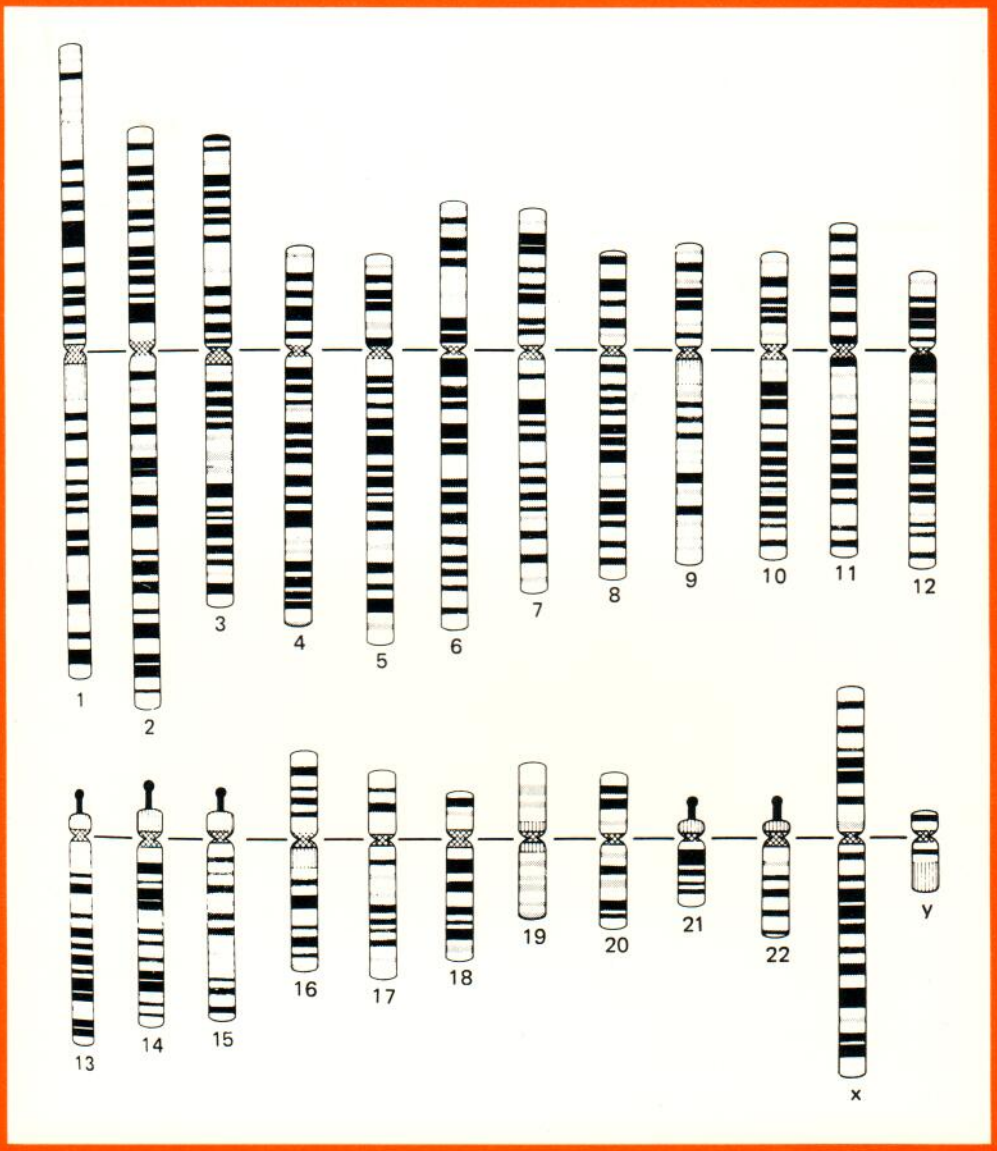
Boston Biomedical Research Institute

1990 Annual Report

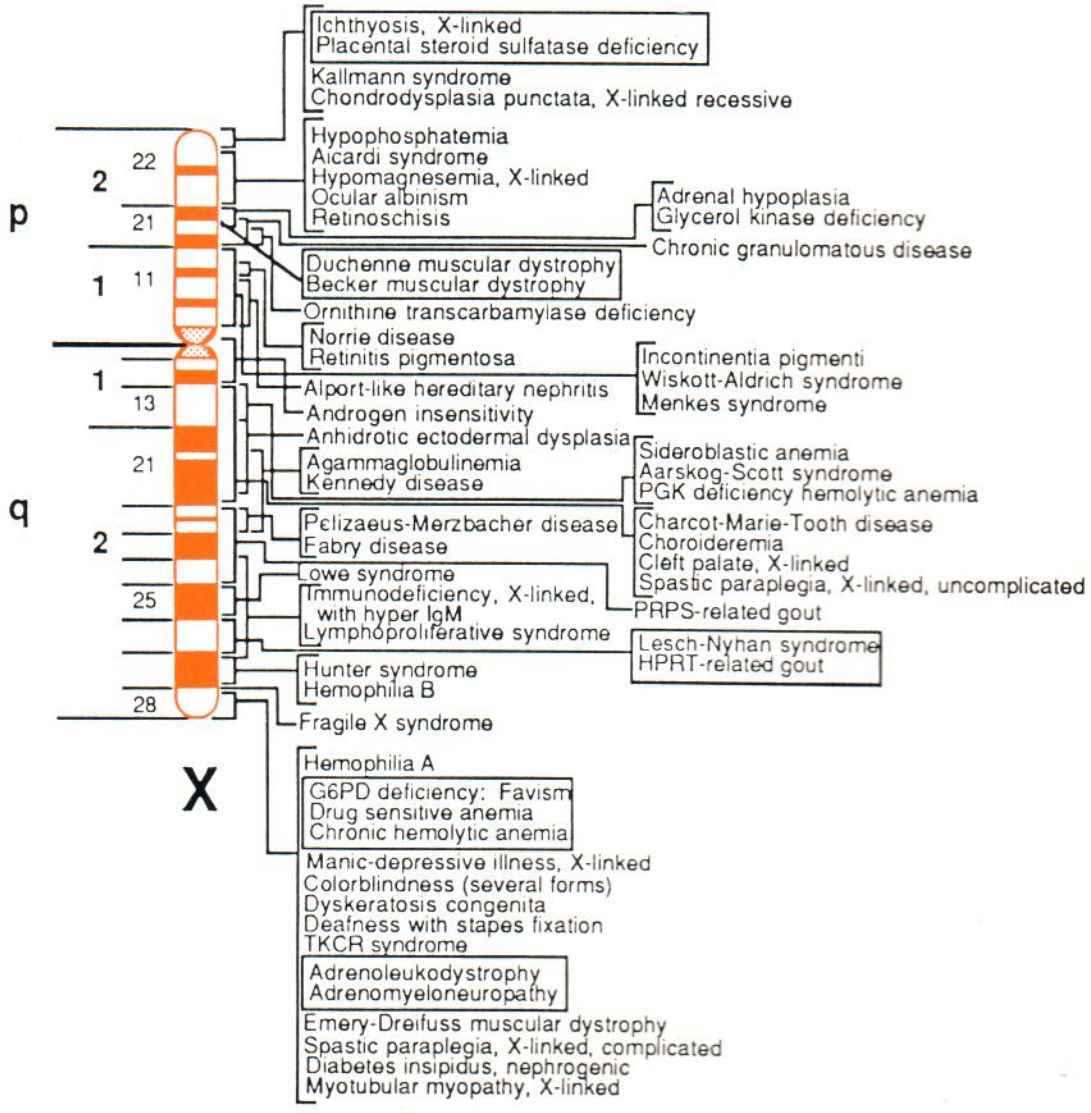


Cover:

Diagram of the human chromosomes, with the characteristic pattern of bands which can be revealed by a specific staining procedure. All normal human cells except the sperm and egg contain 46 chromosomes: A pair each of chromosomes 1–22 and either a pair of X chromosomes (in females) or a single copy each of the X and Y chromosomes (in males).

More than 3,000 inherited diseases are known to be due to specific mutations on one of the chromosomes. Rapid progress is being made in mapping the mutations responsible for inherited diseases to specific locations on the chromosomes. Indeed, the genes whose mutation leads to three of the most common genetic disorders—Duchenne muscular dystrophy, cystic fibrosis, and neurofibromatosis—have been identified and characterized within the last 2–3 years. This triumph of basic biomedical research makes possible the early diagnosis of these diseases and, by helping us understand their cause, may ultimately contribute to their management and treatment.

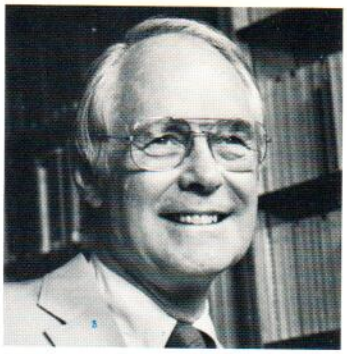
Below is a diagram of the X chromosome, together with a list of diseases that are due to mutations of the X chromosome and the approximate location of these mutations. The identification of these and other genes and their mechanism of action is one of the great challenges of molecular genetics. [From Scriver et al. (1989) The Metabolic Basis of Inherited Disease, McGraw Hill, New York.]



Boston Biomedical Research Institute

is an independent, non-profit organization with a staff of M.D. and Ph.D. investigators who carry out a broad program of basic research in biology and medicine, and provide highly specialized training for future physicians and scientists. For two decades the Institute has maintained its position among the leaders in the world-wide effort to prevent and cure disease. Areas currently under investigation range from the study of birth defects to the biology of aging. The findings of Institute scientists are used by others in clinical projects including those aimed at helping people suffering from cancer and diseases of the heart, muscles, liver, and eye. The Institute's research programs will ultimately bring lasting benefits to the future well-being of mankind.

Contents



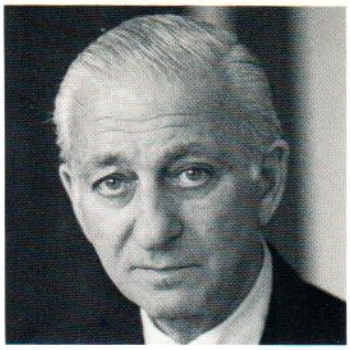
As with most annual reports, this 1990 report of Boston Biomedical Research Institute takes a look at the year past, but it also seeks to inform about some of the ongoing work of the Institute. While the following pages may seem a bit technical, I hope the language is reasonably understandable to the layman and non-specialist scientist; if not, I must share the blame as I read the proof and sought clarification of terms and phrases which were not understandable to this layman.

