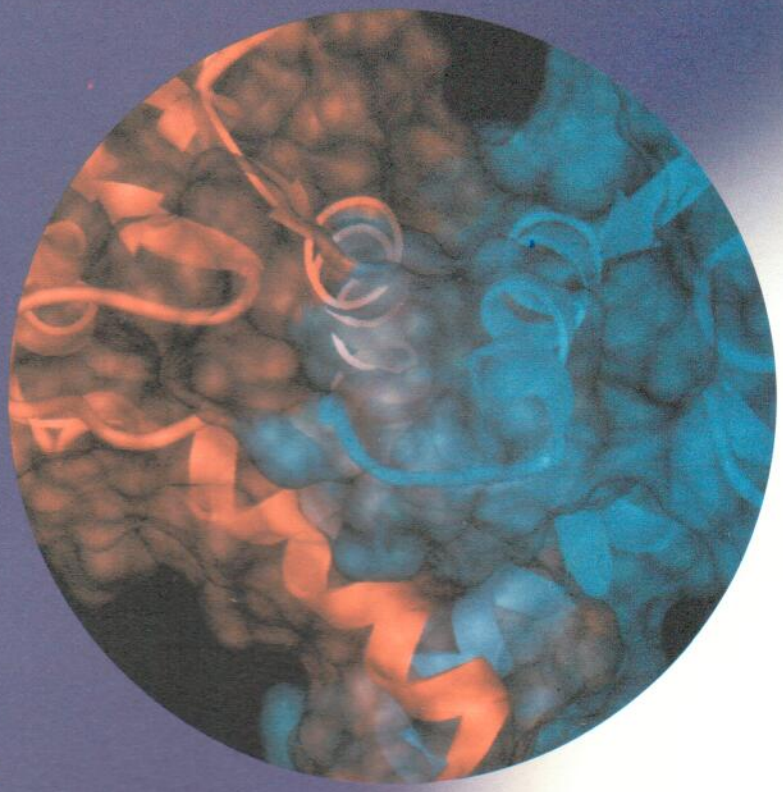


BOSTON BIOMEDICAL RESEARCH INSTITUTE

Annual Report

1996

About Boston Biomedical Research Institute

The Boston Biomedical Research Institute (BBRI) is dedicated to basic biomedical research to promote the understanding, treatment and prevention of specific human diseases. The areas of investigation concern the structure and function of muscle proteins, mechanisms of cell communication, and the control of cell growth and gene function. A major focus is muscle cell biology which has implications for muscle-related diseases such as hypertension, stroke, and heart failure. When appropriate, the Institute collaborates in clinical studies to apply the results of basic research to problems of human health and the cure of disease. Boston Biomedical is an independent, not-for-profit institution.

In its 25 years as an independent research organization, BBRI has established a tradition of excellence in biological research conducted in an intellectually exciting environment. BBRI's faculty consists of 25 principal investigators supported by a staff of 50 research associates, technicians, post-doctoral scientists in training, and students. While the true measure of the Institute's success is in how its work has changed people's lives, it is worth noting that BBRI ranked among the top 20 independent research institutes in the United States in terms of publications cited by other scientists. BBRI scientists have the intellectual freedom to break out of traditional academic disciplines, and investigators with diverse backgrounds and approaches can interact with each other to focus on a common research program. Scientists are encouraged to follow new paths, stimulated by these interdisciplinary interactions, in the hope of fostering unexpected discoveries.

Contents

Cover Photograph: The cover is a portion of a photograph of the calcyclin dimer, subunits shown in red and blue as both ribbon diagrams and transparent van der Waals. *from Potts et al. Nature Structural Biology 2 790-796 (1995)* 124 KB JPEG. The photograph was supplied courtesy of Dr. Walter Chazin, The Scripps Research Institute, and was design and produced by graduate student, Jarrod Smith.

A BRIEF HISTORY OF BOSTON BIOMEDICAL RESEARCH INSTITUTE

1950 The Retina Foundation is founded by Charles Schepens.

1951 The laboratory of the Retina Foundation is established in a tenement house on 30 Chambers Street of Boston's old West End, with Endre Balazs as the first full-time member of the research staff.

1952 John Gergely joins the Foundation to initiate a program in protein chemistry which subsequently became the basis of an internationally prominent muscle research program.

1962 The Institute of Biological and Medical Sciences of the Retina Foundation moves into a new building at 20 Staniford Street in Boston. The building was erected, at the cost of $2 million, on land made available by the Boston Redevelopment Authority.

1964-66 The research facilities at 20 Staniford Street are enlarged and scientists in other areas of basic biomedical research, such as bioenergetics and developmental biology, are recruited so as to provide a well-rounded biomedical research program to complement the Institute's clinical eye research efforts.

1970 The Retina Foundation is split into two separate institutions: the Boston Biomedical Research Institute, which is granted a rent-free 50-year lease of one-half the space at 20 Staniford Street, and the Eye Research Institute of the Retina Foundation, which is now known as the Schepens Eye Research Institute.

1972-79 BBRI's muscle research program makes fundamental contributions to the characterization of the proteins that constitute skeletal muscle. These included the elucidation of the role of the troponins, which are important regulatory components of skeletal and heart muscle and have come to play a key role in the early diagnosis of heart attacks.

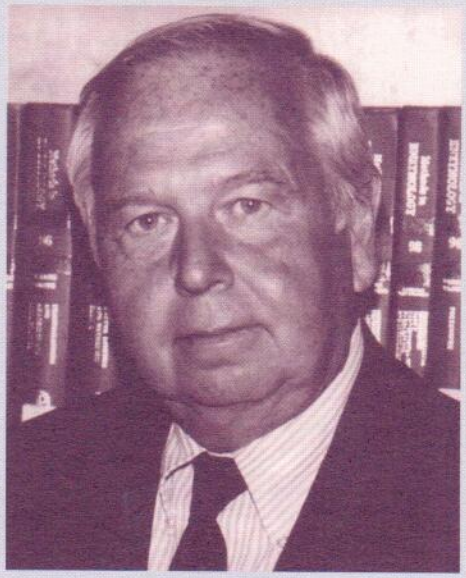
1982 BBRI files its first patent application in the area of immunotechnology and receives corporate research support for further research in this field. This patented technology has now been licensed to a biopharmaceutical company for use in cancer immunotherapy.

1990 The techniques of molecular genetics are applied to BBRI's muscle research program and contribute to the elucidation of the regulatory role of troponin C in muscle contraction.

1992 A major program in smooth muscle research is initiated at BBRI with the support of a $6 million program project grant from the NIH.

1995 With the appointment of Kathleen Morgan as BBRI's Director, the Institute focuses on three major areas relevant to muscle research – cell motility, cell communication and cell growth – and begins an aggressive faculty recruitment program in these research fields.

1996 A challenge grant from the Amelia Peabody Charitable Trust provides the cornerstone for the establishment of a major structural biology facility at BBRI for the analysis of proteins at the atomic level.



Message from the President

The ultimate aim of the innovative research carried out at Boston Biomedical Research Institute is the prevention of disease and the maintenance of health. We strive not only to extend the average life span, but also to improve the quality of life for all.

This Annual Report describes several of the remarkable projects underway by BBRI scientists and the breadth of collaborative programs with research hospitals in the Boston area as well as with other research laboratories throughout the United States. In total, our research agenda documents the uniqueness of BBRI as a leader in the field of basic biomedical research.

Scientific innovation is both complex and costly. Both private and public resources are essential to support the skill and dedication of scientists by providing the efficient scientific equipment and related resources.

BBRI is grateful to the many individuals, foundations, and corporations who provide sorely-needed capital to sustain our efforts. Likewise, we recognize the crucial role of public spending in support of basic biomedical research through the highly-competitive research grant programs of the National Institutes of Health (NIH). Significantly, our faculty is composed of many scientists who have brought distinction to BBRI by earning research grants from NIH. Unfortunately, such public grants do not cover the cost of initiating new research programs by attracting and supporting promising new scientists who are just beginning to establish the credentials and reputations with which to compete for grants in future years.

Thus it remains the challenge for each of us, as believers in the promise of earnest scientific research, to support BBRI with financial contributions that enable us to sustain the challenging agenda of promising work ahead.

