The analysis of voltage recordings from the cortical surface of the brain of a cat, 8 channels of data will be digitized over 5 seconds for 1,000 words per second. The analysis will consist of the computation of:

1. probability density and probability distributions.
2. joint probability density and probability distribution.
3. cross correlations and autocorrelations.
4. cross spectral density functions.
5. Fourier transforms of data.
6. eigenvalues for Schroedinger time dependent wave equation.
7. diagonal from 3 by 3 Hermitian coherency matrix.
8. the display of recorded data upon television set for photographing.

The analysis is designed to focus upon differences in phase, amplitude and frequency between recordings under different conditions of stimulation. The differences are also to be translated into quantum mechanical form.

The ACME system has also been used in this laboratory for analyzing comparison of single units (neurons). A number of statistical programs have been written utilizing subroutine's made available from ACME for this analysis.
INDIVIDUAL USER PROJECT DESCRIPTION

<table>
<thead>
<tr>
<th>INVESTIGATOR:</th>
<th>DEPARTMENT:</th>
<th>INSTITUTION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edward D. Dolezal Jr., M.D.</td>
<td>Surgery (Div. of Urology)</td>
<td>Stanford Computation Center, Stanford Medical School</td>
</tr>
</tbody>
</table>

FIELD OF INVESTIGATION: UROLOGY

PROJECT TITLE: THE APPLICATION OF COMPUTERS TO UROLOGY

AMOUNT OF RESOURCE USAGE: 39779

PROJECT DESCRIPTION
(Approximately 300 words)

During the past nine months we have had the opportunity to explore the application of computers to urology in the following areas of investigation:

1. Text Processing -
   - Patient History and Physical Examination
   - Scientific Manuscripts

2. Data Processing -
   - Renal Function Study (Calculation and Interpretation)
   - Angiotensin Determination

3. T.V. Graphic Display and Teaching Machine (Computer Based)

4. Progress under development -
   - Urinary Infection Study
   - Neurogenic Bladder Patient Review
   - Ureteral Peristalsis Study (On-line data processing)

Please see accompanying descriptive material for details of each project.
In this research project we are investigating factors which affect frequencies of genes controlling various human heritable characteristics. A group of Mayan Indian isolates are being studied in the Lake Atitlán region in Guatemala. A high infant mortality rate, the age distribution of these populations and of mortality in these populations, and preliminary sero-epidemiologic studies indicate the harsh environment of these communities.

We are collecting from a number of these communities demographic information concerning fertility and migration, genealogic information, data on significant causes of pre-reproductive morbidity and mortality by means of physical examinations and sero-epidemiologic indicators, and information about polymorphisms of blood by laboratory examination of blood specimens. We are emphasizing data collection from individuals in nuclear family units so that we may undertake segregation analysis of polymorphisms. Studies of distributions of gene frequencies are also being undertaken. Demographic data and information about morbidity and mortality will be used to analyze variation in gene frequency distributions and to analyze distortion of segregation frequencies.

The Stanford University Medical School computer system (ACME) is used to process and analyze the large amount of data being generated from these studies. A complete census is performed for each community for identifying inhabitants participating in the study, for demographic data for our analysis, and for establishing nuclear families and relationships of various individuals in the community. These data are processed by computer at Stanford. Computer analysis of the genetic data is also being undertaken.

At present the Indian community, San Antonio Palopó, consisting of Cakchiquel speakers, is being studied.
INDIVIDUAL USER PROJECT DESCRIPTION

INVESTIGATOR:  
K. COLLINS

DEPARTMENT:  
BIOCHEMISTRY

INSTITUTION:  
Stanford Computation Center
Stanford Medical Center

FIELD OF INVESTIGATION:  
PROTEIN CHEMISTRY

PROJECT TITLE:  
ATCase

AMOUNT OF RESOURCE USAGE:  
32670

PROJECT DESCRIPTION  
(Approximately 300 words)

ATCase contains two types of programs and data files. One type is used in conjunction with an amino acid analyzer, to process data gotten from the analyzer. The second type is used in conjunction with ultraviolet spectral studies of the E. coli enzyme aspartate transcarbamylase (ATCase).

