

HIGHLIGHTS OF THE YEAR

Research Highlights

The Tumor Virus Program

Much to my satisfaction, the 1996 review of the Lab's the DNA Tumor Virus Program Project Grant resulted in renewal of this funding for the fifth time. As the term of the grant is five years, we enter our 26th year with this Program Project Grant, good through the year 2001.

This grant was established 25 years ago by Jim Watson and Joe Sambrook to use DNA tumor viruses to study cancer. In 1968, the Lab changed direction toward the study of DNA viruses that infect mammalian cells. Jim recruited Joe Sambrook, among others, to pursue these studies and in 1971 the first application was made for a large (\$1 million) program project grant. This program project continues to be a cornerstone of cancer research at the Lab to this day. Over the years this grant has supported the studies of Joe Sambrook, Richard Roberts, Robert Tjian, Michael Botchan, Phillip Sharp, Louise Chow, Earl Ruley, Ed Harlow, Terri Grodzicker, Michael Mathews, Yakov Gluzman, and myself, as well as many others. It was this grant that supported Richard Roberts' studies on split genes that resulted in his winning the Nobel Prize in 1993 with Phillip Sharp.

The Program Project continues to use DNA tumor viruses to probe how normal cells become cancer cells and now includes Winship Herr, Arne Stenlund, Adrian Krainer, Ryuji Kobayashi, and myself. Additional components of cancer research recently added to the grant are studies by Carol Greider into the involvement of telomerase in tumor progression and a multifaceted approach aimed at understanding the mechanisms and regulation of programmed cell death (apoptosis) in cancer cells by Scott Lowe (a former Cold Spring Harbor Fellow), and Yuri Lazebnik. Apoptosis involves a mechanism—built into every cell—that will cause the cell to self-destruct when it is triggered. This process is vital to



Yuri Lazebnik and Scott Lowe

development, ridding organisms of unnecessary cells (i.e., webs from human embryo fingers and toes, and tails from tadpoles as they become frogs) and also by destroying damaged or diseased cells. Most conventional cancer therapies work by triggering apoptosis, and Scott and Yuri each study different aspects of this process.

Scott Lowe reported, early in the year, the discovery of an important characteristic of the p53 gene—a known tumor suppressor. Cells at the center of solid tumors usually die from hypoxia, a lack of oxygen that results from the dense cellular overcrowding caused by the rampant cell division that is characteristic of cancer. Some cells, however, survive in these hypoxic conditions, and Scott, with Tom Graeber and colleagues at Stanford University School of Medicine, has shown that it is the cells with a p53 mutation that survive. Scott had shown previously that cells with a p53 mutation are immune to the effects of conventional cancer therapies. Together these studies provide a link between tumor growth and resistance to cancer therapy; tumor cells which acquire p53 mutations would survive hypoxic conditions and simultaneously become less susceptible to cancer therapy.

Yuri Lazebnik, who studies the mechanisms involved in the execution of programmed cell death, has also focused on drug resistance in cancer cells, and is looking for ways to by-pass this therapeutic obstacle. Because conventional cancer therapy typically triggers apoptosis by damaging the cell to the point that it self-destructs, Yuri is trying to understand why this machinery is not active in some tumor cells despite the presence of the cell death signal. In addition, he is trying to discover how the latent signal in tumor cells can be activated.

Yuri uses an experimental cell-free system that he developed by mixing cytoplasmic extract from a cell with purified nuclei. Howard Fearnhead of Yuri's lab made an interesting observation in the cell-free system. When he used an extract from normal cells there were no changes to the nuclei, but the addition of an extract from untreated, drug-resistant tumor cells caused apoptotic changes in the nuclei—they began to fragment in the same way as nuclei in dying cells. This indicated that drug-resistant cells have the apoptotic machinery, but they cannot sense the triggering signal that is present. In collaboration with Scott Lowe, Yuri's lab traced the origin of this signal and found that it is generated by the very same oncogene that transformed the cell to become drug-resistant. Yuri's lab is now working to further identify the oncogene-generated activity. The hope is that this knowledge could be used to find a way to selectively activate apoptosis in cancer cells.

Cell Cycle

Studies of the cell cycle are also an important component of cancer research and this year cell cycle studies in yeast and in mammalian cancer cells complimented one another. Bruce Futcher's lab has been working to understand how the essential cyclin-dependent protein kinase (CDK) complex (Cdc28-Cln) controls commitment to cell division in yeast, a popular model organism for cancer research. They were particularly interested in how Cdc28-Cln promotes DNA replication. They knew of a protein, Sic1, that inhibits other CDK protein kinases that are necessary for DNA replication. Last year, postdoctoral researcher Brandt Schneider

and graduate student Qing-Hong Yang in the Futcher lab showed that the Cdc28-Cln complex places phosphates on Sic1, following which the phosphorylated Sic1 is attacked by enzymes that digest the protein, thereby allowing DNA replication to begin. In cells that have Sic1, the Cln proteins were essential for replication. A striking observation was that mutant yeast cells lacking Sic1 could commit to DNA replication and cell division even when they lacked the Cln proteins. These results show that the only essential activity of the Cln-like cyclins and the CDK partner CDC28, is to control an inhibitor (sic1) of cyclin CDKs that regulate DNA replication.

These studies complement David Beach's work on the cell cycle in mammalian cells. Beach's lab and others have shown that the Retinoblastoma protein (Rb), an important tumor suppressor which inhibits entry into the cell cycle, is itself inhibited by the Cdk4-Cyclin D protein kinase complex—which is similar to the yeast Cdc28-Cln complex. Beach's lab has found that while Cdk4-Cyclin D is normally essential for DNA replication, it is dispensable in mutants lacking Rb. Furthermore, they have shown that another tumor suppressor protein, p16, regulates Cdk4-cyclin D activity by functioning as a CDK inhibitor.

Many clinical studies have shown that the p16 tumor suppressor is mutated in a wide variety of human cancers. In collaboration with Ron DePinho's laboratory at the Albert Einstein College of Medicine, the gene that encodes p16 has been mutated in a line of mice so that the mice no longer express the protein. These mice develop tumors of various types at a very high rate, providing proof of the role of p16 as a tumor suppressor. These "knock-out" mice will provide a valuable animal model for the study of human cancer therapy.

Phosphatases

In other cell cycle work, David Beach and Konstantin Galaktionov made the important discovery of the regulatory target of the *myc* onco-gene. That *myc* is an oncogene has long been known, as has its role in cell cycle: the Myc protein is a driving force in cell division, and in partnership with a protein called Max, can promote either oncogenic transformation (cancer) or apoptosis (programed cell death). Myc is known to be a transcription factor for controlling gene expression, but the critical target genes whose expression it regulates remained obscure. David and Konstantin have found that the *cdc25A* protein is the target of Myc's function. They were studying Cdc25A because their earlier studies in yeast showed that it was an important CDK regulator, a so-called protein phosphatase. Interestingly, elevated levels of *cdc25A* have been found in a significant number of breast tumors and other cancers, making these cell cycle components a prime target for anti-cancer drug discovery efforts.

Nicholas Tonks' lab has continued to move forward in their work on the role of protein tyrosine phosphatases (PTPases). These enzymes catalyze dephosphorylation—the removal of phosphate groups from molecules which have been phosphorylated by protein kinases. In 1994, Nick and then-Cold Spring Harbor Fellow and X-ray crystallographer David Barford determined the first three-dimensional structure of a PTPase: the human PTPase 1B (PTP1B). The crystal structure of a

molecule frequently sheds a great deal of light on how the molecule might function—scientists can then see which domains are exposed on the surface, where potential binding sites are located, etc. This information can then be used to develop molecules that effectively block specific actions or interactions. In 1995, Nick and David (by then at Oxford University) built on their success with another "first:" they solved the structure of PTP1B bound to a phosphorylated substrate (the molecule on which an enzyme acts).

In order to accomplish this, Nick and Postdoctoral Fellow Andrew Flint developed a mutant that would bind to its substrate but *not* dephosphorylate it, and David crystallized and solved the structure of the bound pair. These structures of PTP1B demonstrated that the unique signature motif that is the defining feature of the PTP enzyme family acts as a rigid cradle structure that binds to the phosphate group on a target substrate. The motif lies at the base of a cleft on the surface of the protein and when the substrate binds, the cleft closes, locking the substrate within the enzyme.

These studies are illuminating *how* a PTPase works; the next question was *with what* does it work? It has long been thought that there were a limited number of PTPases each of which dephosphorylated a great many substrates. Nick and his colleagues suspected, and have now shown, that PTPases are actually very selective. Together they have developed "substrate-trapping" mutants for a variety of PTPases, like the one used to solve the structure of the PTP1B substrate complex. By expressing substrate-trapping mutants in cells, they can see which substrates the phosphatases recognize. They have made the surprising discovery that many PTPs examined in a physiological context are exquisitely selective, binding consistently to only a small number of substrates. This work has implications for the development of finely targeted therapeutics, as phosphorylation and dephosphorylation are critical to many cellular processes including cell growth, proliferation, and differentiation.