We hope you will enjoy reading this report and rediscovering how "connected" BBRI is to the extensive scientific network of projects in the Boston area and beyond.

Without your support and encouragement, it is unlikely that we could fully meet the challenges ahead...but with your support and encouragement, I am confident that we will not fail in our search for innovations that improve life throughout the world.

Edgar G. Davis

Message from the Director

At this writing, I have been working at the BBRI for almost 2 years, and it has been a considerable source of satisfaction to see how the Institute has moved forward in that time. For over 25 years, BBRI has been a leader in the field of muscle research and has made significant contributions to the understanding of the structural and molecular biology of muscle contraction and the regulation of cell growth and gene function. I am pleased to say that, working with BBRI faculty, staff and trustees, we are beginning to implement a new, five-year Strategic Plan. As part of this plan, I have been working hard to accelerate recruitment efforts. These efforts have already added four new faculty members as well as a third research group whose goal is to understand the processes of cell communication.

Our primary mission continues to be the performance of fundamental biomedical research, which promotes the understanding, treatment, and prevention of human diseases. I want to emphasize that "basic" research will continue to be our main focus as we move into the next five years. Those associated with BBRI realize that, in order for new therapeutics to continue to be created into the 21st century, groundbreaking basic research must be performed today. Often, however, the average person fails to understand that when new information is put into the beginning of the R & D "pipeline", it is only after verification, applied research and clinical trials are performed that a new practical application comes out the other end – and this process commonly takes 10 – 20 years.

A new initiative at the BBRI over the last year and a half, that I have greatly enjoyed facilitating, has been the encouragement of scientific collaborations with our research colleagues in the Boston area hospitals. The goal of these collaborations is to "shorten the pipeline" – so that the new knowledge discovered today will see practical application at the most rapid possible pace. In the future, I hope to see the initiation of new collaborations with scientists in pharmaceutical firms and biotechnology companies to even further accelerate the pace at which our fundamental research can result in practical benefit.

This issue of the Annual Report focuses on just a few of the new BBRI collaborative initiatives that have recently begun. The scientists involved have been very excited about the prospect of being able to see the practical benefit of cutting-edge basic work in a wide variety of clinical settings, as well as the enjoyment that always results from "tossing ideas around" with other scientists from different backgrounds. I hope you enjoy reading about these new ventures.

Kathleen G Morgan

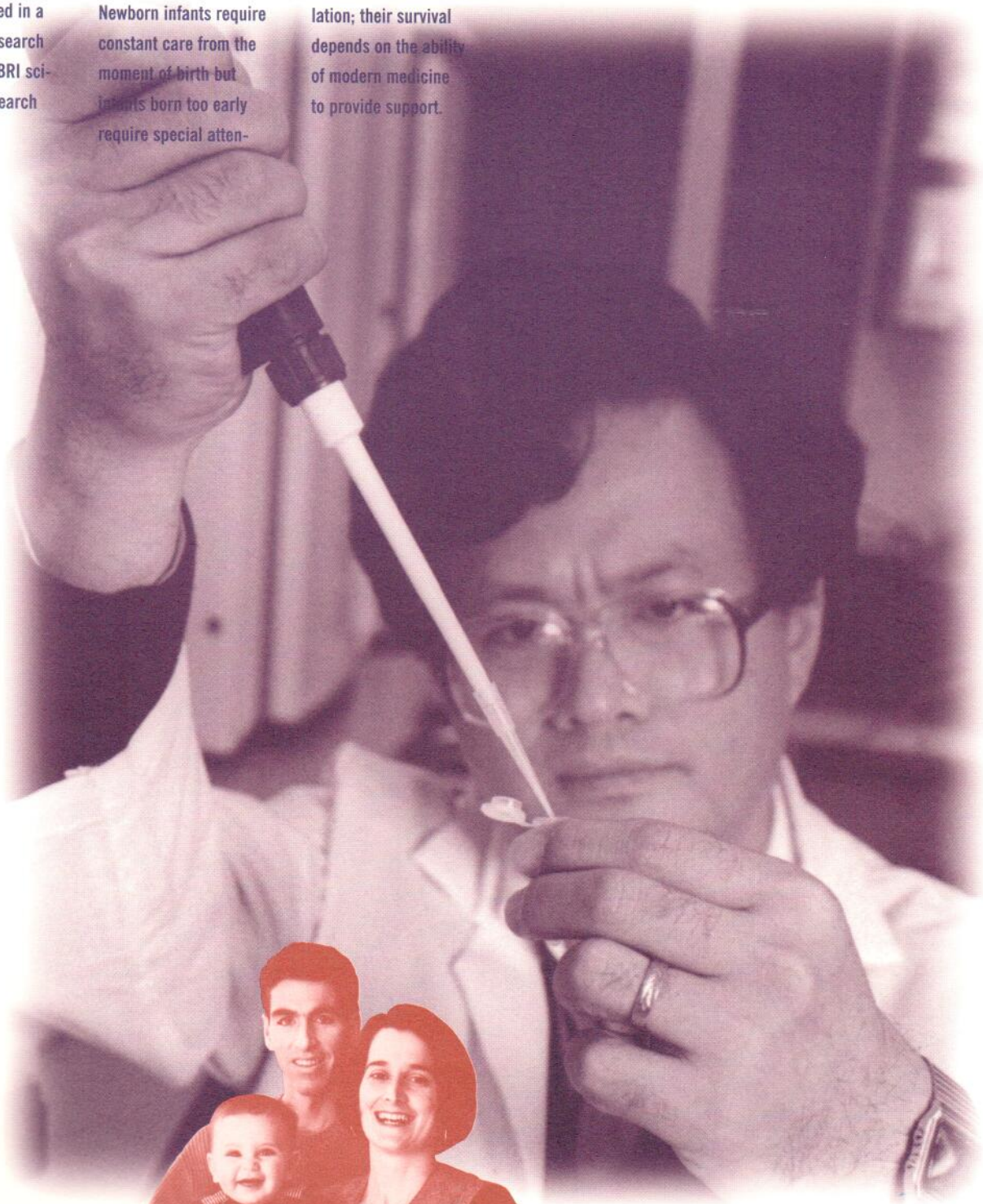
Kathleen G. Morgan

"Babies are truly wonderful gifts – and healthy babies are the most precious gifts of all."

Hope A. Ricciotti, M.D., Beth Israel Hospital

Hope A. Ricciotti, M.D., a physician in the Obstetrics/Gynecology Department at Beth Israel Hospital in Boston as well as an Instructor at Harvard Medical School, is currently involved in a collaborative research initiative with BBRI scientists. This research collaboration is focused on the role that proteins in the human uterus may play in the labor/birth process. The goal is to better understand labor and premature labor so that effective interventions may be developed.

Newborn infants require constant care from the moment of birth but infants born too early require special attention, because their development in the uterus is incomplete. They may have trouble breathing or their hearts may need stimulation; their survival depends on the ability of modern medicine to provide support.



Premature Labor

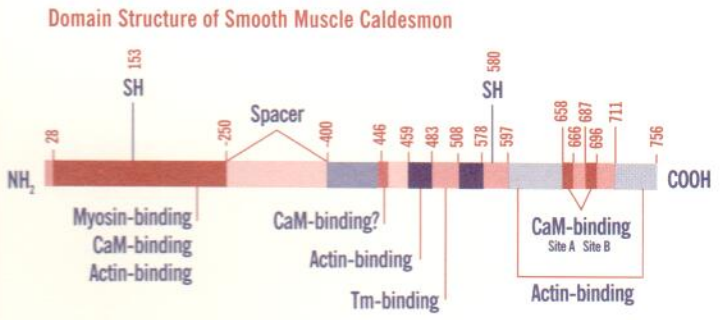
Even though the treatment for premature infants has dramatically improved in the last decade, the treatments for premature labor have not. In fact, the incidence of premature birth has not changed dramatically in the past 25 years. Greater understanding about the underlying causes of premature labor is needed before effective treatments can be developed.