First type: An amino acid analyzer is used in our research group for a wide variety of studies in protein chemistry. These include structure-function studies on (borne) ribonuclease, structure-function studies on (E.coli) aspartate transcarbamylase, and extensive studies on the development of procedures for the sequential degradation of peptides and proteins. Thus the analyzer is heavily used by a number of people working on several projects. The analysis of the chromatograms obtained from the amino acid analyzer is laborious and tedious when done by hand. Thus ACME, in conjunction with some other automatic equipment, has been adapted to make these analyses fast, accurate, and dependable. The peaks on the chromatograms are either measured automatically (by an integrator attached to the analyzer) or, if necessary, measured by hand. This data is then fed into an ACME program ("AAanal"), which then processes the data. The features of the program include the following:

a. The input may be either H-W (hand measured) or I (automatically integrated) data.

b. Either the most recently determined set of constants normalization factors for each peak of the chromatogram or the average of the last ten sets (stored in the computer) may be used.

c. The program determines the total weight of the sample analyzed.

d. The amount (in millimicromoles) of each amino acid in the sample is computed.
e. The micromoles of each residue per mg. protein in the sample may be computed.

f. All the data can be corrected (automatically) for tryp to plan destruction.

g. The number of residues of each amino acid in the protein can be computed, and the molar ratios of the amino acids, normalized to any residue, can be determined.

h. The program can deal with 23 amino acids and derivatives, or the 17 commonly occurring acid-stable residues.

Thus the use of ACME has allowed large amounts of data that would have had to be calculated by hand be processed by the computer - with resulting improvements in speed and accuracy, and in the increased versatility.

Second type: ACME is being used to create ultraviolet difference spectra from model compounds to simulate spectra generated on studies of the mechanism of action of the catalytic subunit of aspartate transcarbamylase. The studies have not progressed far enough to evaluate their effectiveness, but the outlook is good that this application will prove meaningful and enlightening in the system being studied. Such a simulation study with model compounds could not be undertaken in any systematic way without access to a computer.
The adrenal gland is involved in the response to stress. In the newborn rat, there is a brief period of poor response to stress by the adrenal gland. As one parameter, we are measuring the capacity of the adrenal gland to synthesize steroid hormones.

From the glands of newborn rats of a particular age group we prepare an enzyme system that catalyzes the conversion of cholesterol to pregnenolone, the hormone precursor. The rate of this conversion is an indicator of the amount of enzyme present in the glands. We follow the rate of conversion by using cholesterol labeled with two different radioactive isotopes and calculating the change in isotope ratio. From each incubation more than ten samples are withdrawn, counted in duplicate for the two isotopes and recounted with a radioactive standard. Thus, about 100 different counts are generated with each incubation.

We use ACME to compute the ratio of the two isotopes for each sample (by averaging duplicate counts and correcting for overlapping counts) and to store these results along with other information about the incubation. Various other programs are used to work on the information stored in the data file and to produce the rate of enzymatic conversion by fitting the best line through the experimental points and by determining the slope and its confidence interval. All this derived information is stored in another data file. To date over 125 incubations ranging over the ages of 1 to 46 days have been carried out and treated in this manner. The project was started in Oct. 1967.

All the information of a set of similar experiments has been retrieved, and a significant pattern of development of the enzyme system has been discerned. Another program analyzes the entire set of experiments and generates a mathematical function that describes the pattern of development. This developmental pattern of the enzyme system was found to correlate closely with the pattern of stress responsiveness described for the adrenal gland of the neonatal rat. A report of these findings has been submitted for publication in Science (1969).
Our project is to develop a control system for an artificial heart. The technique will be to telemeter out blood pressure and flow information from an experimental animal whose heart has been denervated by cardiac autotransplantation. The data will be analyzed and reduced on the 360/50. A mathematical model will then be built which will simulate the data. This model will form a comparison model to the live animal which will then form the trajectory for a controller. A mathematical model will be built into a real time computer such that the heart rate of this animal will be controlled according to the model and according to the biologic stress.

Calculations done are blood volume, renal plasma flow, cardiac output and Fournier analyses.