Transcription Control

Another important cellular process is transcription—the formation of a complementary strand of RNA based upon one of the two strands of DNA. But the *in vivo* study of DNA transcription is difficult because basal transcription factors are vital to cells' survival. Disruption of their function can lead to cell death, making experimentation difficult. Two Cold Spring Harbor scientists, Winship Herr and Nouria Hernandez, study the components of this vital process and their interactions. Some transcription factors, the proteins required to initiate or regulate transcription, recognize the promoter region of the DNA where transcription begins. A key regulatory element in the promoter region of the DNA is known as the TATA box.

Both Winship and Nouria study the TATA box-binding protein (TBP) and its interaction with other transcription factors. Winship's lab developed a new system to study the relationship between TBP and the transcription factor TFIIB in human cells by building on the work of Kevin Struhl of Harvard Medical School. Kevin developed an altered promoter

(TGTA instead of TATA) and an altered TBP binding protein that was engineered to match it. In this system, transcription continued to occur, yet the potentially lethal consequences of disrupting the endogenous transcription machinery were circumvented. Bill Tansey in Winship's lab took this approach an important step forward: using this altered TGTA box/TBP pair, they developed a new altered pair of basal transcription factors—TBP and TFIIB—that works in concert with the original TGTA box/TBP pair. This "sequential altered specificity" has enabled Winship's group to study TFIIB in living cells, which was previously not possible in human cells.

Nouria reported interesting results in her work on the interaction between TBP and another group of transcription factors, the small nuclear RNA (snRNA)-activating protein complex (SNAP_c), that binds to the U6 RNA polymerase III promoter. TBP consists of a conserved domain long thought to be the only functional region of the protein, while it also contains a non-conserved amino-terminal region long thought to be less, if at all, useful. Nouria has shown that upon truncating the TBP protein to eliminate the amino-terminal domain, the TBP bound much better to the TATA box. In addition, truncation of the amino-terminal domain resulted in strongly diminished binding of SNAP_c to its binding site next to the TATA box on the DNA. Her results indicate two previously unknown roles for the non-conserved region of TBP: inhibiting TBP's binding to the DNA and interacting with another member of the transcription machinery (SNAP_c) to promote its binding to the U6 promoter. Hence, the presence of this previously unrecognized component is essential to U6 transcription.

Neurofibromatosis

In cancer studies at Cold Spring Harbor, the *ras* oncogene, first discovered by Cold Spring Harbor's Michael Wigler and a group at MIT in 1981, has been the focus of much research. *ras* is critical to control of growth and development in healthy cells, and when mutated contributes to the formation of tumors. In an exciting interplay between cancer and neuroscience research, a member of our neurobiology team discovered a role for the Ras protein in processes of learning and memory. In related research, the same lab also made an important discovery regarding Neurofibromatosis (NF), a disease that causes learning disabilities in children and tumors in adults.

In 1995 Yi Zhong showed that the *ras* pathway was a mediating factor in the transmission of certain (G-protein-coupled) neurological impulses. In 1996, Yi's studies moved toward the investigation of the relationship between *ras* and the Neurofibromatosis type I (NF1) tumor suppressor gene. NF1 is one of the most commonly inherited neurological disorders in humans. The disease is characterized by tumors (frequently benign), developmental abnormalities, including reduced height, and in many patients (30-45%) specific learning disabilities.

The activity of *ras* determines the response of cells to a number of signals, including growth factors, that mediate cell proliferation, growth, and differentiation. *ras* activity can be inhibited by a number of proteins including NF1. Since it is known that elevated *ras* activity causes cancer



Yi Zhong

in many human tissues, the diminished inhibition of ras activity in NF patients may well contribute to the development of NF symptoms. However, the story has become even more interesting as Yi Zhong has discovered that the NF1 protein also controls another biochemical pathway in addition to inhibiting the activity of ras. Yi's lab obtained mutant *Drosophila* that lacked the NF1 gene from Andre Bernards at the Massachusetts General Hospital in Boston and uncovered a link between NF1 and the cyclic AMP signaling pathway. The latter pathway was previously shown by Tim Tully and Jerry Yin of CSH and others to control learning and memory in *Drosophila*. Yi found that the NF1 defect could be eliminated by providing small molecules that could activate the cyclic AMP pathway. These results suggest these small molecules as candidate drugs for treatment of NF.

Alcino Silva, who has done important work with mice, has uncovered a mouse model for the study of learning and memory deficits associated with NF. He obtained a line of NF1+/- mice (one good copy of the gene and one defective) from Tyler Jacks, a collaborator at MIT, and demonstrated learning difficulties similar to those in human NF patients. The development of a mammalian model for the NF disease is facilitating extensive studies of NF that would not be possible in human subjects. These mice will also be valuable in assessing the effects of drugs that affect the cyclic AMP pathway. I am particularly pleased that these exciting results on NF come so soon after the watershed meeting on NF research held at the Banbury Conference Center in late 1995.

In another research project, Alcino continues to study the role of the CREB protein, a target of cyclic AMP, in learning and memory in mice. This year, he had the very exciting success of achieving behavioral rescue in CREB mutant, learning-impaired mice. He demonstrated conclusively that by modifying training regimens for the CREB mutants he was able to overcome profound long-term memory deficits. In these studies Alcino altered the number of training sessions and the length of the rest interval between them. This work follows from the elegant studies on the role of CREB in learning and memory by Tim Tully and Jerry Yin. These examples of successful behavioral rescue through modified training have tremendous implications for the treatment of memory disorders.

Neuronal Learning

In other neurobiology research, Hollis Cline and Roberto Malinow have made great strides in understanding the changes that take place in synapses during development of the neuronal networks and during learning and memory processing. Holly studies the development and stabilization of neurons and synapses while Robert looks at the molecular mechanisms involved in synaptic plasticity—that is, the changes that take place at synapses during learning and the formation of memories.

Holly's laboratory at CSHL is one of a few laboratories in the world to have succeeded in using confocal microscopy to observe changes in live neurons over the course of several days. She uses high-speed microscopy techniques and DiI, a fluorescent dye, in anesthetized *Xenopus* frog tadpoles. By watching neurons grow over time, this group has been able to document some remarkable aspects of their development. They saw and photographed developing neurons sending out axon branches

like branches on a tree, but the surprising result of these studies was that most branches extended by the developing neuron were also retracted, in a process of reaching and withdrawing that continued for days, until the cell established a set of extensions with which it was happy. The factors that determine which branches were stabilized in the end remain under investigation.

Once a synapse (a connection between an axon and a receptor cell) is formed, synaptic transmission, the passing of neurological impulses, may begin. Holly and Robert found that newly formed synaptic connections use a type of glutamate receptor called the NMDA receptor. When a synapse matures, it gains a second type of neurotransmitter receptor known as AMPA receptors. They've determined that this process is dependent on the entry of calcium into the cell and subsequent activation of the enzyme CaMKII, which in turn stimulates the arrival of AMPA receptors. The exciting result of subsequent experiments showed that when CaMKII is inserted into a developing neuron, the cell then develops characteristics of a mature cell—the branches stabilize and the synapses acquire the second receptor, AMPA.

Robert's group studies the role of AMPA receptors in a process called LTP, for long-term potentiation. LTP is the strengthening of a neural pathway, a physiological change that takes place with repeated or very strong impulses across a neural pathway. This group studies LTP in the hippocampal region of the rat brain. The hippocampus is a region of the mammalian brain that is implicated in learning and memory. It has been shown that when the hippocampus is damaged, the ability to form long-term memory is impaired; when it is destroyed on both sides of the brain, the ability to form new memories is lost. As LTP is thought to be a critical part of the learning and memory processes, this continued work into the mechanisms of LTP should provide valuable insight into these vital brain functions.

Grigori Enikolopov has expanded on his earlier finding that nitric oxide (NO) acts as a regulator of cell proliferation and differentiation. Initially Grisha and Natalia "Natasha" Peunova showed that NO acts as a molecular switch to tell neuronal precursor cells to stop dividing and to begin developing into, and functioning as, nerve cells. In experiments designed to test the role of NO in other cells in developing *Drosophila*, Grisha, Natasha, and Boris Kuzin, a visiting scientist from Moscow, have shown that NO also controls organ size during development of an intact organism. Flies in whom the expression of NO was suppressed during larval development displayed substantially larger organs including eyes, wings, genitalia, and legs. The diameter of some leg segments has been 3–4 times that of normal flies, leading to the nickname "Schwarzenegger flies," as they are affectionately known among lab staff.

Tim Tully and Jerry Yin's quest to isolate new genes involved in the biology of memory was boosted this year by generous support from the Hartford Foundation. The Hartford Foundation is concerned with issues related to aging and is especially enthusiastic about the learning and memory work. The long-term hope of this collaboration is that new genetic information will yield a greater understanding of the causes of aging-related memory dysfunction. As part of this effort, the Hartford Foundation will also support two Banbury meetings—one in 1997 on cognitive functioning and one in 2000 on aging and cognitive dysfunction.

