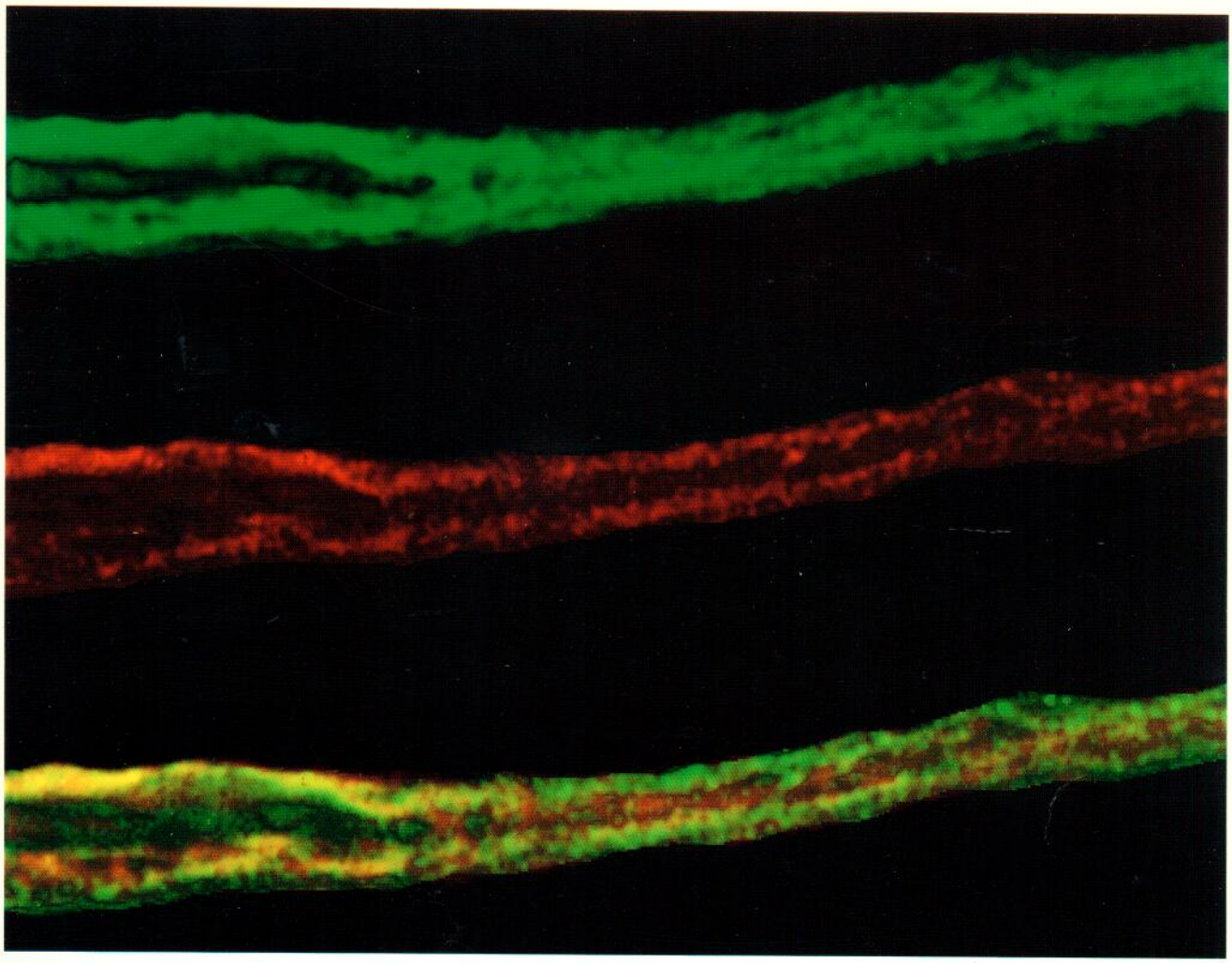
BBRI – Begins Its Second Quarter Century
New Visions – New Faculty – New Research Initiatives



Boston
Biomedical
Research
Institute

1995 Annual Report

BOSTON BIOMEDICAL RESEARCH INSTITUTE (BBRI) is dedicated to basic biomedical research, which promotes the understanding, treatment and prevention of human diseases. The areas of investigation concern the structure and function of muscle proteins, the mechanisms of membrane transport and signal transduction, and the control of cell growth. A major focus is muscle cell biology, which has implications for neuromuscular and other muscle-related diseases such as asthma, hypertension, malignant hyperthermia and gastrointestinal disorders. When appropriate, the Institute collaborates in clinical studies of patients to apply the results of basic research to problems of human health and the cure of disease. Boston Biomedical Research Institute is an independent, not-for-profit institution.

Cover.
Mapping the internal skeleton of a smooth muscle cell.
Top: Immunofluorescent localization of desmin in a vascular smooth muscle cell.
Middle: Immunofluorescent localization of the beta isoform of actin in the same cell.
Bottom: Computer-generated superimposition of the upper two images, where areas of overlap are coded yellow in an intensity proportional to the degree of overlap.

— Image acquisition, computer deconvolution, and photography by Christopher Parker.

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"If only we knew" must be a phrase repeated thousands of times as scientists, physicians and patients grapple with the frustration of today's relatively limited treatments for many humanly tragic and economically costly illnesses. The list of the completely unsolved goes on: coronary heart disease, multiple cancers, Alzheimer's disease, AIDS, diabetes, and many others.

Of course, much progress has been and is being made by dedicated scientists around the world in developing new and improved medicines and treatments. Yet, at some point in their work, further breakthroughs are inevitably blocked by the limits of the most fundamental of knowledge – or "basic research" regarding the intricacies of the human body and the inherent nature of specific illnesses.