In his report John Gergely has called attention to the tightening up of NIH funding for basic research projects. This is a continuing source of concern to the Trustees, as we are seeing grants go unfunded, or be delayed or be funded at lower levels, notwithstanding the continued high scores by most of our staff applications. This naturally puts more pressure on our limited capital funds, which in prior years we have been able to accumulate gradually. While it is appropriate to devote some of these funds to respond to the current restrictive federal funding policies, this, of course, means our "endowment" is not growing as it should. Longer range responses to this situation must be found; and the Trustees are very much aware of this challenge which we hope to meet in a number of ways.

As reported last year, we have embarked on a major recruitment effort for a senior and well recognized scientist, and the Trustees have approved the allocation of significant funds to help finance the salary of such a person, who would head a new department and would be expected to have an important role in the future leadership of BBRI. While this is a major commitment of our modest funds, it is felt to be a necessary and most worthwhile investment in the future of the Institute. It is hoped that the right person will invigorate our scientific activities and also be able to attract both government and private funding. Thanks to the efforts of Elkan Blout who heads the Search Committee, the appropriate Harvard Medical School committee has approved the proposal that this scientist also have an appointment as a professor in one of the Departments at the Medical School. Thus, Harvard will join us in the search which we hope and expect will enhance the Search Committee's ability to attract able candidates.

We are continually grateful for the generous contributions of our many supporters who are listed elsewhere in this report; in these stringent times their help is more than ever needed. In the months ahead we will no doubt be seeking more support from old and new friends as we work to build up our funds to cover the widening gap between our costs and the government funding for our work.

John B. French



In this annual report as in those of prior years we try to present some aspects of the Institute's work which illustrate rapid advances in biomedical research. A new feature of this report is the listing of scientific articles published by members of the staff in the past year. While some titles may be unintelligible to the lay reader we hope that this list—of what is really our product—may help to portray our research activities and the multiple interactions among scientists in a more tangible way.