Plant Genome Research

This year, with strong support from Laboratory Board Chairman David Luke III, Cold Spring Harbor scientists Richard McCombie and Rob Martienssen entered into a global collaboration that is determined to sequence the entire genome of a flowering plant, *Arabidopsis thaliana*, by the year 2004. Under a grant of \$12.7 million from the National Science Foundation (NSF), the Department of Energy (DOE), and the Department of Agriculture (USDA), three U.S. groups, one European consortium, and one Japanese laboratory have divided up the total genome in order to organize a thorough project with no duplication of effort.

Arabidopsis is a popular model organism for plant genetics research. It is a small plant in the mustard family, and has one of the smallest plant genomes and the highest gene density so far identified in a flowering plant.

There are three U.S. groups participating in the project: one is a consortium of sequencing labs headed by Cold Spring Harbor and including groups from Washington University, in St. Louis, Missouri, and Applied Biosystems, Inc., located in Foster City, California. The other two U.S. groups are The Institute for Genomic Research in Rockville, Maryland, and the Consortium of Stanford University, University of Pennsylvania, and University of California at Berkeley. Our overseas collaborators are the European Scientists Sequencing *Arabidopsis* (ESSA), a 17-lab consortium under the direction of Mike Bevan, of the John Innes Center, and the Kazusa DNA Research Institute in Japan, headed by Satoshi Tabata.

The project will result in the first genome sequence of a higher plant and will provide a complete catalog of all the genes involved in the plant life cycle, from seed to flower and fruit. Results garnered by the participants will be made available to the global plant research community almost immediately via the World Wide Web. The resulting knowledge will have agricultural implications for virtually all crops, including wheat and corn, and will be immediately applicable to all economically important plant species.

These numerous and varied good results in our Labs have allowed us to end the year on a very positive tide. As the new year begins, I can already see continued success coming from these research programs.

Symposium

The 61st annual Cold Spring Harbor Symposium on Quantitative Biology, held May 29–June 5, marked the sixth time that the Symposium has been dedicated to topics on neurobiology; beginning with The Neuron in 1952, followed by Sensory Receptors in 1965, The Synapse in 1975, Molecular Neurobiology in 1983, and The Brain in 1990, heralding President Bush's "Decade of the Brain." Each of these meetings has rendered a clearer understanding of the complex nature of the brain and nervous system. This year's meeting, Function and Dysfunction of the Nervous System, was no exception. Talks focused on integration of neural systems and diseases of the nervous system. Sessions on psychiatric diseases, addiction, neurodegenerative diseases, Alzheimer's, learning and memory, and neuronal dysfunction indicated strong potential for the application to human disease. This Symposium parallels the Laboratory's deep commitment to neurobiology.



V.S. Ramachandran

During the Symposium, the annual Dorcas Cummings Lecture was given by Vilayanur S. Ramachandran, Professor of Neurosciences and Psychology, Director of the Brain and Perception Laboratory, and Co-director of the newly formed Center for Research on Brain and Cognition at University of California, San Diego. His research focuses on an interest in human visual perception and behavioral neurology (the study of patients with focal brain damage). His talk, *Illusions of Body Image in Neurology: What they reveal of human nature*, explored his most recent interest, which examines behavioral correlates of neural plasticity including phenomena such as "phantom limbs," anosognosia or "denial of paralysis," and anorexia nervosa. Most of these syndromes have been known since the turn of the century and treated as enigmatic curiosities on which there has been little research done. Ramachandran has brought them from the clinic to the laboratory and shown that an intensive study of these patients can often provide valuable new insights into the functional organization of the normal human brain. Nearly 300 supporters of the Laboratory, as well as the scientists attending the symposium, attended the lecture.

The Reginald G. Harris Lecture, inaugurated in 1995 and named for the former Laboratory director who initiated the CSH Symposium in 1933, was presented by Richard Axel of the Center for Neurobiology and Behavior at the College of Physicians and Surgeons, Columbia University. His talk entitled *The Molecular Biology of Smell* opened the Sensory Perception session.

On the eighth and final day, Zach W. Hall, Director of the National Institute of Neurological Disorder and Stroke at the NIH, delivered an eloquent and comprehensive summary. He talked about the dual role of Cold Spring Harbor—first, symbolically, as the place where new science begins, and secondly, as a place of unprecedented scientific excitement. His summary was based on two major themes—the link between behavior and biology, and the success of being able to attack brain disease in humans.

Banbury Conference Center

Banbury Center highlights DNA: The chemistry and biology of DNA are fundamental to so much of our research and to biomedical research throughout the world. It is remarkable that even after so many years of intensive study, we are still discovering novel properties of the molecule and intriguing aspects of its biology. In 1995, Rich Roberts and Xiaodong Cheng, here at the Laboratory, described how an enzyme-DNA methylase that modifies the activities of DNA alters the structure of the double helix in a totally unexpected way. In the same way that an old-fashioned juke box "flipped" a record out of the stack to be played, so the enzyme makes accessible the base it is modifying by "flipping" it out of the helix. The 1996 Banbury meeting DNA Base Flipping: How and Why reviewed new evidence that "base flipping" may be not be restricted to DNA methylases but may be a more general mechanism used by other enzymes for interactions with DNA molecules as well.

Banbury Center hosted an historic meeting on the topic of telomerase in 1994. Work in Carol Greider's lab at Cold Spring Harbor and other laboratories has shown that telomere replication may play important roles

in both cancer and aging. Telomerase is the enzyme that is used by the cell to sustain telomeres (the ends of chromosomes) and this field has become a very "hot" area of research. The follow-up meeting in 1996, *Telomeres and Telomerase*, drew many of the participants of the 1994 meeting together with researchers new to the topic. The 1996 meeting, like the earlier meeting, provided an opportunity for the presentation and discussion of new data, unpublished and controversial.

One of the most remarkable meetings of the year dealt with one of the oldest problems in molecular biology: how RNA molecules are made from the appropriate genes and at the appropriate times. The field has reached a stage of development where critical review and synthesis are needed, and the Banbury meeting *Mechanisms of Transcriptional Initiation* succeeded in providing at least the critical review. The meeting was notable for its organization, the schedule being developed as the meeting progressed, with speakers being limited to just a few minutes and just a few slides.

The Executives' Conference

This series of meetings continues to be a pleasant surprise. Each year sets such high standards for the following year, that it is not clear how we will be able to find new topics of sufficient interest. It is a measure of the vitality and vigor of biomedical research that new subjects are continually appearing. Human Development—a topic much in the news now with the cloning of a sheep—was the topic for 1996, and covered human embryonic development, the development of gender differences, and the fertilization and manipulation of human embryos in vitro.

Education for Nonscientists at Banbury Center

Among the most influential meetings held at Banbury Center were those funded by the Alfred P. Sloan Foundation for workshops on biomedical research for Congressional staff and science journalists. In 1996, the Federal Judicial Center in Washington, D.C. brought federal and state judges to Banbury to learn about many aspects of science in the courtroom. Topics ranged from the history and philosophy of scientific practice to issues of direct application, such as the use of statistical evidence and how courts understand risk assessment. Genetics was not neglected, with talks on eugenics, genetics, and social implications of the Human Genome Project. One issue that was raised repeatedly concerned expert witnesses and how to establish their credibility in litigation where fees for testimony speak very loudly.

In November, the Banbury Center hosted a workshop for science journalists similar in format to previous meetings funded by the Sloan Foundation. This time supported by funds from the Lab's Department of Public Affairs, the title of the meeting was *Genetics of Human Behavior*. Talks addressed genetic factors involved in such "behavioral" issues as alcoholism, homosexuality, aggressive behavior, and learning and memory. The meeting was a stimulating and educational experience for more than 20 science writers.

Board of Trustees

Individual trustees Charles Dolan, Owen Smith, and Henry Wendt as well as scientific trustee Shirley Tilghman each concluded a full term on the Board in 1996. I look forward to continued advice and interaction with these friends and colleagues.

Mary D. Lindsay, a friend and advocate for more than 40 years and a board member as often as the bylaws allow since 1971, has concluded her most recent term. She had been a member of the Executive Committee since the early 1980s and since 1992 was vice chairman of the Board. Over the years, Mary has served on most board committees. Among her longest and most valued tenure was her active role on the Building Committee. In November, the Board elected Mary Lindsay an honorary trustee for life.

Most recently Mary's long-held commitment to the young scientists and their families came to fruition in the establishment of child care here. Ground breaking, demolition and renovation of the De Forest Stables has begun to make way for what will become a fine facility to serve the youngsters of our staff.

The election of five new individual trustees and one scientific trustee in 1996 continues the strong board participation that the Laboratory has grown to depend on. C. Thomas Caskey, M.D., senior vice president of research for Merck Research Laboratories in West Point, Pennsylvania, not only brings his extensive research experience in mammalian genetics and inherited diseases but his astute business acumen in the area of biotechnology. Helen Dolan, longtime resident of nearby Oyster Bay, continues to represent the ever charitable Dolan family, who continue to be close friends of the Laboratory. Lola Grace is a financial consultant specializing in financial institutions and has already made a tremendous contribution with her outstanding leadership of the Emanuel Ax Gala in October and her avid encouragement of Lab partnerships with local private and public schools. Lola continues the strong association between the Grace family and our Board. Leon Polsky, a lawyer residing in New York City, has extensive legal and judicial experience to bring to the Laboratory. Mr. Polsky is the son-in-law of the late, revered trustee Lita Annenberg Hazen. William Matheson, retired since 1992 after practicing law in New York City for 42 years, has established with Mrs. Matheson the Matheson Endowment for Neuroscience. The Mathesons make their home in Florida.

