HIGHLIGHTS OF THE YEAR

The research and education programs at the Laboratory remain strong and vibrant. The recruitment of the first students in the Watson School of Biological Sciences and the completion of their intensive core courses highlighted progress this year. The DNA Learning Center introduced new, Web-based educational tools, and the meetings and courses programs at the main campus and the Banbury Center continued to provide a valuable service to the scientific community. Significantly, the Laboratory Press saw the continued development of its exciting textbook-publishing program as part of the Laboratory's goal to promote innovative teaching programs for graduate students and senior undergraduate students. These educational programs occur in the surrounding of a strong research environment, with research and education braided together in a common enterprise.

Research

Neuroscience

Roberto Malinow

Roberto Malinow and Karel Svoboda have continued to push the limits of brain imaging by observing the changes that occur in individual neurons as they respond to electrical stimuli. Combining their expertise in electrophysiology and high-resolution imaging of the brain, they study the cellular events that underlie "synaptic plasticity"—the ability of brain neurons to reorganize their connections in response to experience, such as during learning and consolidation of memories. In particular, Roberto and Karel are exploring the mechanisms involved in long-term potentiation (LTP), the strengthening of synaptic connections between nerve cells in response to trained stimuli. Their studies focus on a region of the brain involved in learning and memory called the hippocampus, a region required for a form of memory called declarative memory, or the conscious memory of learned events.

Karel Svoboda

This year, Roberto and Karel studied the distribution of AMPA receptors within dendrites, a nerve cell property they suspect contributes to LTP. AMPA and other receptors mediate the effects of glutamate, a key neurotransmitter that is one chemical which crosses the synapse or gap between neurons. They first engineered hippocampal neurons to express a fluorescent version of the AMPA receptor so they could track its movement within the processes called dendrites that branch from the neuronal cell. They used a high-resolution optical-maging system called two-photon laser-scanning microscopy, both before and after electrical stimulation.

Before stimulation, AMPA receptors were distributed evenly along the branch-like shafts of dendrites, but were largely restricted from the dendritic spines that project from shafts and are where the synapses lie. After stimulation, however, AMPA receptors moved rapidly into the spines. Synapses are typically located at the tips of spines, but without functional AMPA receptors, such synapses are inactive, or "silent." Therefore, the movement of AMPA receptors into dendritic spines may contribute to LTP, at least in part, by converting silent synapses to

active synapses. Moreover, evidence from Roberto's lab suggests that the constant replenishment of AMPA receptors at synapses may be involved in maintaining synapses in an active state over long periods of time. It is an intriguing possibility that this form of synaptic plasticity may underlie the development of the brain's neuronal network and function of neurons in an adult brain.

Roberto and Karel's studies provide some of the first real-time, high-resolution images of the events that are likely to power the restructuring of vast neural networks within an important site for learning and memory in the brain.

Yi Zhong

Yi Zhong and his colleagues are also studying the neurological basis of learning and memory, but in the fruit fly *Drosophila*. They have recently focused their efforts on explaining the puzzling observation that a human disease called neurofibromatosis causes both cancer and learning defects.

Neurofibromatosis is one of the most common inherited genetic disorders affecting humans. The disease is characterized by discoloration and tumors of the skin and is caused by mutations in the *NF1* gene. *NF1* encodes a protein that inhibits the activity of the Ras protooncogene product, another protein that is altered in many human tumors. Thus, when the *NF1* gene is mutated, the resulting uncontrolled activity of Ras can lead to cancer. But how mutations in *NF1* lead to cancer and learning defects was unknown.

From previous work, Yi knew that an enzyme called adenylyl cyclase was required for learning in *Drosophila*. He also knew that adenylyl cyclase activity was stimulated by the *Drosophila* NF1 protein (human and *Drosophila* NF1 are remarkably similar, so much so that human NF1 can substitute for its *Drosophila* counterpart in transgeneic flies). Yi and his colleagues first established that *Drosophila*—like humans and mice—requires NF1 for learning (in this case, learning to avoid a particular odor that was paired with a small electrical shock).

It was first necessary to determine whether the defects in adult flies lacking NF1 were an indirect result of developmental abnormalities due to the loss of NF1 activity as the brain develops. But experiments demonstrated that the learning defect in flies lacking NF1 could be corrected during adulthood by a burst of NF1 from an externally controlled gene. Then, in a series of elegant experiments, Yi showed that the effects of NF1 on learning are mediated by the enzyme protein kinase A, an enzyme that lies downstream from NF1 and adenylyl cyclase in the regulatory pathway controlling learning. Since protein kinase A is a well-characterized enzyme, the studies suggest that by activating it, the learning deficit could be reversed.

Yi's studies reveal the role of NF1 in a new mechanism that contributes to normal learning and memory in *Drosophila*. Because this pathway is conserved from fruit flies to humans, there is a distinct possibility that pharmacological intervention in the adenylyl cyclase pathway might reverse the NF1 defect in humans.

Virus-induced Pathogenicity: The Case of HIV

The genomes of human and simian immunodeficiency viruses, HIV and SIV, encode several auxiliary proteins that modulate the function of infected cells and optimize virus propagation in part by enabling infected cells to evade the host's antiviral immune response. Determining how these auxiliary proteins work is therefore important for understanding the pathogenesis of AIDS and how an effective vaccine might be formulated.

Jacek Skowronski and his colleagues are studying how one of these auxiliary proteins, Nef, promotes HIV infection. The Nef proteins of HIV and SIV are similar, and each fulfills multiple roles in the course of viral infection. The goal of the experiments in Jacek's laboratory is to determine how Nef interacts with protein sorting and signal transduction machinery in T cells and macrophages, two immune system cell types that are infected by HIV.

Jacek and his colleagues have found that Nef is required for the "down-regulation" or removal of particular host-cell proteins from the cell surface (CD4 and class I MHC proteins). Moreover, a collaboration with scientists at Erlangen University (Germany) and Harvard University has led to the identification of certain mutations in Nef that selectively disrupt its ability to down-regulate CD4, thereby greatly decreasing viral replication during the acute phase of viral infection.

One future challenge for the Skowronski group is to determine precisely how down-regulation of CD4 and class I MHC by Nef promotes viral propagation. One possibility is that by removing CD4 and MHC I from the cell surface, Nef enables HIV-infected cells to evade the body's immune response. Alternatively, Nef might be required to optimize host-cell survival so that the virus has a chance to reproduce before it kills the cell.

Cancer Research: Regulation of Cell Death

The genetically programmed death of cells is a normal part of growth and development. In addition, programmed cell death, or "apoptosis," safeguards organisms from cancer by triggering the self-destruction of precancerous cells. A hallmark of many types of cancer is a defect in apoptosis that allows precancerous cells to survive and proliferate, and eventually form a tumor.

Yuri Lazebnik and his colleagues are exploring the possibility that restoring the ability of cancer cells to self-destruct via apoptosis might be an effective therapeutic strategy. They study a family of enzymes called caspases that act in a proteolytic cascade to execute programmed cell death. Among several known caspases, caspases 2, 8, and 9 are thought to be "initiator" caspases. In response to cellular self-destruct signals, these caspases trigger a chain reaction in which a series of "effector" caspases are converted from an inactive to an active form. Once activated, effector caspases cleave key cellular proteins, and cell death follows due to destruction of DNA, disruption of nuclear structure, and disintegration of cells into small vesicles.

Previous work from Yuri's lab suggested that a caspase cascade leading to self-destruction remains functional in cancer cells, but it is uncoupled from the signal that triggers its activation. To study this critical link between a cell death signal and the caspase-mediated cell death machinery, Yuri and his colleagues purified a cellular factor that could trigger caspase-mediated apoptosis. They found that a known protein called APAF-1 (*ap*optosis *a*ctivation *f*actor-*1*) plus caspase-9 are key components in triggering apoptosis in tumor cells. Another lab had shown that APAF-1 stimulated the biochemical activity of caspase-9, but precisely how APAF-1 worked on caspase-9 remained a puzzle.

