identification of a gene locus for $\gamma G_1$ immunoglobulin H chains and its linkage to the H chain chromosome region in the mouse. Proc. of Natl. Acad. of Sci. 58:188-194.
8. Tyan, M. L., L. J. Cole & L. A. Herzenberg. 1967. Fetal liver cells: a source of specific immunoglobulin production in radiation chimeras, pp. 87-89. In J. Dausett, J. Hambruger, G. Mathe (Eds.) Advance in transplantation. Proc. 1st Intl. Cong. Transpl. Soc., Paris, June 27-30 (Munksgaard, Publisher).
9. Herzenberg, L. A., Leonore A. Herzenberg, R. C. Goodlin & E. C. Rivera. 1967. Immunoglobulin syntehsis in mice: suppression by anti-allotype antibody. J. Exp. Med. 126:701.
10. Herzenberg, L. A. J. D. Minna & Leonore A. Herzenberg. 1967. The chromosome region for immunoglobulin heavy chains in the mouse: allelic electrophoretic mobility differences and allotype suppression. Cold Spring Harbor Symposia on Quantitative Biology 32: 181-186.
11 Herzenberg, L. A. H. O. McDevitt & Leonore A. Herzenberg. 1968. Genetics of antibodies. Ann. Rev. of Genetics 2:209-244.
12. Tyan, M. L. & L. A. Herzenberg. 1968. Ontogeny of the mouse immune system. II. Immunoglobulin-producing cells. J. of Immunol. 101:446-450.
13. Tyan, M. L., H. O. McDevitt & L. A. Herzenberg. 1968. Genetic control of the antibody response to a synthetic polypeptide: transfer of response with spleen cells or lymphoid precursors. Abstract and paper submitted to 2nd Intl. Transpl. Cong. N.Y., Sept. 1968.
14. Herzenberg, L. A. and M. L. Tyan. 1968. Genetics of antibody formation: role of thymus in the evolution of the immune response. 12th Intl. Cong. of Genetics, Tokyo, Japan, Aug. 19-28.
15. Tyan, M. L. & L. A. Herzenberg. 1968. Immunoglobulin production by embryonic tissues: thymus independent. Proc. of Soc. for Exp. Biol. & Med. 128;952-954
16. Herzenberg, L. A. 1969. Rabbit Aa locus allotypes: quantitative comparisons in IgG, IgA, and IgM by inhibition of precipitation. Fed. Proc., p. 435 (abstract)
17. Hulett, H. R., W. A. Bonner, J. Barrett and L. A. Herzenberg. 1969. Cell sorting: automated separation of mammalian cells as a function of intracellular fluorescence. Science 166;747.
18. Tyan, M. L., L. A. Herzenberg & P. R. Gibbs. 1969. Lympoid precurosors: thymus independent antibody production. J. of Immunol. 103;1283.
19. L'age=Stehr, J. and L. A. Herzenberg. 1970. Immunological memory in mice. I. Physical separation and partial characterizationof memory cells for different Ig classes from each other and from antibody producing cells. J. of Exp. Med. 131:1093-1108.
20. Jacobson, E. B., J. L'age-Stehr & L. A. Herzenberg. 1970. Immunological memory in mice: II. Cell interactions in the secondary immune response studied by means of Ig allotype markers. J. of Exp. Med. 131:1109-1120.
21. Hulett, H. R., L. A. Herzenberg, W. A. Bonner, and P. L. Wolf. Rapid cell-sorter -- a new tool for cell study with clinical applications. Laboratory Investigations (abstract in press) Presented at 59th Annual Meeting of International Academy of Pathology, St. Louis, Missouri, March, 1970.