I am happy to welcome once again Dr. Arnold Levine, who served as a trustee from 1976–1980. Codiscoverer of the important p53 tumor suppressor protein, he studies virus-induced oncogenesis and cancer biology at Princeton University in the Department of Molecular Biology.

To trustee and dear friend Wendy Russell, we all extend our heartfelt sympathy at the loss of her beloved husband Bill Russell. In the short time that we knew Bill, it was clear that he had fast become the same avid proponent of the Laboratory as is his enthusiastic wife.

Robertson Research Fund

The Robertson Research Fund was established by the Robertson family of Lloyd Harbor in 1973. The initial gift from Charles Robertson was nearly \$8 million and coincided with the transfer of the Robertson property on



Mary D. Lindsay

Banbury Lane to the Laboratory. The site of our Banbury Conference Center, this property is further supported by a maintenance fund, also created by the Robertsons.

Two years later in 1975, the Banbury Fund—the Robertson family's private foundation—established the Marie H. Robertson Memorial Fund to support neuroscience research at Cold Spring Harbor. This year, the Marie Robertson fund distributed \$125,000 to support Tim Tully and his work on learning and memory in *Drosophila*; a new postdoctoral researcher for Alcino Silva, who studies learning and memory in mice; two neurobiology seminars (given by Josh Gordon of University of California, San Francisco and Menahem Segal of the Fogarty International Center in Bethesda, Maryland); and a Banbury Meeting on Genetic Approaches to Learning and Memory.

In 1996 the Robertson Research Fund—its value now up to \$59 million—distributed \$1.8 million to basic research at Cold Spring Harbor. These funds provided research program support directly to 20 scientists; very important supplemental support for the Lab's postdoctoral fellows; and support for graduate students and our seminar program. These most generous gifts continue to have a monumental impact on science at the Laboratory.

Major Gifts

The Laboratory's research programs received strong support in 1996. Plant research received a second substantial gift from Laboratory Board Chairman David L. Luke III and his wife Fanny, who gave \$362,250 to *Arabidopsis* research. In 1995, Mr. Luke and Westvaco Corporation provided seed money of \$290,000 to establish a plant sequencing project at Cold Spring Harbor. This gift allowed the Lab to become a major player in an important international collaboration to sequence the genome of the plant *Arabidopsis thaliana*. In additional plant research support, Pioneer Hi-Bred International, Inc. gave \$80,000 to support Research Investigator Joseph Colosanti.

The Arnold and Mabel Beckman Foundation supported structural biologist Leemor Joshua-Tor with a \$200,000 new investigator grant; the Mellam Family Foundation provided \$200,000 to Nick Tonks for his work with PTPases; the Pew Scholars Program in the biomedical sciences gave \$200,000 to Tatsuya Hirano in a four-year scholarship for research on the dynamics of chromosome structure; the Oliver S. & Jenny R. Donaldson Charitable Trust gave \$125,000 to Michael Hengartner for his work on programmed cell death; the Swartz Foundation gave \$77,274 to help establish a computational neurobiology research program at the Laboratory; the Charles A. Dana Foundation supported Tom Marr in his research into the genetic basis of manic-depressive illness with \$194,000; while Glaxo-Wellcome, Inc. gave \$100,000 for postdoctoral fellows working on cell cycle and apoptosis in laboratories headed by Yuri Lazebnik, Michael Hengartner, and David Beach. *1 in 9: The Long Island Breast Cancer Action Coalition* gave \$50,000 to Michael Wigler's lab for breast cancer research; Mr. and Mrs. Alan Seligson gave \$35,000 to the ongoing Andrew Seligson Memorial Fellowship; the Goldring Family Foundation gave \$30,000 for a Postdoctoral Fellow in my laboratory; Oxnard Foundation donated \$20,000 to muscular dystrophy research;

and the Lauri Strauss Leukemia Foundation granted \$15,000 to Nick Tonks through their Felix Schnyder Memorial Fund.

Gifts to neuroscience research were numerous. We are particularly grateful to Marjorie A. and William L. Matheson for establishing The Matheson Endowment Fund for Neuroscience with gifts totaling \$2,869,227. The John A. Hartford Foundation gave \$320,082 to Tim Tully; Lita Annenberg Hazen Foundation provided \$200,000 to Neurobiology research; the McKnight Endowment Fund for Neuroscience gave \$150,000 to Jerry Yin, and the G. Harold and Leila Y. Mathers Charitable Foundation donated \$126,750 to Robert Malinow. New York Community Trust gifted \$60,000 to Alcino Silva, and the National Neurofibromatosis Foundation granted Alcino \$50,000, while the Volkswagen Foundation gave him \$32,808. Both the Helen Hoffritz Foundation gift of \$20,000 and the Ep-pley Foundation for Research gift of \$15,000 went to support Holly Cline's research into neuronal growth.

Badly needed equipment money was received from The Oliver S. & Jenny R. Donaldson Charitable Trust, who gave \$100,000 to Dick McCombie for an automated DNA Sequencer (used in both cancer and plant research), William and Maude Pritchard Charitable Trust who gave \$75,000 for neurobiology equipment, and the Slocum Estate gave \$8,000 for other essential equipment.

In the earliest stages of fund-raising for the Cold Spring Harbor Laboratory Advanced Imaging Facility and associated start-up costs, we received in 1996 generous commitments of \$300,000 from the William Stamps Farish Fund and \$250,000 from the Gladys and Roland Harriman Foundation. The Lucille P. Markey Charitable Trust gave \$500,000 to Karel Svoboda, a young neurobiologist who will join us in 1997 as we begin our new imaging effort.

The Emanuel Ax Gala was the most successful fund-raiser in Lab history. Major gifts to this event include the Anderson Group, \$10,000; Mr. and Mrs. Charles Dolan, \$10,000; Mrs. Oliver R. Grace, \$10,000; Mr. and Mrs. John S. Grace, \$5,000; J.P. Morgan and Co., Inc., \$5,000; Mr. and Mrs. Edwin S. Marks, \$5,000; Mr. and Mrs. William R. Miller, \$5,000; Mr. and Mrs. Thomas A. Saunders III, \$5,000; Mr. and Mrs. Douglas A. Soref, \$5,000. A complete list of contributions to the gala may be found in the financial section at back.

Donations to the Second Century Endowment Fund included \$393,000 from the estate of Eric Ridder, \$50,000 from the Banbury Fund, \$49,960 from Henry Wilmerding, and \$43,871 from Robert L. Garland by way of a contribution to the pooled income fund.

Carol Large, chairman of the capital campaign for the Mary D. Lindsay Child Care Center held a marvelous kick-off luncheon on September 18 for a very enthusiastic committee. By the end of 1996, more than \$620,000 had been raised. Board members, CSHL Association directors, and members of the committee were responsible for contributing nearly half toward the \$1-million goal. Individuals and foundations have shown their support for Lab families with generous donations: Edwin Marks, \$185,553; The Weezie Foundation, \$75,000; Mr. and Mrs. Robert G. Merrill, \$54,380; Anonymous, \$50,000; Mr. and Mrs. David L. Luke III, \$50,000; Mrs. John H. Livingston, \$26,468; David H. Koch Charitable Trust, \$25,000; Mr. and Mrs. James M. Large, \$20,000; Dr. and Mrs. James D. Watson, \$20,000; Schiff Foundation, \$15,000; Dickey Family,

\$12,000; Mr. and Mrs. Peter O. A. Solbert, \$10,171; G. Morgan Browne, \$10,000; Hyde and Watson Foundation, \$10,000; Mr. and Mrs. Robert V. Lindsay, \$10,000; Mrs. Donald A. Straus, \$10,000; Mr. and Mrs. Howard Phipps, Jr., \$10,000; Mr. Arthur C. Merrill, \$7,500; Mr. and Mrs. Henry Wendt, \$7,500; Mr. and Mrs. John P. Cleary, \$5,000; Mr. and Mrs. Edward H. Gerry, \$5,000; and Mr. and Mrs. Robert D. Lindsay, \$5,000. A complete list of donors may be found in the financial section of this report.

DNA Learning Center

The DNALC received its 100,000th visitor in 1996. While this would be a yearly or even quarterly statistic for a large science center, the numbers alone do not tell the whole story. Half of all visitors, overwhelmingly precollege students from the New York metropolitan area, participated in a two-to-three hour laboratory experience. Visitation has tripled since opening in 1988—to 22,720 students, teachers, and families in 1996. Also over this period, the lab clientele has shifted from almost entirely high school students to more than half middle school students. Lab field trips were increased by 30% in 1996 by adding more afternoon sessions for middle school students. However, with double or triple booking virtually every school day between October 1 and June 15, the Bio2000 Laboratory has reached saturation. The DNALC's educational reach was further expanded with the opening of its own World Wide Web site (<http://darwin.cshl.org>). By year's end the site was receiving more than 10,000 "virtual" visitors per month, including representatives from more than 50 countries.

