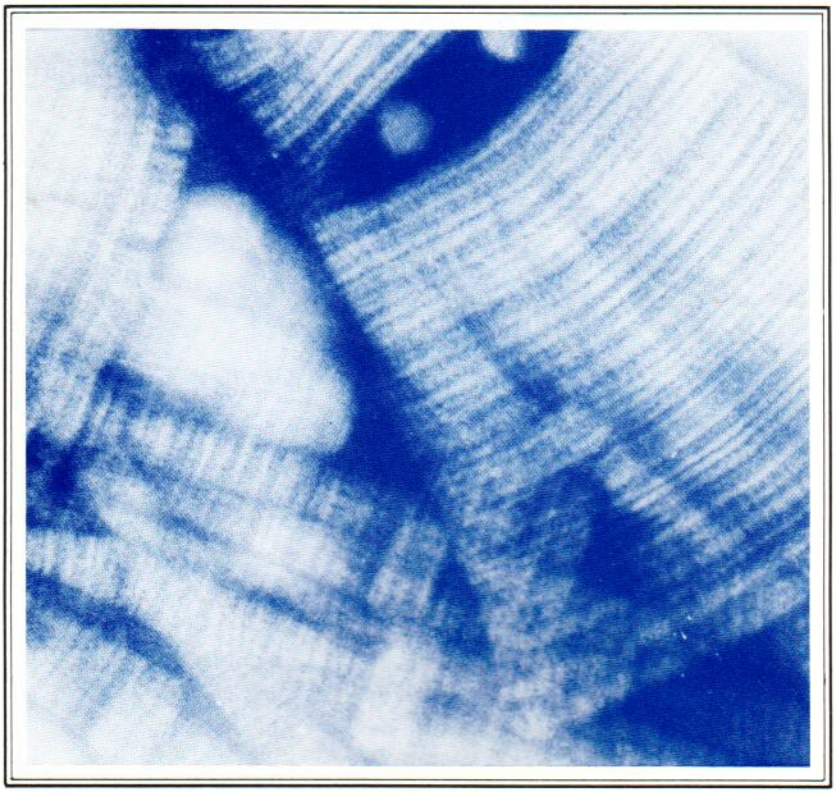
Boston Biomedical Research Institute



ANNUAL REPORT

BOSTON BIOMEDICAL RESEARCH INSTITUTE

Contents

Boston Biomedical Research Institute
is an independent, non-profit organization committed to the
prevention and cure of disease through basic research.

Report of the President

John A. Shane

On behalf of the Officers and Trustees of the Institute, I am extremely pleased to report that 1981 was a year of substantial change, activity and progress for Boston Biomedical Research Institute.

Over the past year, the Officers, Trustees and Corporation Members have contributed many hours and have actively participated in the affairs of the Institute. For example, more than twenty-two committee meetings were held during the year. More important than the contribution of time, however, has been the thought, planning and organization which have been contributed by this group to the Institute.

Financially, the Institute is in sound condition. Despite a continuing reduction in the amount of real research funds (adjusted for inflation) available from government-sponsoring agencies and despite increased competition for these funds, a record $4. 2 million in grant revenues was received by BBRI in 1981. Through careful control of expenses coupled with donations and other income, a surplus of approximately $318,000 was realized during the year. The Institute's balance sheet remains strong with no short or long-term debt outstanding. In this respect, the Institute has performed better than most commercial genetic engineering ventures which have been formed in the past few years.

Under the guidance of the Development Committee and the able management of Penelope W. Stohn, the Development Office had a particularly constructive year. In addition to broadening the scope and content of the traditional annual meeting, scientific dinner meeting, and spring meeting, frequent luncheons were held for friends of the Institute, the Wing Ding jazz concert was organized and held in the spring, three issues of *News From The Institute* were published and approximately thirty proposals were prepared and submitted to selected foundations. As a result of this activity, and more, a record $96,776 was raised for the Institute from annual gifts, and BBRI has become more widely known. In addition, on 2 July 1981, The Frederick J. Kennedy Memorial Foundation made a generous grant of $100,000 to the Institute toward the creation of new laboratory space. This project is discussed in more detail in the Executive Director's report.

A major step in the possible future direction of the Institute was taken in June when the Trustees directed the creation of the Commercial Committee to determine whether BBRI should participate in some way in the commercialization of medical research. In September, this Committee made the following recommendations which were unanimously approved by the Trustees:

"A. The Committee unanimously recommends that BBRI Trustees approve, in principle, the concept of forming an affiliated but independent corporation with its own separate management and capitalization. In return for its initiative in forming this corporation and for providing ongoing advice and guidance to it, BBRI would become a significant shareholder of the venture. This affiliated corporation would seek sponsored research contracts from industry, and would pursue commercialization of biological and medical developments, sponsored at BBRI or elsewhere, or in its own facilities, and would be free to seek assistance from BBRI or others in pursuing its objectives.

B. If the Trustees act favorably on this recommendation, then:
(1) Their action should be reviewed by the Institute's Scientific Advisory Board, and also its Committee on Research to obtain their general reaction to the proposal, as well as specific ideas and suggestions which will be helpful in the detailed implementation of the proposal. (2) The Commercial Committee should be charged with preparing a detailed proposal to implement the recommendation, including proposed management and capitalization, and the proposed initial relationship between BBRI and the corporation. This proposal should come back to the Trustees for review and approval. "

Two subcommittees of the Commercial Committee are currently working on the implementation of these recommendations.

The present financial, organizational and professional strengths which the Institute enjoys can be attributed to the contributions of many, but none more than David C. Crockett. Mr. Crockett was Chairman of the Institute from November 1968 until November 1980, when he chose not to stand for reelection.

Mr. Crockett's contributions to the Institute have been broad and numerous and run from sharing his wonderful sense of humor, to most effective fundraising and exhortation. He has no peer in conducting an annual meeting with style, purpose and interest. He has graciously agreed to continue as a Trustee of the Institute and is serving on the Development Committee. William Tyler, Mr. Crockett's successor as Chairman, served as President of the Institute from 1971 until 1977 and provides important continuing leadership and guidance.

In accordance with traditional practice, Dr. Peter Davison's two-year term as Executive Director of the Institute will conclude at the time of this year's annual meeting, when he will be succeeded by Dr. D. Rao Sanadi. I would like to express my particular appreciation and admiration to Dr. Davison for his outstanding leadership during the past two years.