☆U.S.GPO: 1970 - 379-849

22. Riblet, Roy J. and L. A. Herzenberg. 1970. Mouse lysozyme: production by a monocytoma, isolation, an comparisons with other lysozyme. Science 168:1595
23. Herzenberg, L. A. Gene interactions in immunoglobulins (in press). Presented at Symposium on Anti-Human Gamma Globulins, Lund, Sweden, Oct. 1969.
24. Herzenberg, L. A. 1970. From cell biology to immunology -- a short trip. J. of Cellular Physiology 76: 303-310.
25. Merrill, J. T., N. Veizades, H. R. Hulett, P. L. Wolf and L. A. Herzenberg. 1971. An improved cell-volume analyzer. Review of Scientific Instruments 42:1157-1163.
26. Bechtol, K. B., T. G. Wegmann, B. W. Chesebro, L. A. Herzenberg & H. O. McDevitt. 1971. The antibody response to (T,G) -A--L in tetraparental mice. Federation Proceedings, p. 1531 (abstract).
27. Riblet, R. J., L. A. Herzenberg & L. A. Herzenberg. 1971. Active allotype suppression in a cell transfer system. Federation Proceedings, p. 2552. (abstract)
28. Bonner, W. A., H. R. Hulett & L. A. Herzenberg. 1971. Highspeed sorting of fluorescence labelled cells. Federation Proceedings, p. EIO. (abstract)
29. Mitchell, G. F., E. O. Chan, M. S. Noble, I. L. WEissman, R. I. Mishell and L. A. Herzenberg. 1971. Specific immunological memory to heterologous erythrocyt s in both T-cell and B-cell populations and requirement for T-cell in expression of B-cell memory. Evidence using Anti θ and anti-allotype sera with congenic mice. J. Exp. Med., in press.

30. Mitchell, G. F. R. I. Mishell and L. A. Herzenberg. 1971. Studies on the influence of T-cells in antibody production. Presented at the 1st International Congres of Immunology, Washington D.C., August, 1971.
31. Herzenberg, Leonore, E. B. Jacobson, L. A. Herzenberg, and R. J. Riblet. 1971. Chronic allotype suppression in mice: an active regulatory process. New York Academy of Sciences. In press.
32. Herzenberg, L. A. 1971. Immunoglobulin genetics in cellular immunology. New York Academy of Sciences. In press.

Selected publications before 1967:

1. Herzenberg, L. A. and Leonore A. Herzenberg. 1959. Adaptationto lactose. Nutrition Review 17:65-67.
2. Herzenberg, L. A. 1959. Studies on the induction of beta-galactosidase in a cryptic strain of escherichia coli. Biochimica et Biophysica Acta 31:525-538.
3. Herzenberg, L. A. and Leonore A. Herzenberg. 1961. Association of H-2 antigens with the cell membrane fraction of mouse liver. Proc. of Natl. Acad. of Sci. 47:762-767.
4. Herzenberg, Leonard A. 1962. Part I. Steps toward a gentics of somatic cells in culture. Part II. Maternal isoimmunization as a result of breeding in the mouse
5. CAnn, H. M. and L. A. Herzenberg. 1963. In vitro studies of mammalian somatic cell variation II. Isoimmune cytotoxicity with a cultured mouse lymphoma and selection of resistant variants. J. of Exp. Med. 117:267-284.
6. Wunderlich, J. and L. A. Herzenberg. 1963. Genetics of a gamma globulin iso= antigen (allotype) in the mouse. Proc. of Natl. Acad. of Sci. 49:592-598.
7. Erickson, R. P., D. K. Tachibana, L. A. Herzenberg and L. T. Rosenberg. 1964. A single gene controlling hemolytic complement and a serum antigen in the amouse. J. of Immunol. 92:611-615.
8. Hereenberg, L. A. 1964. A chromosome region for gamma $2_A$ and beta $2_A$ globulin H chain isoantigens in th mouse. Cold Spring Harbor Symposium of Quantitative Biology 29:455-464.

Total number of publications: 75.