At BBRI, our mission has been and will continue to be to accelerate the pursuit of basic science and to speed its ultimate application to solutions of specific biomedical questions.

BBRI is blessed with a distinguished and dedicated faculty. Their pre-eminent record of discovery is documented by a wide array of achievements, publications, and grants earned amidst the enormous competitive pressures for funding in today's environment of restricted public budgets at the NIH and industrial budget constraints in an era of health care "cost containment."

During the past year, BBRI was extremely fortunate to have attracted Dr. Kathleen Morgan as Director and Chief Executive Officer. Dr. Morgan has brought an extraordinary degree of collegiality, creativity, and courage that extends the historical traditions of past leadership excellence. In general, BBRI enters its second quarter century with a solid foundation on which to confront and conquer the challenges ahead. Attracting the human, physical, and financial resources to carry out our vision and mission is an exciting prospect. Thus, we wish to share with you the following brief summary of our strategic vision, its practical implications, and the initiatives we are likely to pursue to assure that adequate resources are in place to enable us to fulfill our potential for service:

1. BBRI will continue to build upon its reputation as a preeminent international center for smooth muscle research. In doing so, we anticipate developing strong programs in two additional and interacting areas of basic science – cellular communications and cell growth. Both fields are relevant to our focus on muscle research because, as you will read in this annual report, smooth muscle cells do grow and do receive signals that communicate a message to either grow or move. Such knowledge represents the essential "linkage" that inevitably exists between the "basic research" typified by BBRI. and the potential for other academic and industrial scientists in "applied research" to develop newer and better treatments for such conditions as vascular spasm, heart failure, and coronary heart disease.

So, to the question of 'What good is the basic research done at BBRI?' our response is the hearty hope that lives will be saved or extended some day because of the insights contributed by BBRI investigators!

2. The requirements necessary to continue our quest for world-class research discoveries are obvious. BBRI will need to recruit two additional scientists in each of the next five years so as to augment our current investigative capacity. To sustain our competitive position in structural biology, we will establish a High Resolution Structural Biology Facility.

Inevitably, the increase in faculty and equipment essential to enable us to keep in the forefront of significant research will lead to considerations for new and expanded space. We view this need with optimism and confidence that a well-designed proposal will be convincing to funding sources because of the track record of BBRI to deliver significant science.

3. The ongoing and increasing need for financial resources implicit in our future plans are challenges we accept gladly. We believe in our competitive record, the quality of our research, and our ability to define programs in which individuals, corporations, and foundations will invest the "seed money" essential to recruit new scientists, acquire new equipment, and expand the laboratory facilities essential to the conduct of future exciting scientific research agendas.

With a clear strategic vision and practical plans for implementation, we ask each one of you who reads this annual report for the opportunity to meet or speak directly with you about the Institute, and to seek your suggestions, counsel, and support.

As you will note from the enclosed response card, we wish to learn to know you, and we hope you wish to learn to know us. Whether it be a telephone chat, a "drop-by" for coffee, or a "working lunch" with our Director, our scientists or a Board member, we hope you will take the time from your busy schedules to check us out, give us the opportunity to show you why we believe that we justify your serious consideration to support our work and, above all, to convince you that you can make a difference in helping us accelerate the search for discovery and the improvement of the human condition.

Edgar G. Davis

Report of the Director

As I write this I am reminded of the Chinese curse regarding living in interesting times. These are certainly "interesting times" for the BBRI. The promise of biomedical research has never been greater. In the last decade, the progress in reducing cardiovascular disease alone has been remarkable. The breakthroughs that have evolved from basic biomedical research support have included: thrombolytic drugs to treat acute heart attacks, HMG-CoA reductase inhibitors to reduce cholesterol levels, ACE inhibitors for heart failure, implantable defibrillators, calcium channel blockers, and coronary angioplasty. These advances have significantly increased the cost effectiveness of therapy as well as the quality of patients' lives.

At the same time, the future of the basic biomedical infrastructure in this country has never been more fragile. The success rate of meritorious new grant "RO1" applications to the NIH is now 1 in 10 (Science, July 7, 1995, p.13). At the time the BBRI was founded, essentially all meritorious grants were being funded.

Fortunately BBRI investigators continue to succeed at 2-3 times the national average in their applications for funding. In the most recent round of reviews, two of our scientists have ranked in the top 2-3 % nationwide — Dr. Sam Lehrer and Dr. Len Adam, who is one of our new recruits and is joining the Institute as of September 1.

Although I have been "on board" for only eight months at this writing, I have already seen dramatic changes occurring in the Institute. We have recruited two new faculty members: Dr. Michael Sherman from Harvard Medical School and Dr. Leonard Adam from the Krannert Institute at University of Indiana. Their research is highlighted in this Report and will add significant depth and breadth to our existing programs in motility, cell communication and cell signaling. Additionally, a reading of the following report will make clear that their basic research is likely to have considerable impact of practical importance in the area of cardiovascular medicine.

In the last eight months we have also opened, here at BBRI, a new Office of Technology Transfer under the supervision of Skip Irving with the Massachusetts Biotechnology Research Institute. This office has not only provided assistance in matters of sponsored research agreements, patents and technology transfer agreements, but has also proactively conducted a survey of our existing technology at the Institute and is moving forward in advising us in seeking corporate partners in future developments on this new frontier.

We are now in the midst of searches for a new Director of Development, an Assistant Director/Controller and an additional new faculty member. The Development search has been particularly challenging in the effort to identify an individual with the ability to imbue in others the vision which many of you already share and actively support: the recognition of the need for and value of investment in Basic Science. Immediately, we will add a new faculty member in the exciting area of "non-muscle motility" (a topic of future newsletters), but we will also begin, next year, a campaign to expand our Structural Biology Program into the realm of high resolution technology (more on this later). Thus I can readily promise that the future year will provide continuing growth and progress at the BBRI.