The conduct of basic medical research has become more complex, competitive, and fast paced than ever before, and there appears to be no slowing in this rate of change. You should be assured that those connected with the Institute have been equal to the tasks at hand and are preparing for the future in a constructive and intelligent manner.

Report of the Executive Director

Peter F. Davison, Ph. D.

In the course of the year we have welcomed to the Institute ten post-doctoral fellows from the United States and from five foreign countries. In turn, four fellows have left the Institute, most to return home. Six staff members have also left BBRI. Dr. Robert Lee resigned recently to take a faculty appointment at Colorado State University. Dr. David Morgan returned to Australia, and Dr. Keizaburo Miki to Japan. Dr. Robert Burrows joined the staff of the Eye Research Institute. Drs. Ray Houghton and Ruth Emyanitoff joined the staffs of New England Nuclear Corporation and Genex Corporation, respectively.

We welcome to the faculty of the Institute Dr. Michael Pringle from London University, England and Dr. Jen-Shiang Hong from Brandeis University to the Cell Physiology Department, and Dr. Edward Galbavy from the University of Florida to the Fine Structure Department.

Although this has been a good financial year, as described in the President's report, close scrutiny of grants receivable and awards promised for next year suggests that this satisfactory record may not continue. There is no doubt that we will face a serious problem if the Administration's proposal to cut 12% from the NIH budget is applied to grant funds, and if the proposal is accepted by Congress. The problem is not unique to this Institute, but is shared by all universities, medical schools and research institutes in most of the western world, where economic problems have forced governments to slash budgets for higher education and research. BBRI's Trustees and the staff are attempting to counter this threat to our research programs by building improved facilities for research, and devising ways to broaden the base of financial support for research.

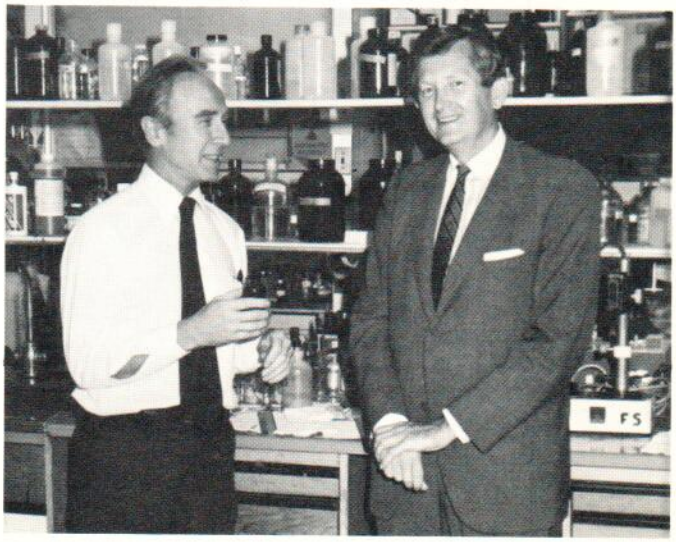
With the support of large grants from the Fred M. Roddy Foundation and The Frederick J. Kennedy Memorial Foundation and the help of many smaller donations, laboratories are being renovated in the Institute's basement. The improvements include a special laboratory and facilities for developing monoclonal antibodies, a research tool that will have enormous impact in many fields of study as well as in diagnostic and clinical use. An improved darkroom, storage for flammable chemicals, a computer center, and larger laboratories are also under construction or already in use. In addition some laboratories on the third floor will be redesigned to accommodate research displaced by the basement area renovation. Another development is the installation of a larger computer with connections to all research departments. Some of the scientific applications of the computer are described later in this report.

The second initiative, seeking a broader funding base, is a matter that was delegated by the Trustees to a sub-committee which is seeking ways to obtain a limited level of commercial or private sponsorship for basic research, and for the development of the products of that research. A growing number of organizations have found commercial sponsors—Harvard Medical School (Monsanto), Massachusetts General Hospital (Hoechst) and Massachusetts Institute of Technology (Exxon)—to name a few. Among these giants the Institute is dwarfed by size but not, I believe, by enterprise.

The juxtaposition of basic research and sponsored research has conjured up apprehension among many people, and it has been widely discussed in faculty meetings, newspapers, and journals. Our Trustees are concerned that such activity does not threaten the character of the Institute or its staff, or the breadth of its research programs. On the other hand, they urge that our dependency on the federal dollar should diminish. Ideally, the Institute would like the opportunity to allow our scientific staff to undertake research problems sponsored by for-profit organizations as an alternative to the support from voluntary health agencies and the federal government.

Commercial organizations usually establish research contracts and claim patent priorities for discoveries in the course of the work that they sponsor. This is not a novel feature for work at the Institute because much NIH research is performed through contracts with patent limitations. However, commercially-sponsored research at BBRI could cause concern if there is demand for secrecy between staff members about experimental discoveries or if the contracts could be regarded as exploitation of facilities that were provided with dollars from donors and the federal government.

Scientists with skills in academic biochemistry and basic biomedical research are in demand because of the present commercial enthusiasm for the products and capabilities of these sciences. At the same time, university faculties and enrollments are shrinking. We must take care that in this climate the objectives of the Institute are not subverted for transient advantages. I have confidence in the wisdom of our President, Mr. John Shane, the committees reviewing this venture, Trustees and staff to guide us through a period of readjustment while we maintain our ultimate objectives of using basic biological research for the improved health of mankind.