☆U.S.GPO: 1970 – 376-696

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Bert S. Kopell, M. D. | Chief, Psyt. Research & Training Division, VA Hospital Palo Alto, California | 2/11/31 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| New York, New York | USA | ☒ Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Univ. of Geneva, Geneva, Switzerland | Medical Baccalaureate | 1953 | Medical Science |
| Univ. of Geneva, Geneva, Switzerland | M. D. | 1958 | |
| Maimonides Hospital, New York | Rotating Intern | 1958-59 | |

**HONORS**

Psychiatry Career Teaching Award--July, 1966 - June, 1968
Diplomate of American Board of Psychiatry & Neurology in Psychiatry, 1966

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Electrophysiological Studies of Drugs | Collaborator |

**RESEARCH SUPPORT** *(See instructions)*

1. Current Research Support
   a. 20% effort VA Part 1 funds "Electrocortical Measurement of Set and Attention in Psychiatric Patients". Grant terminates 6/20/72, $15,000 for F. Y. 1972.
   b. 10% effort to: MH 19918; total direct costs for May 1, 1971 to April 30, 1972--$115,062.
2. Pending Applications
   a. 40% effort "Brain Responses, Behavior and Drug States in Man: A General Research Proposal". Total amount requested for current year $154,134. Total requested for a 5-yr. period $635,801. To NIMH and the VA (See Below)

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

| | |
|---|---|
| 1970-Present | Chief, Psychiatry Research & Training Div., VA Hospital, Palo Alto, CA. |
| 1970-Present | Assoc. Professor, Stanford University Sch. of Medicine, Dept. Psychiatry |
| 1969-Present | Director, Medical Student Training Program in Psych., Stanford Univ. |
| 1968-Present | Director, Human Perception Lab., Stanford Univ. Sch. of Med., Dept. Psychi. |
| 1965-1970 | Assist. Professor, Stanford Univ. Sch. of Med., Dept. Psychiatry |
| 1964-1966 | Research Associate, Palo Alto Veterans Administration Hospital |
| 1964-1965 | Instructor, Stanford Univ. Sch. of Medicine, Dept. of Psychiatry |
| 1962-1964 | Chief, Psychiatric Services, Westover Air Force Base, Massachusetts |
| 1959-1962 | Resident, University of Colorado, Denver, Colorado |
| 1958-1959 | Rotating Intern, Maimondes Hospital, New York |

See representative publications

2. Pending Applications (continued)
   b. 20% effort "Brain Responses in Alcoholics During Drinking Cycle". Total amount requested for current year $73,607. Total requested for a 3-yr. period $222,699. Submitted to NIMH.

## PUBLICATIONS

Stilson, D. W. and Kopell, B. S. The recognition of visual signals in the presence of visual noise by psychiatric patients. J. Ner. Ment. Dis., 139: 209-221, 1964.

Kopell, B. S., Noble, E. P. and Silverman, J. The effect of thiamytal and methamphetamine on the two-flash fusion threshold. Life Sciences, 4:2211-14, 1965.

Stilson, D. W., Kopell, B. S., Vandenbergh, R., and Downs, M P. Perceptual recognition in the presence of noise by psychiatric patients. J. Nerv. Ment. Dis., 142: 235-247, 1966.

Noble, E. P., Silbergeld, S., Kopell, B. S., McKinney, W., Wittner, W. K., and Butte, J. C. The effects of physiologic doses of corticosteroid on catecholamine metabolism in man. J. Psychiat. Res., 6: 159-167, 1968.

Kopell, B. S. and Wittner, W. K. The effects of chlorpromazine and methamphetamine on visual signal from noise detection. J. Nerv. Ment. Dis., 147:418-24, 1968.

Hilf, F. and Kopell, B. S Non-contingent reinforcement and certainty. Psychonomic Science, 11: 211-213, 1968.

Macpherson, L. and Kopell, B. S. Systems approach to the measurement of slow evoked potential changes. Med. Biol. Eng., 6: 673-65, 1968.

Kopell, B. S., Lunde, D. T., Clayton, R. B., and Moos, R. H. Variations in some measures of arousal during the menstrual cycle. J. Nerv. Ment. Dis., 148: 180-187, 1969.