The past year has been both a good and a bad one. The good thing about it is that science has flourished in the international community as well as at BBRI. Genes for hereditary diseases such as muscular dystrophy, cystic fibrosis, and neurofibromatosis have been identified, and the structures of the proteins they encode are being unraveled. The past year also marked the filling in of some significant gaps in our knowledge of the proteins involved in muscle contraction and regulation, including the elucidation of the structure of one of the key proteins of the contractile apparatus, actin, on the atomic scale. Scientists at BBRI too have been doing their share of making new discoveries published in prestigious journals, some of which—e.g. Nature and Science—take only about 7% of the submitted manuscripts. Two recent publications by BBRI scientists in the periodical Nature have attracted special comments by their editorial writers as research highlights.

On the negative side is the inadequate Federal funding for basic science, which affects BBRI together with all academic and research institutions in the U.S. Whereas ten years ago nearly 40% of peer review approved applications were funded, during the past year the number has dropped to close to 15% and sometimes even less. I should add that it is a matter of pride to BBRI that several of our applications have scored in this high range and have received funding for the next five years. A number of investigators, however, both here and in other institutions, are put on what one might call a waiting list because of the shortage of funds so that it has almost become the rule that a few months' delay in funding is routine. Needless to say, this places a great deal of financial burden on BBRI and our sister institutions. Not only does the current funding policy present great difficulties for those who are now engaged in the scientific enterprise, it is also a dangerous threat to the future growth of biomedical research, because a large number of young people will be deterred from entering careers in biomedical research. Some of you perhaps have read accounts of the woes of young faculty members in various universities, who were among the brightest post-doctoral students but have not been able to receive funding of their first NIH research grant application. In Congressional hearings it has been pointed out that notwithstanding the large resources that universities and research institutions have had to invest in recent additions to their faculties, there is a great danger that these investments will die on the vine if no radical change in funding policies occurs.

BBRI is fortunate in having an enthusiastic Board of Trustees and supportive Corporation, and we hope that members of these boards will continue to help in sustaining our scientific venture. The role of private, unrestricted funds will be even more important in the future than in the past. Additionally, well informed lay supporters of academic and research institutions can and must play a crucial role in influencing public policy so as to maintain the vigor and preeminence of research in the United States.

John Gergely, M.D., Ph.D.

REAPING THE HARVEST OF THE ERA OF MOLECULAR BIOLOGY

ANSWERS TO MANY BASIC PROBLEMS OF BIOLOGY—NATURE OF GROWTH, MECHANISM OF DUPLICATION OF VIRUSES AND GENES, ACTION OF ENZYMES, MECHANISM OF PHYSIOLOGICAL ACTION OF DRUGS, HORMONES, AND VITAMINS, STRUCTURE AND ACTION OF NERVE AND BRAIN TISSUE—MAY LIE IN THE KNOWLEDGE OF MOLECULAR STRUCTURE...

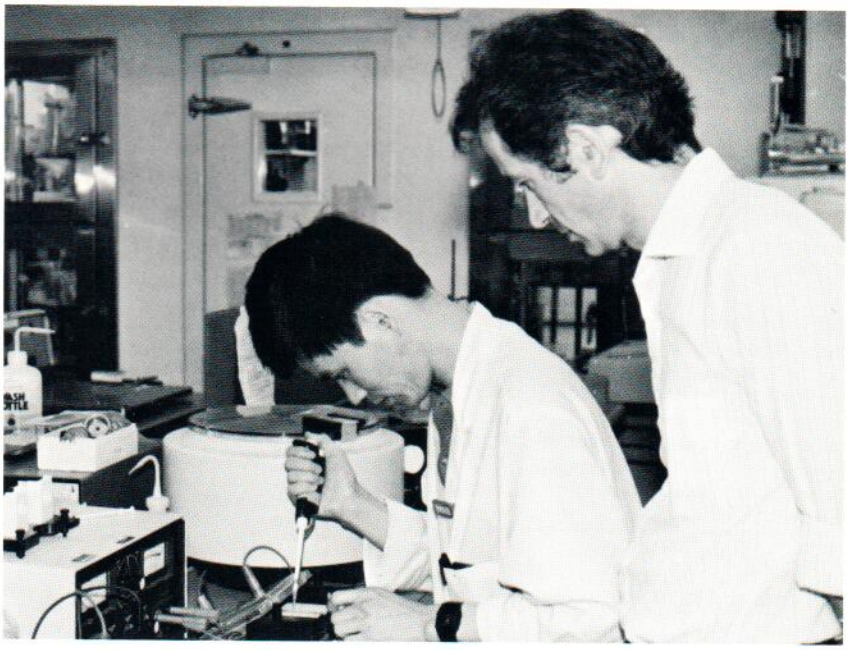
LINUS PAULING, 1946

Pauling made this prophetic remark at the dawn of the era of molecular biology. In less than half a century the study of molecular structure has yielded unprecedented insights into the nature of life processes and the aberrations that give rise to disease. As new experimental approaches to the study of biological molecules were developed, it became possible to attack ever more complex biological problems. Especially important have been the recent advances in molecular genetics, which have made possible the analysis and manipulation of genes that specify the structure of the molecular components of the cell. The "new genetics" has revolutionized the study of biological processes, opening the door to investigations which in 1946 would have been considered in the realm of science fiction.

One important class of molecular components of the cell that have been the subject of intense investigation by BBRI scientists are the protein molecules that constitute the muscle fibers and are responsible for movement and its control. Not only is the study of motion one of the great challenges of modern biology, but it may provide important insights into the causes and perhaps the treatment of diseases manifested in abnormal muscle function, such as muscular dystrophy. Although much progress has been made through the study of the structures of muscle protein molecules, the ability to manipulate the genes of these proteins by the methods of molecular genetics is opening important new lines of investigation.

MOLECULAR BIOLOGY—The study of the structure of the molecules that constitute living matter, especially of their 3-dimensional shapes and the way in which different molecules interact to form the complex structures and shapes of living organisms.

MOLECULAR GENETICS—The analysis and test-tube manipulation of genes that allow the elucidation and modification of their function. It includes the design of new genes by combining various portions of different DNA molecules or by artificial mutation and transferring genes from one organism to another.



Zenon Grabarek and Ruo-Ying Tan analyzing a mutant form of the muscle protein troponin C.

ORGANISM—A living being, which may consist of only a single cell (a "unicellular" organism), for example a bacterium or yeast, or of many cells (a "multicellular" organism) such as plants and animals. The genome of multicellular organisms is many times larger than that of unicellular ones because it must encode the components of many different kinds of cells, and dictate the way these cells are organized into tissues and organs and how the organism develops from an embryo into an adult plant or animal.