We are also investigating the rhythmic characteristics of arrhythmics using large volumes of interbeat intervals to characterize the populations.
This project title was used for:

1. Learning how to code in Acme/Pl.

2. Statistical evaluation of the relationship between antemortem and postmortem values of electrolytes in serum and with postmortem specimens of vitreous and cerebrospinal fluids. While we were able to confirm the semi-quantitative findings of earlier authors, our expectation of being able to quantate antemortem serum electrolyte concentrations was not attained. Substantial use of Acme statistical subroutines was made to show the independence of antemortem and postmortem values within acceptable range.

3. Laser microprobe analysis of single cells. It was decided to organize data in the form of scatter diagrams and plots. It was not clear which parameters were of substantial importance in obtaining "accurate" results. Furthermore, results subjectively assessed as aberrant had been rejected, leading to non-correction of microprobe system defects though quite good results.

By introducing raw data into the computer, a better sample of microprobe output was obtained, and graphical analysis certainly assisted in excluding some supposed inter-relationships, between laser output and pmf difference for example. In this way the development of an efficient microprobe has been accelerated. Initial programming of a 2471 output scatter diagram was time consuming and a run cost about 150 page minutes for 10 data points. Subsequently the program has been improved to where 200 data points with their mean and standard deviation per X line are plotted for 50 page minutes. Use of this later program is project laser has saved an estimated greater than 10,000 page minutes when compared to the cost for original scatter diagram program. The effect of organic matrix in plasma and self absorption on cation determinations is now clearer.

Effect of oxygen concentration on exfoliated bronchial epithelial cells. Here the data had greater variance than even in the electrolyte concentration project, smoothing routines and trigonometric interpolation was performed. The results were
ambiguous.

4. Several extensive programs for manipulation and filing of alphanumeric and numeric data were built. The aim initially was to write a sufficiently generalized program to cope with most of the procedures I was being asked to deal with. These programs cost too much to run, and occupied a great quantity of the system's memory. The project title is now being used to file programs for subsequent partial or complete copying into other projects in an attempt to conserve programming time.
# PROJECT DESCRIPTION

## Individual User Project Description

<table>
<thead>
<tr>
<th>Investigator:</th>
<th>Department:</th>
<th>Institution:</th>
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| Enlander, Derek | Pathology | Stanford Computation Center  
|               |             | Stanford Medical School |

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<th>Field of Investigation:</th>
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<td>Data Retrieval</td>
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## Project Description

(Approximately 300 words)

Retrieval of autopsy data and hospital records from various parameters. Program will be suitable for use by secretarial staff insertion of data daily and then programmer retrieval of data from any image parameter e.g. diagnosis, hospital record no., etc. Corelation of data between cases will be available.
The Veterans Administration Cooperative Analgesic Study is a cooperative clinical pharmacological study in five VA Hospitals. It has the following aims:

A. To evaluate compounds now in use for analgesic and sedative activity, and to verify under controlled conditions the claims for efficacy and side effect liability.

B. To evaluate newer analgesics of the non-addicting oral type and to place them in their proper hierarchy with standard drugs namely morphine.

C. To investigate the methodologic problems by use of modern computers and statistics.

D. To stimulate new research into the area of analgesic and sedative evaluation, and to provide a framework for the teaching of clinical pharmacology within the Department of Anesthesia.

This study is conducted by the Anesthesia Section of the various involved Veterans Administration Hospitals under the direction of the Chief of Anesthesia and assisted by Nurse Observers. The Nurse Observer has been trained in the standard method of patient interview for subjective and objective pain evaluation in patients, and for followup and interviews for nighttime sedation. The study is oriented to postoperative surgical patients and patients in whom chronic pain is a problem, or in patients with chronic hospital care requiring nighttime sedation. Double blind crossover techniques are used, except when dose ranging is done. Medications are prepared in identically-appearing form, randomized and numbered serially. Patients are selected according to prescribed methods and questioned for efficacy and side effects.
Protocols and forms for collection and management have been devised. The data is collected from all the hospitals at the data collection center here in Palo Alto VA Hospital and is input directly through the 2711 Terminal to the Acme System at Stanford. Data is error checked immediately upon entry into the system and error checking reports are redistributed to the participating institutions. At the present time, our data file includes programs for error checking our data, analyzing for means, analysis of variance and potency, confidence curves and orthogonal comparisons. In addition, we are contemplating the use of additional programs which will use the linear hypothesis for obtaining relative potencies in those studies where order effects are important.