Kathleen G Morgan

Kathleen G. Morgan, Ph.D.

BBRI – The Second Quarter Century

New Visions – New Faculty – New Research Initiatives

BBRI is well known in scientific circles for its contributions to understanding the structural and molecular biology of muscle contraction. Over the past 25 years, BBRI investigators have pioneered the application of state-of-the-art technologies to probe, at the molecular level, the mechanisms of muscle contraction and its regulation. BBRI's work on the characterization of the proteins that participate in the control of muscle contraction and on the interaction of these proteins with calcium has advanced our knowledge of this important biological process. It has also laid the foundation for therapeutics aimed at regulating the flow of calcium to skeletal, cardiac, and vascular muscle. The "calcium channel blocker" drugs whose development benefited from this research have been used in the treatment of cardiovascular disease in millions of patients worldwide.

Biomedical research in the cardiovascular field alone saves $12 billion a year — an amount that exceeds the entire proposed NIH budget for the next fiscal year.

As BBRI begins its second quarter-century, it is embarking on new research initiatives that will keep it at the forefront of scientific discovery. Under the leadership of Dr. Kathleen Morgan, BBRI's new Director, the Institute is expanding its research efforts in the area of smooth muscle and establishing, with Boston-area hospitals, a strong interdisciplinary program that focuses its concerted effort on smooth muscle tissue.

Investigators working in Dr. Morgan's (second from left) laboratory: Mr. Christopher Parker, Dr. Regent LaPorte, Mr. Michael Reddy, Dr. Arie Horowitz, Dr. Michael Taggart, Dr. Constance Menice.

To supplement BBRI's already strong program in smooth muscle research while maintaining the Institute's broad expertise in cell and molecular biology, BBRI initiated earlier this year an aggressive search for new faculty with a focus on three research areas: (1) Muscle contraction and cell motility, (2) communication between and within cells, and (3) control of cell growth. By adding a new faculty member in each of these areas, we aimed to establish research programs that complemented each other as well as the ongoing research. Indeed, the three research areas named above are highly interdependent: the contraction of smooth muscle and the growth of smooth muscle cells depend on signals communicated between smooth muscle and other cells. The recruitment initiative proceeded more rapidly than anticipated, owing to the large number of outstanding candidates who competed for the advertised faculty positions, a testimony to the high standing of BBRI in the scientific community. Two new faculty appointments have now been made, and Dr. Morgan's vision of a strong, interdisciplinary yet highly integrated program of research will begin to take shape this autumn when two new research laboratories — in addition to that of Dr. Morgan, which has been operating since January — will be inaugurated.

This report describes the three new research programs that are being established at BBRI in 1995: Dr. Kathleen Morgan's, which deals primarily with the mechanisms of communication within the smooth muscle cell; Dr. Leonard Adam's, which focuses on the biochemistry of smooth muscle contraction; and Dr. Michael Sherman's, which is concerned with the role of an interesting new class of proteins in the control of growth. From these descriptions, it will become apparent that the contractile function of muscle, cell communication, and cell growth are highly interdependent processes, and that the three new research programs are not self-contained but will much benefit from interacting with each other and with those programs already ongoing at BBRI.

What Is Smooth Muscle?

The body contains three types of muscle: skeletal muscle — that moves the arms and legs; cardiac muscle — that makes the heart beat; and smooth muscle — that makes up the walls of most of the hollow organs of the body — and does just about everything else! There are six types of smooth muscle:

- vascular smooth muscle
- respiratory smooth muscle
- gastrointestinal smooth muscle
- urinary smooth muscle
- reproductive smooth muscle
- ocular smooth muscle

Each type of smooth muscle represents a different vital function for the body, and when any of these functions goes awry, the result is an entire class of diseases. For example, over-activity of the smooth muscle of blood vessels results in hypertension or vascular spasm. In the respiratory system, smooth muscle malfunction can cause asthma, and so on. The study of smooth muscle function and its control addresses many unsolved biological problems, whose solutions will have an important impact on the understanding and treatment of some of our most common and debilitating diseases.

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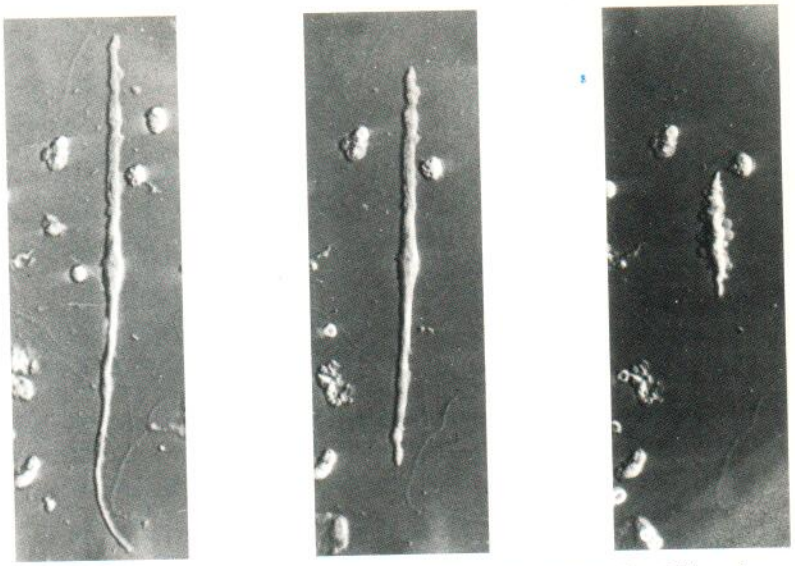

A single isolated vascular smooth muscle cell shortens in response to the addition of adrenaline-like chemicals.