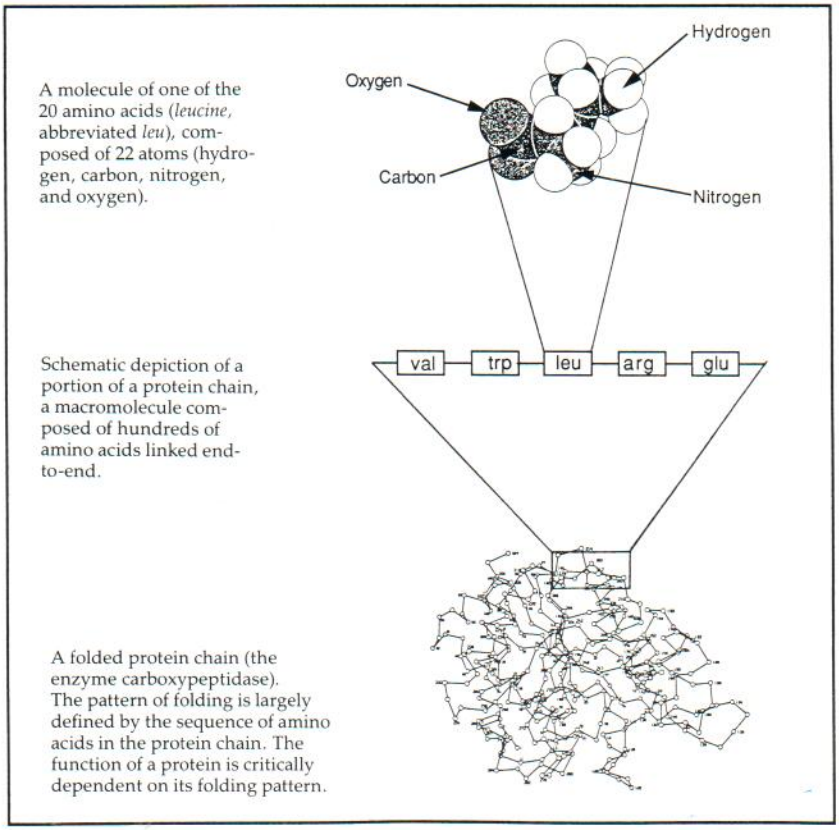
CELL—The basic unit of an organism, containing a full complement of genetic material (the "genome") and the machinery needed to reproduce it. Cells are surrounded by membranes or walls and can either be free-living, such as bacteria or amoebae, or associate with other cells as part of an organism. All the cells of an organism have identical genomes.

GENE—The unit of genetic information. The information contained in a gene is encoded in the sequence of nucleotides in DNA and usually specifies the sequence of amino acids in a protein. The amino acid sequence of every protein in a cell is specified by a different gene.

GENOME—The totality of all the genes of an organism. The genome encodes all inherited traits of an organism, including the structures of all its component parts and the instructions for their assembly, as well as many aspects of growth and behavior. All cells of an organism contain identical genomes and each time a cell divides, the genome is precisely duplicated.

Most of the working parts of the cell are proteins, very large molecules (often referred to as macromolecules) composed of many thousands of atoms. The proteins are assembled from 20 different kinds of building blocks, linked together end-to-end in long chains. These building blocks are called amino acids, which themselves are small molecules consisting of 10–30 atoms each. Every cell contains at least 10,000 different proteins, which contain a selection of the same set of 20 amino acids but differ in the number of each of the amino acids and the order in which these are arranged along the protein chain. Each protein chain is folded on itself in a complex but highly specific 3-dimensional pattern.

The proteins have many different functions. Some of them are important structural components of the organism, both inside and outside the cells. Others serve as moving parts, for example the proteins of muscle; or as pumps in cell membranes and organs such as the kidney and intestines; or as receivers and transmitters of information in the sensory organs, the nervous system, and at the surface of almost every cell; or as defenders of the body in the immune system. However, by far the largest number of proteins serve as enzymes, the catalysts which make possible the many chemical reactions that occur in every cell. These thousands of exquisitely controlled reactions are collectively known as metabolism and allow organisms—from bacteria to man—to grow and multiply, to move, and to respond to the outside world.

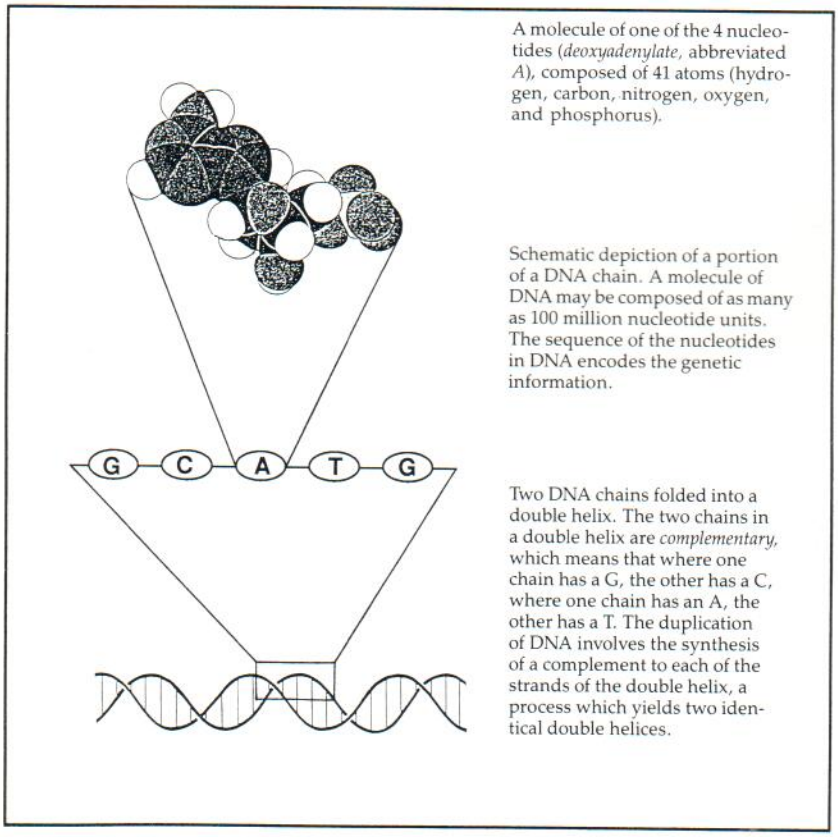


A protein molecule (bottom) with exploded views (center and top) showing successively smaller components.