Moos, R. H., Kopell, B. S., Melges, F. T., Yalom, I. D., Lunde, D. T., Clayton, R. B., and Hamburg, D. A. Fluctuations in symptoms and mood during the menstrual cycle. J. Psychosom. Res., 13 37-44, 1969.

Kopell, B. S., Wittner, W. K. and Warrick, G. The effects of stimulus differences, light intensity and selective attention on the amplitude of the visual averaged evoked potential in man. Electroenceph. Clin. Neurophysiol., 26:619-22, 1969.

Kopell, B. S. The role of progestins and progesterone in brain function and behavior. In The Metabolic Effects of Gonadal Hormones and Contraceptive Steroids, Hilton A. Salhanick (ed.), New York: Plenum Press, 1969.

Kopell, B. S., Wittner, W. K., Lunde, D. T., Warrick, G., and Edwards, D. Cortisol effects on the averaged evoked potential, alpha rhythm, time estimation, and the two-flash fusion threshold. Psychosom. Med., 32: 39-49, 1970.

Roth, W. T. and Kopell, B S. The auditory evoked response to repeated stimuli during a vigilance task. Psychophysiology, 6: 301-309, 1969.

Hilf, F. D., Wittner, W. K., Kopell, B. S. Feedback utilization styles of paranoid patients. J. Nerv. Ment. Dis., 149: 491-495, 1969.

Roth, W. T., Kopell, B. S., and Bertozzi, P. E. Effects of attention on averaged evoked response to speech sounds. Electroenceph. Clin. Neurophysiol., 29: 38-46, 1970.

Bert S. Kopell, M. D.
Publications Continued

Kopell, B. S , Wittner, W. K., Lunde, D. T., Warrick, G. and Edwards, D. Influence of triiodothyronine on selective attention as measured by the averaged evoked potential in man. Psychosom. Med., 32: 495-502, 1970.

Zarcone, V., de la Pena, A., Kopell, B. S., and Dement, W. Visual evoked response following REM deprivation. Psychophysiology, 7: 301, 1970.

Kopell, B. S., Zarcone, V., de la Pena, A., and Dement, W. C Changes in selective attention as measured by the visual averaged evoked potential following REM deprivation in man. Electroenceph. Clin. Neurophysiol., 32: 322-325, 1972.

Macpherson, L., Hutchings, M. D., and Kopell, B. S. An electrically operated skin resistance switch. Psychophysiology, 8: 673-675, 1971.

Macpherson, L. and Kopell, B. S. A zero-setter and voltage reference unit for EEG amplifier systems. Psychophysiology, in press. (1972).

Tinklenberg, J. R., Kopell, B. S., Hollister, L. E., and Melges, F. T. A comparison of the effects of marihuana and ethanol on memory, evoked potential, and contingent negative variation. Psychopharmacology Bulletin, in press. (1972).

Corby, J. C. and Kopell, B. S. Blink and eye movement EEG artifacts. Psychopyhsiology, in press. (1972).

Kopell, B. S., Maxim, P., and Koran, L. Influence of lithium on selective attention as measured by the averaged evoked potential in man. Submitted and accepted for publication by Psychopharmacologia.

Kopell, B. S., Wittner, W. K., Lunde, D. T., and Wolcott, L. L. Effect of amphetamines and barbiturates on selective attention as measured by the averaged evoked response. In preparation.

Kopell, B. S , Tinklenberg, J. R and Hollister, L. E. Effects of marijuana and alcohol on the contingent negative variation. In preparation. To be submitted to Archives of General Psychiatry.

Kopell, B. S., Wittner, W. K., and Lunde, D. T. Influence of amphetamines and barbiturates on contingent negative variation. In preparation. To be submitted to Psychopharmacologia.

Corby, J. C. and Kopell, B. S. Effect of predictability on evoked response enhancement in selective attention. In preparation.

Lunde, D. T., Costell, R., Wittner, W. K. and Kopell, B. S. The electrocorticol expression of sexual object preference in non-deviant male and female subjects. In preparation. To be submitted to Science.

Moos, R., Clayton, R., Kopell, B. S. and Hamburg, D. A. Progesterone and menstrual cycle symptomatology. In preparation.

# BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Walton T. Roth, M.D. | Chief of Psychiatric Consultation Services | 2/23/39 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Topeka, Kansas | USA | ☒ Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Harvard College | B.A. | 1961 | Biochemistry |
| New York University School of Medicine | M.D. | 1965 | |

**HONORS**

Harvard National Scholar, 1957-1961
N.Y.U. Merit Scholar, 1961-1965
AOA Medical Honor Society, elected 1965
Diplomate of American Board of Psychiatry and Neurology in Psychiatry, 1972

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Human Electrophysiology | Collaborator |

**RESEARCH SUPPORT** *(See instructions)*

1. Current Research
   None
2. Pending Applications
   a. 50% effort "Brain responses in alcoholics during drinking cycle". Total amount requested for current year $73,607. Total requested for a 3-year period $222,699. Submitted to NIMH.
   b. 50% effort "Brain responses, behavior and drug states in man: a general research proposal". Total amount requested for current year $154,134. Total requested for a 5-year period $635,801. To NIMH and VA.

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

| | |
|---|---|
| 1971 - Present | Chief of Psychiatric Consultation Services, V.A. Hospital, Palo Alto, Ca. |
| 1969 - 1971 | National Institutes of Mental Health, Clinical Associate |
| 1966 - 1969 | Resident in Psychiatry, Stanford Hospital |
| 1965 - 1966 | Intern in Medicine, North Carolina Memorial Hospital |
| 1964 | National Science Foundation Summer Fellowship, The Worcester Foundation for Experimental Biology |
| 1960 | National Science Foundation Summer Fellowship, Harvard |

See Representative Publications

Publications, Walton T. Roth, M.D.

Roth, W.T. The effect of LSD, mescaline, and d-amphetamine on the evoked "secondary discharge". Psychopharmacologia (Berl.), 9: 253-258, 1966.

Roth, W.T. and Kopell, B.S. The auditory evoked response to repeated stimuli during a vigilance task. Psychophysiology, 6: 301-309, 1969.

Roth, W.T., Kopell, B.S., and Bertozzi, P.E. The effect of attention on the average evoked response to speech sounds. Electroenceph. clin. Neurophysiol., 29: 38-46, 1970.

Stillman, R., Roth, W.T., Colby, K.M., and Rosenbaum, C.P. An on-line computer system for initial psychiatric inventory. Amer. J. Psychiat., 125: 7, Jan. 1969 suppl., 8-11.

Roth, W.T. and Cannon, E.H. Some features of the auditory evoked response in schizophrenics. Arch. Gen. Psychiat., in press, 1972.

Roth, W.T., Galanter, M., Weingartner, H., Vaughan, T., and Wyatt, R. The effect of marijuana and synthetic delta-9-THC on the auditory evoked response and background EEG in humans. Submitted for publication, 1972a.

Roth. W.T. Auditory evoked responses to unpredictable stimuli. Submitted for publication, 1972b.

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Ronald D. Jamtgaard | Facility Director (ACME) | May 2, 1933 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Sioux Falls, South Dakota | USA | ☒ Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Augustana College, Sioux Falls, S.D. | A.B. | 1957 | |
| University of Minnesota | | | coursework for M.A. in Pub. Admin. |
| University of Minnesota | | | |

**HONORS**

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Biomedical computing, communications systems | Management Support |

**RESEARCH SUPPORT** *(See instructions)*

ACME Computing Facility, Stanford School of Medicine 95% time RR00311
S.U. Medical Center Computer Planning Funds 5%

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1970-present Director, Advanced Computer for MEdical Research (ACME) Stanford Medical School, Stanford Computation Center, Stanford University.

1969-1970 Manager of Administrative Services, Radiation Division, Varian Associates, Palo Alto, California.

1967-1969 Inter-Facility Associate Director, Stanford Computation Center, Stanford University.

1966- Executive Assistant to Director (Dr. W.K.H. Panofsky) Stanford Linear Accelerator Center, Stanford University.