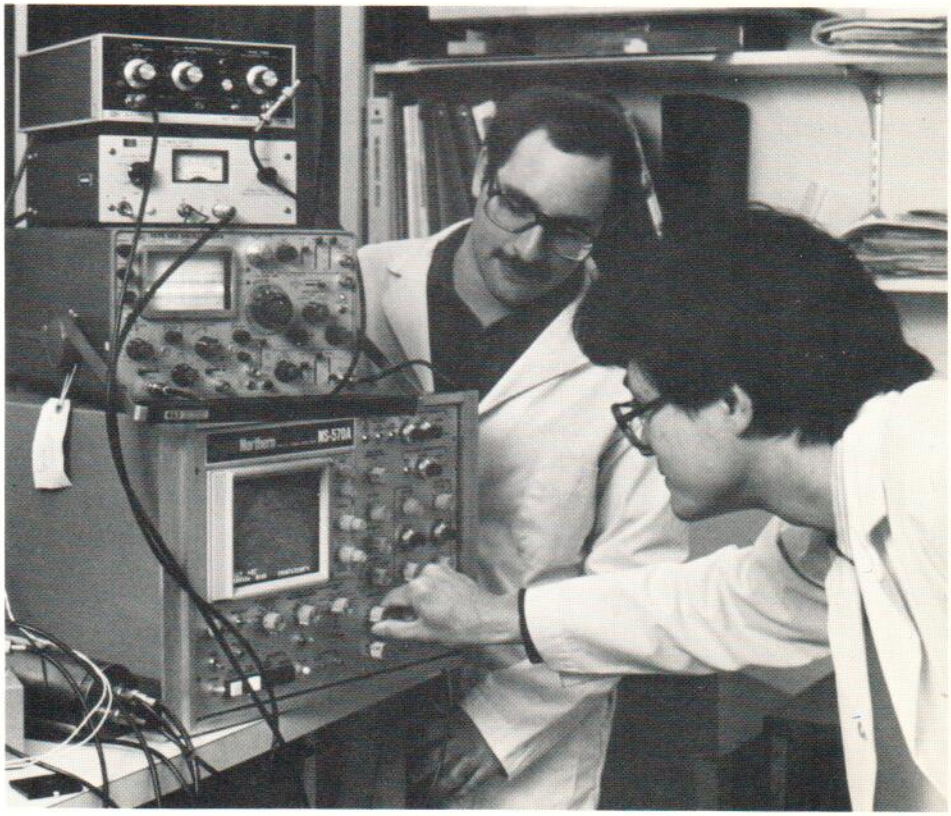
"In completing one discovery we never fail to get an imperfect knowledge of others of which we could have no idea before, so that we cannot solve one doubt without creating several new ones."

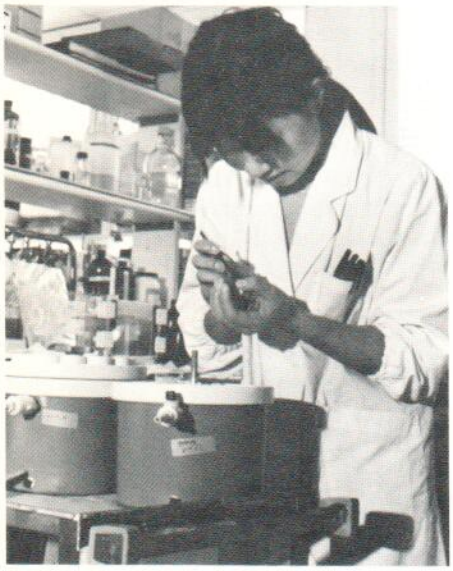
Joseph Priestly

Fluorescence Spectroscopy

When light is shone on certain substances, it can be reemitted through a process known as *fluorescence*. For centuries scientists have used fluorescence to study the nature of materials. Over the past 15 years biochemists have been using the *fluorescent probe* technique to study the structure and function of macromolecules such as proteins and nucleic acids. The strategy behind this technique consists of three parts. First, probes that contain two functional segments—one fluorescent and the other chemically reactive—are selected. Then the probe is chemically attached through its reactive segment to specific locations in a protein. Finally, light is shone on the complex and the properties of the light reemitted by the probe are examined. The properties of the reemitted light give us information about the environment of the probe. This method is not unlike the unmanned space exploration program in which a probe is sent to a specific location. Once planted, it is then asked to examine the environment surrounding it, and beam the information back to the exploration team at home.

At BBRI this technique is being used by various investigators to study the mechanism of muscle action. For example, Dr. Jack Seidel uses the fluorescence of the amino acid tryptophan to study the enzymatic properties of myosin, a major muscle protein. Dr. Mario Rosemblatt uses fluorescently tagged antibodies to identify structural elements in the membranes of muscle. Dr. Sherwin Lehrer fluorescently labels the regulatory protein tropomyosin to study its structural and functional transitions.

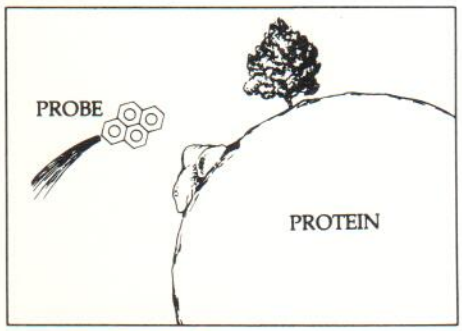




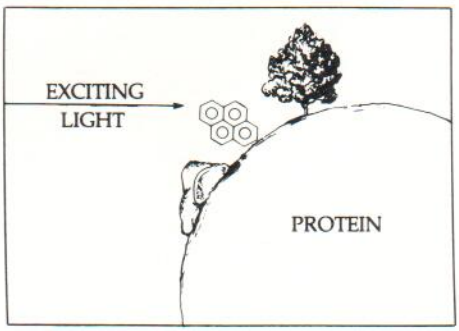
In a study conducted by Dr. Terence Tao, a fluorescent probe was attached to a unique site in actin filaments. The fluorescence of the attached probe was examined in the absence or presence of the quencher acrylamide. A quencher is a fluorescence antagonist which, when allowed to collide with the probe, renders it non-fluorescent. The extent of quenching reflects the degree to which the probe is exposed to the external environment. When other muscle proteins interact with actin, one can expect the probe to be shielded from collisions with quenchers in the external medium. This method, therefore, provides a means to study the interaction between actin and muscle proteins.

Finally, Drs. Terence Tao, Sherwin Lehrer, Paul Leavis, John Gergely and Albert Wang are collaborating to use the excitation energy transfer method to map the distances between sites in various protein components of muscle. In this method, two different probes are placed at two sites. The labelled components are then reconstituted to form a functional system in vitro. When this doubly labelled system is illuminated one probe may transfer its excitation energy to the second. The extent to which this occurs depends on the distance separating the two probes. The proximity between any two labelled sites of the muscle proteins can, therefore, be estimated by measuring the extent of energy transfer. It is hoped that such studies will yield a better understanding of the spatial relationships between muscle proteins.