In September, the DNALC celebrated the opening of the McClintock Exhibit, a tribute to the late Barbara McClintock and the Nobel Prize-winning work that she did during five decades at Cold Spring Harbor. The display consists of a recreation of Barbara's laboratory bench and includes original equipment, books and personal effects that had been archived since Barbara's death in 1992. It also includes a biography, her awards, and a video tape of Barbara's acceptance speech at the Nobel Ceremony in Stockholm in 1983.

The enthusiasm for DNALC programs was matched by the exceptionally strong support of Long Island businesses represented on the Corporate Advisory Board. This body, chaired by John Leahy of Chase Manhattan Bank, raised \$147,000 in support of the DNALC's programs for local students. This contribution equaled 17% of 1996 operating costs. Looking toward the DNALC's 10th anniversary in 1997, we will have to consider ways to insure that it maintains its position as the world's leader in gene education. This will include enlarging the DNALC facility, expanding genetic information available at its WWW site, and convincing the state government to accept some responsibility in providing annual support for this unique New York resource.

Scientific Honors

Carol Greider and her work on telomerase have received considerable recognition in recent months. In addition to a good deal of attention from the popular press, Carol has been lauded by several prestigious organi-



Winship Herr (right) accepts Laboratory's award from Herbert Zaretsky, American Cancer Society

zations. She was awarded the American Society for Cell Biology's (ASCB) first Glenn Foundation Award. The American Society for Biochemistry and Molecular Biology (ASBMB) honored Carol with the Schering Plough Award, an award reserved for researchers who are within ten years of receiving their Ph.D. Perhaps most exciting, and indeed challenging, was her appointment by President Clinton to the newly established National Bioethics Advisory Commission (NBAC). This appointment came just in time to allow Carol to be a guiding force in deciding how the Clinton administration will deal with ethical issues related to the cloning of mammals.

David Beach, highly respected for his work in understanding control of the cell division cycle and its implications for cancer, was elected this year a Fellow of the Royal Society—the United Kingdom's prestigious national academy of science. Founded in 1660, the Society promotes improvements in natural knowledge. David attended the admission day ceremony in London on June 6 and received the certificate of fellowship.

Michael Hengartner, a young apoptosis researcher, was awarded the Pharmacia Biotech Prize for Young Scientists. Sponsored by the American Association for the Advancement of Science (AAAS), this honor recognizes outstanding molecular biologists at the earliest stage of their careers.

Structural biologist Leemor Joshua-Tor, who arrived at Cold Spring Harbor in late 1994, received the Beckman Young Investigator Award. Leemor uses X-ray crystallography and biochemistry to study the structure and function of cellular proteins and enzymes.

And finally, the Laboratory was honored when the Long Island division of the American Cancer Society bestowed its special Excellence in Research Award on the Laboratory for its "leading edge research program in cancer biology."

Cold Spring Harbor Laboratory Press

Eight books and two videos were published this year. Notable new titles included the Symposium volume on Protein Kinesis and two new volumes in the CSHL Monograph series. *DNA Replication in Eukaryotic Cells*, edited by Melvin DePamphilis, is composed of three sections (concepts, proteins, and systems) so it serves as an introduction to this important topic for scientists-in-training and as a core reference work for experienced investigators. *Epigenetic Mechanisms of Gene Regulation*, edited by Vincenzo Russo, Robert Martienssen, and Arthur Riggs, discusses our current understanding of the observation first made by Barbara McClintock in maize, that heritable changes in gene function cannot all be explained by changes in DNA sequence. The mechanisms underlying these phenomena are reviewed in the many species in which they are now known to occur. Also notable was the reissue of an expanded edition of Horace Freeland Judson's absorbing history of the development of molecular biology, *The Eighth Day of Creation*. The additional material in this edition includes challenging essays on the lives and scientific contributions of Rosalind Franklin and Erwin Chargaff.

In December, Nancy Ford, the book program's managing editor, announced her decision to retire after 24 years' of extraordinary service to the Laboratory. She played a leading role in the creation of the book



Trudy Calabrese



Cathy Soref



John Cleary

publishing program at Cold Spring Harbor and is remembered with affection and admiration by many of the authors and editors with whom she produced so many outstanding contributions to the scientific literature.

The journal program continued to strengthen. All three journals had increased circulation and the impact factor of *Genes & Development* rose for the eighth consecutive year, placing it among the six most influential science journals in the world.

Cold Spring Harbor Laboratory Association

The Cold Spring Harbor Laboratory Association, under the skillfull leadership of President John Cleary, again enriched the Laboratory with its many activities. Three dynamic and enthusiastic directors were elected to the CSHL Association in 1996: Trudy Calabrese, Tony Kemper, and Cathy Soref. Tony and Cathy have contributed greatly to the growth and continued success of the Next Generation Initiative (NGI) while Trudy put her efforts toward raising funds for the capital campaign for our child care center and developing new contacts for our annual membership drive.

The NGI program has generated new and renewed interest in the Lab. The focus of this program is to encourage people in their thirties and forties to become interested in science at the Lab and to encourage new membership in the CSHL Association. At an NGI lecture on January 19, 1997, I presented an overall view of our research program and history and Tim Tully described the newest findings in learning and memory in *Drosophila*. Following the program, five private dinner parties were given, echoing the very successful dinner parties held annually since 1954 following the Dorcas Cummings lecture.

The traditional and highly regarded Symposium Dinner Parties were a notable success under the 1996 leadership of Vernon Merrill, a director of the Association. Twenty-two hosts and hostesses opened their homes to personal guests, visiting and Lab scientists for an evening of exceptional food and lively intellectual exchange.

The Association's annual membership total of well over \$600,000 was gratifying in light of the fact that a major capital campaign for the child care center and the Emanuel Ax benefit were under way concurrent with the fall membership drive.

Allen Oliff, M.D., executive director of Cancer Research at Merck Research Laboratory, addressed the Association members at their Annual Meeting in February. His lecture, *Anti-cancer Agents Directed Against Oncogene Targets*, provided an enlightening discussion of the long and complicated process involved in turning basic scientific knowledge into therapeutic clinical treatments.

The Association orchestrated a variety of other special events during the course of the year. On May 5, a concert by pianist and writer, Carol Montparker, was complimented by an exhibition of the works of Stan Brodsky, noted artist and teacher. This provided a double treat for the Association members and friends who attended.

On October 13, our good friend Dr. Cynthia J. MacKay and Dr. Peter Gouras, her collaborator from Columbia-Presbyterian Hospital, presented a much-needed discussion of macular degeneration, the number one cause of legal blindness in people over 65 in the United States. The lecture drew an inquisitive audience to hear about retinal cell transplantation, a new treatment for this debilitating affliction. A lively question and answer session followed; this lecture made a valuable contribution to our friends and neighbors.

On November 17, 1996, Dr. David Grimaldi, Curator and Chairman of the Department of Entomology at the American Museum of Natural History, presented an informative lecture on *Amber: A Scientific Renaissance*, to a packed house of adults and children. His focus was on both the history and biology of this ancient resin. Afterward, Dr. Grimaldi remained in the lobby to sign copies of his book, *Amber: Window to the Past*, and to continue answering individual questions from the guests about their own pieces of amber.

Also in November, this year's Major Donor Cocktail Party was graciously hosted by former Laboratory trustee Owen Smith and his wife Bernadette in their beautiful home, *Whispering Laurels*, for major donors and Laboratory scientists.

President's Council

The President's Council was formed three years ago in an effort to bring together a small group of individuals interested in science and the work



Barry Gordon, Bluma Appel,
Ueli Grossniklaus, J.D. Watson

at Cold Spring Harbor Laboratory. Members of the President's Council provide support for the Cold Spring Harbor Fellows program through an annual commitment of \$25,000. This funding is critical to the Lab's continued initiative to attract top young scientists fresh from their Ph.D. studies. These fellowships allow new researchers to pursue their own research, rather than assisting in the laboratory of an established scientist.

A major feature of the Council is an annual meeting that brings together this select group of leaders from business, finance, and science to discuss the latest developments in genetic research and biotechnology. The Council's 1996 meeting, held May 17-18, commenced with lunch on Friday at Ballybung, the home of Jim and Liz Watson, and was followed by thought-provoking lectures on learning and memory by Drs. Tom Marr and Alcino Silva of Cold Spring Harbor Laboratory. The keynote speaker, Dr. Barry Gordon, Associate Professor of Neurology and Cognitive Science at John Hopkins University Medical School, opened the evening session with his talk on *Remembering and Forgetting*. Saturday's highlights included lectures by Dr. Eric Kandel, Howard Hughes Medical Institute and Columbia University; Dr. Tim Tully, Cold Spring Harbor Laboratory, Dr. Paula Tallal, Center for Molecular and Behavioral Neuroscience, Rutgers University; and Dr. Earl Hunt, University of Washington. The mix of minds—leaders in the business world and in the scientific community—evoked interesting insights as well as provocative discussions. The meeting ended on Saturday with the guests gathering once again at Ballybung for a parting luncheon.