1961-1966 Budget Officer, Stanford Linear Accelerator Center, Stanford University.

1958-1961 Management Trainee, Field Office Liaison Officer and Budget Analyst U.S. Atomic Energy Commission at Germantown, Maryland, and Idaho Falls, Idaho.

SE... PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Gio C.M. Wiederhold | Lecturer, Consultant, and Senior Systems Designer | June 24, 1936 |
| **PLACE OF BIRTH (City, State, Country)** | **PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)** | **SEX** |
| Varese, Italy | Permanent Resident Alien | ☒ Male ☐ Female |

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| TMS Technicum, Rotterdam, Holland<br>U.C. Berkeley, Calif. 1960-64 | B.S. | 1957 | Aeronautical Eng.<br>Coursework in heuristic programming, compiler design, etc. |

**HONORS**

Graduated cum laude from TMS Technicum.
Listed in WHO's WHO IN AMERICA, vol . 35, 1968-69.

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Use of computers in data reduction and medical applications of computers. | Technical Staff |

**RESEARCH SUPPORT** *(See instructions)*

ACME Computing Facility, Computation Center, Stanford University. Supported under the Biotechnology Resources Branch of NIH, Grant No. RR00311-06.(30% time)

Department of Surgery, Div. of Cariovascular Surgery, S.U. Medical Center, Stanford University, consultant. (10% time)

Hospital Data Processing, S.U. Hospital, Stanford University, technical assistant. (60% time)

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1970-present: User Services Manager, ACME and consultant to Director, S.U. Hospital, ADP.
1965-70: Director, ACME Facility, Stanford Computation Center.
1965-present: Lecturer, Computer Science Dept., Stanford University.
1964-65: Visiting Professor, Indian Inst. of Technology, Kanpur, India under USAID.
1961-64: Head of Programming, U.C. Berkeley, Calif.
1958-61: IBM Service Bureau Corp., New York and San Jose, Programmer.
1958: SHAPE Air Defense Technical Center, Europe - technical assistant.

Consultant to American Cyanamid Co. (1961-date); Optimum Systems Inc. (1967-date); Syntex Corp. (1968); U.C. Berkeley Center for Research and Management Science ( 1968-69); Reeves Telecom Corp., N.Y. and Detroit (1969-70). Consultant, National Center for Health Services, USPHS. Consultant, Polymorphic Corp., Palo Alto, Calif.

Bibliography:

1) Wiederhold, G., Loewner, P. et al.: CSI/CSO Insurance Rate Tables. SBC Corp., 1959.
2) Wiederhold, G. and Tsao, C. C.: A program for evaluation equilibrium combustion. Kinetics, Equilibrium and Performance of High-Temperture Systems, 1962.
3) Wiederhold, G. and Potter, R. L.: Computation of the equilibrium composition of multi-component chemical systems. American Cyanamid Co., Stamford, Conn., 1962.
4) Wiederhold, G.: Control language for an interactive time-sharing system. SHARE TSS/67 Control Language Comm., 1966.

(continued)

Bibliography (continued)

5) Wiederhold, G.: Internal Documentation, U.C. Computer Center, Berkeley, Calif., 1962-65. FORFOR: A timesharing compiler system design; programming using Assembly Macros; FXMS: An error traceback procedure for FORTRAN IV and MAP Programs; MORT: A collection of Text Manipulating Procedures; Proposal for simple system allowing direct access to the computer; STUDENT: A Fast FORTRAN IV Compiler.

6) Wiederhold, G.: A Summary of the ACME System. ONR Computer and Psychobiology Conference Proceedings, Monterey, Calif., May 17, 1966.

7) Wiederhold, G.: A Summary of the ACME System. Conversation with a 50 Conference Proceedings, Chicago, Ill., October 31 - November 1, 1966.

8) Sanders, W.J., and Wiederhold, G., et al.: An Advanced Computer System for Medical Research. AFIPS Conference Proceedings 31, Anaheim, Calif., 1967.