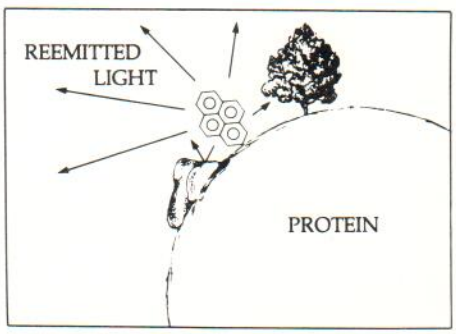
Terence Tao



1. ATTACHMENT:
A fluorescent probe is sent to a specific location in a protein.



2. ILLUMINATION:
Once attached, the probe is illuminated with exciting light.



3. FLUORESCENCE:
Information on the environment around the probe is contained in the light reemitted by the probe.

Rapid Kinetics

When two chemicals interact, a certain amount of time elapses before the formation of the final product. The mathematical description of the progress of the reaction provides information on the nature of the reactants, the mechanism of the reaction, and the chemical environment in which it occurs. In many biological processes the rate of the reaction is very rapid, and chemical intermediates which may have lifetimes of a few thousandths of a second can be detected only by special techniques. The study of rapid kinetics involves the fast mixing of two solutions with different chemical compositions and the detection of the intermediates formed in the initial phase of the reaction.

In one application of rapid kinetics, the *chemical quench method*, a solution containing an enzyme is rapidly mixed with another solution containing an *effector chemical*. The two are allowed to react for a specified time, after which a third reagent (e. g. acid) is added to stop or "quench" the reaction. This process is repeated to obtain a series of different time points, and the chemical products in each solution are analyzed. This procedure provides a series of "snapshots" of the reaction and permits the time course of the reaction to be reconstructed, as a motion picture is constructed from a series of isolated frames.

In order to understand the complex orchestration of reactions that govern muscle contraction, BBRI scientists Drs. Noriaki Ikemoto and Terrence Scott are using the chemical quench technique to analyze the rates at which calcium is pumped across muscle membranes. Calcium controls muscle contraction; the strength and duration of contraction are determined by the interaction of calcium with regulatory proteins in the contractile machinery. Evidence suggests that this interplay of reaction is defective in many neuromuscular diseases, such as malignant hyperthermia.

Using this technique, Drs. Cecilia Hidalgo and Noriaki Ikemoto are examining the rates of formation of enzyme-phosphate complexes in the calcium pump protein to relate changes in the rate of this enzyme's activity to the transport of calcium.

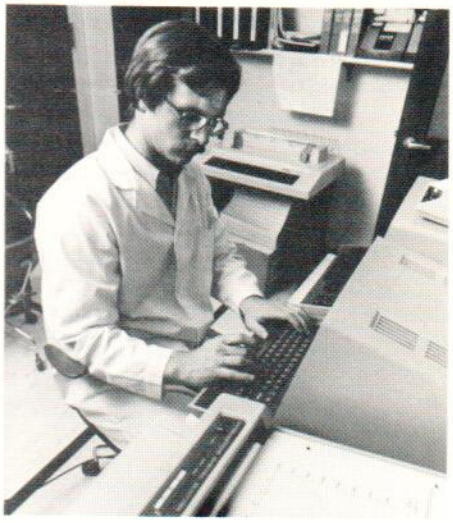
"This procedure provides a series of 'snapshots' of the reaction and permits the time course of the reaction to be reconstructed, as a motion picture is constructed from a series of isolated frames."

In an alternate technology, the *stopped-flow technique*, the course of a reaction is continuously monitored by a light beam. As the reaction proceeds, either some of the beam's energy is lost (absorption) or light is reemitted (fluorescence). These light signals are sampled and analyzed by computer programs developed at BBRI by Dr. Scott. He and Dr. Ikemoto employ this technique to elucidate how calcium is transported across muscle membranes and to relate this movement to changes in the molecular shape of the protein serving as the calcium "pump" in these membranes.

Many crucial physiological responses which occur at velocities of thousandths of a second can be seen only by means of the rapid kinetics technique. Drs. John Gergely, Paul Leavis, Zenon Grabarek and Albert Wang are using this technique to analyze muscle proteins and metal interactions. The determination of the rates of these processes is important to the understanding of the mechanism which regulates muscle contraction and relaxation. The investigators are studying the velocity and strength of calcium binding to muscle regulatory proteins, using rare earth metals in place of calcium. These metals emit light when stimulated by a beam, and emissions change in a characteristic fashion when the metals are bound to the proteins.

It is expected that analysis of these individual regulatory events will shed light on their possible malfunctions in various disease states such as heart disease and muscular dystrophy.

Terrence Scott



Saturation Transfer EPR

Originally a tool for physicists and physical chemists, electron paramagnetic resonance (EPR) has become important in biomedical research to determine the motion of various components of the living cell. The technique involves the rigid attachment of a chemical probe, which acts as a tiny magnet, to a protein or a membrane. The rotation or flexing of the probe reflects the motion of the protein or the fluidity of the membrane. These motions are too slow to be measured by the conventional EPR method. A new variant of this technique, however, Saturation Transfer EPR, is sensitive to molecular rotation occurring at a frequency of 1,000 to 10,000,000 cycles per second and, therefore, encompasses the frequencies at which the crossbridges of muscle and protein of the cell membrane rotate.

Currently accepted models of muscle contraction involve successive attachment, rotation, and detachment of a crossbridge connecting the myosin and actin filaments of the muscle. The muscle shortens as the myosin filament rows its way along the actin filament. Little has been known, however, until recently about the rotation of the crossbridge—how fast does it rotate and at how large an angle can it swing through?

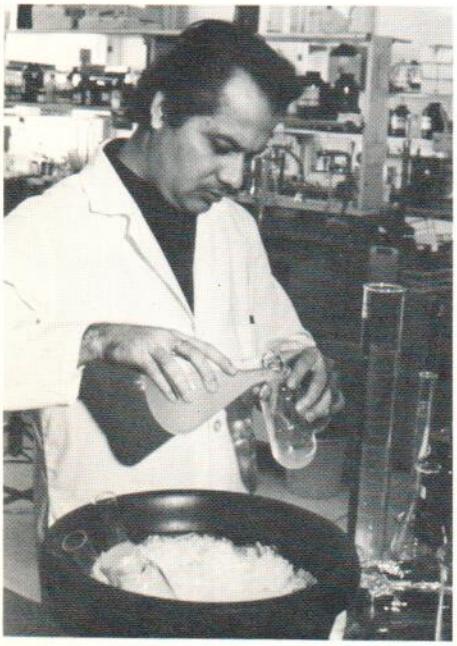
The experimental approach used by Drs. Barbara Manuck, Jack Seidel and John Gergely involves magnetic labelling of the crossbridges and studying their rotation in pure solutions of contractile proteins, in myofibrils representing individual units of the contractile systems, and in muscle fibers where the contractile system is virtually intact. When crossbridges are assembled into myosin filaments, they move at a rate of about 100,000 cycles per second, but when bound to actin filaments they are slowed to 1,000 cycles per second. Since this is the same rate at which actin moves, we conclude that the crossbridge rotation, relative to the actin filament, is completely stopped when the crossbridge binds to the actin filament. This rigid immobilization of bound crossbridges has also been found in myofibrils. Recent evidence indicates that it also occurs in muscle fibers.