How Do Smooth Muscle Cells Process Signals?

Although we now have a fairly good understanding of the mechanisms by which an electrical signal from your brain tells the skeletal muscle in your arms and legs to move, or by which the pacemaker cells in your heart tell the cardiac muscle cells to beat, we are only beginning to understand the pathways by which a signal such as the adrenaline released in response to a sudden fall in the stock market is communicated to the contractile proteins inside the vascular smooth muscle to switch them "on", contract a blood vessel and raise your blood pressure.

How Can Smooth Muscle Be Studied?

Dr. Morgan's laboratory has developed methods for isolating single smooth muscle cells from the walls of blood vessels. By the use of these methods, the single smooth muscle cells on the stage of a microscope act in the same manner as they would inside the blood vessel wall. They show the same ability to contract and shorten dramatically in response to the sorts of signals to which they would be exposed inside the body. In the body, these smooth muscle cells would wrap around an organ such as the stomach or a blood vessel. When the cell shortens to a quarter of its initial length, it is easy to picture the dramatic decrease this would cause in the volume of the stomach or the size of the blood vessel lumen.

One of the ways Dr. Morgan is trying to elucidate the pathways of intracellular communication is to use brief treatment of the isolated cells with detergents so as to perforate the outer layer of the cell. Then small proteins that are suspected to be important regulators of smooth muscle contraction can be added to the interior of the cell. Alternatively, altered or mutant forms of these proteins that can act as antagonists of the protein of interest can be added to see if they interfere with contraction of the cell. These studies are being performed in collaboration with two other smooth muscle researchers at the BBRI, Drs. Albert Wang and Terry Tao. From these collaborative studies, this group has recently collected information implicating two newly discovered proteins in the physiological regulation of contraction of smooth muscle: *caldesmon and calponin*.

Another way of determining the mechanism of cell communication is to add fluorescent tags to the molecules of interest and to use image restoration methods literally to watch their travels through the cell. These cells are very small (a one hundred thousandth of an inch thick), so the digital imaging techniques being used in Dr. Morgan's laboratory are being performed with the use of microscopes, but they utilize the same technology that is used by astronomers to resolve distant stars in the night sky or by clinicians to see the fine details of the distribution of a radioactive tracer in the heart during an angiogram.

Constance Bergh-Menice studying proteins from a blood vessel.

Dr. Morgan's group is currently very interested in the possible role of a special group of proteins in communicating signals to smooth muscle contractile filaments to tell the cell to contract. These proteins cause the addition of a phosphate group to other proteins and are called "kinases" because the addition of the phosphate group often "energizes" the other proteins. Both Dr. Morgan and Dr. Adam suspect that a relatively newly discovered kinase, "MAP kinase", is important in regulating smooth muscle contraction. These two scientists are working in collaboration to determine the role of this kinase in the smooth muscle cell and to determine new therapeutic agents to promote or block the activity of this kinase. Dr. Adam is using biochemical methods to study this problem (see below) while Dr. Morgan is using cellular techniques.

By following the traffic of important proteins within the smooth muscle cell, Dr. Morgan's group has been able to test which proteins are "in the right place at the right time" to communicate a message from the cell membrane (which forms a barrier between the outside world and the contents of the cell) to the contractile proteins in the interior of the cell. After applying a chemical stimulus to the outside of an isolated cell, her group has seen the movement of specific proteins from the interior of the cell to the membrane. Then, apparently after picking up the "message," the protein leaves the membrane and travels to the contractile filaments where it somehow communicates the message for the filaments to start moving and cause the shortening of the cell. Dr. Morgan's group is very interested in "who" is directing the traffic of signals within the cell as well as how those signals are transmitted from one part of the cell to another part of the same cell.

Chris Parker "deconvolving" an image of a vascular smooth muscle cell.

Arterial blood pressure and blood flow are two very tightly controlled processes within the body. Blood flow changes occur in part by constriction and relaxation of the smooth muscle lining the blood vessels. Alterations in blood pressure are necessary to accommodate changes in body position and to maintain an adequate flow of oxygen and nutrients to all organs of the body. Pathological changes in blood pressure, especially high blood pressure, can lead to such dramatic medical problems as stroke and heart disease, which, combined, are the leading causes of death in this country. Clearly, a better understanding of what is involved in the control of blood pressure will ultimately lead to better treatment modalities and, hopefully, lower morbidity and mortality.

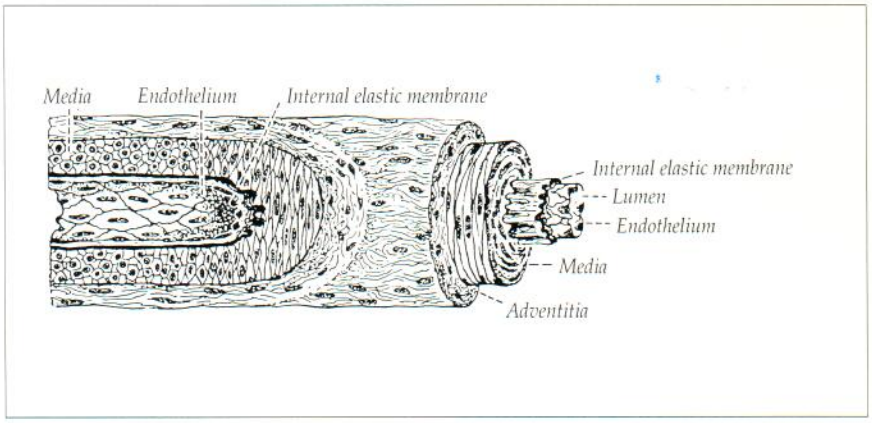

Diagram of the structure of an artery.