9) Brietbard, G.Y., and Wiederhold, G.: PL/ACME: An Incremental Compiler for a Subset of PL/1. IFIP68 Congress Proceedings, Edinburgh, Scotland, August 1968.

10) Wiederhold, G. and Hundley, L.: A Time-Shared Data Acquisition System. Digest 1969 IEEE Computer Group Conf. on Real-Time Systems, IEEE, Minneapolis, Minn., pp. 190-196, June 1969.

11) Wiederhold, G.: Setting Up a General Purpose Data Acquisition System. Proceedings of IBM Scientific Computing Symposium on Computers in Chemistry, Data Processing Division, White Plains, New York, August 1969.

12) Wiederhold, G.: An Advanced Computer System for Medical Research. Proceedings of IBM Japan Computer Science Symposium, Research and Computer System, Tokyo, Japan, pp. B1-B15, November 1969.

13) Crouse, L. and Wiederhold, G.: An Advanced Computer System for Real-Time Medical Applications. Computer in Biomedical Research (Academic Press), vol. 2, 6, December 1969.

14) Wiederhold, G.: Internal Documentation (ACME Notes), Stanford Computation Center, ACME Computer Facility, Stanford, Calif., November 1965 - present.

15) Wiederhold, G.: Medical Uses of Computer (in Japanese) presented in Tokyo, Japan, November 1969, published in IBM Review No. 27, February 1970.

16) Wiederhold, G., Brietbard, G.: A Method for Increasing the Modularity of Large Systems. IEEE Computer Group News, vol. 3, 2, March-April 1970.

17) Girardi, S., Frey, R., Wiederhold, G.: A Filing System for Medical Research. Presented at Journees Internationales d'Informatique Medicale de Toulouse, France, March 4-6, 1970, and at The Eighth Annual Symposium on Biomathematics and Computer Science in the Life Sciences, Houston, Texas, March 23-24, 1970.

18) Crouse, L. and Wiederhold, G.: Interactive Use of a Timesharing System for Medical Laboratory Supports, San Diego Biomedical Symposium Computing On-Line, April 6-8, 1970.

19) Wiederhold, G., and Ehrman, J.: An inferred syntax and semantics of PL/S. Submitted to Sigplan Notices, A Journal of the ACM, September 1971.

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE *(Mo., Day, Yr.)* |
|---|---|---|
| Hundley, Lee | Assistant Director, ACME | January 31, 1931 |
| **PLACE OF BIRTH** *(City, State, Country)* | **PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)* | **SEX** |
| Dallas, Texas | USA | ☒ Male ☐ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Southern Methodist University, Dallas, Tex.<br>San Jose State College, S.J., Calif. | B.S. | 1960 | Electrical Engineer coursework for MA |

**HONORS**

Sigma Tau - Engineering Honorary Fraternity
Eta Kappa Nu - Electrical Engineering Honorary Fraternity
Graduated second in a class of 92 from Southern Methodist University

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Biomedical Computing Applications | Technical Staff |

**RESEARCH SUPPORT** *(See instructions)*

ACME Computing Facility, Stanford School of Medicine 100% time RR00311

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevent to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

| | |
|---|---|
| 1967-present | Assistant Director ACME Computing Facility, Stanford University |
| 1966-67 | Manager, Systems Engineering-Programming Manager, Data Pathing, Inc. Los Altos, Calif. |
| 1961-1966 | Research Engineer, Instrumentation Research Laboratory, Genetics Department, Stanford School of Medicine. |
| 1959-1961 | Research Scientist, University of Texas Southwestern Medical School. |

**Publications:**

Montgomery, P. O'B. and Hundley, L. L.: "The Use of Television in Scanning Techniques for Ultraviolet Irradiation of Cells." Digest of Technical Papers, 12th Annual Conference on Electrical Techniques in Med. and Biol. November 10-12, 1959, 19.

Hundley, L. L. and Montgomery, P. O'B: "Flying Spot Techniques in Microscopy." Digest of Technical Papers, 12th Annual Conference on Electrical Techniques in Med. & Biol. November 10-12, 1959, 20-21.