Members of the President's Council include Christopher Alafi, Alafi Capital; Abraham Appel, Appel Consultants; Peter L. Bloom, General Atlantic Partners; James T. Conneen, A.T. Hudson & Co.; Michel David-Weill, Lazard Freres & Co.; Frederick Frank, Lehman Brothers, Inc.; Leo A. Guthart, ADEMCO; Charles E. Harris, Harris & Harris Group, Inc.; Walter B. Kissinger, Long Island Research Institute; Donald A. Pels, Pelsco, Inc.; George B. Rathmann, ICOS Corporation; Hubert J. P. Schoemaker, Centocor, Inc.; James H. Simons, Renaissance Technologies Corp.; and Sigi Ziering, Diagnostic Products Corporation.

A Very Special Benefit

On October 13, 1996 renowned concert pianist Emanuel Ax provided a most memorable evening. In addition to surpassing all previous events in its success as a fund-raiser, the evening was a spectacular musical, culinary, and visual experience. The outstanding performance of Mr. Ax and a formal dinner for the 350 attendees were enhanced by the dramatic decorations brought in for the event. Shelley Galehouse King Broven's faux art added the finishing touches. Gala Chairman Lola Grace, with co-chairmen Hope Lapsley, Carol Large, and Cathy Soref and a committee of 75 pulled off a stellar event, which raised over \$134,000, with great style.

Concerts

Grace Auditorium was the setting for many other musical performances during our meeting season. On April 27, at the meeting on zebrafish,



Emanuel Ax
and J.D. Watson



Lola Grace



Carol Greider



pianist Max Levinson performed a moving and enjoyable piano recital. This concert was sponsored by a gift from Dr. Mark Ptashne.

Young Artists concerts included violinist Joseph Lin on August 17, accompanied by Benjamin Loeb on piano and held during the Cancer Genetics meeting. On August 24, Todd Palmer, clarinetist, and Margaret Kampmeier, pianist, performed during Bacteria and Phage, and Mikhail Yanovitsky gave a piano concert on September 7 during Translational Control. In addition, Andrew Russo, an invited guest of Liz Watson, performed a piano recital in the intimate Davenport Music Room on September 22.

Child Care Realized

A long-held desire to provide child care to our staff is finally a reality. Several hurdles were cleared in 1996—the Village Board approved our plan for the renovation of the DeForest Stables at the north end of Bungtown Road. A ground breaking on June 23, complete with golden shovel and balloons, was attended by Village and Laboratory Trustees as well as our Laurel Hollow neighbors and members of our extended Lab family. Among the speakers were Sheri Lucero from Centerbrook Architects and Mimi Leshin, recently retired director of the Long Island/National Employee Assistance Providers Inc., and an expert on child care in the workplace.

A Laboratory committee, chaired by Cheryl Sinclair, director of human resources, comprised of scientists, trustees, staff, and outside experts, was charged with recommending appropriate child care. After exhaustive research which included impromptu site visits, interviews and comparative proposals, the committee recommended the selection of Rainbow Chimes, Inc. This child care provider was established in 1980 under the leadership of Kathleen Roche, R.N., founder and executive director and Laura Ludlum, associate director since 1985. Rainbow Chimes provided site consultation, family orientation, and workshops for youngsters both here at the Laboratory and at their location in Huntington. Kathleen Roche and her team bring the right kind of flexibility and quality needed by our Lab families. The Mary D. Lindsay Child Care Center will be open

to our infants, toddlers and pre-schoolers in summer 1997. The dedication is planned for June 21, 1997.

Gavin Borden Visiting Fellow

The Gavin Borden Visiting Fellow pays tribute to the late Gavin Borden, founder of Garland Publishing. Included in Garland's list are textbooks for graduate students, the most successful of which is the popular *Molecular Biology of the Cell* by Alberts et al. The Borden Fellow is chosen each year by our graduate students, and speaks to and visits with the students and staff. This year's Visiting Fellow was Martin Raff, an author of *MBC* and professor of biology at the University College of London. He opened his talk with warm reflections on time spent with Gavin Borden, who died most prematurely at only 52 years of age, then went on to offer an eloquent discussion of the control of cell numbers during development. Using the central nervous system as an example, glial cells specifically, Raff explored the many components that must be in place for proper control of cell division and differentiation. The evening lecture was followed by a dinner in the Clarkson dining room. The following day, Dr. Raff met in seminar with the graduate students.



Martin Raff

Undergraduate Research Program

The Laboratory's summer Undergraduate Research Program (URP), initiated in 1959, has matriculated 462 students, affectionately known as URPs. Many have gone on to productive careers in the biological sciences. The program exposes students to hands-on experimental approaches to science and to a greater degree of understanding of the issues involved in biochemistry, genetics, and in molecular and cellular biology.

In 1996, administration of this program passed from Assistant Director Winship Herr, who ran the program for the last 10 years, to scientist Michael Hengartner.

Twenty-two students were chosen from more than 280 applicants for this year's Undergraduate Research Program. On March 7, 1996 the Lab received a \$1 million gift to the URP endowment from Burroughs Wellcome. In addition to the Wellcome Fund, the 1996 program was supported by Jephson Educational Trust, Cornelius N. Bliss Memorial Fund, Share-It-Now-Foundation, Nathan Springer, Donald J. Sutherland, Dr. Ira Herskowitz, Angus P. McIntyre, David B. Kaback, and the Qosina Corporation. A list of the students, their schools, mentors and research projects may be found in the Undergraduate Research Program section of this annual report.

Partners for the Future (PFF)

Through this program, designed to introduce high school students to the world of basic research, the Lab welcomed five teenagers again this year. The students work October through March with scientist mentors from the Lab, on original research projects. I am pleased to welcome Cablevision as the first corporate partner for the PFF program, and am

grateful for their forethought in establishing this partnership. This year their corporate sponsorship funded Sophia Virani of Herricks High School, who worked with Hong Ma on plant genetics. The other participants, their high schools, and Lab mentors are: Jana Steiger, Oyster Bay High School (with Peter Nestler); David Nussbaum, Half Hollow Hills High School West (Michael Regulski); Robert Wlodarczyk, Hauppauge High School (John Connolly); and Maddalena Pizzirusso, Sewanhaka High School (Erich Grotewold).

Project WISE

For the second consecutive year, Cold Spring Harbor Laboratory took part in Project WISE—Women in Science and Engineering. Orchestrated by SUNY Stony Brook and funded by a grant from the National Science Foundation, the project involves several Long Island institutions—SUNY, CSHL, Brookhaven National Laboratory, and the American Association of University Women—each helping to expose bright young women to the world of science. The program for female high school students requires the student's participation during each of her four high school years—9th through 12th grade. The Lab instructs the 10th graders in molecular biology and genetics, offering a foundation upon which they can build a future in technology and the sciences.

Mary Horton of our Grants Department ably managed our involvement in this ambitious program, which includes two trips to the DNA Learning Center, dinners with Lab scientists, and visits to CSHL labs. Mentors in 1996 were staff investigators Holly Cline and Michael Hengartner; post-doctoral fellows Karen Buchkovich, Alyson Kass-Eisler, Michele Cleary, and John Horton; and research technician Stephanie Smith.

Educational Outreach

The Laboratory's responsibility to local private and public schools continues to expand through Lab tours, nature walks, chats on the internet with and lectures by Lab scientists.

Eastwoods School pre-K children visited Xiaodong Cheng's X-ray crystallography lab, the third grade learned about Tim Tully's flies, and their eighth graders worked with combinatorial chemist Peter Nestler and postdoctoral researcher John Horton. In addition, each class took at least one historical tour and an annual hunt along our beaches. The Inter-school Exchange, a consortium of local private schools made up of Eastwoods, Portledge, Friends Academy, Holy Child, Greenvale and Buckley Country Day School, is a group who shares community resources. CSHL Association director Cathy Soref has been coordinating the Lab's contribution to this group as a scientific resource. As well, Friends Academy shared a special evening program with Lab staff Alyson Cass Eisler, Brandt Schnieder and Mona Spector which included e-mail follow up with those scientists.

For West Side School, within the Cold Spring Harbor School District, we conducted three Science Nights. At each event a CSH scientist addressed a group of elementary school children and their parents and teachers. On April 1, visiting scientist Sandy Williams presented *Heart Attack? Genes to the Rescue*. On May 20, Alcino Silva talked to a group

about learning and memory in mice, and Carol Greider ended the series on June 17, discussing *You and Your Chromosomes*.

For the second year, we cooperated with Cold Spring Harbor High School as they hosted a group of Japanese high school students and their teachers. The group spoke little English, but worked with a Japanese English teacher as translator. When the vocabulary for a scientific tour of Cold Spring Harbor Lab was beyond the translator's vocabulary, we were fortunate to have the help of research investigators Akila Mayeda and Shou Waga, and postdoctoral researcher Kyoko Hidaka, who discussed our history, science, and educational programs with the group.