Anatomical Considerations To Blood Vessel Constriction

A blood vessel contains three distinct anatomical parts. The portion of the vessel closest to the lumen, through which the blood flows, is the endothelium. The endothelium is usually only a single cell layer thick yet serves a very important process in vascular biology. The cells in the endothelium constitute a barrier that keeps chemicals as well as blood cells from passing to the underlying tissue and prevents clotting within the blood vessels. The endothelial cells also release signals that control the contractile state of the blood vessel. Underlying the endothelial cells, the next anatomical layer of the blood vessel is the media. The medial portion of the blood vessel is comprised, predominantly, of *smooth muscle* cells and makes up the bulk of the mass of an artery. The outside layer of an artery is the adventitia that contains fibroblasts. The cells in this portion of the artery do not normally undergo contraction and relaxation, and the function of the adventitia is poorly understood.

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Mechanisms of Blood Vessel Contraction

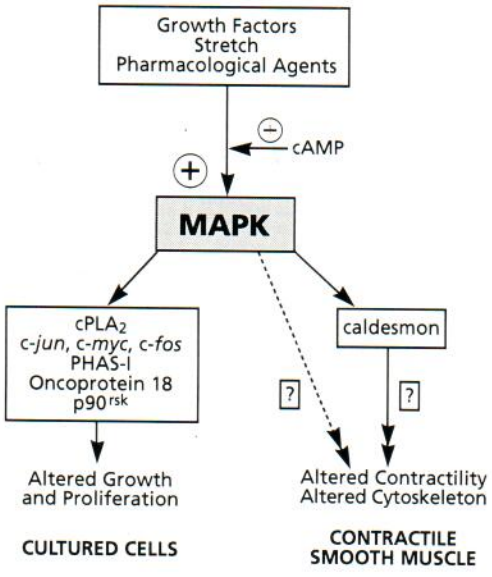
Smooth muscle cells contain, within the cytoplasm, filaments termed thick and thin filaments. The thick filaments are comprised, predominantly, of the protein myosin; thin filaments contain actin. Myosin is a "motor" protein that, by cyclic shape changes, can move along the "tracks" provided by the actin filaments. Contraction results from cyclic binding of myosin to actin and a movement of these two filament systems in apposition to one another. The biochemical mechanisms that control this process ultimately control the contractile state of the blood vessel and hence the blood pressure and blood flow to vital organs of the body.

Regulation of the contractile state of smooth muscle is based in part on the modification of the myosin motor. Earlier work performed in Dr. Morgan's laboratory showed that, when vascular smooth muscle cells are activated to contract, the calcium ion concentration in the vascular smooth muscle cells increases. We now know that calcium is the signal that activates another kinase that causes a molecule of phosphate to be incorporated into myosin. While this is a complex biochemical process, which has taken years to identify, the end result is an increase in the rate of movement of the myosin motor. As the motor pulls on the actin, attached to the outer edges of the cell, the smooth muscle cell shortens, and the cells wrapped around the blood vessel will act to pinch off blood flowing through the vessel and thus increase blood pressure.

Dr. Leonard Adam, who joined the BBRI September 1 from the Krannert Institute in Indiana.

While the modification of the myosin motor is one biochemical mechanism ultimately regulating cell contractility, there are several situations where smooth muscle is known to contract without having this process happen. Therefore another, unknown, process must exist in the smooth muscle cell that accounts for the contraction of the cells under these conditions. In particular, a significant amount of evidence has led to the suggestion that a protein sitting on the actin thin filament tracks, *caldesmon*, may also regulate smooth muscle contraction. Dr. Adam has shown that phosphate is also incorporated into caldesmon during the course of smooth muscle contraction, in this case catalyzed by the mitogen-activated protein kinase (MAPK).

MAPK is activated in smooth muscle in response to a number of stimuli, including drugs that increase blood pressure, chemicals released from blood clots, as well as the sort of stretch exerted on a blood vessel undergoing angioplasty. In addition, a number of factors released by the endothelium of blood vessels are known to be activators of MAPK. Current collaborative work between the muscle and signal transduction groups at the BBRI involves determining the mechanisms for and consequences of activation of this enzyme in smooth muscle. Interestingly, this enzyme has been shown to play a role not only in smooth muscle contraction but also in smooth muscle growth. How the cell knows whether MAPK is telling it to contract or to grow is unknown.



The central role of MAPK in the contraction and growth of smooth muscle of blood vessels.

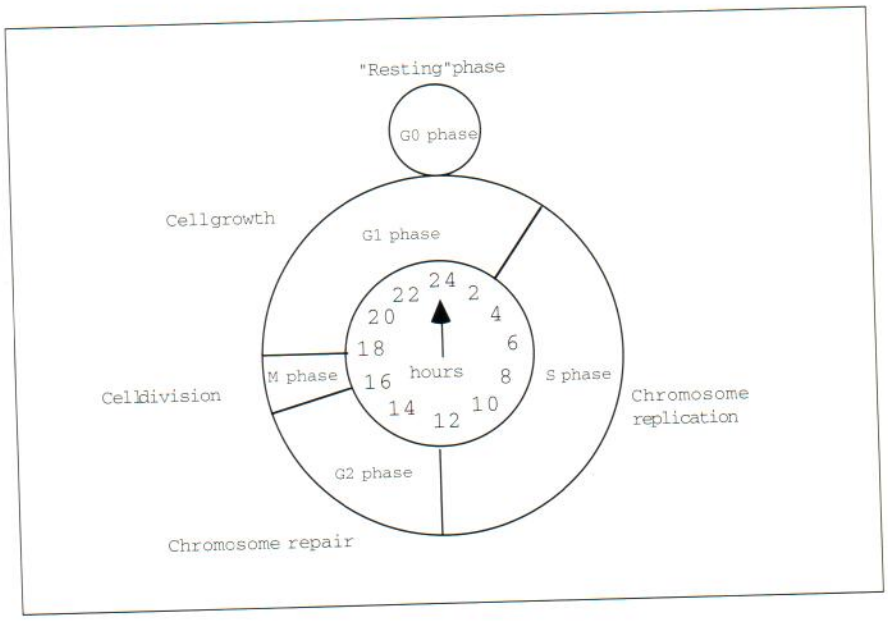
Why Study Cell Growth?