This suggests that the motion of the crossbridge when bound to the actin filament is controlled by the flexing of a small part of the actin filament. This hypothesis might eventually provide a better understanding of the development of contractile force, but requires further testing under conditions more closely resembling those present in contracting muscle.

The *sarcoplasmic reticulum* is a membranous reservoir for calcium in muscle. When calcium is released into the cytoplasm, contraction ensues. When it is pumped back into the reservoir the muscle relaxes. An enzyme in the membrane uses the chemical energy of ATP to transport calcium from the cytoplasm to the reservoir. Dr. Cecilia Hidalgo has attached a magnetic probe to the calcium pump enzyme in this membrane. The movement of this enzyme within the membrane occurs at a rate of one thousand cycles per second. Changes in composition of the membrane alter both the rate at which ATP is used to pump calcium and the rate of movement of the enzyme. The exact nature of this movement and its importance to the calcium transport across the membrane are under investigation.

Dr. Michael Pringle is studying another molecular pump which transports protons across the mitochondrial membrane. The mitochondrial pump is composed of two components: one which activates the pump and one which transports protons. The mechanism by which protons are pumped through the membrane during the hydrolysis of ATP remains unknown, and there is much speculation concerning the role of protein-lipid interactions in the process. Saturation Transfer EPR is being used to study the motion of these components and that of the entire complex to determine the mechanism by which the pump works. Studies in model membranes will show whether motions of the proteins correlate with the active and passive flow of protons across the mitochondrial membrane. Through the use of this powerful technique for studying the dynamic behavior of cellular components we shall continue to increase our understanding of normal and diseased cells.

Jack Seidel



Computer Interfacing

Computers have become an indispensible tool for the modern researcher. BBRI has kept pace with current trends and now has a computing facility based on a Digital Equipment Corporation PDP-11/44 minicomputer, which aids investigators in data acquisition, analysis, and system modeling. In addition to the main computer, several microcomputers are in use to control experiments and gather data for individual projects. The crucial link between two computers or between an instrument and a microcomputer is called an *interface* and permits intercommunication.

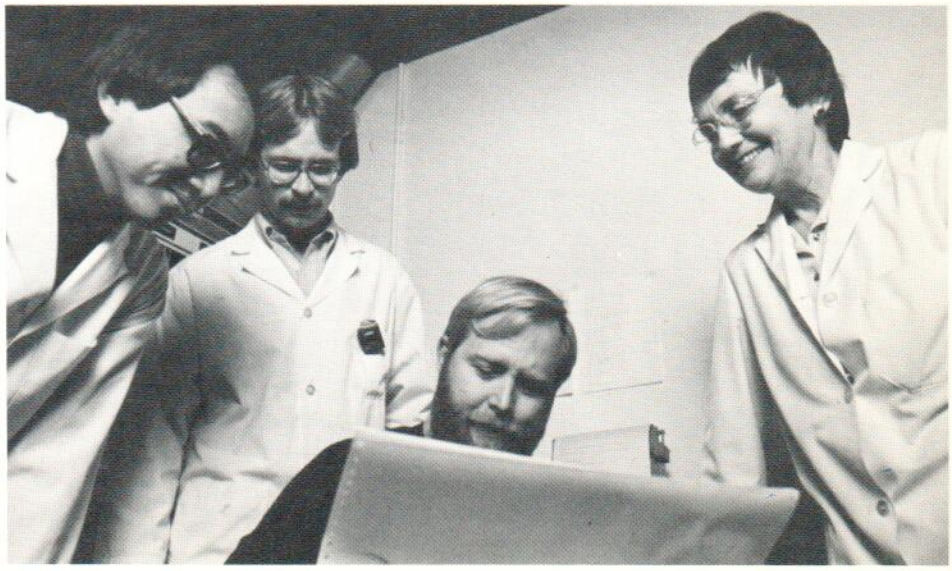
One of the functions of an interface is to convert the continuously variable *analog* signals from the real world into the individual *digital* packets, known as *bytes*, required by the computer. In most cases, the microcomputers are interfaced to the larger PDP-11/44 system so that data acquired by a microcomputer can be analyzed on the larger system. An interface is also required between an instrument and microcomputer. Several of the microcomputers can be interconnected to facilitate data transfer. The relationships between these components are represented in the accompanying diagram.

The microcomputer provides the added capability of altering the experimental conditions based on information it receives from the various signals it monitors. The rapidity with which the microcomputers can respond allows feedback to occur within a ten-thousandth of a second.

Dr. Terence Tao uses AIM-65 and PDP-11/03 microcomputers for data acquisition and analysis in his studies of fluorescence energy transfer and fluorescence lifetimes. In these experiments, a solution of muscle proteins under investigation is illuminated with an extremely brief (less than one billionth of a second) flash of intense light. In turn, the light emitted from the sample by fluorescence is collected by a photomultiplier tube and sent by the interface to the microcomputer. These data are then transferred to the PDP-11/44 for analysis required to relate the properties of muscle proteins in solution to their function in the living tissue.

Dr. Terrence Scott uses a PDP-11/03 microcomputer for data acquisition and analysis in studies of the enzyme kinetics of the calcium transport system of the sarcoplasmic reticulum, as discussed on pages 8 and 9.

The computer is also being used at BBRI to study the mechanisms involved in the development and aging process. Dr. Barbara Wright and