Effector caspases are synthesized as inactive precursors that are activated upon cleavage by other "upstream" caspases. For example, caspase-3 (an effector caspase) is cleaved and activated by caspase-9 (an initiator caspase), but how the initiator caspase is cleaved and activated was unclear. The observation that APAF-1 can bind directly to caspase-9 led some scientists to believe that APAF-1 brings two different caspase-9 molecules together, which then cleave and activate each other. To the contrary, Yuri and his colleagues have now

shown that APAF-1 is a regulatory subunit that is in a complex with caspase-9 and causes a 1000-fold increase in caspase-9 activity, probably by triggering the ability of individual caspase-9 molecules to cleave and activate themselves. Now that the process whereby the APAF-1/caspase-9 "holoenzyme" activates the cell death machinery has been investigated, it is possible to investigate ways to recouple this machinery to the self-destruct signals that are generated in cancer cells, but are normally ignored.

Controlling Cell Shape

During development and throughout adulthood, animal cells within multicellular organisms proliferate, migrate various distances, and take up residence as parts of tissues and organs. The regulation of this dynamic process involves the ability of cells to sense and respond to diffusible growth factors and the extracellular matrix (ECM) that surrounds them. Metastatic cancer cells become independent of growth factors for their survival and break free from their extracellular matrix moorings to invade areas of the body outside their normal domain.

David Helfman studies how growth factors and the interaction of cells with the ECM regulate oncogene-mediated signal transduction pathways. In particular, he investigates how growth factors regulate the contractility of the actin/myosin cytoskeleton of cells. All cells have such a system, but it is particularly effective in muscle cells since actin and myosin are responsible for muscle cell contractions. David is interested in how increased contractility stimulates cell-ECM interactions and promotes the growth and survival of cells in part by blocking programmed cell death.

David has discovered that overexpressing a cytoskeletal protein called caldesmon inhibits contractility and interferes with the formation of "focal adhesions," the structures that mediate cell-ECM interactions. His results (obtained in collaboration with Alex Bershadsky of the Weizmann Institute, Rehovot, Israel) identify a new pathway for the regulation of cytoskeletal function, and they suggest that caldesmon can counteract some of the stimulatory effects of the Ras oncogene product on cell growth. Moreover, they provide new information about how the movement of nonmuscle cells is controlled. David's finding that caldesmon affects focal adhesion formation is also important for understanding adhesion-dependent signaling, a process in which the cell's attachment to a substrate triggers changes in cell physiology that promote cell growth and survival.

Epigenetic Inheritance of Gene Expression

Not all clones are created equal. As genetically identical cells (such as those in an embryo) multiply, different sets of genes are switched on and others off, giving rise to cells and tissues with distinctive properties (e.g., liver versus muscle).

Such differential gene expression is often established by alterations in the large-scale architecture, or chromatin structure, of DNA. For example, transcriptionally silent regions of DNA are packaged into forms of chromatin that may be less accessible to certain transcription factors. In contrast, transcriptionally active regions of DNA adopt alternate chromatin structures that may be more accessible to certain transcription factors. A particular DNA sequence can be silent or active, depending on its position within the genome or the type of cell in which it resides. Such states of chromatin are said to be epigenetic because they can

be inherited in a stable manner. Examples occur in inactivation of one of the X chromosomes in female mammals, in certain human cancers, and in parental imprinting of genes.

Shiv Grewal and his colleagues use a powerful model system in the fission yeast *Schizosaccharomyces pombe* to study how the active and silenced states of gene expression are established. Working at the National Cancer Institute, Shiv and former CSHL scientist Amar Klar showed that in a particular region of the fission yeast genome, active and silent states of gene expression can be stably inherited through mitosis (cell division) and, remarkably, through meiosis (the division leading to spores or gametes for the next generation). These findings were striking because scientists had generally believed that different states of chromatin structure were erased during meiosis to enable unbiased gene expression after the fusion of gametes.

In essence, Shiv found that the Mendelian inheritance of traits sometimes depends not only on the faithful replication of DNA sequences, but also on the transmission of higher orders of chromatin structure. The "gene" in these instances is thus not only DNA, but DNA plus associated proteins. Shiv has proposed a chromatin replication model in which both the DNA molecule and higher-order chromatin structure are duplicated.

Since joining the faculty of CSHL in 1998, Shiv has tested several predictions of the chromatin replication model. He has found that among several potential candidates, a particular protein, Swi6, is critical for establishing a silenced state of chromatin structure and that Swi6 is required to maintain silencing through multiple mitotic cell divisions or meiosis.

Histone proteins are major determinants of chromatin structure, and the chemical modification of histones (e.g., acetylation) is known to affect chromatin structure. Shiv has observed that an enzyme that de-acetylates histones, Clr3, is required—in addition to Swi6—for the silenced state of chromatin structure to be maintained. He also showed that Swi6 binding is enriched in a silenced region of DNA and that the histones bound to silenced DNA are less acetylated than are histones bound to the identical region of DNA when it is active.

Because proteins homologous to Swi6 and Clr3 exist in organisms as diverse as fungi, *Drosophila*, and humans, mechanisms for the inheritance of chromatin structure akin to that studied by Shiv are likely to be widespread in nature. In fact, there are proteins in mammalian cells that function like Swi6, and in my own laboratory, we have found that these mammalian cell proteins are bound to a chromatin assembly factor (CAF-1) that is itself tethered to one of the proteins responsible for replicating DNA, called PCNA. Thus, there exists a direct biochemical link between the inheritance of DNA and the inheritance of chromatin. Interestingly, mutations in CAF-1 in the budding yeast *Saccharomyces cerevisiae* cause defects in epigenetic inheritance.

Regulation of Transcription in Cancers

The control of transcription itself is likely a major contributor to progression in human cancers and indeed, many oncogene products are errant transcription factors. Bill Tansey and his colleagues study cell proliferation and how defects in the regulation of transcription can lead to cancer.

The c-*myc* gene encodes a transcription factor that plays a critical role in promoting normal cellular proliferation. Because the Myc transcription factor is a potent cell proliferation stimulator, the level of Myc within cells is normally tightly controlled. An unfortunate consequence of the power of Myc to stimulate cell proliferation is that unregulated Myc activity can lead to cancer.

The amount of Myc protein in cells is determined not only by how much Myc is synthesized in a given time frame, but also by how quickly it is destroyed. Bill is studying how the destruction of the Myc protein is regulated and how defects in this process lead to abnormally high levels of Myc, and potentially to cancer.

First, Bill showed that Myc is normally destroyed by the proteasome, a large complex of enzymes that cuts proteins targeted for destruction into small pieces. This process—called ubiquitin-mediated proteolysis—enables the abundance of many different kinds of proteins, including Myc, to be adjusted in response to particular cellular conditions.

Next, Bill mapped the regions of the Myc protein necessary to target it for destruction by the proteasome. He found that a region encompassing the amino-terminal third of the Myc protein was sufficient to promote the destruction of Myc. Significantly, mutations in this region of Myc are associated with Burkitt's lymphoma, plasmacytomas, and other kinds of cancer. Bill and his colleagues tested five such cancer-associated mutations of Myc and found that four of them blocked Myc degradation. These observations raise the possibility that the mutations contribute to cancer by blocking Myc degradation, thereby increasing the levels of Myc in cells and causing them to promote cell division.

Finally, Bill found that the region required for Myc degradation overlaps with the domain of Myc that mediates its function in activating transcription of certain genes. Thus, he uncovered an intriguing underlying connection between two processes—proteolysis and transcriptional activation—that had not previously been characterized. This connection between proteolysis and transcriptional activation appears to be common in short-lived regulators of gene expression.

Cell Biology in the Nucleus

David Spector and his colleagues are studying the dynamic movements of molecular assemblages that mediate two essential, intimately connected processes in the cell nucleus: transcription and pre-messenger RNA (pre-mRNA) splicing.

Transcription is the process whereby the enzyme RNA polymerase synthesizes RNA molecules from DNA templates. During transcription, RNA polymerase proceeds from one end of a gene to the other, synthesizing a continuously elongating pre-mRNA molecule as it moves along the DNA.

Pre-mRNA molecules contain sequences that encode protein, called exons, as well as noncoding pieces of RNA called introns that are removed by the splicing machinery of the nucleus. Interestingly, splicing often begins before the synthesis of pre-mRNA molecules is completed, i.e., as pre-mRNA molecules emerge from the transcription apparatus. This year, David and his colleagues have discovered important new information about the components of the splicing machinery and how its mode of action is linked to gene transcription.