Like the plumbing in our homes, the blood vessels in our bodies occasionally need to be repaired so as to remove an obstruction or to stop a leak. All too commonly, smooth muscle cells proliferate into the lumen of the blood vessel, leading to a life-threatening narrowing of the arteries. The irony is that this unwarranted growth of smooth muscle cells, termed restenosis or graft failure, usually follows medical intervention whose aim was to remove obstructions from the arteries by angioplasty or bypass surgery. Indeed, restenosis and graft failure are the major factors that limit the long-term success of invasive medical intervention for the correction of arterial blockage and affect thousands of patients every year. At this time, there is unfortunately no way to predict the occurrence of these complications nor an effective preventive treatment. Intriguingly, the body itself sometimes is able to bypass the obstruction by sprouting new, collateral, vessels by a process termed angiogenesis. Unfortunately, the factors that determine whether new vessels are sprouted or whether old vessels are occluded are not yet known. All progress in this direction must await a more complete understanding of the mechanisms that control the growth of smooth muscle cells, and this is why BBRI gives high priority to studying the control of cell growth.

It is ironic that this unwarranted growth of smooth muscle cells, termed restenosis or graft failure, usually follows medical intervention whose aim was to remove obstructions from the arteries by angioplasty or bypass surgery.

The Cell Cycle

Most of the cells in our bodies are not multiplying at any given time but are in a "resting" state called G0 in which they can remain for days, months, or years. (Actually, the term "resting" is a misnomer, for the cells are working very hard, carrying out their specific functions in the body.) It is only in response to certain signals that a cell is stimulated to proliferate by dividing into two new cells. Cell division is a very carefully controlled process because it requires the accurate duplication of the cell's chromosomes and their equal distribution between the two daughter cells, lest mutations or chromosomal abnormalities should occur. Cells achieve the orderly occurrence of cell division by organizing its many steps into a cyclic process, the so-called cell cycle, which is depicted in the diagram below.



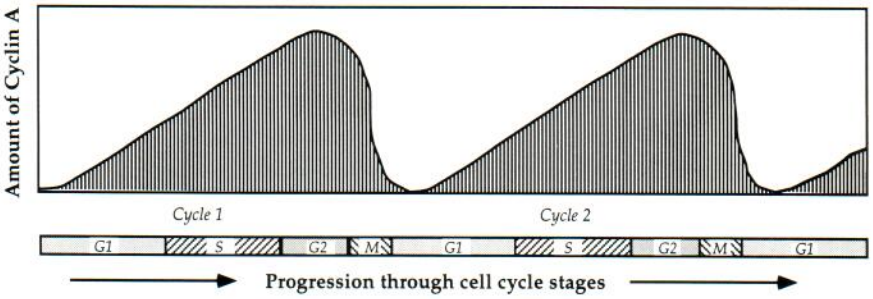
In response to a growth stimulus, a cell leaves the "resting" state called G0 and enters G1 phase of the cell cycle, setting into operation a molecular clockwork that moves the cell in turn into S phase, where the machinery for DNA synthesis is cranked up and put to work replicating the chromosomes, then into G2 phase, where the replicated chromosomes undergo a quality control process to check whether errors have been made in replicating the genetic information and to correct those that have occurred; into M phase, where the newly replicated chromosomes are transported to opposite poles as the cell undergoes division to yield two identical daughter cells; and, finally, back into G1 phase, where the daughter cells grow until they have attained the size of the parent and can either reenter the resting state, G0, or undergo another round of the division cycle, depending on whether the cells continue receiving signals to go on dividing. (An exception to this rule is cancer cells, which are permanently turned on owing to a mutation and therefore continue to proliferate even in the absence of external growth signals.)

The Cyclins Are The Molecular Clocks Of The Cell

A typical human cell needs about 24 hours to traverse the cell cycle and allocates this time to the various cell cycle phases in roughly the proportions shown in our diagram. This time is the same whether a cell grows in its normal place in the body or is isolated in a culture dish, suggesting that the cell cycle is controlled by a built-in clockwork. The identification of this molecular clock has been one of the great challenges of modern cell biology. An important breakthrough came about 10 years ago with the discovery of the cyclins, which are proteins that gradually build up to critical levels inside the cell and then are rapidly degraded at specific points in the cell cycle, reminiscent of the oscillators that control the movement of clocks. This is illustrated in the diagram below for one of the cyclins, cyclin A, which sets the time for the transition from M phase to G1:

Dr. Michael Sherman, who joined the BBRI this summer from the Harvard Medical School.

The mechanisms by which the cyclins control progression through the cell cycle are a subject of very active investigation, and it is now clear that they exert their effect by modulating the action of protein kinases which transfer phosphate groups to proteins. As you may recall from the descriptions of Dr. Morgan's and Dr. Adam's research in the preceding sections of this report, protein phosphorylation by protein kinases (and subsequent dephosphorylation by protein phosphatases) is a key element in the transduction of signals within the cells and can set in motion many different processes which range from muscle contraction to DNA replication.



What Makes The Cell's Molecular Alarm Clocks Ring?