A collaborative research initiative between BBRI scientists Albert Wang and Kathleen Morgan and scientists and physicians at the Obstetrics Department of Beth Israel Hospital is targeted at exploring the regulation of contraction of the human uterus. The uterus and other hollow organs of the body are composed primarily of smooth muscle. Smooth muscle is called involuntary muscle because it responds to stimuli but is not under conscious control; inappropriate contraction or relaxation of this type of muscle is responsible for a number of diseases of internal organs and abnormalities, including premature labor.

The regulation of smooth muscle contraction is still one of the great mysteries of modern biology and one of the challenges that these scientists are confronting. It is suspected that two newly discovered proteins, caldesmon and calponin, regulate the contraction and relaxation of the smooth muscle and, thus, may be potential targets for novel therapeutic interventions. Just precisely what role these proteins play, however, is still being investigated. Because the question of how these proteins do what they do remains unanswered, BBRI's investigators are approaching the challenge in several ways: determining the structure-function relationship of caldesmon; characterizing its interactions with other protein components; and understanding how these proteins are regulated.

As mentioned, it is suspected that the smooth muscle protein, caldesmon, may have a regulatory role in the contraction of smooth muscle. However, other than test tube evidence, there are few published studies in the literature pointing to a functional role for caldesmon; a leading paper on this subject has been co-authored by Drs. Morgan and Wang. Of the six types of smooth muscle: vascular, respiratory, gastrointestinal, urinary, reproductive, and ocular, the focus of this premature labor collaborative project by Drs. Morgan, Ricciotti, and Wang is on the role of smooth muscle in the female reproductive system, and the implications of the regulation of smooth muscle contraction on the labor and birth processes. Four years ago, a research group in Texas showed, through the use of antibodies, that there was a higher level of caldesmon present in the uterus during pregnancy. This finding was confirmed by the scientists at BBRI and Beth Israel Hospital, who also discovered that the level of caldesmon falls back to normal, once labor sets in. This is true both in normal and pre-term labor, and gives additional support for the important role of caldesmon. Caldesmon, therefore, seems to be an active component in the regulation of contraction during labor by keeping the uterus quiet during pregnancy.

The clinical implication of this study is that, through the understanding and manipulation of the contraction regulator, caldesmon, pre-term labor could be treated or avoided, thereby reducing risks to the baby – or conversely, contractions and labor could be induced if necessary. In either case, the control of the onset of labor would be controlled by the use of caldesmon as a potential therapeutic target.



This is an exciting collaboration, as it coordinates BBRI's basic research expertise and understanding with the clinical and medical experience of colleagues at Beth Israel Hospital. As Albert Wang says, 'This is a truly exciting study because it has such potential to provide therapeutic intervention on one of the most fundamentally important human functions: to give birth. To be able to have an impact by helping women have healthier babies.... what could be more relevant?"

Arthritis and Inflammation

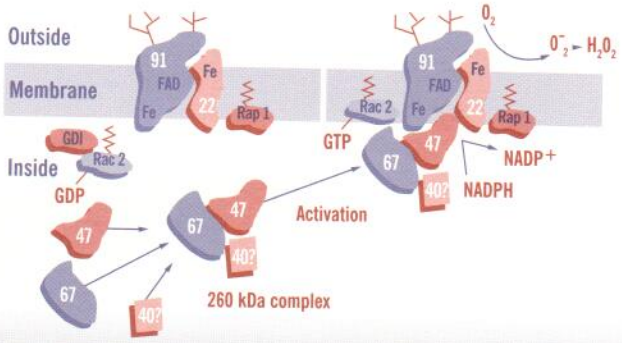
In one of his essays*, Lewis Thomas remarked that the ill effects of many bacterial or viral infections are not caused by the infectious agent itself but by the violence of the patient's defense mechanisms. The cells in our bodies, especially the white cells and macrophages, whose function is to destroy "foreign" cells such as bacteria or tumor cells, respond to chemical signals emitted by the foreign invaders and set in motion an elaborate machinery for killing the intruders. Unfortunately for us, the signal transduction pathways that are involved in this process are exquisitely sensitive and tend to overreact. Many symptoms of infectious disease, for example, the symptoms of the common cold, are inflicted by "friendly fire" which causes damage to our own cells. This is also the cause of many chronic diseases, which often appear many years after the bacterial infection that elicited the response: rheumatoid arthritis, multiples sclerosis, lupus, and many more. If we knew how to control the signal transduction pathways that elicit this misguided defense response, we might be able to reduce the pain caused by these chronic conditions.

In the past few years, the signal transduction pathways in human cells have been the subject of intense investigation, and one of the triumphs of this research is that we can now begin to develop drugs against specific components of these pathways so as to modulate the response to a particular signal. This is the focus of a collaborative project between BBRI Senior Scientist John Badwey, Ph.D., and Dwight Robinson, M.D., Professor of Medicine in the Arthritis Unit of the Massachusetts General Hospital. Together with BBRI Research Fellow Jian P. Lian, Ph.D., and RiYun Huang, M.D., Drs. Badwey and Robinson are examining the pathway by which signals from microbes cause white blood cells to produce toxins such as hydrogen peroxide (the chemical used in hair bleach) and hypochlorous acid (the active ingredient of Clorox). Although these toxins are very effective in killing invading microbes, they are also responsible for inflammatory reactions, including rheumatoid arthritis.

Dr. Badwey's research at BBRI over the past 8 years has contributed much to the understanding of the complex signal transduction pathway by which white blood cells, when they sense a nearby microorganism, trigger the switch that turns on the machinery for producing the toxic hydrogen peroxide and superoxide. One of Dr. Badwey's key contributions was the discovery that the link between sensing the signal and manufacturing the product is a complex series of reactions in which phosphates are either added or removed from highly specific proteins. These proteins represent the chain of command that conveys the message to the cell's toxin factory, and Dr. Badwey has identified many of the enzymes that modify them. The enzymes that add phosphates, called protein kinases, and those that remove phosphates, called protein phosphatases, represent ideal molecular targets for drugs that might modulate signal transduction. Dr. Badwey's collaboration with Dr. Robinson aims to identify such drugs and study how they might be used to alter the signal transduction pathway so as to moderate or inhibit the production of hydrogen peroxide and superoxide.

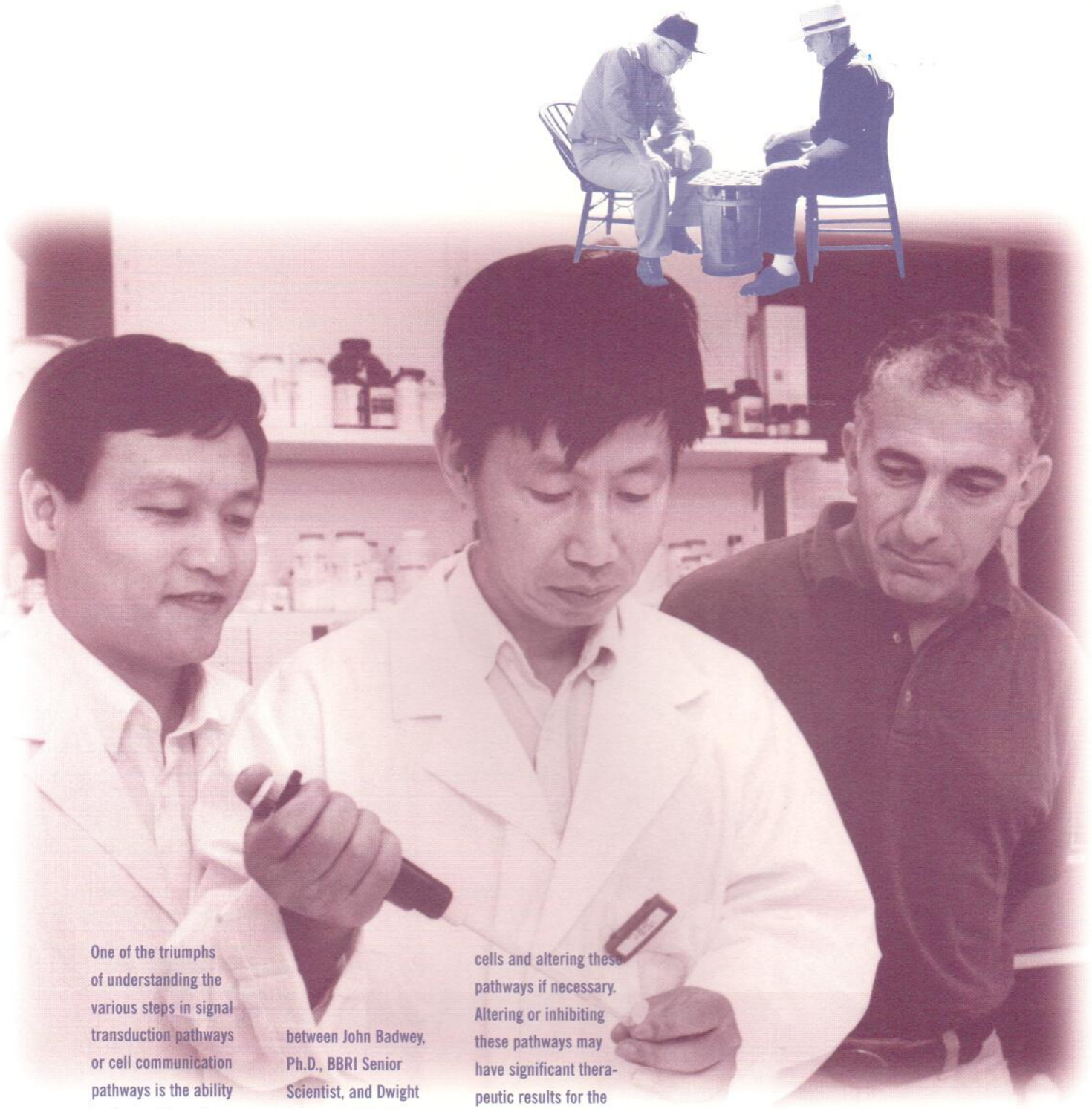
*Lewis Thomas: "On Disease" in *The Medusa and Snail*, Viking Press, New York, NY 1979