They showed that truncating the carboxy-terminal domain (CTD) of RNA polymerase prevents the targeting of the splicing machinery to transcription sites and eliminates pre-mRNA splicing. These results indicate that the splicing machinery is recruited to transcription sites by binding to the CTD of RNA polymerase. In essence, the splicing machinery gains easy access to pre-mRNA transcripts by piggybacking on the enzyme that makes the transcripts.

Abundant evidence indicates that splicing factors are assembled and/or stored in large multiprotein complexes called interchromatin granule clusters (IGCs). But in the 40 years since IGCs were described, only a single attempt to purify and characterize them in detail

has been published. David and his colleagues have now succeeded in purifying IGCs, and they have used mass spectroscopy protein sequencing, in collaboration with former CSHL staff member Scott Paterson at Amgen Corporation, to identify over 100 different protein components of these complexes. In addition to several known splicing factors—whose presence in IGCs was known or expected—many were known transcription factors whose presence in IGCs was surprising. In addition, 12 new proteins of unknown function were identified as IGC components and are the subject of ongoing study in David's lab.

Structural Biology

The phenomenon of splicing of pre-mRNA was discovered at CSHL, and Adrian Krainer's laboratory continues to investigate the biochemistry of this process and how different genes are spliced into alternative mRNAs by excising different introns. In collaboration with structural biologist Rui-Ming Xu, Adrian and his colleagues use X-ray crystallography to study—at the atomic level—the precise structural basis of the protein-RNA interactions that mediate pre-mRNA splicing.

Human hnRNP A1 is an abundant, versatile protein that both binds to the single-stranded regions of DNA present at the ends of chromosomes (called telomeres) and, as Adrian's lab discovered, regulates the use of alternative 5 splice sites, probably by binding to pre-mRNA (although how and where is uncertain).

Rui-Ming and his colleagues, in collaboration with Adrian's lab, have solved the crystal structure of UP1 (a part of human hnRNP A1) which is complexed with telomeric DNA. The structure reveals an interesting "railroad tie" mode of DNA binding in which two antiparallel single-stranded DNA molecules (the rails) bind to the surface of two antiparallel, oblong molecules of UP1 (the ties) oriented at right angles to the DNA. The structure provides a simple and elegant model for how hnRNP A1 binds to telomeres. Moreover, it suggests how hnRNP A1 might bring two strands of RNA into close proximity during the process of pre-mRNA splicing.

Rui-Ming's work with Adrian demonstrates the synergy that can result when structural and molecular biologists collaborate to address a given problem. Two other CSHL scientists, Xiaodong Cheng (now at Emory University) and Winship Herr, benefited in a similar way from their collaborative effort this year to determine the crystal structure of the herpes simplex virus (HSV) transcriptional regulatory protein VP16.

Viruses commandeer the transcriptional machinery of host cells, which they use for the expression of their own genes. During HSV infection, viral gene expression occurs in three classically defined phases: immediate early, delayed early, and late. This cascade of viral gene expression is triggered by VP16, a potent activator of immediate-early gene transcription that is released into cells upon infection. Following its release into cells, VP16 binds to a host cell protein called HCF (*h*ost *c*ell *f*actor). Then the VP16/HCF complex binds—in combination with a second host cell protein called Oct-1—to the DNA target present in the promoters of HSV immediate-early genes. The transcription of these genes is thus activated, and a productive viral infection ensues. VP16 also happens to be one of the most commonly utilized transcription factors for activating genes that have been introduced by experimenters into cells.

To investigate further the role of VP16 in mediating viral gene expression, Xiaodong, Winship, and their colleagues determined the structure of the conserved core of the VP16

molecule using X-ray crystallography. They discovered that VP16 is shaped rather like a chair. The scientists were able to define what parts of VP16 are involved in a particular function by determining where mutations that specifically disrupt one VP16 function but not another map on the surface of the protein. For example, Xiaodong and Winship found that three mutations known to block the assembly of virus particles all cluster on one side of VP16. In contrast, a mutation known to block the interaction of VP16 with Oct-1 maps on the other side of the protein.

Xiaodong and Winship also identified a region of VP16 likely to bind to DNA by examining the charge distribution on the surface of VP16. DNA is negatively charged. Because like charges repel, protein surfaces that bind DNA are usually positively charged. The seat of the VP16 chair-like structure has such a positively charged surface. This region is further implicated in DNA binding by evidence from Winship's lab that mutations in the seat bottom disrupt VP16's DNA-binding activity. In short, DNA sits on the VP16 seat.

Studies of VP16, Oct-1, and HCF by Winship and his colleagues have revealed a great deal of information about how transcription is regulated. The added dimension of structural information provides an even clearer view of how the molecules that mediate this complex and dynamic process interact with each other and with DNA.

X-ray crystallographic data sets for the structures of both hnRNP A1 and VP16 were collected at Brookhaven National Laboratory, where we now maintain a dedicated high-energy beam-line. Our proximity to Brookhaven allows our structural biologists to have immediate access to this natural resource.

Bioinformatics

Lincoln Stein and his colleagues develop computer software programs that enable biologists to organize, work with, and make sense of the vast amounts of information that are becoming available from human and other genome sequencing projects.

Bioinformatics (the application of computer science to the analysis of biological information) is a relatively young field. Ten years ago, the comparison of a newly discovered DNA sequence with known sequences usually required several hours on a personal computer and considerable input by the investigator. Today, the same exercise—which provides clues about the potential function of an uncharacterized sequence of DNA—takes a few seconds and is conducted by scientists all over the world via the Internet. The impact of bioinformatics on the future of basic science, medicine, and agriculture is difficult to overestimate.

Lincoln Stein

One of Lincoln's first projects was a user-friendly database that allows biologists to analyze the nematode worm *Caenorhabditis elegans* genome in several ways, such as to determine what genes are expressed in a particular cell type or what human genes are homologous to a particular *C. elegans* gene. This database currently receives 25,000 "hits" per week and was recognized by a computer chamber of commerce, LISTNET, as the "Best Software of 1999 Developed by a Large Company" on Long Island (and there are some very large computer companies on Long Island).

Lincoln and his colleagues have recently joined a multi-institutional consortium whose goal is to map *s*ingle *n*ucleotide *p*olymorphisms, or SNPs, that are distributed throughout the human genome. SNPs are variations (polymorphisms) among different individuals that occur in sequences of DNA. Although the majority of SNPs

have no physiological consequences, a particular SNP might be located near a mutation that *is* of great physiological consequence (e.g., disease-causing mutation). SNPs are therefore extremely useful as markers for genetic disease, for the development of reagents to diagnose genetic disease, and for the cloning of disease-related genes. In addition, SNPs are invaluable to scientists interested in tracing the flow of genetic information through human populations on global and regional scales.

Lincoln and his colleagues have developed software and hardware systems for storing, analyzing, and disseminating the large amounts of information currently being generated by the SNP consortium. A 1.5-ton uninterruptible power supply, a closet-sized 1-terabyte storage array, and a high-performance cluster of 40 individual computers linked together in a "parallel processing" configuration are now all part of the daily operation in Lincoln's lab.

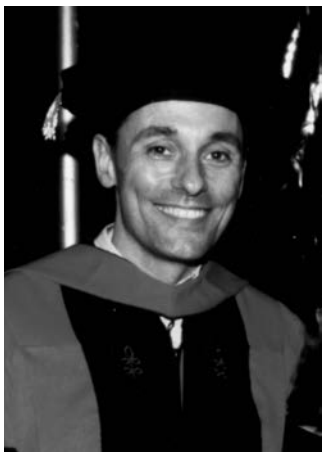
Symposium LXIV

On June 2–9, our activities centered around the 64th annual CSHL Symposium, entitled Signaling and Gene Expression in the Immune System. On Sunday, June 6, meeting attendee Irving Weissman, of Stanford University School of Medicine, delivered the annual Dorcas Cummings Lecture to a scientific and public audience. His talk "Repairing the Body: The Promise of Blood and Tissue Stem Cells" addressed a topic that is much in the news because of its great potential in repairing human disease tissues. Judging by the enthusiastic reaction of the audience, the lecture was very well received and timely.