Subsequent methodologic studies will be made much easier by immediate turnaround and storage capabilities of the 360/50. In addition, we plan to use our data for historical controls using Bayesian theories of statistics and eventually hope to have output of patient histories from the data inputed on the computer forms.
Two computation activities concerning the relationship between the electrical behavior of single intracellular slow potentials and simultaneously recorded macropotentials (EEG) in a human subject were pursued. Dr. Frank Morrell, Chairman, Department of Neurology provided the data.

In one, transfer function and coherence function computations were performed using the intracellular data as input data and the EEG as output data. The objective was to reconcile Dr. Ross Adey's (UCLA) contentions that there was no significant coherence between the intracellular slow potentials and the EEG and Dr. Morrell's demonstration of significant coherence between particular EEG wave complexes and intracellular potentials. (Reference in 1966 Intensive Study Program of the Neurosciences Research Program, Rockefeller Univ. Press 1967). The computational results achieved demonstrated that the relationship between the intracellular potential and the EEG was linear and time varying. This result is compatible with both the Adey and Morrell findings and reconciles the two points of view. (The results were communicated in
results suggest that EXG records can be synthesized arbitrarily well by this means. The computational results therefore suggest that what happens at any instant in the macropotential (synchronous behavior) is duplicated throughout the time course of the individual cell intracellular potential. In effect therefore, at least under the circumstances examined, it appears that the macropotential can be interpreted as being primarily due to the summation or average of the intracellular potentials within the field of the macroprobe. Additional experimental and computational studies are contemplated to further understand this phenomenon.

In both cases, the investigation could not be conducted without the use of large scale digital computations.
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<tr>
<td>David Godwin</td>
<td>Radiology-Surgery</td>
<td>Stanford Computation Center</td>
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<td>Stanford Medical School</td>
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**FIELD OF INVESTIGATION**: Cancer Records  
**PROJECT TITLE**: Adrenalectomy

**AMOUNT OF RESOURCE USAGE**: 23,462

**PROJECT DESCRIPTION**
(Approximately 300 words)

Pilot Analysis of Case Records of Adrenalectomy for Storage, Analysis, and Review.
ACME is used for general laboratory computations of several kinds, primarily those in which exhaustive calculations are required following experiments of several days' duration. These uses are all in connection with project Biochemical Mechanisms in Drug Addiction, supported by NIMH. Statistical packages are also used routinely. Some of the studies concern drug-induced activity of mice, measured in photoelectric counter cages at successive drug injections. Other studies involve tissue distribution of radioactive levorphanol in the mouse. Yet other studies concern binding of radioactive levorphanol under various conditions to subcellular fractions of mouse brain homogenates.

ACME is also used for miscellaneous purposes in connection with graduate student training; a number of student projects are handled on this same project account.
INDIVIDUAL USER PROJECT DESCRIPTION

INVESTIGATOR: Leonard A. Herzenberg
DEPARTMENT: Genetics
INSTITUTION: Stanford Computation Center
Stanford Medical Center

FIELD OF INVESTIGATION: Genetics and Immunology
PROJECT TITLE: "PIGGY"

AMOUNT OF RESOURCE USAGE: 12,655

PROJECT DESCRIPTION
(Approximately 300 words)

Our laboratory is engaged in quantitative studies on immunoglobulins in antibody in production/mice. ACME has been used to calculate immunoglobulin levels from raw data obtained in experiments, to predict immunoglobulin levels from theoretical curves, to calculate geometric means for antibody assays and operations to convert raw data to useable experimental results. In addition some work has already begun to use ACME to keep track of individual histories of thousands of mice maintained in this laboratory. The program to draw pedigree charts for all of the inbred strains is already in operation. Other programs to study the immunologic history are in process of preparation. It is hoped that programs will be developed to make information retrieval for antisera testing easier and quicker.
This project consists mainly of programs for the analysis of cyclic graphs to allow the enumeration of the ring structures of chemistry. Programs analyze the trivalent cyclic graphs.