The Phagocyte NADPH Oxidase System



"Inhibitors of this kind of inflammatory reaction would find important therapeutic uses, both in moderating inflammation associated with infections and allergic responses and in controlling chronic inflammatory conditions such as rheumatoid arthritis."

John Badwey, Ph.D., Senior Scientist, BBRI

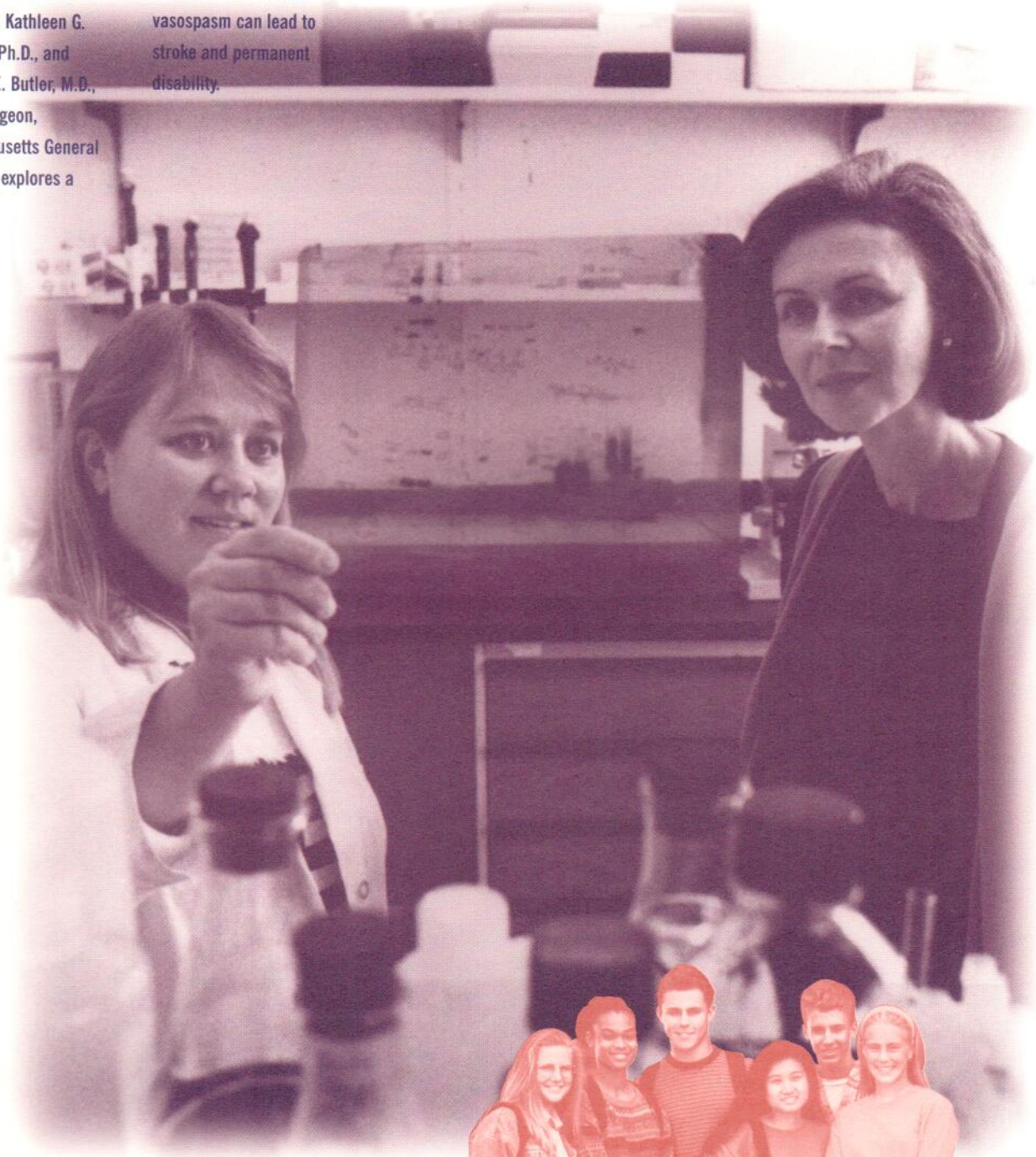


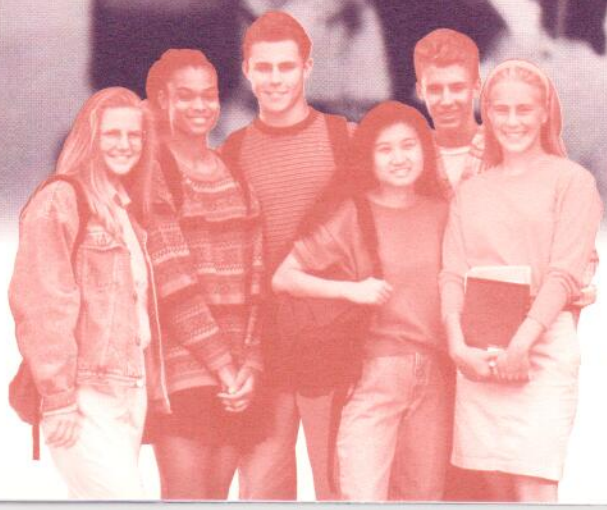
One of the triumphs of understanding the various steps in signal transduction pathways or cell communication pathways is the ability to change the pathway – or stop it altogether – if the health of a patient is in jeopardy. A collaborative research project between John Badwey, Ph.D., BBRI Senior Scientist, and Dwight Robinson, M.D., Massachusetts General Hospital, is focused on understanding the signal transduction pathways in human cells and altering these pathways if necessary. Altering or inhibiting these pathways may have significant therapeutic results for the development of new anti-inflammatory treatments for debilitating diseases such as arthritis.

"The brain, particularly the human brain, is perhaps one of the greatest – and least comprehensible – wonders of existence. It is this continuing mystery of why the brain does what it does, and how it does what it does that makes it so alluring – and yet so frustrating."

William E. Butler, M.D., Massachusetts General Hospital

The basis of a collaborative research initiative between BBRI's Director and Senior Scientist, Kathleen G. Morgan, Ph.D., and William E. Butler, M.D., Neurosurgeon, Massachusetts General Hospital, explores a specific and devastating disorder of the brain called cerebral vasospasm, which is, literally, a spasm of certain blood vessels in the brain. Cerebral vasospasm can lead to stroke and permanent disability.