Irving Weissman

Watson School of Biological Sciences

The Laboratory's graduate school—the Watson School of Biological Sciences—became a reality this year. Recruitment of the inaugural class was an outstanding success. The six new students arrived late in the summer, beginning classes on September 7. The two core courses—Scientific Reasoning and Logic and Scientific Exposition and Ethics—were supplemented by specialized minicourses and provided an overview of the current state of biology in many fields. The lecturing presented a new challenge to most CSHL scientific faculty and quite happily, everyone involved rose beautifully to the occasion. The huge success of the program is in large measure due to the tireless efforts of Winship Herr and Lilian Gann, both of whom have transformed graduate education at CSHL and we hope beyond.



Winship Herr

In our first official celebration of the Watson School, the Laboratory held a convocation on November 5 at which we bestowed the honorary degree of Doctor of Science *honoris causa* on three esteemed scientists: David Baltimore, president of the California Institute of Technology; Gerald Fink, director of the Whitehead Institute for Biomedical Research and American Cancer Society Professor of Genetics at the Massachusetts Institute of Technology; and Seymour Benzer, the James Griffin Boswell Professor of Neuroscience at the California Institute of Technology. Each of them played a significant part in the education programs at the Laboratory, from under-

graduate research to postgraduate courses. Their citations and acceptance speeches after receiving the degree are printed in the Watson School of Biological Sciences section of this Annual Report.

In November, Jim Watson delivered a series of lectures to commemorate the opening of the graduate school. The lectures were held in Grace Auditorium in anticipation of the sizable audience that might be attracted to hear Jim talk, and we were not disappointed. On each of four evenings, Jim spoke to a full house. The lectures were entitled "Discovering the Double Helix" (Nov. 2); "George Gamow and His Combinatorial Approach to the Genetic Code" (Nov. 9); "Finding the Genes of DNA Tumor Viruses Which Unlock Cellular DNA Synthesis" (Nov. 16); and "Recombinant DNA and the Beginnings of the Human Genome Project" (Nov. 22). These lectures have been captured on videotape and will be available to future students.

Watson School Gala

The Laboratory hosted a gala fund-raiser in Grace Auditorium on October 5th to raise money for the Watson School of Biological Sciences. We were extremely fortunate to have Lola Grace as the gala chairman. Thanks to the efforts of Laboratory Trustee Mark Ptashne, we attracted three of the world's greatest classical musicians—pianist Emanuel Ax, violinist Midori, and cellist Yo-Yo Ma—to perform a joint program of Mendelssohn. Before the exceptional ensemble performance, the audience was treated to a tasting dinner featuring cuisine prepared by chefs from three of New York City's top gourmet restaurants—Charlie Palmer of Aureole (who was present to serve his culinary creations), Daniel Boulud of Daniel, and

(*Top left*) Lola Grace, with daughter Lola and Yo-Yo Ma; (*bottom left*) Chefs of LeBernadin; (*right*) Midori, Emanual Ax, Yo-Yo Ma.

Eric Ripert of Le Bernardin. Exquisite wines, contributed by Iron Horse Vineyard, stunning displays of flowers by J. Barry Ferguson Flowers Ltd., and gifts from Tiffany, Estée Lauder, and Sony Classical helped make the evening a spectacular success for the 350 attendees. The evening was phenomenal, raising more than $750,000 for the Watson School. We must thank Lola once again for organizing such a unique event in our lives.

URP 40th Anniversary Reunion

In August, the Laboratory held a two-day reunion for alumni of the Undergraduate Research Program (URP) in celebration of the program's 40th anniversary. More than 70 people returned to reminisce about living and working at the Laboratory. The event included talks by 14 former URPs and a keynote talk by former URP and Nobel prize winner David Baltimore. Their stories gave current scientists a glimpse of days gone by along Bungtown Road, including parties at the beach, trips to New York City, and, of course, a memorable science experience.

First URP Director Arthur Chovnick and former URP Gerry Rubin

Banbury Center

The first Banbury Center Executives' Conference was held 13 years ago in 1986 and the topic of the meeting was genomics. Although that word had not been invented at the time, the idea of sequencing the human genome had been discussed at the Cold Spring Harbor Symposium earlier the same year, and speakers at that first Executive Conference went on to become leaders of various genome projects. 1999 seemed the right time to review the state of genomics; it was a milestone year in the history of genome research due to the completion of the first sequence of a human chromosome. Among the speakers at the 1999 meeting were Lee Hood of the University of Washington in Seattle and David Botstein of Stanford University, both of whom spoke at the 1986 Banbury meeting. We heard about advances in sequencing, potential applications of data, and the controversies over patenting and commercialization of DNA sequences. Once again, we are indebted to Sandy Warner, chairman of J.P. Morgan and Co., and David Demming for their enthusiastic support of this unique meeting.

Banbury Center has a long history of meetings on human genetic disorders, beginning with a 1982 meeting about the application of recombinant DNA techniques to these disorders. These meetings are of immense immediate value for the discussion of data and ideas, and they also ultimately promote further research. In 1999, we hosted a meeting on ataxia telangectasia (AT), a progressive degenerative disorder involving DNA repair, characterized by degeneration of the brain, lack of muscle control, and immunodeficiency. The meeting was funded by the AT Children's Project. The Children's Project has been a driving force in promoting research on AT, and research sponsored by the Project has led to remarkable advances in our understanding of the basic mechanisms of AT, especially through the identification of the ATM (mutated AT gene) protein. The Banbury AT meeting was designed to encourage critical analysis of the current body of knowledge concerning the protein's structure and function, with particular focus placed on its role in nerve cells. In addition, participants discussed possible applications of current data to the design of new therapies using genes or stem cells.

Banbury's J.P. Morgan Conference

In addition to hosting straightforward scientific meetings, Banbury Center also has a long history of hosting meetings that deal with controversial topics in biology that have important societal implications. In earlier years, these topics dealt largely with environmental carcinogenesis and risk assessment. More recently, we have examined and reviewed possible difficulties arising from new developments in human genetics. In 1999, we focused on xenotransplantation, the transplantation of tissues or organs between species (e.g., from animals to humans). Xenotransplantation raised many of the same issues raised by recombinant DNA technology in the mid 1970s. How, for example, will we deal with what are—for the present at least—unquantifiable risks? In the case of xenotransplantation, one such risk is the transmission of unknown viruses from pig tissues to human transplant recipients. The ambience of a Banbury Center meeting, with 30–40 participants from diverse backgrounds gathered in an intimate setting, is particularly conducive to discussion of such controversial topics.

DNA Learning Center

Student visits to the DNA Learning Center (DNALC) plateaued at 30,000, as all available lab space was used at full capacity. Meanwhile, over 380,000 people visited the DNALC Internet sites, a threefold increase from 1998. The majority visited the animated genetics primer, *DNA from the Beginning*, which went online in January 1999 and was funded by the Josiah Macy, Jr. Foundation. It has proved immensely popular with teachers, students, and casual Web surfers.

Several other Internet projects neared completion during 1999. The *Image Archive of the American Eugenics Movement* is a searchable database of over 1200 photos and docu-

Creators of the *Image Archive of the American Eugenics Movement*. (*Back row, left to right)* Chun-hua Yang, Susan Conova, Shirley Chan, Matthew Christensen; (*front row, left to right)* David Micklos, Susan Lauter, Jan Witkowski.

ments from this dark period in the history of science. It is fitting that Cold Spring Harbor Laboratory be the source of such information, as, indeed, the Eugenics Record Office (ERO) was founded in 1910 by Charles B. Davenport, then director of the Biological Laboratory (which later became CSHL). He set up the headquarters for American eugenics research on land adjacent to the Carnegie Institute's Station for Experimental Evolution (of which he was also director). The ERO was closed in 1940 when the Carnegie Institute withdrew its support.

The new eugenics Web site features a unique interface that displays controversial documents about sterilization, racial stereotyping, and immigration restriction, along with contextual explanations that help users understand how and why the science went so wrong. In a different vein, *Bioservers* offer simple bioinformatics tools that allow students to "mine" information from DNA—including using their own DNA to reconstruct human evolution.

A mobile bioinformatics teaching lab, *VectorNet*, is being constructed under a new $500,000 grant from the Howard Hughes Medical Institute. Ten lap-top computers will connect to a local server running the entire DNALC Web site, bioinformatics software, and gene databases—providing an Internet experience without an Internet connection! During the academic year, *VectorNet* will be deployed in selected New York City schools; during the summer, it will be used to conduct teacher-training workshops at sites around the United States.