The function of proteins depends critically on the order in which their amino acid building blocks are arranged. The individuality of a living organism depends on the nature of its proteins and is defined by a blueprint which serves as guide for the synthesis of all proteins. This blueprint is called the genome and consists of many genes, each of which contains the information that specifies the amino acid sequence of a particular protein. The genes are composed of DNA, macromolecules like proteins but containing only four kinds of building blocks. The DNA building blocks are called nucleotides and are connected end-to-end in long chains. Genes are made up of two such chains, which are wound around each other as a double helix and have the capacity for self-duplication with the help of the proper cellular machinery.

It is the sequence of nucleotides in each gene that dictates the order in which the amino acids are arranged in the corresponding protein. Just as different combinations of dots and dashes specify the 26 letters of the alphabet in the Morse code, the genetic code specifies the 20 amino acids in proteins by various combinations of the 4 nucleotides of DNA. One of the great achievements of modern biology was the deciphering of the genetic code in the 1960's. As a result, we can now look at the nucleotide sequence of the DNA from a particular gene and deduce the amino acid sequence of the protein for which that gene serves as the blueprint.

Because cells also have the machinery for duplicating their genomes, DNA with all its genetic information can be passed on from generation to generation, assuring that the proteins of every individual reflect the parental heritage. If the gene for a particular protein has experienced a mutation, the mutated gene will be transmitted from parent to offspring. Mutant genes usually encode altered proteins. If the altered protein is defective in its function, the mutation may lead to diseases such as sickle cell anemia, muscular dystrophy, or cystic fibrosis. The tragedy of genetic diseases is that the child who has the misfortune to receive the defective gene from its parents is doomed to lead a life marred by handicaps, suffering, or early death. However, through the techniques of molecular genetics, it has become relatively easy to read the nucleotide sequence of genes, and this gives us the power to recognize mutations in particular genes and thus screen for genetic defects prenatally to determine whether the child would be normal or afflicted by the disease.



A molecule of one of the 4 nucleotides (*deoxyadenylate*, abbreviated *A*), composed of 41 atoms (hydrogen, carbon, nitrogen, oxygen, and phosphorus).

Schematic depiction of a portion of a DNA chain. A molecule of DNA may be composed of as many as 100 million nucleotide units. The sequence of the nucleotides in DNA encodes the genetic information.

Two DNA chains folded into a double helix. The two chains in a double helix are *complementary*, which means that where one chain has a G, the other has a C, where one chain has an A, the other has a T. The duplication of DNA involves the synthesis of a complement to each of the strands of the double helix, a process which yields two identical double helices.

A DNA molecule (bottom) with exploded views (center and top) showing successively smaller components.

The Morse Code			The Genetic Code		
· · ·	=	S	A T G	=	Methionine (met)
- - -	=	O	T T A	=	Leucine (leu)
- · -	=	D	C A G	=	Glutamine (gln)
	etc.			*etc.*	

A Morse code message:

·-·	·	···	·	·-	·-·	·-··	····
R	E	S	E	A	R	C	H

A genetic message:

DNA	-A-T-G	-G-A-A	-C-A-G	-A-A-T	-T-T-A-
PROTEIN	- met -	glu -	gln -	asn -	leu -

[Part of the message for the enzyme aspartokinase, elucidated at BBRI]

ARTIFICIAL MUTATIONS HELP US UNDERSTAND HOW CALCIUM CONTROLS MUSCLE CONTRACTION

A great deal can be learned about the function of a protein by analyzing the changes in mutant proteins that interfere with their function. For example, much of what we know about the function of hemoglobin, the protein that carries oxygen from the lungs to the tissues, has come from the analysis of the hemoglobins of patients who have inherited a defective hemoglobin gene. Today, however, we no longer need to wait until a patient is found with a genetic defect in the protein we wish to study. Instead, we can use molecular genetics to construct a mutant gene in the test tube, insert it into a microbial or animal cell, and study the altered protein produced under the direction of the mutant gene.

Molecular genetics thus provides a powerful tool for studying the various pieces of the cellular machinery at the molecular level. For instance, to study a mechanical system, one interchanges and modifies one or more parts and thereby arrives at the optimal operating mode and finds out about the basic behavior of the system. In biology, we can do this by using molecular genetics techniques to produce a modified gene with an artificial mutation, introducing the gene into suitable bacteria and letting the bacteria do the job of producing the modified protein, a job which would be very laborious if it had to be done by classical organic chemistry.

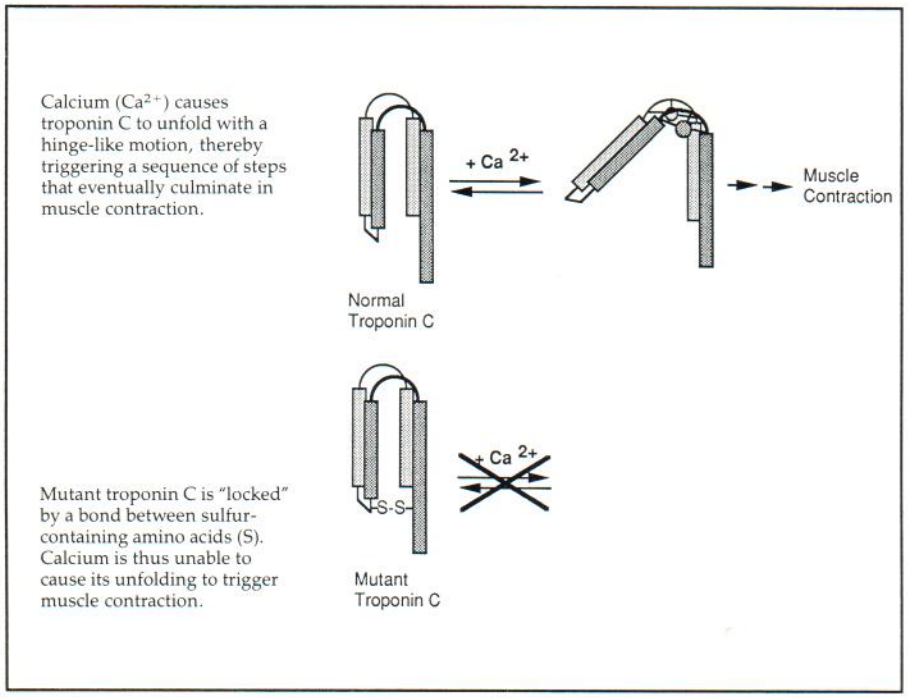
MUTATION—A change in the sequence or number of nucleotides contained in a gene. A mutation may be caused by the damage of DNA through some environmental agent, such as ultraviolet light or a toxic chemical, by an error in DNA replication, or artifically in the laboratory by the chemical modification of DNA. If the gene in which a mutation occurs codes for a protein, the mutation may lead to an alteration of the protein. Mutations that occur in reproductive cells are inherited and may give rise to genetic diseases. On the other hand, artificial mutations produced in the laboratory are important tools for studying basic life processes. The manipulation of genes by artificial mutation is often referred to as "genetic engineering."