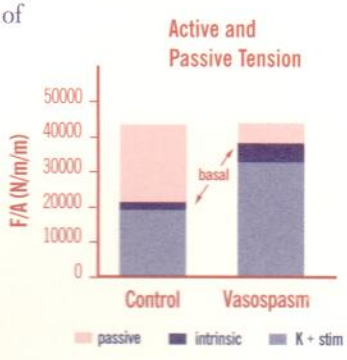
Brain Injury and Stroke

Cerebral vasospasm occurs primarily as a consequence of the rupture of a cerebral aneurysm, but it can also be the result of a head injury or a complication of brain surgery. When a head injury is involved, the patient may develop, after the initial traumatic brain injury, what is called "secondary" or delayed brain injury. This is a result of disturbances in the circulation of blood in the brain and can occur two days or more after the accident. Traumatic brain injury is a frequent cause of death and disability in all age groups, but it is particularly prevalent in adolescents and young adults.

The rupture of an aneurysm or head trauma causes blood to spill into the space below the arachnoid membrane, which is the middle of the three coverings of the brain and spinal cord. The arachnoid membrane also covers the space through which the brain's blood vessels pass. The pooling of blood in this area is called a subarachnoid hemorrhage. The spilled blood has a toxic effect on the blood vessels it surrounds and causes them to clamp shut, resulting in a cerebral vasospasm. The cerebral vasospasm cuts off the blood flow to a portion of the brain, which often leads to a stroke.

A particularly frustrating aspect of this condition is that the cerebral vasospasm may occur as late as 15 days after the blood vessel injury. For example, a patient may have successful brain surgery to correct a cerebral aneurysm and then suffer a stroke from a cerebral vasospasm 2 weeks later. The physician knows that it is apt to happen but is unable to prevent it. This consequence is, needless to say, devastating.

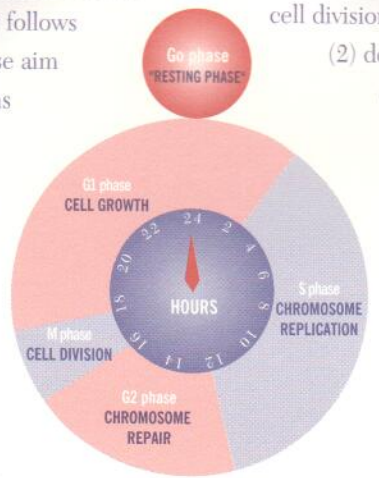
"There are two components of vasospasm that we are examining: an active component and a passive component," explains Dr. Morgan. The active component is the result of contraction of the smooth muscle cells that make up the walls of the blood vessel. Dr. Butler recently published his finding that the active component involved an elevation in the calcium concentration in the smooth muscle cells. This elevated calcium level turns on a biochemical cascade that leads to contraction of the cells and an active pinching-off of the blood flow going through the vessel. This finding provides an important clue, but how the changes in calcium levels occur and how to reverse them still need to be determined. Clinical trials with calcium channel blockers have met with little success. In fact, there is no satisfactorily effective drug therapy to treat this devastating condition.



The passive component of vasospasm is a scarring of the blood vessel wall and also contributes to the irreversible nature of the closure of the vessel. Smooth muscle cells and other similar cell types may also contribute to the development of this passive component, but we need a better understanding of how these cells function before we can identify useful therapeutic targets to reverse this process.

Cardiovascular Disease

It is critical that basic research and medical technology collaborate and combine forces to achieve the goal of improved health for all. One such collaboration between faculty of BBRI and the Cardiology Division of Beth Israel Hospital is focused on studies of a new protein, calcyclin, and the possible use of this protein in therapeutic interventions to treat restenosis. Restenosis is the unwarranted growth of smooth muscle cells which can lead to a life-threatening narrowing of the arteries. The irony of restenosis is that this regrowth of cells and the reocclusion of a diseased coronary artery follows medical intervention whose aim was to remove obstructions from the arteries by balloon angioplasty or bypass surgery. In fact, restenosis is one of the major factors that limits the long-term success of invasive medical intervention for the correction of arterial blockage and affects thousands of patients every year. This is why BBRI gives high priority to studying the control of cell growth.



The Cell Cycle

A current collaborative research project between BBRI Senior Scientist, Albert Wang, Ph.D., and Michael Simons, M.D., Cardiovascular Division, Beth Israel Hospital, is examining calcyclin, a new protein that binds calcium. Calcyclin is a member of a large family of small calcium-binding proteins found in smooth muscle that are suspected to regulate the ability of cells to contract. However, the level of this protein fluctuates inside the cell depending on what stage the cell is at during the cell cycle. Initial information indicates that when the cell is actively dividing, the level of calcyclin is high; and, conversely, when the cell is quiet, the level of calcyclin is low.

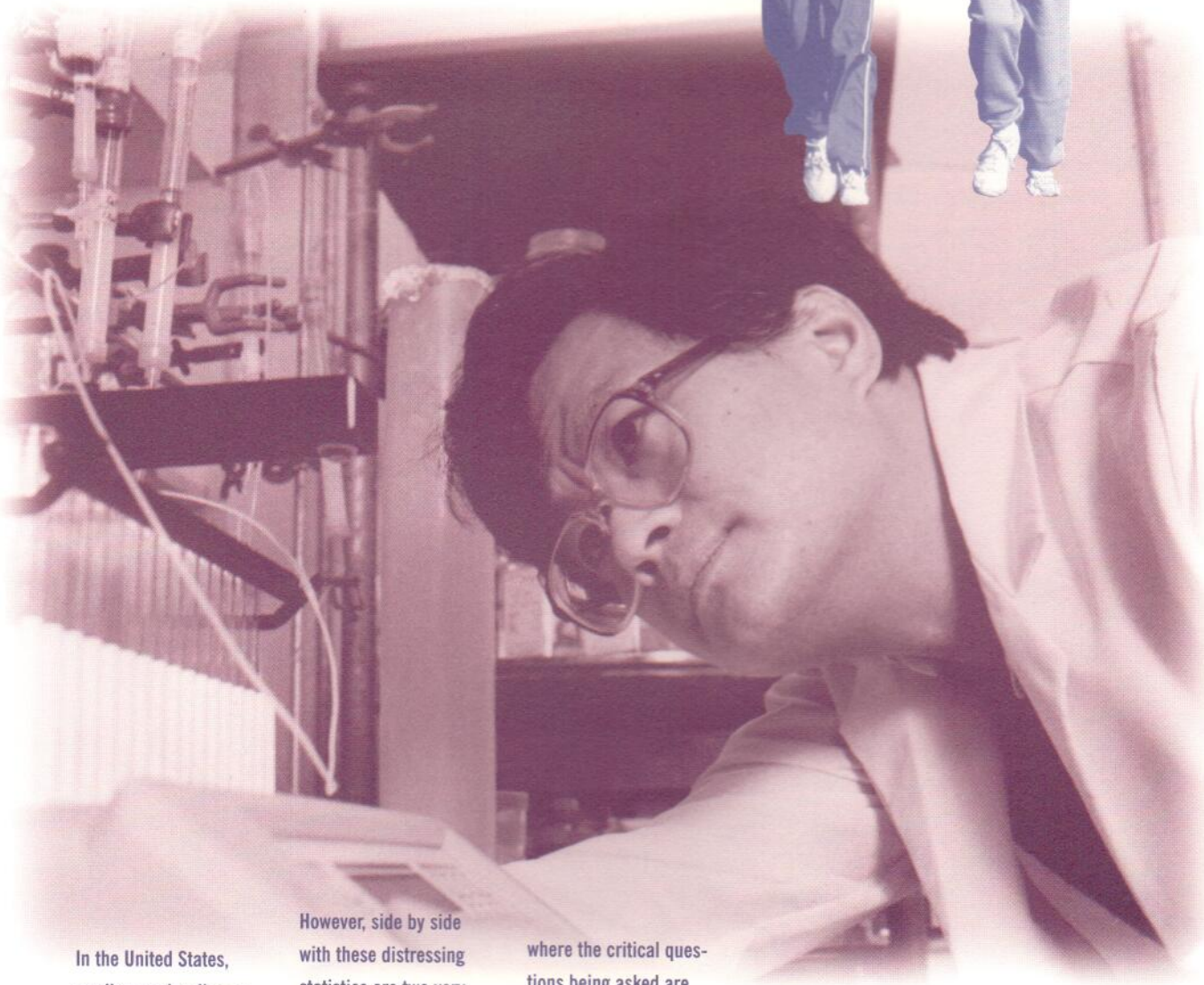
There are two primary questions that have emerged in this new study of calcyclin: (1) does it actually change or enhance the cell division rate or the cell cycle and (2) does it also regulate the activity of contractile proteins?