CSHL Press

Financially, the year was satisfactory, with a 6% increase in revenues and an operating surplus gained through publication of new books, improved journal advertising revenue, and aggressive marketing efforts. More importantly, the Press continued to serve the scientific community by providing high-quality publications.

The Press published eight new books and a videotape, including the monograph *Prion Biology and Diseases*; the manual *Imaging Neurons*; and the advanced-level textbooks *Essentials of Glycobiology* and *Transcriptional Regulation in Eukaryotes*. Also notable was a collection of the outstanding research papers published at the Laboratory from 1903 to 1968, *Illuminating Life*, which should become a valuable teaching tool. Over 240 titles are in

print, with a strong backlist led by *Using Antibodies* and *At the Bench*. A new, targeted sales program boosted orders through major resellers.

The journal program continued to flourish. *Genes & Development* (*G&D*), *Genome Research* (*GR*), and *Learning & Memory* (*L&M*) increased or maintained subscription levels. Advertising revenues were 30% higher. All three journals were offered more manuscripts than ever before. The impact factors of *G&D* and *GR*, as measured by citation analysis, rose substantially, and *G&D* maintained its rank among the top ten primary research journals. Online editions of all three journals were enhanced by new software tools, and *GR* developed the capacity to publish papers online well ahead of print.

The Protein Society selected CSHL Press from a list of ten candidates as the next publisher of its journal *Protein Science*. The contract is for the period 2001–2005.

A new program to develop and publish textbooks for undergraduates was initiated early in the year. Five promising projects were identified, including a book on evolution, and approaches to potential authors were made. Outlines of prospective books are being developed.

In 1997, the Laboratory purchased the lovely residence of Anne and Wally Meier (daughter and son-in-law of Charles Robertson) adjacent to the Conference Center on our Banbury estate. The house has now been altered to serve as a writing center for authors of the new textbooks. Alex Gann joined our staff as senior editor of textbooks, and his office is located in Meier House as well. Alex earned a Ph.D. in molecular biology after working on restriction enzymes in Noreen Murray's lab at Edinburgh University in Scotland. He did postdoctoral research at Harvard, studying mechanisms of gene regulation with Mark Ptashne, and at University College London, working on newt limb regeneration with Jeremy Brockes. Most recently, he was a lecturer in developmental biology at Lancaster University in England.

Gavin Borden Visiting Fellow

Joseph L. Goldstein, M.D., of University of Texas Southwestern Medical Center and a Nobel laureate for his research on cholesterol metabolism that led to cholesterol-lowering drugs, was the Gavin Borden Visiting Fellow this year. Dr. Goldstein's lecture, held on March 11, was entitled "A Proteolytic Pathway That Controls Cholesterol Content of Membranes, Cells, and Blood."

Joseph L. Goldstein

Titia de Lange, Roel Nusse, Harold Varmus, Steve Hughes, Suzanne Ortiz

Varmus Birthday Celebration

On December 12, 74 scientists gathered at Cold Spring Harbor Laboratory to celebrate the 60th birthday of Harold E. Varmus, M.D., director of the National Institutes of Health. Harold has since become President of Memorial Sloan-Kettering Cancer Center in New York City. He has been coming to meetings at CSHL for over a quarter century and is well known for his research accomplishments—including the discovery of cellular oncogenes with Mike Bishop that garnered them a Noble prize—as well as for his extraordinary leadership. As director of the NIH, Harold stressed the importance of biomedical research for the improvement of the human condition, and oversaw a dramatic increase in public support of biomedical science.

Harold Varmus's birthday celebration at the Laboratory, which took the form of a two-day symposium on cancer cell biology, was organized by Steve Hughes of the National Cancer Institute (NCI); Titia de Lange of Rockefeller University; Roel Nusse, HHMI investigator at Stanford University Medical Center; all former Varmus laboratory members; and Suzanne Oritz of Varmus' lab. at the NCI. Prominent speakers included long-time collaborator Mike Bishop, fellow retrovirologists David Baltimore and Peter Vogt, and former high school mate Gerry Fink.

Undergraduate Research Program (URPs)

The 1999 summer Undergraduate Research Program consisted of 26 students—12 women, 14 men—from 12 countries. They were chosen from among 520 applicants from around the world. The objective of the program is to provide a greater understanding of the principles of biology. It instills in the students an awareness of major topics of investigation, helps develop intellectual tools necessary for modern research, exposes students to the process of research, and allows them to meet top scientists who visit CSHL.

The program received financial support in 1999 from the C. Bliss Memorial Fund, Burroughs Wellcome Fund, Jephson Educational Trust, Dorcas Cummings Memorial

Lecture, Grace Professorship, and the URP Endowment (composed of the Burroughs Welcome Fund, Emmanuel Ax Fund, Garfield Fund, Libby Fund, Olney Fellowship, Shakespeare Fellowship, Von Stade Fellowship, Glass Fund, and the Read Fund).

Partners for the Future

The Partners for the Future program was established in 1990 to give outstanding high school seniors the opportunity to work on original research projects in a laboratory under the supervision of a scientist-mentor. The students spend a minimum of ten hours per week at the Laboratory, beginning in October, and at the conclusion of the program in March, present a scientific summary to an audience of scientists, teachers, and parents. In the process, the students gain valuable research experience and are paid a stipend for their efforts. This program is supported by the DNA Learning Center Corporate Advisory Board from proceeds of their annual fund and golf tournament.

The participants for the 1999/2000 school year were David Rubenstein, Bethpage High School (mentor: Yuri Lazebnik); Michelle Kollmeier, Half Hollow Hills High School West (mentor: Marja Timmermans); Jeffrey Winer, Plainview–Old Bethpage J.F.K. High School (mentor: Masaaki Hamaguchi); Justin Singer, Jericho High School (mentor: Eric Drier); Laura Roche, Cold Spring Harbor High School (mentor: Michael Hengartner); and Michel John Maloof, Garden City High School (mentor: Frances Hannan).

Board of Trustees

C. Thomas Caskey concluded his term on the Board of Trustees in 1999. Since 1996, Tom brought extensive research experience to the Board of Trustees, particularly in the area of human genetics. Tom first visited the Laboratory in the late 1960s to attend a Phage Course. We shall miss his always active participation at Board meetings.

Three new members were elected to the Board in 1999: Robert Lindsay is a managing general partner with Bessemer Partners where he is involved with overseeing the private equity investment activities of Bessemer Securities Corporation. Robert grew up here in Laurel Hollow and his family has had a long-running relationship with the Laboratory—his father, Robert V. Lindsey, served as a Trustee on the Laboratory's Board and treasurer and vice president of LIBA (now CSHLA), and his aunt, Mary D. Lindsay, served as vice chairman on the Laboratory's Board. Ed Scolnick is president of Merck Research Laboratories, and executive vice president of science and technology for Merck and Co., Inc. Before that, he was at the National Cancer Institute where he discovered the viral *RAS* oncogene. Arthur Spiro is president of AMSTEX Enterprises, Inc., a company that deals in corporate and business marketing, planning, acquisitions, mergers, textile patents, investments, licenses and leases. He is also adjunct professor of entrepreneurial studies at the College of Business and Public Affairs at Clemson University in South Carolina.

David L. Luke III

On April 23, former Chairman of the Board of Trustees David L. Luke III was honored at a dinner at the Piping Rock Club in Locust Valley. The dinner was held in appreciation of his contributions to the Laboratory during his 12-year tenure on the Board, and for his role in the establishment of the

Watson School. The keynote speaker was Vartan Gregorian, president of the Carnegie Corporation of New York and former president of Brown University. Ed Harlow of Massachusetts General Hospital Cancer Center and Harvard Medical School offered thoughtful remarks as well. A special treat during the evening was a performance by Kitty Carlyle Hart, whose voice and vocal style from a time past were flawless.

Mr. Luke is now an honorary trustee of the Laboratory and chairs the ongoing $32 million capital campaign to endow the Watson School.