Other tours included Westbury Friends School (Westbury), Sacred Heart Academy (Hempstead), Greenvale School (Glen Head), and assorted other schools and universities. For each of these tours we ask two or more scientists to take a break from their research and show the students and teachers around their laboratory. Our scientists are gracious hosts to these groups and their participation enriches the experience for our visitors.

Winterthur Visit

On June 19, our trustee Wendy Russell, a member of Winterthur Museum and Gardens, helped arrange for the Lab to be part of a special Winterthur visit to Long Island's North Shore. Their schedule included Old Westbury Gardens, the Planting Fields Arboretum, the model railroad and gardens of Mr. and Mrs. Henry Harris, Jr., as well as private gardens of local garden club members. Here at the Lab they visited our DNA Learning Center, heard from lab scientists, and took a tour by car of the grounds.



(Photo by M. Cyril Morris)

Advocates for Cancer Research

Our relationship with the very dynamic grass roots organization *1 in 9: The Long Island Breast Cancer Action Coalition* continues to flourish, as does Mike Wigler's research that they help support. Susan Cooper and Wendy Goldstein again attended the annual Michael Scott Barish Sand Soccer Tournament in Long Beach, where hundreds of children play soccer to support the work of *1 in 9*. More than a dozen Lab staff took

part in their walk-a-thon in Eisenhower Park on May 19, at which Nassau County Executive Tom Gulotta dedicated the Garden of Hope in memory of the founding members of *1 in 9* who lost their battle with breast cancer. At their second annual black-tie dinner dance at the Seawane Club in Hewlett Harbor, Jim Watson was honored in the good company of New York State Senator Joseph L. Bruno, Nassau County Executive Thomas S. Gulotta, and proactive union leader Joseph Scalamandre. During this elegant event, *1 in 9* president Geri Barish presented the Laboratory with a \$50,000 check toward the *1 in 9* grant in support of cancer research in the Wigler lab. We were honored to be there and continue to be deeply grateful for their support.

Capital Projects

Our buildings and grounds staff (the new Facilities department), housed for many years in the garage-style buildings facing the harbor on the Lab's lower roadway, has officially outgrown its space. To that end, we have completed renovation of the former Kurahara House and begun construction of two adjacent barns approved for construction by the Village of Laurel Hollow on June 17, 1996. This new complex, located at the north end of the campus west of Bungtown Road, will consolidate all facilities, functions and staff, including painters, landscapers, security, electricians, grounds keepers, plumbers and others. The Richards Complex is named for former director of buildings and grounds Jack Richards, who continues to serve part-time as director of construction.

Bungtown Road was once again paved in 1996. While it is, in fact, a public road, the Lab has for many years maintained, plowed and otherwise cared for our "main road." This is a benefit to the Lab and our neighbors alike.



Record Snow

The early months of 1996 were marked by the most profound snowfall in the history of the Laboratory. On the eighth day of January, the "Blizzard of '96" deposited more than 20 inches of snow into 50 mph winds, closing schools throughout the area and many local roads. While most Laboratory staff stayed home for a "snow day," dedicated members of our Facilities Department braved the elements and traveled to the Lab to clear walks and roads on Lab grounds, and mechanics arrived to assure support for labs where research continued through the storm. On April 10, yet another foot of snow blanketed the grounds during the twentieth snow storm of the season, making the winter of '95/'96 the snowiest on record. The Facilities staff worked tirelessly to keep the campus safe and clear, and for this we are most appreciative.

Long-Term Service

At a festive poolside celebration at Banbury Center, Bill Keen, our comptroller who has kept the Laboratory financially responsible year after year, celebrated 25 years with not a single adverse institutional audit report. Bill calmly manages the complex nature of our funding with skill and



*Top row: John Maroney, Bruce Stillman,
James D. Watson, Rodney Chisum, Peter Stahl
Middle row: Bill Keen, Pat Kurfess, Dorothy Brown
Front row: Roberta Salant, Elizabeth Ritcey, Phil Renna*

humor. John Maroney, assistant administrative director/manager of commercial relationship, also marked a quarter century of service. John began in 1971 as a laboratory technician for James Lab, where he learned the buying skills necessary for a 1975 promotion to the Lab's purchasing manager. In 1982 John assumed the position of assistant administrative director. In 1989 he earned his law degree, which he applies to his biotechnology licensing responsibilities.

Chief accountant Guy Cozza, groundsman Joseph Ellis, administrative assistant Roberta Salant, assistant director of facilities Peter Stahl, and media maker in Demerec Lab Margaret Wallace each celebrated 20 year milestones.

The Press' senior technical editor Dotty Brown; James lab aide Rodney Chisum; senior scientist David Helfman, who was overseas on sabbatical for most of the year; grants specialist Pat Kurfess; carpenter Joseph Pirnak; senior photo technician Phil Renna, and editorial coordinator Liz Ritcey each celebrated 15-year anniversaries with the Lab.

The evening ended with a presentation of gifts to honor each person's service.

Changes in Scientific Staff

Turnover in scientific staff is to be expected in a rigorous and dynamic scientific research institution such as Cold Spring Harbor Laboratory. This year, after more than two decades at Cold Spring Harbor, senior scientist Mike Mathews left us for the University of Medicine and Dentistry of New Jersey (UMDNJ) in Newark, where he accepted a position as Professor and Chairman of the Department of Biochemistry and Molecular Biology. Mike arrived here in 1974 as an early member of the "tumor virus group" and was studying diverse aspects of regulation of gene expression in recent years. I was most fortunate to work with him as a Postdoctoral Fellow when I first came to the Laboratory and I wish him well in his new position. Also, Venkatesan "Sundar" Sundaresan left after ten years of plant research with us. Sundar was instrumental in establishing the current plant genetics research program at the Lab. Together with Rob Martienssen he developed the use of Barbara McClintock's transposons from maize to study plant development and gene expres-



*Mike Mathews
(Photo by Susan Cooper)*

sion in *Arabidopsis*. Sundar has gone on to become Director of the Institute of Molecular Biology at National University of Singapore.

Kim Arndt, an Associate Investigator who studied cell cycle in yeast and had been with us since 1988, left for a position as Principal Scientist with Wyeth-Ayerst Research Laboratory in Pearl River, New York. Staff Associate Akiya Watakabe left David Helfman's lab to join the faculty of the National Institute for Basic Biology in Okazaki, Japan.

Ronald Pruzan, visiting scientist from Geron Corporation, wrapped up his stay in Carol Greider's lab. He has returned to Geron, the biotech company in Menlo, California that is working to develop Carol's work on telomerase into clinical applications.

Arrivals

We had ten new visiting scientists join our staff this year. One, Clifford Yen, did postdoctoral research here in Rich Roberts' lab in 1978-1982 and is now looking at genetic mutations in human cancers using RDA (representational difference analysis) in Michael Wigler's lab. Daniel Bush came for his sabbatical from USDA-ARJ and the University of Illinois to do plant research with Rob Martienssen; Ai-Ping Dong, from Northeast Normal University in China, is working with X-ray crystallographer Xiaodong Cheng; Satoshi Kida came from the University of Tokyo to study learning and memory in Alcino Silva's lab; Umberto Piarulli arrived from the Organicae Industriale in Milano, Italy, to work in combinatorial chemistry with Peter Nestler. Grigori Enikolopov has been hosting several visiting scientists—Vladimir Scheinker came from C.P.G., Inc. in Lincoln Park, New Jersey, to study the role of nitric oxide in differentiation, and Olga Zatsepina came to join her husband Boris Kuzin, who has been a visiting scientist in Grisha's lab intermittently since 1994. Venkatesan Sundaresan had two visiting scientists studying plant genetics with him in 1996—Wei-Cai Yang from Wageningen University in the Netherlands and De Ye from Institute of Molecular Agrobiology in Singapore.

As usual, we also had a great infusion of youthful intellect. Twenty-three labs took in one or more new postdoctoral researchers this year, for a total of 33. Fourteen new graduate students also joined labs at Cold Spring Harbor.

Promotions

Promotions this year included plant geneticist Ulrich "Ueli" Grossniklaus, who studies plant reproductive biology and development; cancer researchers Greg Hannon, who studies cell cycle, and Scott Lowe, who studies apoptosis and cancer therapy resistance; X-ray crystallographer Rui-Ming Xu; and genome computer scientist Michael Zhang. Each was promoted to Assistant Investigator.