In research, every answer usually leads to a new question. The discovery of the cyclins was a major step forward in understanding how the cell cycle is regulated, but it raised the interesting question: What causes the sudden degradation of cyclin which triggers the transition from one cell cycle phase to the next? Dr. Michael Sherman, who has joined the BBRI faculty this summer after a period of postdoctoral training at the Harvard Medical School, is addressing this question by examining the degradation of a G1 cyclin, known as Cln3 in scientific jargon, that triggers the transition from G1 phase to S. The study of Cln3 was of particular interest because this cyclin seems to be the earliest cyclin to be activated in the cell division cycle and therefore may represent the cell's master clock.

Chaperoning The Cell's Molecular Clock

There is no end to surprises in basic research — serendipity is the mainstay of discovery. Another project on which Dr. Sherman was working dealt with an interesting group of proteins known as molecular chaperones. The chaperones were given this curious name because their task is to guide the folding of other proteins. Proteins are synthesized as one-dimensional amino acid sequences but cannot function until folded into the correct three-dimensional shapes. Although this folding process can occur spontaneously, it is often inefficient and sometimes goes awry and ends with the wrong structure. In such cases, the assistance of the molecular chaperones in the folding of proteins is of great importance to the cell. Another context in which the molecular chaperones play an important role is in the recovery from environmental stress, such as high temperatures. Under heat stress or other extreme conditions, many proteins become partially unfolded ("denatured") and the chaperones help them to return to their natural states — this is why the chaperones are sometimes also referred to as heat-shock proteins.

What does all this have to do with the cell cycle? When his colleagues at the Harvard Medical School discovered that the Cln3 cyclin needs to be phosphorylated before it can be degraded and thereby trigger the alarm for entry into S phase, Dr. Sherman

Dr. Michael Sherman discusses new data with Dr. Anatoli Meriin, a post-doctoral fellow in his laboratory.

decided to study this phosphorylation process in more detail. To his surprise, he discovered that a molecular chaperone had to bind to the Cln3 cyclin before its phosphorylation could occur. So the real triggering event that sets the cell cycle clockwork going is produced by a chaperone which is synthesized by the cell in response to stress such as too little oxygen or damaging free radicals.

This was a very exciting discovery, because we see here the convergence of three basic responses of life: Stress response, represented by the molecular chaperons; signal transduction, represented by protein phosphorylation; and cell growth, represented by the cyclins. Dr. Sherman's work is sure to provide important insights into how these central life processes are integrated. By helping us understand why some cells grow and others don't, it will provide us with the conceptual basis for the development of drugs that can prevent cell growth where it may threaten the life of a patient, such as in restenosis.

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NATIONAL INSTITUTES OF HEALTH

Dr. Badwey	Synergistic stimulation and priming of neutrophils	7/90 - 4/96	$ 865,000
Dr. Badwey	Enzymes modulating second messengers in neutrophils	4/93 - 3/97	645,000
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Mr. Shao	New England Biolabs	9/92 - 8/96	80,000

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Many thanks for your encouragement and support!

Our entire faculty and staff join me in thanking every one of the individuals, foundations, and businesses identified on these two pages for contributing in fiscal 1995 to BBRI's progress in research. Your help is very important to us, and we are grateful to you.

Thanks to you, our Annual Research Fund totalled $259,000 in the year just past. The donations to the Institute have also included valuable pieces of research equipment from The Millipore Foundation, the Polaroid Foundation, and PerSeptive Biosystems, and a fellowship for a Ph.D. student from New England Biolabs. In addition, present and former faculty members joined with Trustees to contribute over $31,000 to a Research Fellowship honoring BBRI's Dr. John Gergely, co-founder of the Institute. We hope now to raise the endowment funds needed to perpetuate the Fellowship.

As so often in the past, Ernie Henderson has again been extraordinarily generous to the Institute. In recognition of his leadership in the support of the Institute's mission, Ernie Henderson was selected to become the first member of BBRI's Founders Society.

The year 1995 has seen a number of important advances here at the Institute, as described in the letters of the President and Director at the beginning of this report. Now, as the momentum builds and Dr. Morgan completes her first year as Director, we look forward to further enhancement of BBRI's position as a world-renowned center of excellence in basic biomedical research. We will continue to need your partnership in our endeavors. All of us working together can make Dr. Morgan's ambitious visions for BBRI a reality.

Edgar G. Davis
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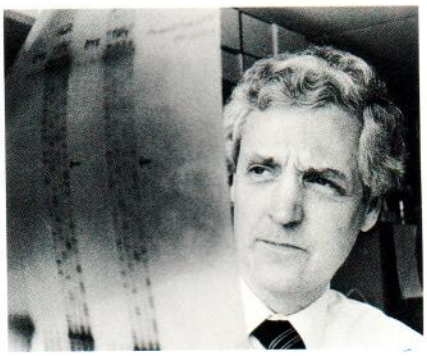