Kitty Carlyle Hart

CSHL Association

The CSHL Association (CSHLA) held its annual meeting on February 2. The membership thanked its retiring directors—W. Dillaway Ayres, David C. Clark, Carol E. Large, Phillip M. Satow, Jordan Saunders, and Lisa Schiff—and elected James Spingarn as president of the CSHLA, and Mary Alice Kolodner, Eileen Pulling, and Larry Remmel as new directors.

The meeting featured a lecture by scientist and author Edward O. Wilson of Harvard University. His lecture was entitled "Consilience: Science Meets the Arts." After the meeting, members of Next Generation Initiative (NGI) were invited to the DNA Learning Center for a special presentation on DNA science by DNALC Director Dave Micklos and then-Assistant Director John Kruper. On March 7, the CSHLA sponsored a lecture by John, introducing the DNA Learning Center's new Web site, *DNA from the Beginning*, the Internet's first authoritative genetics primer.

Fanny Elder, Ann Seifert, E.O. Wilson

On April 17, the Association held a Jazz Benefit. The performance featured Stanley Turrentine and Kenny Blake on saxophone, Harold Betters on trombone, Kevin Moore and Max Leake on piano, Paul Thompson on bass, and John Uskridge and Roger Humphries on drums. The evening included an elegant dinner and raised money in support of young scientists' research at the Laboratory.

The annual major donors cocktail party was held in the Locust Valley home of Carolyn and Ollie Grace. The elegant setting provided an enjoyable opportunity for Laboratory scientists to mingle with those whose generosity helps support their work.

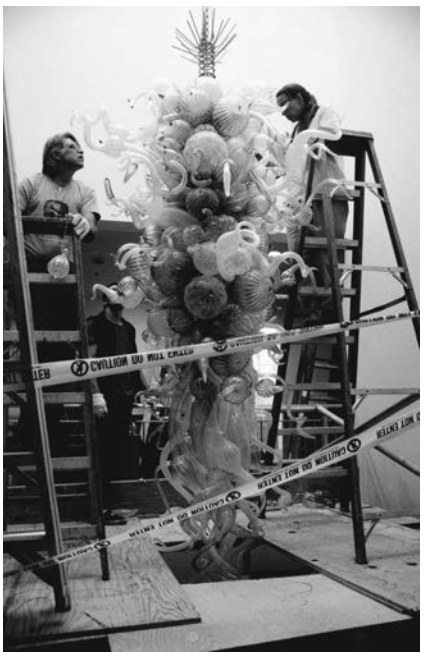
DNALC Corporate Advisory Board (CAB)

Each year the DNALC Corporate Advisory Board (CAB), now chaired by Jack Leahy, supports the DNALC to the extent of 10% of its operating budget by means of a golf tournament and annual fund.

On October 24, Jim and Liz Watson hosted an evening of cocktails and supper at Ballybung to thank members of the CAB for their support and to introduce potential new candidates for the CAB.

Dedication of the Luke Building

Nancy Marks and Liz Watson at
Marks Laboratory Dedication



Assembly of the Chihuly glass chandelier

Building Projects

Genome Research Center at Woodbury

Renovations are under way at Cold Spring Harbor Laboratory's new Genome Research Center at Woodbury. Located on a 12-acre site, 7 miles south of the Laboratory's main campus, the Genome Research Center will enable the Laboratory to expand its basic research initiatives in genomics and other gene-based technologies. Upon its completion, the Genome Research Center at Woodbury will be a 72,000-square-foot facility, outfitted with state-of-the-art scientific technology.

Research in the center will initially focus on sequencing the *Arabidopsis*, rice, and mouse genomes; identifying genes that are mutated in breast and other cancers; bioinformatics; and establishing a facility funded by the National Science Foundation for identifying mutants of maize. The administrative offices of the CSHL Press, as well as a 125-seat auditorium and a full-service dining commons, will round out this first-class, scientific complex.

Other Building Projects

Two other major building projects were completed in 1999. On June 12, the David and Fanny Luke Building was dedicated. Located on the lower roadway facing the inner harbor, the Luke Building consists of two renovated, and now attached, buildings: the old Carpenter Shop and the Power House. Designed by Jim Childress of Centerbrook Architects, the Luke Building houses the offices of Development, Human Resources, and Public Affairs.

The dedication on October 17 of the new Nancy and Edwin Marks Laboratory for advanced brain imaging was another milestone in the neuroscience program. The state-of-the-art facility was designed by William H. Grover, FAIA, and Walker Burns, AIA, of Centerbrook Architects, and constructed by contractor E.W. Howell, Inc. The Marks Laboratory consists of the Keck Research Laboratories, the Starr Foundation Teaching Laboratory, the Martha Farish Gerry Seminar Room, and shared space for research and support staff. Scientists Karel Svoboda, Zach Mainen, and Tony Zador are studying various aspects of the brain using advanced imaging and electrophysiology techniques in the Marks Laboratory.

The aesthetic centerpiece of the Marks Laboratory is a magnificent glass chandelier created by renowned glass artist Dale Chihuly. Jim and Liz Watson commissioned the piece, which is fashioned after dendrites, and donated it to the Lab.

We are nearing completion of another research facility—the Samuel Freeman Laboratory. There, scientists will use and develop sophisticated computer applications for studying the brain and its function in a relatively new field known as computational neuroscience. The new building, located just north of Beckman Laboratory and across the courtyard from Marks Laboratory, was made possible by a gift from the Samuel Freeman Charitable Trust, headed by CSHL Trustee Bill Murray. We have already recruited one scientist to do research in that building—Dmitri Chklovskii from the Salk Institute—and are looking forward to a dedication of this building in late Spring 2000.

Robertson Research Fund

Since 1973, the Robertson Research Fund has been the primary in-house support for science at the Laboratory. The fund has grown from approximately $8 million in 1973 to now

more than $96 million. Last year, Robertson funds supported cancer research in the labs of David Helfman, Michael Hengarter, Nouria Hernandez, Tatsuya Hirano, Leemor Joshua-Tor, Scott Lowe, Ryuji Kobayashi, Adrian Krainer, Jacek Skowronski, David Spector, and Rui-Ming Xu; neuroscience research in the labs of Grisha Enikolopov, Jerry Yin, and Yi Zhong; and plant research in Rob Martienssen's lab. In addition, Robertson funds supported new investigators Andy Reiner and Shiv Grewal.

The Marie H. Robertson Memorial Fund, devoted to neuroscience, gave support to Grisha Enikolopov's lab and start-up support to scientist Zach Mainen.

Major Gifts

1999 was an exceptional year for fund-raising. We conducted two major campaigns—one to endow the Watson School of Biological Sciences and the other to fund construction of the Nancy and Edwin Marks Laboratory—and the results for both were on target. We are most fortunate to have such generous and supportive friends.

The Watson School of Biological Sciences

Former chairman of our Board of Trustees, David L. Luke III, is spearheading the campaign to endow the Watson School. The progress to date has been very good. The Dean's Chair was established with a pledge of $1,175,000 from the Lita Annenberg Hazen Charitable Trust and $500,000 from the Annenberg Foundation, both made possible by Leon and Cynthia Polsky.

Mr. and Mrs. Leslie C. Quick, Jr., established the Fund for Innovative Graduate Education with a $1 million gift (bringing their gifts to the graduate school to $2.3 million), and Nicholas Forstmann pledged $500,000 in support of a core course, Scientific Exposition and Ethics.

Student fellowships were established by Mr. and Mrs. William A. Miller and The William Stamps Farish Fund, each with a $1 million pledge. Curt Engelhorn established fellowships for European students, known as Engelhorn Scholars, with a $5 million gift through the European Foundation for the Advancement of Medicine.

Faculty lectureships were established by Mr. and Mrs. George W. Cutting, Mr. and Mrs. Norris Darrell, Jr., Mr. and Mrs. Edward H. Gerry, the Esther A. & Joseph Klingenstein Fund, Mary D. Lindsay, and Quick & Reilly Group, with gifts of $300,000 each.

Visiting lectureships were provided by Mr. and Mrs. John P. Cleary, Mr. and Mrs. Edward H. Gerry, and The Seraph Foundation, with gifts of $100,000 each.

Gifts to support the School infrastructure were also appreciated. David H. Deming and Henry U. Harris each gave $50,000 toward the renovation of the students' residence, the Knight House.