Postdoctoral Departures

The following postdoctoral researchers moved on during 1996. Some went on to accept new positions elsewhere, others are continuing their postdoctoral research. Four departed from David Beach's lab; two to continue postdoctoral research—James Hudson at the Institute of Child

Health in London; and Koji Okamoto at Columbia University in New York—and two to research positions: Maureen Caligiuri as a scientist with Mitotix, Inc. in Cambridge, Massachusetts and Johannes Hofmann as a staff scientist at the Basel Institute of Immunology in Switzerland. Two of Mike Mathews' researchers—Tsafira Pe'ery and Yegnanarayana Ramanathan—accompanied him to UMDNJ while two others went on to continued postdoctoral research elsewhere: Huey-Jane Liao to SUNY Stony Brook Pathology Department and Mingsong Liu to University of California at San Francisco, Department of Medicine. Chantal Autexier and Karen Buchkovich left the Greider lab—Chantal to become a senior fellow at BioChem Pharma, Inc. in Chomedey, Canada and Karen to a Research Assistant Professorship at University of Illinois at Chicago; Michael Berg left the Stenlund lab to become a researcher at the Swedish University of Agricultural Sciences; and Hui-Zhi Cai left Ryuji Kobayashi's lab. Paul Kaufman and Rong Li departed from my lab—Paul to become a Staff Scientist for Lawrence Berkeley National Laboratory and Assistant Professor at the University of California—Berkeley and Rong to an Assistant Professorship at the University of Virginia, Department of Biochemistry in Charlottesville. Angus Wilson left the Winship Herr lab to assume an Assistant Professorship at NYU Medical Center in New York. Kim Arndt's lab saw two postdoc departures: Flavio Della Seta went on to become Maitre de Conference for the French University, Institute of Molecular Genetics in Montpellier, and May Luke is now a scientist with Berlex Biosciences in Richmond, California; Andrew Flint finished his postdoc in Nick Tonk's lab and has accepted a position as senior staff scientist at Charybdis Corporation in Bothell, Washington and with him went his wife, postdoc Catherine Flanagan of Hong Ma's. Mario Gimona and Constance Temm-Grove both left David Helfman's lab—Mario to become group leader at the Austrian Academy of Sciences, Institute of Molecular Biology and Connie to accept a position as research specialist at the University of Arizona Department of Animal Science in Tucson. Qing Gu left the Martienssen lab to continue postdoctoral research at University of Tennessee in Knoxville; Akemi Hanamura returned to Japan from the Krainer lab; Kyoko Hidaka finished her postdoctoral work in Bruce Futcher's lab and went on to become a staff scientist at the National Cardiovascular Center Research Institute in Suita, Japan; and Yan-Fen Hu went from Nick Tonks' lab to continue postdoctoral research at the University of Virginia in Charlottesville. Nouria Hernandez's lab said good-bye to two postdoctoral researchers—Renu Mital is continuing postdoctoral studies at the Austrian Academy of Sciences, Institute of Molecular Biology in Salzburg and Frank Pessler is now a medical student at the Ph.D./M.D. program at SUNY Stony Brook. Yukiko Mizukami of Hong Ma's lab is now a visiting postdoc at the University of California at Berkeley in the Department of Plant Biology; Juhan Sedman of Arne Stenlund's lab accepted a position as a research scientist at the Estonian Biocentre in Tartu, Estonia; Barbara Steiner left Bruce Futcher's lab to a continued postdoc at the Zentral Institut für Seelische Gesundheit in Ludwigshafen, Germany; Henry Tobin left the Tully lab and Marie-Luce Vignais left the Gilman lab for continued postdoctoral research at the Institute of Molecular Genetics in Montpellier, France. Wei Wen and Scott Woody also went on to additional postdoctoral research—Wei from the Wigler lab to NYU Medical

Center in New York and Scott from the Sundaresan lab to University of Wisconsin at Madison.

Graduate Students

Many of our graduate students finished their Ph.D.s and have gone on to do their postdoctoral research: from Kim Arndt's lab Andrea Doseff completed her Ph.D. and is now a postdoctoral researcher here in Yuri Lazebnik's lab and Charles DiComo went to do postdoctoral research at Columbia University in New York. Suzana Atanasiuk earned her degree from University of Zurich while working in Winship Herr's lab and has returned to Switzerland. Hai Rao and Kim Gavin earned degrees while doing graduate studies in the my lab—Hai went to a postdoctoral position at the California Institute of Technology in Cal Tech Division of Biology in Pasadena and Kim continues part-time postdoctoral research in my lab and is assistant editor of *Genes & Development*, Dezhi Liao went from the Malinow lab to become a Howard Hughes Medical Institute (HHMI) postdoctoral researcher at Johns Hopkins University in Baltimore and Deborah Taylor went from the Mathews' lab to University of Southern California School of Medicine in Los Angeles. Kathy O'Neill received her Ph.D. and went from Mike Wiglers' lab to a postdoctoral fellowship in Richard Hynes' lab at MIT, and Qing-Hong Yang earned her degree in Bruce Futcher's lab and has gone on to medical school at University of California at San Francisco. Vincenzo Cestari, a graduate student on rotation in the Silva lab, is now a Ph.D. student at University of Rome in Italy.

A Busy Time Ahead

The diversity of the programs at the Laboratory is quite remarkable and I believe the high quality of our research and education is self-evident. Yet, we do not rest on past accomplishments for very long. Only five short years after a considerable expansion of the research at the Laboratory into the exciting area of learning and memory, we find that we are in desperate need of more laboratory space for this program. To take full advantage of the great successes in understanding some of the molecular underpinnings of learning and memory, it has become obvious that we should incorporate new experimental approaches. One such approach is imaging neurons and their function in an intact brain. To visualize neuronal function in live animals would be an enormous benefit, but achieving this goal will require the construction of a new research building to house an imaging center and further technical developments. Having already recruited Dr. Karel Svoboda, a physicist-turned-neurobiologist, to join our faculty in the summer of 1997 and spearhead this new direction, plans are well under way for a handsome imaging building. This project will also enable us to increase the teaching space for the courses, particularly those courses that focus on imaging of the brain. The approval of a new zoning ordinance by the Village of Laurel Hollow early in 1996 will enable careful plans for this project and others to progress.

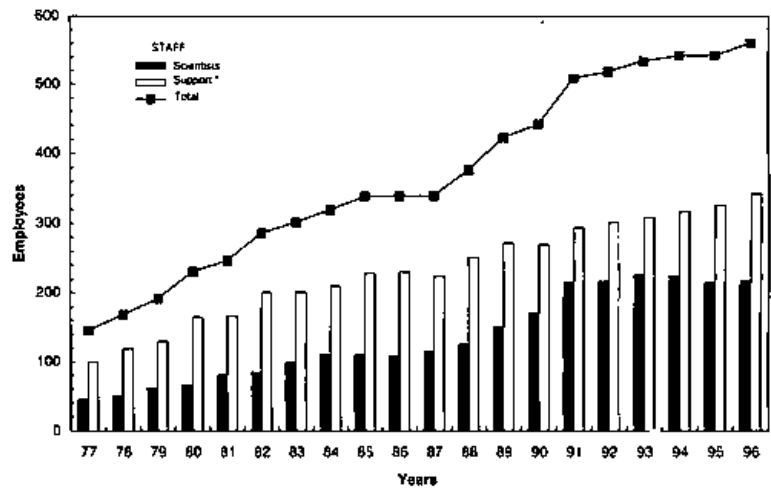
As I look to the immediate future, there will be opportunities to change the direction of the Laboratory in addition to the expansion of our neuro-

science program. A clear opportunity has emerged from the exciting new developments in human cancer genetics, making it necessary to strengthen our research on cancer cell biology and animal physiology. Furthermore, with the modern technologies that are available, it is certain that academic institutions that focus on basic research, such as the Laboratory, should play important roles in taking the basic research to the clinic. Gone are the days when our science rattled around in the scientific literature for some time before it was "picked up" by those more clinically inclined. By judicious choice of collaborations with clinical centers and the biotechnology industry, the gap between our fundamental discoveries and human health should be very narrow indeed.

As an institution, it is imperative that we prepare for such eventualities by continuing to recruit the best young people, provide them with the appropriate facilities, and identify partners with whom we can best synergize. Each of these endeavors is very time consuming on its own, but all are well worth the effort in the long run. In short, life in and around the Laboratory will not be leisurely in the immediate future.

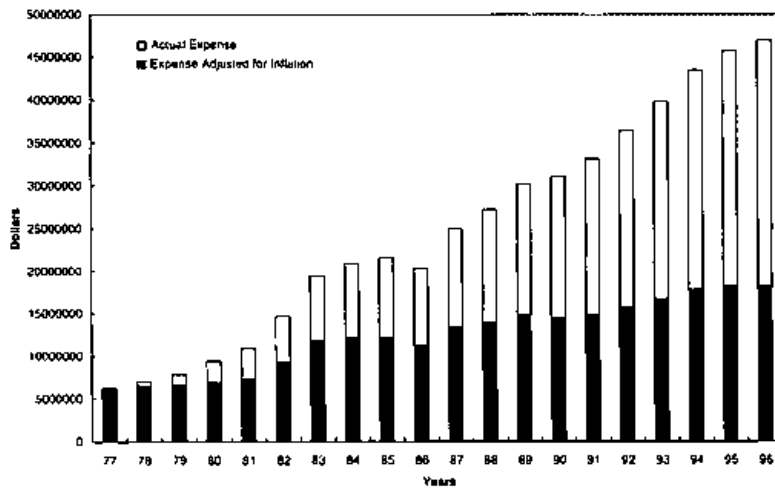
April 22, 1997

Bruce Stillman, Director



* Consists of Full time and Part-time Technical Support, Core Services, Publications, Meetings, Library, Public Affairs, Building and Grounds, Administrative Personnel, Banbury Center and DNA Learning Center

OPERATING EXPENSE



MEETINGS & COURSE PARTICIPANTS