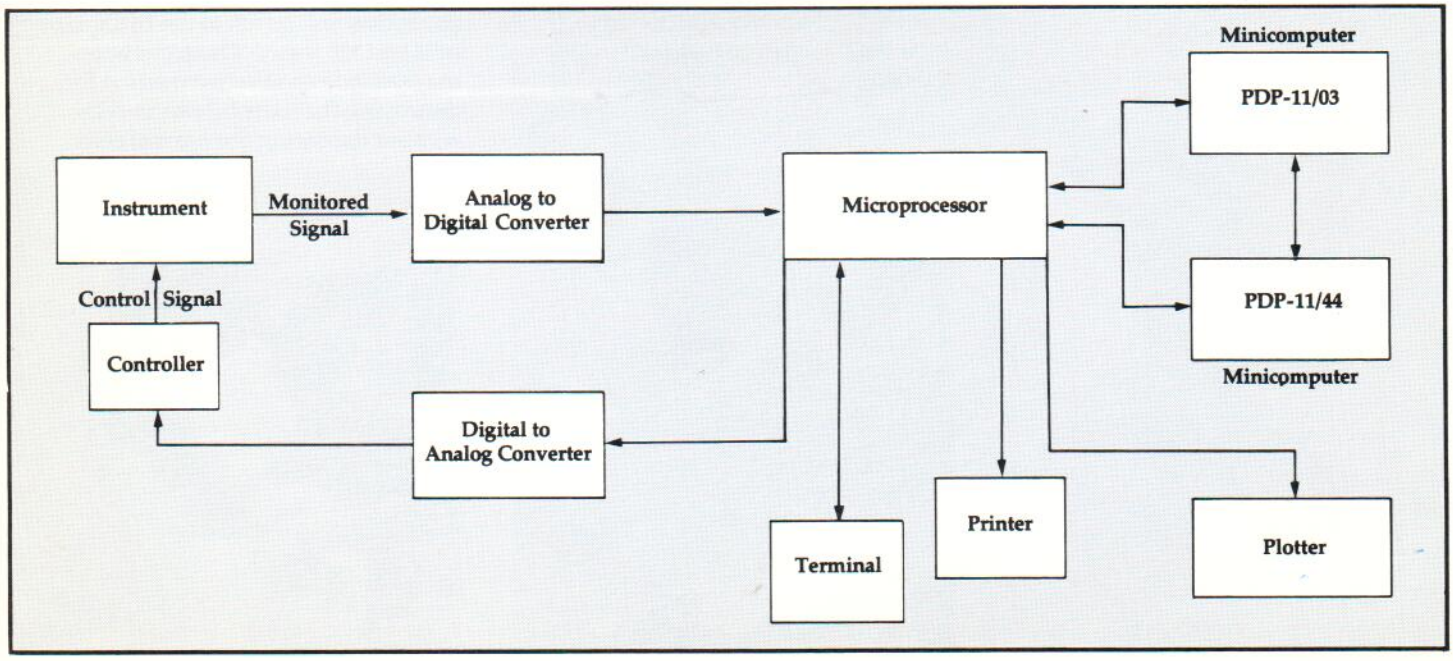
"The fact that many of the computer-based predictions have been substantiated experimentally encourages these investigators to pursue their novel approach."

her colleagues in the Department of Development Biology are currently involved in an in-depth analysis of aging in *Dictyostelium*, a microbial model system with only two cell types. The analysis of *Dictyostelium* metabolism has uncovered so much information that a computer model has become necessary for realistic integration and interpretation of the data. The fact that many of the computer-based predictions have been substantiated experimentally encourages these investigators to pursue their novel approach. Their research on this simple organism will in all likelihood apply to more complex ones.

Dr. Walter Stafford utilizes several microprocessors for instrument control, data acquisition, and data analysis of physical chemical studies of muscle proteins. With a 8080A microprocessor, Dr. Stafford analyzes photographs depicting protein distributions during sedimentation in the ultracentrifuge. The sedimentation behavior of isolated muscle proteins provides information about their size and shape, while the sedimentation behavior of mixtures provides information about interactions between these muscle proteins.

Data taken from these ultracentrifuge photographs are preprocessed by microcomputer and then transferred either to the PDP-11/03 for analysis and plotting or to the PDP-11/44 for analysis by larger programs. A microprocessor control system is being developed for the ultracentrifuge to allow observation of several samples in a single run. The microprocessor will be interfaced to a laser light source which can be switched on and off within a millionth of a second to send pulses of light through each of the samples spinning in the same rotor. By timing the interval between the pulses each sample can be individually observed. This improvement will greatly reduce the number of centrifuge runs necessary to characterize a protein preparation. The same microcomputer system will be interfaced to a scanning ultraviolet spectophotometer on the centrifuge to allow data acquisition for automated analysis. Because it enables researchers to gather vast amounts of data and perform complex analyses, as well as to control experiments with precision, the computer will play an increasingly significant role in BBRI's research programs.

Walter Stafford



Monoclonal Antibodies

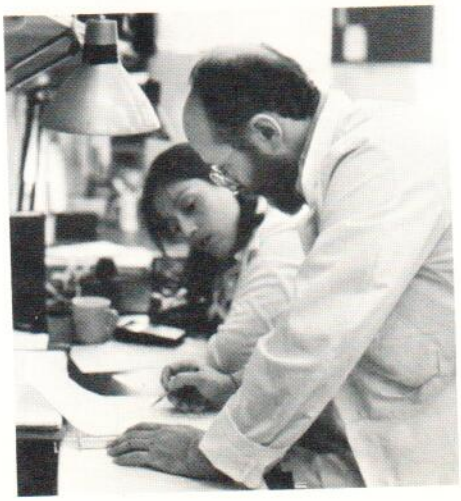
Antibodies are molecules that are produced in response to the presence of particular foreign substances (antigens) in the body. For example, when a person catches "the flu," an illness which is caused by a virus, the immune system recognizes the virus as an invader and produces antibodies that attach to it and inactivate it. The production of antibodies and the neutralization of the virus take about five days.

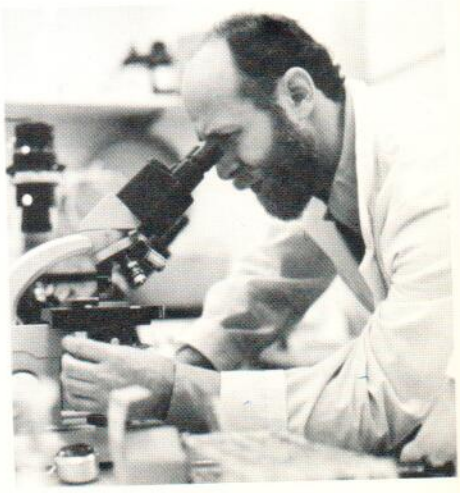
When an antigen is introduced in the body, cells called *lymphocytes* are stimulated. These cells divide and produce plasma cells that secrete the antibody. Usually a single antigen will cause the production of a number of antibodies directed against different parts of the molecule. Thus in the body the antigen is neutralized by a number of antibodies, each present in relatively low concentration in the blood.

A single lymphocyte and its daughter plasma cells—a clone of cells—produce a single type of antibody. These plasma cells normally do not live long. Occasionally, however, one among a population of plasma cells may become cancerous and reproduce repeatedly until it kills the host animal. Such *plasmacytoma* cells can be grown in the laboratory where they may live and divide indefinitely when maintained in culture flasks.