The focus of the work of Dr. Simons is on the first of these questions. Dr. Simons is approaching his exploration of the relationship between calcyclin and cell cycle from a physiological side in an attempt to understand how the calcyclin gene works. Calcyclin is expressed during the G1 phase of cell cycle as the cell is getting ready to begin the DNA synthesis. Previous investigations have shown that an increase in the intracellular calcium level is an important step in progression of the cell cycle to the next phase. Drs. Simons and Wang believe that if the calcium rise is blocked, cell cycle progression will be halted and the cell will not replicate or grow. "If we can put the calcyclin gene where we want it in the smooth muscle cell and activate it when we want to, we should be able to control the cell cycle or growth of the cell, explains Dr. Simons.

Dr. Simons (with Robert Rosenberg, M.D., Chief of the Molecular Medicine Unit, Beth Israel Hospital and Professor of Biology, MIT, and Kathleen G. Morgan, Ph.D., Director, BBRI) has previously published studies showing that another protein, c-myb, regulates cell cycle by altering calcium levels in smooth muscle cells. However, the target of the myb-induced changes in calcium and the mechanisms by which calcium regulates cell cycle are not known. Dr. Simons is working with BBRI scientists to apply this suspected regulatory function of calcyclin also to gene regulation. In other words, Dr. Simons suspects that calcyclin may also be used as a "messenger" between an outside stimulator on a cell surface and regulation inside the cell, in the cell nucleus. This has the potential to develop into gene therapy wherein calcyclin is injected into tissue to stimulate the cells or, conversely, to be removed from cells to inhibit certain cellular functions. Helping us understand why some cells grow and others don't will provide the basis for therapeutic interventions that might prevent life-threatening smooth muscle cell growth, such as in restenosis.

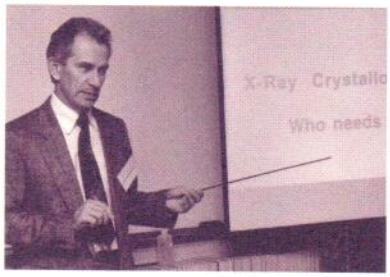
"The fundamental processes controlling cell growth are all the same, whether the cell growth results in restenosis or is somehow involved with the spread of cancer. It is essential that we explore and understand the fundamental mechanisms of the cell cycle – that understanding and awareness will be fundamental information that is applicable to all issues involving cell growth."

Michael Simons, M.D., Beth Israel Hospital



In the United States, cardiovascular disease is the number one cause of death, and coronary heart disease afflicts about 11.2 million Americans.

However, side by side with these distressing statistics are two very positive facts: 1) the future of cardiovascular basic research has never been more promising and 2) science and technology have evolved to a point where the critical questions being asked are beginning to yield answers. These answers are leading the way to improved health and, ultimately, better quality of life for all Americans.

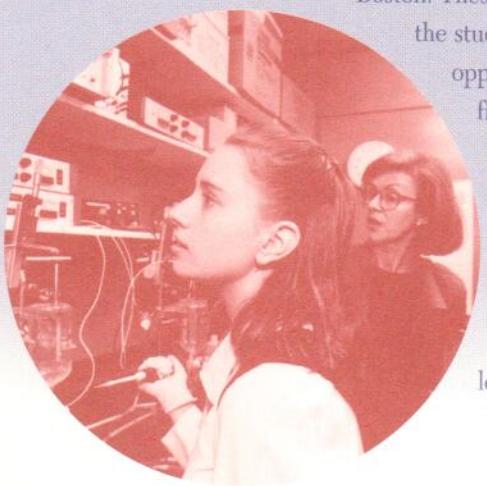


The 1996 Evening of Discovery

The annual "Evening of Discovery" on May 9 brought together BBRI Board members, members of the Corporation, special guests, new acquaintances, BBRI faculty and other friends for research presentations and socializing at BBRI. The evening started with a cocktail reception for all guests and a warm welcome from Jack French, BBRI's Chair of the Board, and Kathleen G. Morgan, Ph.D., BBRI's Director. The guests then moved to three research presentations given by BBRI scientists: "X-Ray Crystallography: Who needs it?" presented by Zenon Grabarek, Ph.D.; "AIDS: The use of Catalytic Antibodies for a Treatment" presented by Victor Raso, Ph.D.; and "Molecular Motors: Nature's Tiniest Motors" by Lynn Coluccio, Ph.D. Each of the presentations was followed by a question-and-answer period. The attendees then reconvened for coffee, dessert, and lively discussions on the talks they had just heard and the relevance of the science to health and disease.

National Youth Leadership Forum on Medicine

On two Mondays during the summer, BBRI hosted a select group of students from the National Youth Leadership Forum on Medicine with a tour of BBRI and introductions to several of our scientists. The National Youth Leadership Forum (NYLF) is a not-for-profit organization that develops specialized and career-oriented programs for outstanding high school juniors and seniors with scholastic merit and strong leadership potential. The National Youth Leadership Forum on Medicine (NYLF/MD) is an eleven-day medical program held each summer in four cities: Boston, Houston-Galveston, San Francisco, and Washington D.C. These outstanding high school students attend conferences at some of the most prominent and technologically advanced medical institutions, including NIH in Washington, D.C., and Massachusetts General Hospital, Harvard Medical School, Beth Israel Hospital, and BBRI in Boston. These on-site visits provide the students with the unique opportunity to witness, firsthand, the research being conducted to combat a specific illness or disease, or to investigate a particular medical issue while simultaneously learning about research-related careers. We were proud to be included as a host organization for these students while they visited Boston, and to have the opportunity to provide information about careers in basic biomedical research.



BBRI Hosts Smooth Muscle Society Meeting

Drs. Leonard Adam and Kathleen Morgan organized this year's Annual Meeting of the New England Smooth Muscle Society, hosted by BBRI on October 5, at the Blake Auditorium of Massachusetts General Hospital. The program ran from 8:30 a.m. until 6:00 p.m. and included 24 scientific presentations on subjects ranging "from membranes to motor proteins," poster viewing, a business meeting of the Society, and a reception at BBRI. The New England Smooth Muscle Society has over 100 members from organizations all over New England that perform research in the field of smooth muscle, including Brown University, University of Vermont, University of Massachusetts Medical Center, Brandeis University, Harvard Medical School, and Harvard School of Public Health.

Development Report

For BBRI's fundraising programs, fiscal year 1996 brought many changes – and as many challenges. In December, 1995, Jackie Findlay retired after 12 years as Director of Development at BBRI. From one who had worked closely with her over the past several years, I will always appreciate her cheerful willingness, dedication, and never ceasing attention to details – and I greatly admire her retirement! In January, 1996, after a national search, Kathleen Carney joined BBRI as the new Director of Development and Public Affairs, as the area of public relations

was "officially" added to the fundraising program for the Institute. Ms. Carney also brought with her Molly Knopf, Development and Public Affairs Coordinator. Working with Dr. Morgan, Dr. Paulus, and Mr. McQuaid (BBRI's new CFO), Ms. Carney has helped put together a five-year Strategic Plan and Financial Forecast, which focuses on new initiatives for the scientific progress of BBRI, as well as for the fundraising, public relations, and financial programs of the Institute. The basis of the Strategic Plan can be simply explained in one word: growth. It is essential that BBRI continue its leadership position in the field of basic biomedical research and move forward on a foundation that is financially secure and publicly acknowledged. Therefore, for those of us who volunteer our time to help BBRI meet this challenge in the next fiscal year, we must reach out even further to our donors and potential donors to explore resources and opportunities for financial support and public awareness that we have not yet discovered. For those of you who have supported us this past year – and further beyond that – my sincerest thanks for your financial commitment.