The main objectives are to indicate all the possible graphs, isomorphisms of superficially different graphs, symmetries within a graph, rational description of each item, rational ordering of the graphs, rational numbering of the vertices and paths and compact, computable notation for each feature.

Each graph is represented as a Hamilton Circuit projected in the boundary of a regular polygon with $n$ vertices. Joining these $n$ vertices and $n/2$ chords, since each vertex is trivalent. The locations of these chords are specified by $n/2$ characters.
INDIVIDUAL USER PROJECT DESCRIPTION

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<th>INSTITUTION:</th>
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<tr>
<td>J. Hwang</td>
<td>GENETICS</td>
<td>Stanford Computation Center</td>
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<td>Stanford Medical School</td>
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FIELD OF INVESTIGATION: GENETICS

PROJECT TITLE: GENLIB1

AMOUNT OF RESOURCE USAGE: 20,079

PROJECT DESCRIPTION
(Approximately 300 words)

This project contains the statistical and miscellaneous programs used by the Genetics Department.

Statistical programs: General statistical analysis for the calculations of sum, mean, standard deviation, the analysis of variance, chi-square, and probability of chi-square distribution, correlation and regression analysis, the normal distribution with the same mean and standard deviation for fitting a curve.

Plotting programs: Plot bar graph in 100 positions, plot of percentage distribution, plot by function scaled to the range of 0 to 100, plot of multivalued function allows the choice and supersition of several characters. Flag is inserted on the chart when underflow or overflow occurred.

Sorting programs: Sorting a vector in ascending order, sort array and alphabetical informations.
### INDIVIDUAL USER PROJECT DESCRIPTION

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<th>INVESTIGATOR:</th>
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<tr>
<td>R.E. Jones</td>
<td>Biochemistry</td>
<td>Stanford Computation Center</td>
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<td>Stanford Medical School</td>
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#### FIELD OF INVESTIGATION

Protein structure

#### PROJECT TITLE:

Nanosecond fluorimetric methods for protein structure determination

#### AMOUNT OF RESOURCE USAGE:

57,050

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### PROJECT DESCRIPTION

*(Approximately 300 words)*

The project under consideration involves the use of a nanosecond fluorimeter designed originally by Shirley, Colyer, Stryer, and Karvin (Rev. Sci. Inst. 38, 488 (1967)). With this instrument the course of fluorescence of various compounds in solution can be followed directly as a function of time, thus furnishing a method for the direct investigation of emission kinetics (through the observation of the total fluorescence) as well as rotational characteristics (through observation of fluorescence depolarization) of the fluorescent moiety. In the case where a fluorescent label is bound covalently or through Van der Waals interaction to a biological macromolecule, characteristics of the macromolecule can be investigated through the behavior of the fluorescence kinetic properties of the small fluorescent label.

In this project the AEIF facility is used for both data collection and data reduction. Data collection is implemented with the 1666 Data Acquisition System and on-line experiments: output from a photomultiplier is projected onto a sampling oscilloscope, the output of which is transmitted to the 1666 after a digital pulse from the 1666 triggers a time sweep in the oscilloscope system. Analog data thus collected is digitalized, stored, and finally the light intensity versus time data is averaged over a series of scans. Further data reduction is accomplished in the 360 by several programs encompassing several data reduction routines. In general, this consists of determining the true course of emission versus time, as the observed emission is convolution of the light source-detector system with the true emission kinetics:

\[ I(t) = \int F(t') \delta(t - t') dt' \]

(where \( I(t) \) is light intensity and \( F(t) \) is the source light pulse as seen by the detection system.)
A program for information retrieval interfacing with the Sanders 720 display. Programs work with multiple files. Files are created by program and store on disk.

Program is called in by IBM 2741 terminal thru ACME. After the compilation by ACME, the execution of the program is initiated on the terminal, all the communication to and from the computer is turned over to Sanders 720 display via the display keyboard.

Program features the option of working with any files, also provides selection of the following actions - create new file, addition of records to the existing files, alter content of any record, delete or insert records, listing any portion of the existing file and search for key words in the file. After each selection is processed user has option of rerunning the program without recompiling.