A new technique of vast importance has been devised to give the antibody-secreting plasma cell the enormous reproductive capacity of the plasmacytoma tumor cell. When plasma cells and tumor cells are fused in the presence of the chemical polyethylene glycol, the progeny of the fused cell pair form a clone that secretes a single type of antibody. If one of these cells is isolated and allowed to multiply in culture bottles, large quantities of "monoclonal antibodies" can be recovered from the culture.

Because monoclonal antibodies bind so specifically to their antigens, they are excellent tools for detecting viruses or bacteria. They can be used also to pick out valuable components from a complex mixture in solution, to inactivate toxins, or to block transplant rejection. One potential use lies in the identification and treatment of cancer. Cancer cells usually have surface molecules (antigens) that are different from those of normal cells. Monoclonal antibodies can be produced that recognize only the malignant antigens. These antibodies can then be linked to cytotoxic agents, chemicals that kill a cell. When this mixture is injected into a patient with cancer, it is hoped that the monoclonal antibodies will attach to the malignant cells and kill them. This technique may provide an effective method for destroying the harmful cancer cells without damaging the normal cells.





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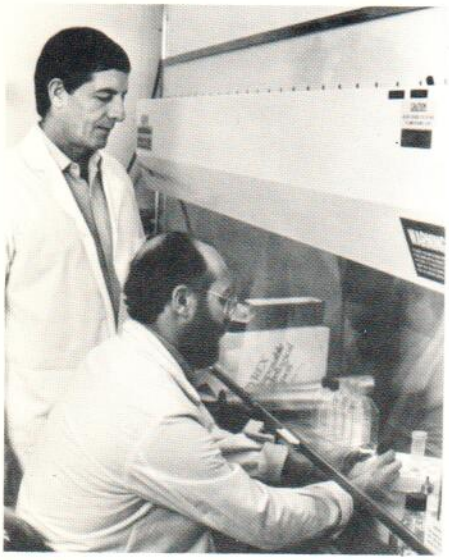


Currently, three of the Departments at BBRI are producing monoclonal antibodies for their research programs. Drs. Peter Davison, Robert Lee and Edward Galbavy are using these antibodies to distinguish the types of collagen present in different tissues of the normal, wounded, or abnormal eye in animals and man. When these antibodies are coupled with dyes or other reagents, the sites in tissue where they bind can be detected with light or electron microscope.

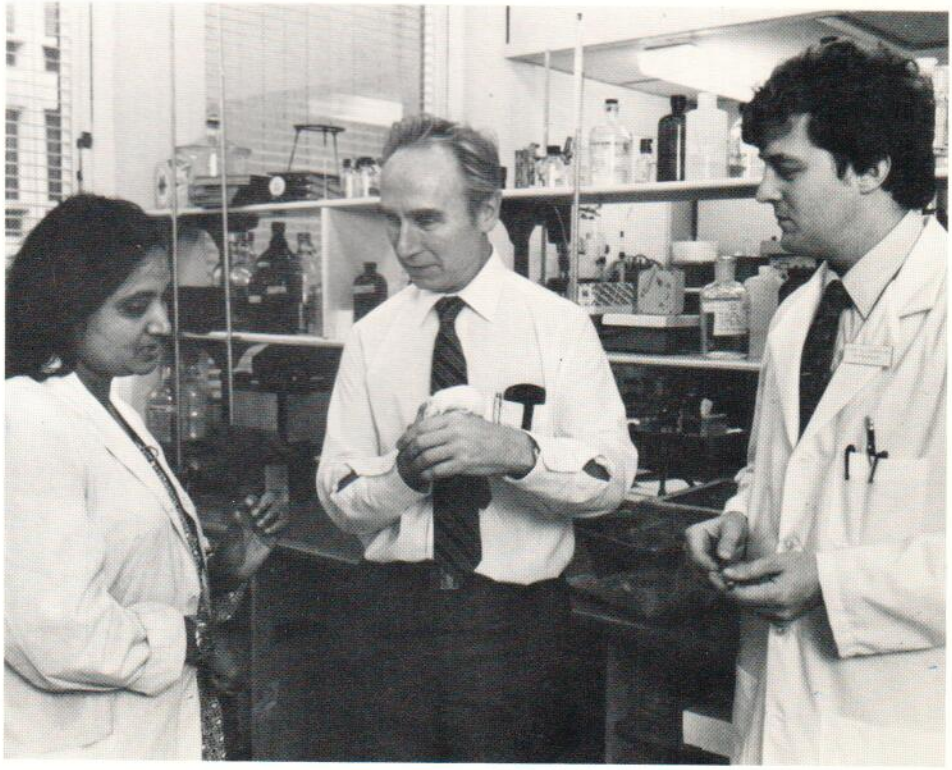
In another type of research, monoclonal antibodies are being used by Dr. Mario Rosemblatt as a tool for understanding the role that different membrane components of skeletal and cardiac muscle play in the process of contraction and relaxation. Dr. Fred Julian will be using monoclonal antibodies to analyze how different portions of the myosin molecule participate in the contractile process of muscle.

It is hoped that the results obtained through the use of monoclonal antibodies in studying diseased muscle will provide information regarding alterations in the normal components of either cardiac or skeletal muscle.

In another program, Dr. Saroj Joshi has prepared several monoclonal antibodies in order to explore the working of the ATP-fueled proton pump present in the membrane of a cell organelle, the *mitochondrion.* This complex pump involves more than ten proteins which may be distinguished and identified by selected antibodies. Selective blocking of these proteins with monoclonal antibodies may elucidate their specific functions.

All of this work will be greatly accelerated by the completion of the hybridoma facility in the basement of BBRI. The laboratories have been redesigned and built, and equipment installed with the help of donations made to the Building Fund by many donors over the past four years. The new facility will allow more Institute researchers to explore the vast experimental possibilities of monoclonal antibodies.