Members of the research team who used artificial mutations to study the control of muscle contraction. From left to right, Zenon Grabarek, Jing Wang, Zhiyan Wang, Terence Tao, John Gergely, Yasuko Mabuchi, Ruo-Ying Tan.

Drs. Zenon Grabarek, Terry Tao, John Gergely, and their associates in BBRI's Department of Muscle Research have recently completed a piece of research of this kind. One step in the regulation of muscle contraction involves a "switch," in actual fact a protein molecule known as troponin C, which is operated by calcium released from cellular storage into the space surrounding the contractile machinery within the cell as the nerve impulse reaches the muscle. X-ray studies in two laboratories, one in Wisconsin and the other in Canada, have led to the suggestion that the switch behaves like a hinged door and that calcium causes the door to open, triggering a sequence of steps that eventually culminate in muscle contraction. Now if the switch indeed operated in this way, then a suitable change in the molecule that would prevent a hinge-like motion should lead to the disruption of its function.

This hypothesis was tested by an experiment based on the hairdresser's art. To give a permanent, hairdressers change the shape of hairs by forming or breaking chemical bonds between pairs of sulfur-containing amino acids in keratin, the major protein of hair. In a similar manner, it should be possible to modulate the shape of the switch protein, the "hinged door," by changing the nucleotide sequence of its gene so that it encodes two sulfur amino acids in strategic positions. When a bond is allowed to form between the sulfur atoms of these amino acids in the muscle protein, the door is locked and it should not be possible to switch on muscle contraction. If by a suitable chemical reaction the bond is broken again, the hinged door should again move freely and muscle contraction should be restored.

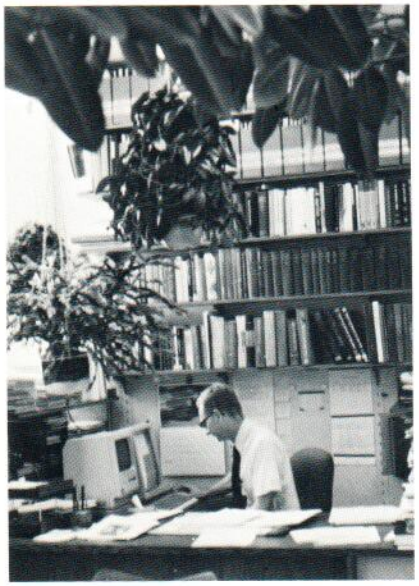
To the great satisfaction of the investigators, it was possible to carry out the modification as described here and, indeed, the results were entirely consistent with the hypothesis that the switch involves a hinge-like motion of the molecule. The beauty of this kind of research is not only that it provides satisfactory experimental support for a hypothesis which then can be used for the further refinement of theories about, in this case, muscle contraction, but that it also opens up ways of understanding possible disease conditions where a congenitally disabled switch may exist.



Terence Tao and Zhiyan Wang discussing a model for the structure of troponin C.

STUDY OF GENE REPLICATION PROVIDES INSIGHTS INTO THE ORIGIN OF MUTATIONS THAT CAUSE MUSCULAR DYSTROPHY

Some mutations that are responsible for inherited diseases occur with exceptional frequency, suggesting that certain genes may be inherently unstable. A case in point is Duchenne muscular dystrophy, which affects one in 3,500 males at birth. An unusual aspect of muscular dystrophy is that about a third of all cases are due to mutations which have occurred within one or two generations and often involve the loss of long segments of DNA. Another unusual feature is the enormous size of the gene in which these mutations occur. It contains more than 2 million nucleotides and is by far the largest human gene known, as large as the entire genome of a typical bacterial cell. The protein produced by the gene has been named dystrophin because its disruption causes muscular dystrophy. What is the cause of the large number of mutations that make muscular dystrophy one of the most common congenital diseases? A clue comes from the work of Dr. Nilima Sarkar in the Department of Metabolic Regulation, who has been studying the problem of the replication of the human genome.



The bytes of information in the books on each of the shelves or on the 50 megabyte hard disc of the Macintosh which Henry Paulus, Director of the Department of Metabolic Regulation, is using correspond approximately to the information stored in a single human chromosome.

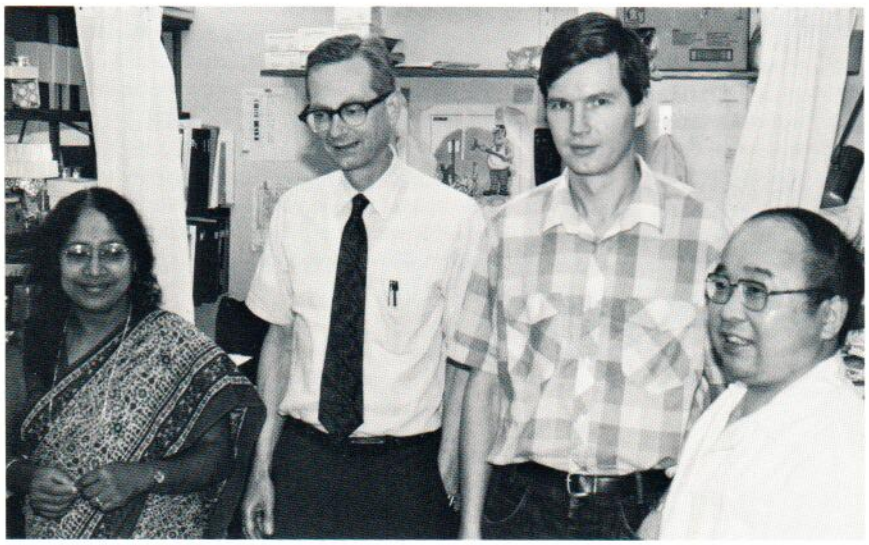
The genetic information stored in the human DNA genome is encoded in 3 billion nucleotide units. To visualize the amount of information this represents, let us imagine that each nucleotide unit is represented by one letter. In that case, the genetic information present in every one of our cells would fill a library of 1,000 large volumes. The duplication of this vast amount of information, which occurs in just 6 hours each time one of our cells divides, poses a logistical problem of staggering proportions. It is analogous to the task of duplicating the library of a medieval monastery within one year. It takes a single monk many years to copy just one volume, and thousands of monks would therefore have to work together, each charged with copying a specific part of one of the thousand books. On examining the copies at the end of the year, we would not be surprised to find pages skipped, transposed, or copied twice, not to speak of transcription errors. The problem of accuracy also confronts the cell when it replicates its DNA, for in order to duplicate the entire genome in the alloted time period of the cell division cycle, copying has to start at thousands of different places. How does the cell assure that every segment of the genome is duplicated once and only once, so that after cell division each daughter cell has a complete copy of the genome?