We have also made progress in our Public Affairs program: three press releases and photo cutlines sent out; the initial formation of a new Public Relations Committee; meetings with local newspaper editors; an updated media contact list; enhanced interaction with Boston-area schools

through site visits; and preliminary contacts with relevant political leaders. All of the seven strategies currently being implemented to launch an enhanced Public Relations program for the Institute will continue into the next fiscal year, and I am hopeful we will continue to see BBRI's visibility and communications expand accordingly.

Fiscal year 1996 finished with $321,000 in BBRI's Annual Fund, an increase of $61,457 or 24% over last fiscal year. Following is a list of our donors. As we move forward into fiscal year 1996, we have many challenges in front of us – but many successes and triumphs behind us. I feel confident we can support BBRI's commitment to growth and progress – with the help of our Board, Corporators, and special friends.

Charles C. Ives
Development Committee Chair

FISCAL YEAR 1996 DONORS

Foundations and businesses which generously gave us their support and encouragement in fiscal 1996:

Analytical Biotechnology Services

The John W. Alden Trust

Anonymous

The Boston Foundation/Leith Family Fund

The Roberta M. Childs Charitable Foundation

Ciba Corning Diagnostics Corporation

The Howard C. Connor Charitable Foundation

Jane B. Cook 1992 Charitable Lead Trust

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Polaroid Foundation

Fred M. Roddy Foundation

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Contributions were given in memory of:

Emily P. Foster by her parents Mr. and Mrs. John S. Foster

Elizabeth Maclean Slayter by her brother Hugh Maclean

Donors to the John Gergely Symposium

Biomatrix Inc.

The Cardiac Society

Ciba Corning Diagnostics Corporation

The Coulter Corporation

Genzyme Corporation

The Japanese Muscle Club

Founders Society

We would like to give special recognition to the members of BBRI's Founders Society:

Ernest Henderson, III

David C. Crockett

Members to the Founders Society are selected because they have exceptional commitment, dedication, and service to the Institute; lifetime giving or commitment of $100,000 or more and/or efforts instrumental in obtaining such gifts for the Institute; and have shown leadership in promoting and facilitating the mission of the Institute to discover and disseminate new biomedical knowledge. We are deeply honored to have these outstanding individuals as members of the BBRI community.

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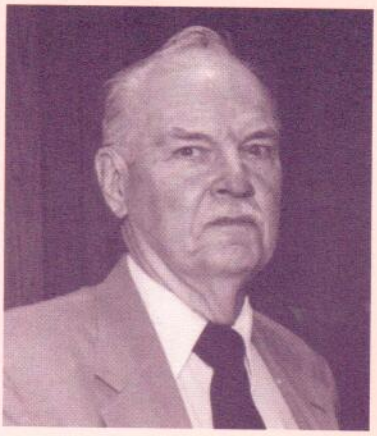
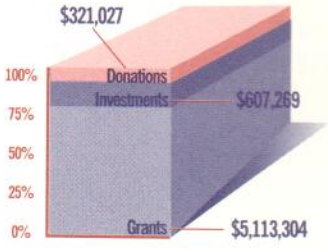
Treasurer's Report



At the close of Boston Biomedical Research Institute's fiscal year 1996, our strong financial position continued to provide a secure foundation for BBRI's strategic initiatives. Following are highlights of the fiscal year's financial performance.

BBRI has three primary sources of revenue: faculty-initiated grants; return on our investment portfolio; and fundraising.

Grants from the National Institutes of Health (NIH) continue to be the major source of funding with grants representing approximately 85% of revenues while annual giving and investment income comprise the balance.

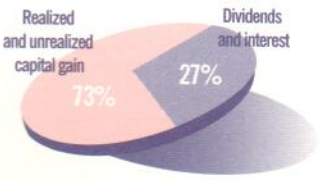


Fiscal Year 1996 Revenue

As a result of the funding squeeze at NIH, we experienced a decline in grant revenue which had an impact on the bottom line. In response, the Board of Trustees recently approved an exciting and comprehensive five-year Strategic Plan, designed to expand the scientific base, seek new revenue alternatives, and refocus intellectual capital toward a common goal. There is no "quick-fix" however, as the grant awarding process is a nine-month cycle at least, and a two-year cycle at most. The Trustees' plan, while aggressive and encouraging, will not produce immediate bottom line benefits. Fiscal 1997 results are expected to reflect that reality.

BBRI continues to build on a solid investment portfolio, which grew to over $7,500,000 with capital gains and dividends of $607,000. 73% of the investment return was comprised of realized and unrealized capital gain, and 27% of dividends and interest.

Investment Returns



Fiscal year 1996 also brought increases in fundraising revenue, which have been reviewed in the Development report. This revenue stream is increasingly valuable to the Institute, as we work to diversify our sources of funding. We all must work together to identify new sources of income and implement programs that will capitalize on these opportunities. One such example is BBRI's Patent and Technology Transfer Committee, which has been actively exploring new collaborations with the biotechnology industry to utilize ideas developed through BBRI's basic research and translate them into clinical uses.

The faculty and administrative team of BBRI are to be commended for working diligently throughout the year to keep expenses in line with budget projections. The Institute continues its tradition of remaining debt free. Due to opportunities presented by changes in government regulations, we are exploring capital equipment financing options not previously available. This may allow us to preserve capital in our investment portfolio while enabling expansion of technological needs.

BBRI's most valuable assets are its people and their ideas! New faculty is being pursued vigorously while accomplished scientists at the Institute renew their focus on funding as well as science. Through its enthusiastic and unanimous adoption of the Strategic Plan, the Board has reaffirmed its commitment to the faculty and the tenants of basic research, and refocused its business priorities.

I would like to take this opportunity to personally thank Vin Raso, our former Controller, upon the occasion of his retirement, for his twenty years of dedicated service to the Institute. I have served as Treasurer for the past thirteen years and Vin's assistance on financial and administrative matters has been invaluable. Vin will continue his service to BBRI as a Corporator and ad hoc advisor, and I am glad we will continue to have the benefit of his advice and guidance.

Respectfully submitted,

Ernest Henderson, III
Treasurer

STATEMENTS OF FINANCIAL POSITION

Boston Biomedical Research Institute

For the Years Ended August 31, 1996 and 1995

Assets	1996	1995
Cash	$ 188,115	$ 970,338
Grants receivable	3,122,380	3,565,016
Pledges receivable	–	800
Investments	7,512,420	7,198,299
Prepayments, deposits and other receivables	25,421	87,693
Property and equipment	1,145,396	1,338,810
Deferred compensation investments	1,220,186	1,426,018
Total assets	$13,213,918	$ 14,586,974
Liabilities and Net Assets		
Accounts payable and accrued expenses	$ 99,969	$ 243,039
Deferred income	3,679,983	4,009,324
Deferred compensation payable	1,220,186	1,426,018
Total liabilities	5,000,138	5,678,381
Net Assets		
Unrestricted	7,599,664	8,243,390
Temporarily restricted	292,704	365,203
Permanently restricted	321,412	300,000
Total net assets	8,213,780	8,908,593
Total liabilities and net assets	$13,213,918	$ 14,586,974

Copies of our complete, audited financial statements, certified by the independent accounting firm of Quin, Rickard & Vecchi, P.C., Certified Public Accountants, are available upon request from the Chief Financial Officer, Boston Biomedical Research Institute.