Montgomery, P. O'B. and Hundley, L. L.: "The Use of Television and Scanning Techniques for Ultraviolet Irradiation Studies of Living Cells." IRE Trans. Med. Electr. ME 7:135-138 July 1960.

Montgomery, P. O'B. and Hundley, L. L.: "The Effects of Selective Ultraviolet Irradiation of the Cytoplasm of Living Cells." Proc. Soc. Exp. Bio. & Med. 105:117-120, Oct. 1960.

Montgomery, P. O'B., Bonner, Wm. A. and Hundley, L. L.: "Flying Spot Microscopy." Encyclopedia of Microscopy, Edited by George L. Clark, Reinhold Publishing Corp. pp. 334-338, 1961.

Montgomery, P. O'B. and Hundley, L. L.: "Ultraviolet Microbeam Irradiation of the Nucleoli of Living Cells." Exp. Cell Res. 24:1-5, 1961.

Montgomery, P. O'B., Bonner, W. A., Hundley, L. L. and Ashworth, C. T.: "Biological Effects of U. V. Irradiation in Chaos Chaos." Royal Microscopical Society. 80:19-24 (PT I) April 1961.

Montgomery, P. O'B. and Hundley, L.L.: "A Flying Spot Interference Television Microscope." Nature. 192:4807, 1059-1060, December 1961.

Montgomery, P. O'B., Van Orden, F., Hundley, L. L., Chapman, C. L. and Cook, J. E.: "Effects of Selective Ultraviolet Irradiation of the Nuclei of Living Cells." Proc. Soc. Exp. Biol. and Med. 108:2, 372-375, Nov. 1961.

Hundley, L. L.: "A Flying Spot Interference Microscope." Annals of the New York Academy of Sciences, Vol. 97, Art. 2, pages 514-515, June 5, 1962.

Levinthal, E., Hundley, L. L., and Lederberg, J.: Life Sciences and Space Research II: "Multivator - A Biochemical Laboratory for Martian Experiments," North Holland Publishing Company, June 3-12, 1963.

Hundley, Coburn, Garwin and Stryer: "A Nanosecond Fluorimeter." Review of Scientific Instruments, 38-488-1967.

**Wiederhold, Gio, Lee Hundley: "A Time-Shared Data Aquisition System" Proceedings of the IEEE Computer Group Conference, March 1970**

SECTION II – PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

*(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)*

| NAME | TITLE | BIRTHDATE (Mo., Day, Yr.) |
|---|---|---|
| Regina Frey | Systems Programmer | September 4, 1937 |
| **PLACE OF BIRTH (City, State, Country)** | **PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)** | **SEX** |
| Newton County, Indiana | USA | ☐ Male ☒ Female |

**EDUCATION** *(Begin with baccalaureate training and include postdoctoral)*

| INSTITUTION AND LOCATION | DEGREE | YEAR CONFERRED | SCIENTIFIC FIELD |
|---|---|---|---|
| Purdue University, Lafayette, Indiana | B.S. | 1959 | Mathematics |

**HONORS**

General Motors and Purdue University Alumni Association Scholarships

| MAJOR RESEARCH INTEREST | ROLE IN PROPOSED PROJECT |
|---|---|
| Biomedical systems computing | Technical Staff |

**RESEARCH SUPPORT** *(See instructions)*

ACME Computing Facility, Stanford University School of Medicine 100% time
NIH BRR Grant RR00311

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE** *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1968-present Systems programmer, ACME Facility, Stanford Computation Center, Stanford University
1964-1967 Programmer, University of California at Berkeley, Linguistics Dept.
1959-1964 Programmer-Analyst, Systems Development Corporation, Santa Monica, Calif.

Education

1959: Programmers Training School, System Development Corporation
1970: Systems Science II, IBM Education

Papers

A Filing System for Medical Research, coauthored, BIOMEDICAL COMPUTING, vol. 2, 1971, Elsenier Publishing Company, Ltd., England.