Dr. Sarkar has developed a procedure for determining the exact time during the cell division cycle at which particular genes are duplicated in cultured human cells. Her method involves tagging the DNA with atoms of mercury as it is being duplicated and measuring the time at which mercury becomes linked to various genes. The results of these experiments show that every gene is duplicated at a specific time, some early, others late, in the cell division cycle. This suggests that the orderly duplication of the genome is accomplished through a time-table which assigns a specific time slot to the replication of each gene.

What would happen if the replication of the human genome did not always follow the time-table precisely? In the case of most human genes, which are small enough to be copied as a single unit, a slightly early or delayed start of replication may be tolerable. But what about a gene such as the dystrophin gene, which is so large that its duplication would take much longer than the time allotted in the cell division cycle unless it were duplicated in several pieces? If a gene is copied in a piecemeal fashion, slight deviations from the replication schedule may seriously interfere with the delicate coordination needed to get the various pieces of the gene replicated on time. As a result, a portion of the gene may not get replicated and one of the daughter cells may receive an incomplete copy similar to the mutant genes seen in many cases of muscular dystrophy. Were this to happen in a reproductive cell, it would lead to a defective sperm or egg and an offspring might inherit the defective gene and thus develop the disease.

Dr. Sarkar, in collaboration with Dr. Henry Paulus, is beginning to explore this possibility by applying her mercury-labelling technique to the study of the replication of the dystrophin gene, to determine whether the pattern of DNA loss in muscular dystrophy patients matches the pattern of gene duplication. If a correlation should be found, this would provide important insights into the origin of genetic diseases, not only of muscular dystrophy but of many other diseases known to be due to the loss of specific gene segments, such as the fragile X syndrome, which is a major cause of mental retardation.

Nilima Sarkar preparing to extract DNA from cultured human cells.



The researchers who are studying the replication of the gene for dystrophin, whose mutation is the cause of Duchenne muscular dystrophy. Left to right, Nilima Sarkar, Henry Paulus, Nikolai Boubnov, Gong-Jie Cao.

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THANK YOU!

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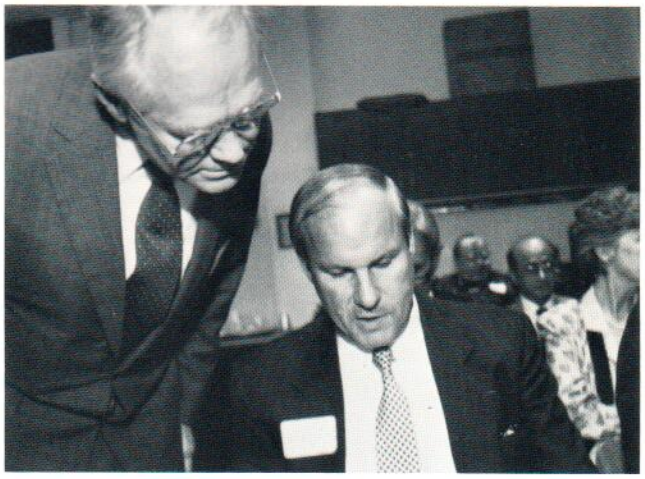

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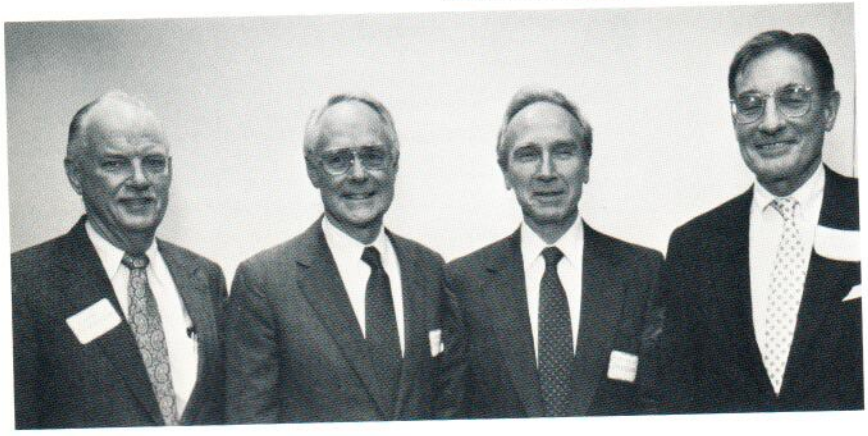

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Yasuko Mabuchi isolating a mutant form of troponin C by high-performance liquid chromatography.