STATEMENTS OF ACTIVITIES

Boston Biomedical Research Institute

For the Years Ended August 31, 1996 and 1995

Changes in Unrestricted Net Assets	1996	1995
Revenues:		
Grants and contracts	$ 5,113,304	$ 6,458,378
Contributions	303,691	214,246
Property and equipment purchased	–	274,347
Investment income	556,968	764,443
Total unrestricted revenue	5,973,963	7,711,414
Net assets released from restrictions	118,724	–
Total unrestricted support	6,092,687	7,711,414
Expenses:		
Salaries and benefits	4,308,640	4,720,396
General support and services	1,156,616	1,047,070
Occupancy costs	998,536	690,000
Property and equipment purchased	–	264,637
Depreciation	206,512	168,202
Fund raising	66,109	88,440
Total expenses	6,736,413	6,978,745
Increase (decrease) in unrestricted assets	(643,726)	732,669
Changes in Temporarily Restricted Net Assets		
Contributions	17,336	81,176
Investment income	28,889	65,571
Net assets released from restrictions	(118,724)	–
Increase (decrease) in temporarily restricted net assets	(72,499)	146,747
Changes in Permanently Restricted Net Assets		
Investment income	21,412	–
Increase in permanently restricted net assets	21,412	–
Increase (decrease) in net assets	(694,813)	879,416
Net assets at beginning of year	8,908,593	8,029,177
Net assets at end of year	$ 8,213,780	$ 8,908,593

GRANTS AND FELLOWSHIPS

Research Grants

National Institutes of Health			
Dr. Adam	MAPK in the contractile phenotype of smooth muscle	3/96 - 2/01	$1,111
Dr. Badwey	Synergistic stimulation and priming of neutrophils	7/90 - 4/96	863
Dr. Badwey	Enzymes modulating second messengers in neutrophils	4/93 - 3/97	643
Dr. Badwey	A novel signalling pathway in neutrophils	5/96 - 4/00	777
Dr. Coleman	ATP binding site photoaffinity probes for F1-ATPase	6/92 - 5/96	798
Dr. Gergely (MERIT)	Biochemistry of muscle contraction	7/89 - 6/97	2,733
Dr. Grabarek	Calcium binding protein/target interactions	6/92 - 12/95	606
Dr. Graceffa	Smooth muscle and non-muscle caldesmon	5/93 - 4/97	728
Dr. Ikemoto	Structure and function of sarcoplasmic reticulum	7/92 - 5/97	1,735
Dr. Joshi	Molecular mechanisms of mitochondrial ATP synthesis	9/92 - 8/96	831
Dr. Lehrer	Tropomyosin and myosin interaction in muscle	12/90 - 11/95	1,651
Dr. Lehrer	Tropomyosin and myosin interaction in muscle	12/95 - 11/00	2,044
Dr. Lu	Structure-function relation in myosin	9/91 - 8/96	869
Dr. Morgan	Regulation of contraction and growth of blood vessels	1/95 - 12/95	209
Dr. Morgan	Regulation of contraction and growth of blood vessels	7/96 - 6/99	713
Dr. Morgan	Contraction of vascular smooth muscle cells	4/95 - 3/97	327
Dr. Paulus	Control of diaminopimelate and lysine biosynthesis	4/93 - 3/97	1,160
Dr. Raso	Targeting toxins with acid-triggered hybrid antibodies	12/89 - 11/95	1,188
Dr. Sarkar	Function of polyadenylate sequences in bacterial RNA	12/93 - 11/97	1,155
Dr. Sherman	Molecular chaperones and protein phosphorylation	5/96 - 4/00	1,067
Dr. Stafford	Engineered anti-breast cancer single chain Fy immunotoxin	6/90 - 11/95	646
Dr. Tao (MERIT)	Proximity relationship among muscle proteins	4/91 - 3/96	1,432
Dr. Tao (MERIT)	Proximity relationship among muscle proteins	5/96 - 3/01	1,747
Dr. Wang (Pro. Proj.)	Molecular mechanism of smooth muscle regulation	9/92 - 8/97	6,000
Dr. Wang	Caldesmon and transmembrane signaling	9/93 - 9/96	60
Dr. Wohlrab	Proton-coupled inorganic phosphate transport	4/92 - 3/97	1,231
American Cancer Society			
Dr. Coluccio	Myosin-I in liver	4/96 - 2/97	187
Dr. Sherman	Role of Hsp70 in ubiquitin-dependent proteolysis	12/95 - 11/96	35
American Heart Association			
Dr. Szymanski	Interaction between calponin and smooth muscle myosin	7/94 - 6/96	59
Medical Foundation			
Dr. Sherman	Molecular chaperones and degradation of oxidatively damaged protein	7/96 - 6/98	100
Muscular Dystrophy Association			
Dr. Ikemoto	Excitation-contraction coupling in malignant hyperthermia	7/94 - 6/97	130
National Science Foundation			
Dr. Stafford	XL-A Analytical ultracentrifuge for the analysis of protein-protein interactions	3/96 - 2/98	158
Sponsored Research			
Dr. Wang	Pharmaceutical Research Laboratory of Kirin Brewery Co., Ltd.	4/96 - 3/97	12

Fellowships

Dr. Ao	American Heart Association, Massachusetts Affiliate	7/94 - 6/96	52
Dr. Shao	New England Biolabs	*9/92 - 8/96	80

**New grants in fiscal 1996*

BBRI'S STAFF

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Kathleen G. Morgan, Ph.D.

Deputy Director
Henry Paulus, Ph.D.

Senior Scientists
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Peter S. Coleman, Ph.D.
John Gergely, M.D., Ph.D., D.Sc.M. (hon.)
Philip J. Graceffa, Ph.D.
Noriaki Ikemoto, Ph.D.
Saroj Joshi, Ph.D.
Paul Leavis, Ph.D.
Sherwin S. Lehrer, Ph.D.
Renne C. Lu, Ph.D.
Kathleen G. Morgan, Ph.D.
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Victor A. Raso, Ph.D.
Nilima Sarkar, Ph.D.
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Terence Tao, Ph.D.
Chih-Lueh Albert Wang, Ph.D.
Hartmut Wohlrab, Ph.D.

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Zenon Grabarek, Ph.D.
Vladimir Z. Volloch, Ph.D.

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Michael Sherman, Ph.D.
Brenda Williams, Ph.D.

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Katherine Sheldon, Ph.D.

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Shu-Qin Jiang, Ph.D.
Yin Luo, Ph.D.
Grazyna Szymanska, Ph.D.
Pawel Szymanski, Ph.D.
Enzhong Wang, Ph.D.
Jing-Lun Wu, Ph.D.

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Gong-Jie Cao, Ph.D.
Chantal Dessy, Ph.D.
Roque El-Hayek, M.D.
Nina Golitsina, Ph.D.
Jolanta Kordowska, Ph.D.
Knut Langsetmo, Ph.D.
Regent LaPorte, Ph.D.
Jian Ping Lian, Ph.D.
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David Meyer, Ph.D.
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Ioanna Petrounia, Ph.D.
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Jen-shiang Hong, Ph.D.
D. Rao Sanadi, Ph.D.
Frank Sreter, M.D., D.V.M., Ph.D.

BBRI Scholar
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Bozena Antoniu, B.S.
Minhua Chai, B.S.
Xiaomei Chen, M.B.
Adelaida D. Carlos, B.S.
Dina Deldon, B.S.
Paula F. Geary, B.S.
Bang Gong, M.B.
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Brett F. Warren, B.S.
Anna G. Wong, B.A.
Ying Zhang, B.S.
Shaobin Zhuang, M.S.

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Sartyapriya Sarkar, Ph.D.
Michael Taggart, Ph.D.

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Sanya Sukduang
Carrie Sougnez

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Chief Financial Officer

Vincent F. Raso, C.P.A.
Controller (Retired 2/96)

Patricia Brouillette
Human Resources Manager

Helene Clinton
Administrative Assistant

Virginia Cahill
Administrative Assistant

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Dir. of Computer Services

Knut Langsetmo, Ph.D.
Asst. Dir. of Computer Services

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Director of Development and Public Affairs

Jacquelyn Findlay
Director of Development (Retired 12/95)

Molly Knopf
Development and Public Affairs Coordinator

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Barbara Zillman

Housekeeping
Maria Bozzella
Constance Giangregorio
Lucille Konjoian (Retired 1/96)
Jian Qing Yang

Editors: Kathleen G. Morgan, Ph.D., Henry Paulus, Ph.D., Kathleen A. Carney and Molly Knopf Designer: Schenkel/Stegman Communications Design Photographs: Steve Gilbert, Studioflex Productions

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