Brain Imaging

Gifts to the neuroscience imaging initiative in 1999 were also significant and most welcome. The Starr Foundation gave $1,100,000 to establish a state-of-the-art teaching lab, and the G. Harold and Leila Y. Mathers Charitable Foundation gave $870,419 in start-up funds for research in Karel Svoboda's laboratory.

Although construction and equipment funds are often the hardest to raise, we were most pleased with extraordinary support from the following people and foundations. Toward con-

struction: The Ira W. DeCamp Foundation gave $500,000; The Weezie Foundation gave $100,000; and Mary D. Lindsay gave $50,000. Toward equipment: the Marks Family Foundation gave $1 million (bringing the Marks' gifts to the brain imaging program to $3.5 million through 1999); the Fannie E. Rippel Foundation gave $355,000; the William E. and Maude S. Pritchard Charitable Trust gave $255,000; and the Fairchild Martindale Foundation gave $50,000.

Samuel Freeman Charitable Trust, through William Murray, initiated a $1 million gift toward the construction of the Samuel Freeman building, which will house our new computational neuroscience program.

Research Support

We received the following generous gifts in support of research in 1999: the Davenport Family Foundation gave $325,000 toward cancer research; the American Cancer Society contributed $360,000 for cancer research; and the Breast Cancer Research Foundation gave $200,000 toward breast cancer research. The Ellison Medical Foundation and the Sidney Kimmel Foundation for Cancer Research each gave $200,000 to cancer research.

The Neurofibromatosis Foundation Inc.—through its Illinois, Mass Bay, and Texas chapters—gave $95,000 to neurofibromatosis research at the Laboratory. The Rita Allen Foundation gave $50,000 to cancer research, and the Seraph Foundation gave $50,000.

In postdoctoral support, we received generous gifts from Mr. and Mrs. Alan Seligson, $70,000; the Helen Hay Whitney Foundation, $69,000; and the Goldring Family Foundation, $60,000.

Plant Research

Our plant research program benefitted from the establishment of a Plant Consortium. Westvaco Corporation, Monsanto, Novartis, and Zenica have pledged $135,000 each per year for four years (1998–2002).

Education Support

In April 1999, the Howard Hughes Medical Institute (HHMI) made a grant of $1.32 million in support of the Laboratory's advanced scientific courses in neuroscience, molecular biology, and structural biology, as well as a new program in advanced imaging techniques. HHMI also made a grant of $500,000 to the DNA Learning Center in support of the new *VectorNet*, a mobile bioinformatics teaching lab that will bring bioinformatics education to students at New York City schools during the academic year and training workshops to teachers across the United States during the summer.

HHMI began funding education at the Laboratory back in 1988, with a grant that enabled the Laboratory to extend its program of summer courses to an intense, nearly year-round schedule, and funds earmarked for the construction of the Hughes Teaching Laboratories in the Beckman Neuroscience Laboratory. HHMI's continued support has been the cornerstone of our excellent educational program, for which we are most grateful.

Mr. and Mrs. David L. Luke III gave a generous contribution of $490,234 toward the David and Fanny Luke Building.

President's Council

The President's Council was formed six years ago, bringing together leaders from business, research, and biotechnology who are interested in science and Cold Spring Harbor Laboratory. Members of the President's Council contribute $25,000 or more annually to support the CSHL Fellows program for top young scientists fresh from their Ph.D. or M.D. studies. The program allows promising young researchers to pursue their own high-level, independent research, rather than pursuing a more traditional postdoctoral fellowship in the laboratory of an established scientist.

The 1999 meeting of the President's Council, held May 14–15, focused on the Evolution of Happiness. It began with a luncheon at Ballybung followed by an afternoon lecture by CSHL scientist Jerry Yin on long-term memory formation. The keynote speaker, Dr. Stanley Watson, Professor of Psychiatry and Co-Director of the Mental Health Institute at the University of Michigan, described the role of the molecule POMC in human psychology. The speakers on Saturday were Dr. Huda Akil also from the University of Michigan, Dr. Jonathan Rees from the University of Newcastle (UK) Medical School, and Dr. Stephen O'Rahilly from the Wellcome Trust Clinical Research Facility in Cambridge. The mix of leaders from the business world and the scientific community evoked interesting insights, as well as provocative discussions. The following were members of the 1999 President's Council:

Abraham Appel, Appel Consultants, Inc.
Peter Bloom, General Atlantic Partners, LLC
Michel David-Weill, Lazard Freres & Co., LLC
Jacob Goldfield, Goldman, Sachs & Co.
Leo A. Guthart, ADEMCO
Charles E. Harris, Harris & Harris Group, Inc.
Walter B. Kissinger, WBK Associates
Thomas J. McGrath, Simpson Thacher & Bartlett
Donald A. Pels, Pelsco, Inc.
James H. Simons, Renaissance Technologies Corporation
Ronald P. Stanton, Transammonia, Inc.
Charles L. Stone, Jr., M.D.
Sigi Ziering, Diagnostics Products Corporation

The Harbor Society

The Harbor Society honors those distinguished individuals who have contributed to the CSHL planned giving program by including the Laboratory in their estate planning. The Harbor Society gained six new members (or member couples) in 1999: Barbara and Arthur Crocker, the estate of Lachlan Braden, Lois Learned, Mr. and Mrs. Karl Runkle, Miss Eleanor Greenan, and Mrs. Lawrence Marks. The annual dinner for the Harbor Society with Jim and Liz Watson was held at Ballybung on May 2. We are most grateful for the foresight and generosity of the Harbor Society members.

Breast Cancer Support

In 1999, there was again outstanding support from breast cancer advocacy groups. Through 1 in 9: the Long Island Breast Cancer Action Coalition—our longest-running breast cancer

donor—we received $100,000 including $10,000 from Rick Shalvoy, proceeds from his Row For a Cure. This organization's support since 1994 has totaled $411,000.

The Lillian Goldman Charitable Trust and Mrs. Lillian Goldman (through The Breast Cancer Research Foundation) gave $200,000 to support breast cancer research in Michael Wigler's lab.

We were also pleased to have the support of several groups for the first time in 1999. The Manhasset Breast Cancer Coalition gave $25,000. The Long Island Foundation for the Elimination of Breast Cancer gave $15,750, and the Elizabeth McFarland Foundation (through the Long Island Foundation for the Elimination of Breast Cancer) gave $20,447. The Long Beach Breast Cancer Coalition gave $500.

Special Events and Public Outreach

Cancer Lecture Series

Richard D. Klausner

The Laboratory hosted a series of four public lectures about cancer given by four of the country's leading cancer specialists. The first, on March 10, featured Richard D. Klausner, M.D., director of the National Cancer Institute. The title was "The War Against Cancer: Where Has Science Brought Us and Where are We Going?" Former Laboratory staff member Douglas Hanahan, Ph.D., of the University of California at San Francisco, delivered the second lecture on October 12, entitled "The Conspiracy of Cancer Cells."

The third talk, held on October 19, was given by Neil Caporaso, M.D., of the National Cancer Institute and was entitled "Cracking the Causes of Cancer: What We Know; What We Don't Know." The series concluded on October 26 with Mark Pegram, M.D., Department of Medicine, Division of Hematology/Oncology, University of California at Los Angeles, speaking about "Targeted Therapy for Breast Cancer."

School Lecture Series

We held three Great Moments in DNA Science lectures in 1999. On April 27, John Kruper of the DNA Learning Center spoke about the fruits of the Human Genome Project in a talk titled "Biology's Gold Rush: Mining Genes from the Human Genome Project." On May 4, Laboratory scientist Michael Greenberg spoke about HIV research in a talk titled "Molecular Studies on HIV Nef, an Essential Viral Protein." On May 11, Laboratory scientist Richard McCombie discussed a critical step in genomic research in "Sequence Analysis of Complex Genomes." These lectures are designed for a teen-aged audience and attract students and teachers from many area high schools.

Other Lectures

On September 26, we hosted a public lecture sponsored by the World Wildlife Fund (WWF) in Grace Auditorium. The president of WWF, Kathryn S. Fuller, talked about "A Living Planet for the next Millennium."

On October 3, the organization Teenspeak, together with the Town of Huntington, held a "Festival Within—A Marathon Poetry Reading" in Grace Auditorium. That event included the participation of several Pulitzer-prize-winning poets.