BOSTON BIOMEDICAL RESEARCH INSTITUTE
BALANCE SHEETS
AUGUST 31, 1990 AND 1989

	1990	1989
ASSETS		
CURRENT ASSETS		
Cash	$ 1,581,156	$ 1,607,384
Grants receivable	3,445,321	4,013,600
Pledges receivable	960	
Prepayments, deposits and other receivables	40,088	38,863
Overhead and fringe benefit adjustment receivable	108,509	
Investments, at market value (cost 1990—$3,542,886 1989—$3,361,020) (note 6)	3,929,465	3,791,190
Total current assets	9,105,499	9,451,037
FIXED ASSETS (notes 1 and 2)		
Leasehold improvements	1,935,632	1,935,632
Research equipment	4,581,469	4,369,513
Furniture and fixtures	48,799	48,799
Total	6,565,900	6,353,944
Less accumulated depreciation	4,958,609	4,607,791
Net fixed assets	1,607,291	1,746,153
	$10,712,790	$11,197,190
LIABILITIES AND FUND BALANCES		
CURRENT LIABILITIES		
Accounts payable and accrued expenses	$ 180,419	$ 141,930
Overhead and fringe benefit adjustment payable		34,499
Deferred grant income (note 5)	3,767,358	4,454,600
Deferred fund (building) (note 5)	115,702	115,702
Total current liabilities	4,063,479	4,746,731
FUND BALANCES (note 1)		
Operating	546,926	587,395
Plant and equipment replacement	3,275,453	2,957,965
Permanent research	604,647	574,573
Fixed assets (notes 1 and 2)	1,607,291	1,746,153
Support of staff members	303,668	288,631
Amelia Peabody staff scientist	311,326	295,742
Total fund balances	6,649,311	6,450,459
	$10,712,790	$11,197,190

See accompanying notes to financial statements.

BOSTON BIOMEDICAL RESEARCH INSTITUTE
STATEMENTS OF REVENUES, EXPENSES AND CHANGES IN FUND BALANCES
FOR THE YEARS ENDED AUGUST 31, 1990 AND 1989

	1990	1989
REVENUES		
Grants	$5,065,122	$5,190,189
Equipment replacement	156,456	143,581
Contributions and pledges		
Unrestricted	143,947	185,353
Restricted availed of in current period	207,891	256,312
Property and equipment purchased (notes 1 and 2)	211,955	190,813
Investment income and appreciation	277,350	777,133
Total	6,062,721	6,743,381
EXPENSES (by department)		
Muscle Research	2,561,922	2,284,887
Cell Physiology	761,899	1,149,475
Fine Structure	657,079	668,334
Metabolic Regulation	894,222	1,018,569
General Research	568,517	492,778
Fund Raising	51,944	54,068
Purchase of fixed assets (note 1)	2,978	80,085
Depreciation (note 2)	350,817	335,290
Write off-subsidiary advances	14,491	141,913
Total	5,863,869	6,225,399
NET ADDITION TO FUNDS	198,852	517,982
FUND BALANCES, BEGINNING OF YEAR (note 1)	6,450,459	5,932,477
FUND BALANCES, END OF YEAR (note 1)	$6,649,311	$6,450,459

See accompanying notes to financial statements.

BOSTON BIOMEDICAL RESEARCH INSTITUTE
NOTES TO FINANCIAL STATEMENTS
AUGUST 31, 1990 AND 1989

(1) - SIGNIFICANT ACCOUNTING POLICIES

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

- Unrestricted funds include two groups representing the portion of expendable funds available for support of operations: a) The operating fund includes unrestricted contributions and investment income less the cost of grants not reimbursed in full by granting agencies, and further reduced by transfers to other funds; b) Other unrestricted funds represent amounts segregated from the operating fund for specific purposes, such as a building program fund, staff support and permanent research funds. These funds are designated for specific purposes by internal direction of the trustees.
- Restricted funds represent resources restricted for research grants or building additions. These funds are deemed to be earned and reported as revenues when the Institute has incurred expenditures in compliance with the specific restrictions. Amounts received but not yet earned are reported as restricted deferred amounts (see note 5).
- Restricted contributions are deferred and recognized as revenues in the period in which they are expended. Restricted contributions received in the current period amounted to $3,850.
- Fixed assets fund represents the depreciated cost of leasehold improvements, equipment and furniture and fixtures.

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

A portion of the overhead chargeable to research grants is deemed to be reimbursement for equipment and is shown as an addition to the Equipment Replacement Fund. This amounted to $156,456 in 1990 and $143,582 in 1989. In addition, $2,978 of equipment was charged to the operating fund in the year ended August 31, 1990, $80,085 in 1989 and added to the plant fund.

(2) - PLANT ASSETS AND DEPRECIATION

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

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

(3) - GOVERNMENT GRANTS

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

(4) - DEFERRED COMPENSATION PLAN

The Institute has a fully funded deferred compensation plan, with funds held by an insurance company as custodian. The assets of the fund and the related deferred compensation liability are not included in the financial statements as they are not intended to be available for operations, but as a segregated retirement fund.

(5) - CHANGES IN DEFERRED RESTRICTED AMOUNTS

	1990			1989
	Building Fund	Grants & Contracts	Total	Total
Balance, beginning of year	$115,702	$4,454,600	$4,570,302	$4,352,287
Additions:				
New grants awarded		4,579,421	4,579,421	5,318,967
Contributions and pledges		3,850	3,850	256,458
Investment income	6,014	22,815	28,829	59,397
	121,716	9,060,686	9,182,402	9,987,109
Deductions:				
Funds expended for designated purposes		5,293,328	5,293,328	5,396,015
Transfer of investment income from Building Fund	6,014		6,014	20,792
Balance, end of the year	$115,702	$3,767,358	$3,883,060	$4,570,302

(6) - INVESTMENTS

Investments consist of corporate and government bonds and listed stocks. Also included is an $800 investment made in 1982 in Boston Biotechnology Corporation. This Company was formed to utilize and commercialize certain technical processes originated at Boston Biomedical Research Institute and elsewhere. The investment holding represents the entire outstanding stock of Boston Biotechnology Corporation and is shown at cost.

INDEPENDENT AUDITOR'S REPORT

Board of Trustees
Boston Biomedical Research Institute
Boston, Massachusetts

I have audited the accompanying balance sheets of Boston Biomedical Research Institute as of August 31, 1990 and 1989, and the related statements of revenues, expenses and changes in fund balances for the years then ended. These financial statements are the responsibility of the Institute's management. My responsibility is to express an opinion on these financial statements based on my audit.

I conducted my audit in accordance with generally accepted auditing standards. Those standards require that I plan and perform the audit to obtain reasonable assurance whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. I believe that my audit provides a reasonable basis for my opinion.

In my opinion, the financial statements referred to in the first paragraph present fairly, in all material respects, the financial position of Boston Biomedical Research Institute as of August 31, 1990 and 1989, and the results of its operations and changes in fund balances for the years then ended in conformity with generally accepted accounting principles.

John Vecchi/Certified Public Accountant
124 Crescent Road, Needham, Massachusetts 02194
(617) 449-5545

October 1, 1990

Credits

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