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Barbara E. Wright

Ernest Henderson with Charles Ives (center) and John Layton

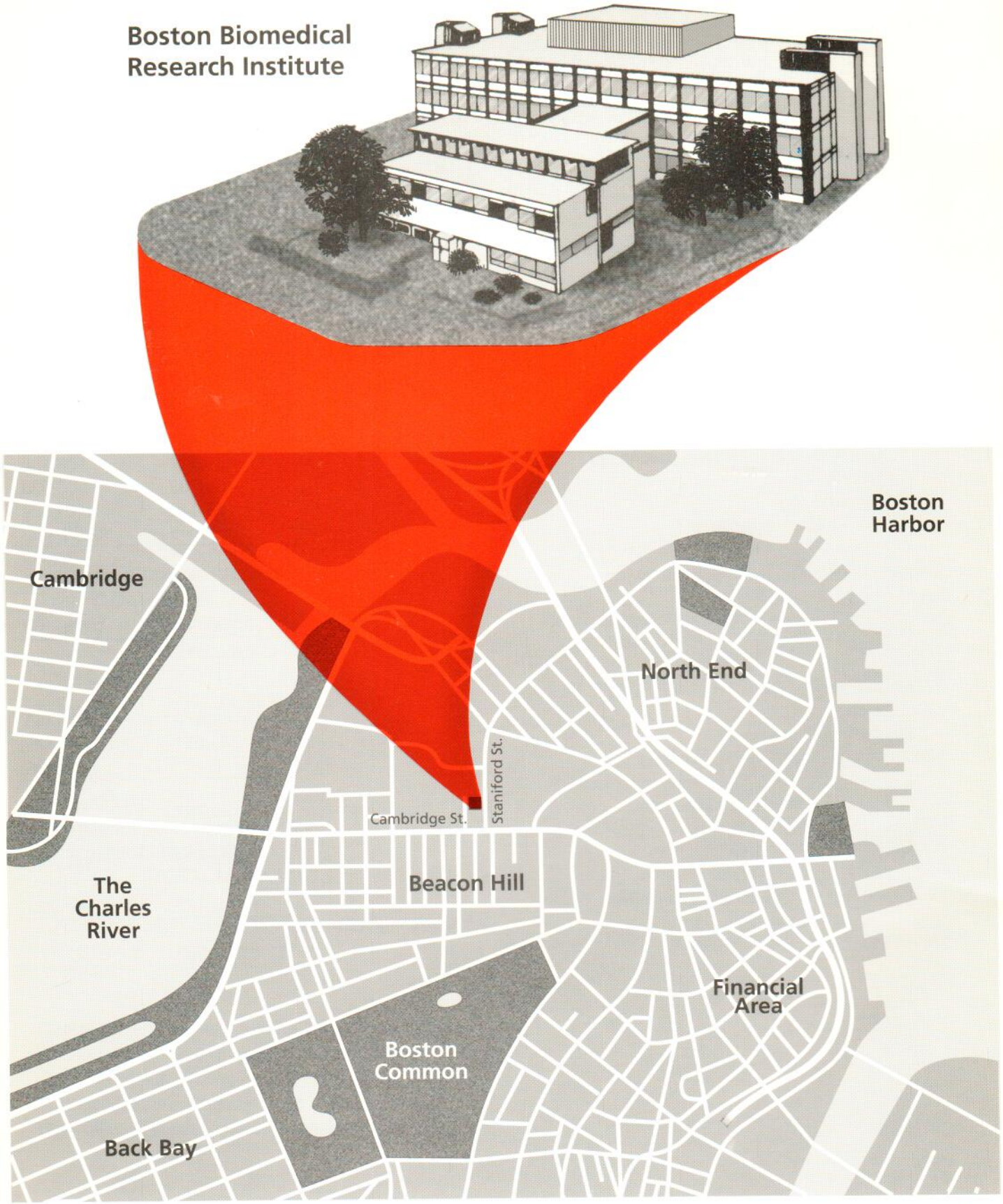
BOSTON BIOMEDICAL RESEARCH INSTITUTE, INC.
STATEMENTS OF FINANCIAL POSITION
AUGUST 31, 1995 AND 1994

	1995	1994
ASSETS		
Cash	$ 970,338	$ 702,641
Grants receivable	3,565,016	5,376,653
Pledges receivable	800	7,075
Investments	7,198,299	6,411,968
Prepayments, deposits and other receivables	87,693	76,287
Property and equipment	1,338,810	1,232,665
Deferred compensation investments	1,426,018	1,214,450
TOTAL ASSETS	$ 14,586,974	$ 15,021,739
LIABILITIES AND NET ASSETS		
Accounts payable and accrued expenses	$ 243,039	$ 114,414
Deferred grant income	4,009,324	5,663,698
Deferred compensation payable	1,426,018	1,214,450
TOTAL LIABILITIES	5,678,381	6,992,562
Net assets		
Unrestricted	8,243,390	7,510,721
Temporarily restricted	365,203	218,456
Permanantly restricted	300,000	300,000
TOTAL NET ASSETS	8,908,593	8,029,177
TOTAL LIABILITIES AND NET ASSETS	$ 14,586,974	$ 15,021,739

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 Controller, Boston Biomedical Research Institute, Inc.

BOSTON BIOMEDICAL RESEARCH INSTITUTE, INC.
STATEMENTS OF ACTIVITIES
FOR THE YEARS ENDED AUGUST 31, 1995 AND 1994

	1995	1994
UNRESTRICTED SUPPORT		
Revenues		
Grants and contracts	$ 6,458,378	$ 6,956,725
Contributions	214,246	160,674
Property and equipment purchased	274,347	108,108
Investment income (loss)	764,443	(40,755)
Total unrestricted support	7,711,414	7,184,752
Expenses		
Salaries and benefits	4,720,396	4,607,890
General support and services	1,047,070	1,196,220
Occupancy costs	690,000	600,000
Property and equipment purchased	264,637	108,108
Depreciation	168,202	188,333
Fund raising	88,440	75,532
Total expenses	6,978,745	6,776,083
	732,669	408,669
Net assets released from restrictions	-	130,499
Increase in unrestricted net assets	732,669	539,168
TEMPORARILY RESTRICTED SUPPORT		
Contributions	81,176	60,750
Investment income (loss)	65,571	(3,495)
Net assets released from restrictions	-	(130,499)
Increase (decrease) in temporarily restricted net assets	146,747	(73,244)
INCREASE IN NET ASSETS	879,416	465,924
NET ASSETS AT BEGINNING OF YEAR	8,029,177	7,563,253
NET ASSETS AT END OF YEAR	$ 8,908,593	$ 8,029,177



Center of Boston

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