Robert E. Lee



BOSTON BIOMEDICAL RESEARCH INSTITUTE
Balance Sheet
August 31, 1981 and 1980

	1981					1980
	Unrestricted Funds		Restricted Funds	Plant Funds	Total All Funds	Total All Funds
	Operating	Other				
ASSETS						
Current assets:						
Cash	$ 6,080	$	$ 172,319	$	$ 178,399	$ 70,296
Grants receivable			3,232,854		3,232,854	3,328,138
Pledges receivable	25,000		100,000		125,000	26,000
Prepayments, deposits and other receivables	56,660				56,660	22,912
Investments, at market value (cost 1981 — $1,212,724 1980 — $1,166,771)	42,078	690,753	443,565		1,176,396	1,164,577
Total current assets	129,818	690,753	3,948,738		4,769,309	4,611,923
Fixed assets: (See Notes 1 and 2)						
Leasehold improvements				1,776,977	1,776,977	1,757,902
Research equipment				2,639,118	2,639,118	2,379,194
Furniture and fixtures				47,129	47,129	47,129
Total				4,463,224	4,463,224	4,184,225
Less accumulated depreciation and amortization				1,902,586	1,902,586	1,596,242
Net fixed assets				2,560,638	2,560,638	2,587,983
Total assets	129,818	690,753	3,948,738	2,560,638	7,329,947	7,199,906
LIABILITIES AND FUND BALANCES						
Current liabilities:						
Accounts payable	12,793				12,793	424
Accrued expenses	40,000				40,000	40,000
Overhead and fringe benefit adjustment payable			37,970		37,970	238,356
Total current liabilities	52,793		37,970		90,763	278,780
Fund balances: (See Note 1)						
Grants and contracts			3,574,600		3,574,600	3,436,653
Operating	77,025				77,025	132,482
Equipment replacement		425,534			425,534	349,808
Permanent research		222,869			222,869	155,455
Building program		42,350	336,168		378,518	258,745
Fixed assets				2,560,638	2,560,638	2,587,983
Total fund balances	77,025	690,753	3,910,768	2,560,638	7,239,184	6,921,126
Total liabilities and fund balances	129,818	690,753	3,948,738	2,560,638	7,329,947	7,199,906

The accompanying notes are an integral part of these financial statements.

BOSTON BIOMEDICAL RESEARCH INSTITUTE
Statement of Revenues, Expenses and Changes in Fund Balances
For the Years Ended August 31, 1981 and 1980

	1981					1980
	Unrestricted Funds		Restricted Funds	Plant Funds	Total All Funds	Total All Funds
	Operating	Other				
Revenues:						
New Grants awarded	$	$	$4,196,071	$	$4,196,071	$4,042,110
Equipment replacement	19,157		43,320		62,477	32,723
Contributions and pledges	95,098		101,678		196,776	(33,164)
Property and equipment purchased (See Notes 1 and 2)				278,999	278,999	177,978
Investment income	11,697	51,170	44,410		107,277	88,561
Total	125,952	51,170	4,385,479	278,999	4,841,600	4,308,208
Expenses: (by department)						
Muscle Research			2,199,502		2,199,502	1,658,049
Cell Physiology			683,136		683,136	533,931
Developmental Biology			318,741		318,741	271,086
Fine Structure			366,984		366,984	468,159
Metabolic Regulation			255,797		255,797	328,290
Bioorganic Chemistry			162,301		162,301	149,371
General Research	19,639		99,328		118,967	108,140
Fund Raising	26,012				26,012	12,497
Purchase of equipment	85,758				85,758	17,428
Depreciation and amortizaton (See Note 2)				306,344	306,344	271,395
Total	131,409		4,085,789	306,344	4,523,542	3,818,346
Net addition (deduction) to fund	(5,457)	51,170	299,690	(27,345)	318,058	489,862
Other changes in fund balances:						
Added to equipment replacement fund		41,970	(41,970)			
Transfer to permanent research	(50,000)	50,000				
Fund balances, beginning of year (See Note 1)	132,482	547,613	3,653,048	2,587,983	6,921,126	6,431,264
Fund balances, end of year (See Note 1)	77,025	690,753	3,910,768	2,560,638	7,239,184	6,921,126

The accompanying notes are an integral part of these financial statements.

BOSTON BIOMEDICAL RESEARCH INSTITUTE

Notes to Financial Statements
August 31, 1981

(1)—Summary of Significant Accounting Policies:

Fund Accounting

The accounts are maintained on the accrual basis and in accordance with the principles of fund accounting. Funds that have similar characteristics have been combined into the following fund groups:

*Unrestricted funds include two groups representing the portion of expendable funds available for support of operations: a) The operating fund includes unrestricted contributions and investment income less the cost of grants not reimbursed in full by granting agencies, and further reduced by transfers to other funds; b) Other unrestricted funds represent reserves transferred from the operating fund, and a building program fund derived from unrestricted contributions.

*Restricted funds represent resources restricted for research grants or building additions. Research grants are added to the fund balance when awarded, and direct charges are deducted when incurred together with the related portion of earned overhead.

*Plant funds represent the undepreciated cost of leasehold improvements, equipment and furniture and fixtures.

Other Matters

All income, gains, and losses arising from the sale, collection, or valuation at market of investments are allocated to the fund owning the assets.

A portion of the overhead chargeable to research grants is deemed to be reimbursement for equipment and is shown as an addition to the Equipment Replacement Fund and the Operating Fund. This amounted to $62,477 in 1981 ($32,723 in 1980). In addition, $85,758 of equipment was charged to the operating fund in the year ended August 31, 1981 and added to the plant fund.

(2)—Plant Assets and Depreciation:

Boston Biomedical Research Institute, under an agreement dated June 16, 1970, shares with Retina Foundation the use of research facilities for fifty years at 20 Staniford Street, Boston, and of a research farm in Townsend, Massachusetts.

The leasehold improvement asset category represents the cost of Boston Biomedical Research Institute's long-term leasehold in the building and improvements, and is being amortized over the 50-year lease term. The furniture and equipment categories represent, at cost, acquisitions from operating funds and restricted research grant awards. Depreciation is primarily on the straight-line basis over the estimated ten year useful life of the assets. All depreciation and amortization is charged to the plant fund.

(3)—Government Grants:

All grant costs billed to the U. S. government and most private grants are subject to audit by the granting agency.

GREENE & COMPANY / *Certified Public Accounts, P. C.*
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Board of Trustees
Boston Biomedical Research Institute
Boston, Massachusetts

We have examined the balance sheet of Boston Biomedical Research Institute as of August 31, 1981 and the related statement of revenues, expenses and changes in fund balances. Our examination was made in accordance with generally accepted auditing standards and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances. We made a similar examination for the preceding year.

In our opinion, the accompanying financial statements present fairly the financial position of Boston Biomedical Research Institute at August 31, 1981, and the results of its operations and changes in fund balances for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

Greene & Company

October 9, 1981

THANK YOU

BBRI is extremely grateful to the individuals and institutions listed below who have made generous contributions during the past fiscal year.

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