While execution is in progress, in addition of the information displayed on the scope, a list of options and selections is printed on the IBM 2741 terminal to keep track of what has been done during each run.
INDIVIDUAL USER PROJECT DESCRIPTION

INVESTIGATOR: SIDNEY LINDES, JR.
DEPARTMENT: GENETICS
INSTITUTION: STANFORD MEDICAL SCHOOL
STANFORD COMPUTATION CENTER

FIELD OF INVESTIGATION: MASS SPECTRAL DATA HANDLING
PROJECT TITLE: MS (MASS SPECTROSCOPY)

AMOUNT OF RESOURCE USAGE: 55,760

PROJECT DESCRIPTION
(Approximately 300 words)

The computer has been used to provide various support functions for research in the area of mass spectral microanalysis of organic materials. The mass spectrometer is run in either of two different modes. The data derived while running in one of these modes is transmitted automatically to the ACME system for storage. The other mode requires operator participation in the transmission.

The stored data is subjected to a variety of interpretative manipulations. In one running mode the mass peak locations are quadratically related to the real running time parameter. Linearization of the mass peak displacement has been performed with the aid of the computer thus simplifying the identification of individual peaks.

A computer driven television unit has been used to facilitate the visual comparison of pairs of mass spectra. The unit incorporates a manual control that positions a spot on the screen. The coordinate of the spot location may be entered into the computer by activation of a switch. The basic display format for the program consists of a central area surrounded by a marginal pattern of zones. A wide selection of program decisions can be made in program execution by directing the spot to different zones. This flexibility enables selection, for example, of the spectra (identified by file numbers) to be displayed for each spectrum; the normalization to be used in the peak height display; the identification of the mass numbers associated with various peaks, etc.
Consultant and programmer. Programs written so far include a scatter plotting routine which plots as many different sets of data as is desired on one graph using a different symbol for each plot; array size checking procedures for approximately 35 statistical subroutines to keep users from writing over the system; and sample programs for an ACME publication which introduces the new user to ACME.
INDIVIDUAL USER PROJECT DESCRIPTION

INVESTIGATOR:  John L. Polascik, M.D.  DEPARTMENT:  Medicine - Endocrine Research

INSTITUTION:  Stanford Medical School  Stanford Computation Center

FIELD OF INVESTIGATION:  Clinical Investigation

PROJECT TITLE:  Reninase and pressure factors in arterial hypertension.

AMOUNT OF RESOURCE USAGE:  41,535

PROJECT DESCRIPTION

(Approximately 300 words)

The Endocrine Unit of the Department of Medicine is engaged in a study of circulating pressor substances, measured under standardized conditions in patients with hypertension. The effects of sodium loading, sodium depletion, and diuretic administration, as well as changes in posture are observed. We have used ADE in several different ways to increase the efficiency of our laboratory work (for example, in the time-consuming calculations of aldosterone measured by the double isotope derivative method). Statistical analysis is being applied to the results. There appear to be several populations of patients with hypertension, some correlated with clinical findings, and others which require further characterization. Correlation between various factors, such as plasma electrolyte concentrations, circulating catecholamine levels, plasma renin activity, and aldosterone secretion, have been calculated. Curve-fitting methods are applied to certain functions which can be described as the sum of exponentials. With the present programs and files, we can organize and use the data from this expanding group of patients, interpreting and utilizing the information for on-going studies.
We are measuring simultaneously the rate of sodium transport and the rate of CO₂ production by the urinary bladder of the toad. Rate of sodium transport is measured as the short circuit current. Rate of CO₂ production is measured as the rate of decrease in conductivity of a dilute NaOH solution as CO₂ is trapped. Outputs proportional to each measure are recorded on a dual channel Varian recorder.

The computer is used to facilitate "continuous" (4 minute interval) comparison of the two variables. By means of the computer we calculate (1) rate of CO₂ production from change in conductivity (not a proportional factor); (2) ratio of short circuit current to rate of CO₂ production a) at each 4 minute interval, b) as increments following change of rate by adding variables (hormones, substrates, drugs), expressed as absolute numbers and as percentage change. We can thus compare changes in metabolism to changes in sodium transport to see how they interrelate. In particular we are studying which changes first in different situations and the different ratios obtained in different situations.