We also continued our Lloyd Harbor Seminars with a lecture by John Coraor of the Heckscher Museum in nearby Huntington on May 20, entitled "The Lives and Works of Arthur Dove and Helen Torr."

Concerts

In addition to the benefit concerts described earlier, we hosted 11 free public concerts during CSHL meetings, when we have a large captive audience. Many meeting participants enjoy the cultural respite from their intense scientific sessions. They were as follows:

April 24	Meng-Chieh Liu, pianist
May 1	Irina Muresanu, violinist, and Tatiana Goncharova, pianist
May 8	Christopher Taylor, pianist
May 15	Judith Ingolfsson, violinist, and Ronald Sat, pianist
May 29	Jennifer Frautschi, violinist, and Benjamin Loeb, pianist
Aug. 21	Ayako Yoshida, violinist, and Andrew Armstrong, pianist
Aug. 28	Dmitri Berlinsky, violinist, and Elena Baksht, pianist
Sept. 4	Sophie Shao, cellist, and Adrienne Kim, pianist
Sept.18	Michael Shih and Patricia Sunwoo, violinists; Ori Kam, violist; and Kristian Reiko Cooper, violoncellist
Oct. 2	Arcadian Trio: Ara Gregorian, violinist; Andrew Russo, pianist; and Raphael Bell, cellist
Oct. 9	Brentano String Quartet: Mark Steinberg and Serena Canin, violinists; Misha Amory, violist; and Nina Maria Lee, cellist

Brentano String Quartet

(*Back row*) Mary Ellen Goldstein, Michael Ockler, Dr. James Watson, Robert Gensel, Dessie Carter, Jim Hope, Bruce Stillman
(*Center rwo*) Daniel Miller, James (Herb) Parsons, Maureen Berejka
(*Front row*) Robert Pace, Carmelita Bautista, Susan Schultz, Katya Davey, Carlos Mendez

Long-term Service

On June 30, employees celebrating milestone anniversaries with the Laboratory were honored at a poolside dinner at Robertson House. Lane Smith, veteran plumber, celebrated 25 years at Cold Spring Harbor Laboratory this past year.

Incredibly to me, I celebrated my 20th anniversary with the Laboratory. Although I had visited the lab in 1978 as a graduate student to speak at the annual CSHL Symposium, I arrived in 1979 to work as postdoctoral fellow in Mike Mathews' lab. The last 20 years have seen great progress in biology at CSHL and I would not have missed a minute of it. All of the following people arrived at the Laboratory that same year, and over the course of two decades, each has had an impact on my life and work at the Laboratory: Maureen Berejka, administrative assistant to the President; Judith Cuddihy, editor for CSHL Press Acquisitions and Development; Katya Davey, hostess for Robertson House; Jim Hope, manager of Food Services; Carlos Mendez, bookkeeper and cash manager; John Meyer, lead painter; Michael Ockler, supervisor of Scientific Art and Photography; James (Herb) Parsons, director of Audiovisual; and Susan Schultz, director of grants contracts.

We also had six people celebrating 15-year anniversaries with the Laboratory: Carmelita Bautista, research associate and facilities manager; Dessie Carter, housekeeper; Robert Gensel, manager of security; Mary Ellen Goldstein, part-time accounts payable supervisor; Daniel Miller, grounds foreman; and Robert Pace, business systems manager.

Changes in Administrative Staff

Maureen Bell joined us as administrative director of the Genomic Research Center. Maureen has a master's degree in biochemistry and an MBA in finance. She was formerly with American International Group (AIG) in New York City as a senior technical services manager. Lilian Gann became assistant dean of the Watson School of Biological Sciences.

Changes in Scientific Staff Titles

Concurrent with the establishment of the Watson School of Biological Sciences, the Laboratory adopted an academic faculty title structure: assistant professor, associate professor, and professor.

Departures

Douglas Conklin went to work at Genetica. Ueli Grossniklaus returned to Switzerland to become a staff scientist at the Friedrich Miescher Institute in Basel. Thomas Misteli (HHMI) became principal investigator at the National Cancer Institute (NIH) at Bethesda, Maryland. Peter Nestler moved back to Germany to accept a position as research scientist at Hoechst Marion Roussel Institute in Frankfurt, Germany. Jing (Jenny) Wang left for a career opportunity at Genica.

New Faculty and Staff

Dmitri Chklovskii was recruited from the Salk Institute as an assistant professor, to initiate studies in computational neuroscience in the newly constructed Samuel Freeman Building. Tony Zador was recruited from the Salk Institute to an assistant professorship, and Zach Mainen, upon completion of his postdoctoral studies with Roberto Malinow and Karel Svoboda at CSHL, was also appointed assistant professor—both as part of the expansion of our neuroscience program. Sang Yong Kim was recruited from the University of Michigan to establish a valuable resource for CSHL scientists: a transgenic mouse and gene targeting facility.

Promotions

Leemor Joshua-Tor and Michael Zhang were both promoted to associate professor. Vivek Mittal completed postdoctoral studies in Nouria Hernandez's lab and was promoted to research investigator in Michael Wigler's lab. Michael Myers was promoted from postdoctoral researcher to senior fellow in Nick Tonks' lab. Zach Mainen (Malinow and Svoboda labs) has been appointed assistant professor here at Cold Spring Harbor Laboratory.

Visiting Scientists

Five visiting scientists joined us this year: Eli Hatchwell came from Wessex Human Genetics Institute at Southampton General Hospital in Southampton, England, to study in Michael Wigler's lab; Boris Kuzin returned from the Russian Academy of Sciences in Moscow to study once again in Grisha Enikolopov's lab; Nathalie Pavy came from Gent University, Belgium in Versailles, France, to study in Lincoln Stein's lab; Hilde Grassmo-Wendler came from the Max Delbrück Centre for Molecular Medicine in Berlin, Germany, to study in Michael Wigler's lab; and Fumio Shiobara came from the National Institute of Agrobiological Resources in Ibaraki, Japan, to study in David Jackson's lab.

Six visiting scientists wrapped up their stays here: Jiaxin An returned from Yi Zhong's lab to his position as professor at the China Academy of Space Technology in Beijing, China; Shern Lin Chew returned from Adrian Krainer's lab to his position as senior lecturer/consultant at St. Bartholomew's Hospital in London; Jyotsna Dhawan returned from David Helfman's lab to India, where she is staff scientist at the Center for Cellular and Molecular Biology in Hyderabod; Imran Siddiqi returned from Ueli Grossniklaus' lab to his position as staff scientist at the Center for Cellular and Molecular Biology in Hyderabod, India; Toshiro Tsukamoto returned from David Spector's lab to Hyogo, Japan where he is a research associate at the Himeji Institute of Technology; and Hannes Buelow, visiting scientist in Linda Van Aelst's lab, left to begin postdoctoral studies with Oliver Hobert at Columbia University in New York City.

Postdoctoral Departures

Christine Berthier (Helfman lab) left to become assistant professor at the University Claude Bernard in Lyon, France.

John Connolly (Tully lab) is continuing his postdoctoral studies at the Foundation Jean Dausset-CEPH in Paris, France.

Francesca Demarchi (Stillman Lab), a visiting postdoc, returned to her postdoctoral position at the ICGEB in Trieste, Italy.

Serge Desnoyers (Hengartner lab) accepted a position as adjunct professor at Laval University in Sainte-Foy, Canada.

Dennis Dong (Wigler lab) is now a staff scientist with ZymoGenetics in Seattle, Washington.

Howard Fearnhead (Lazebnik lab) was appointed principal investigator at the National Cancer Institute Research and Development Center in Frederick, Maryland.

Andrew Fraser (Hengartner lab) is continuing his postdoctoral research in Julie Ahringer's lab at the Wellcome CRC, Cambridge, England.

Anton Gartner (Hengartner lab) accepted an appointment as group leader at the Max Plank Institute in Munich, Germany.

Ilya Ioschikhes (M. Zhang lab) is now an Instructor at the Albert Einstein College of Medicine, Bronx, New York.

Nobuhiro Kashige (Kobayashi lab) accepted an assistant professorship at Fukuoka University, in Japan.

Balazs Lendvai (Svoboda lab) accepted a position as assistant professor at the Institute for Experimental Medicine in Budapest, India.

Hong-Xiang Liu (Krainer lab) went to a research scientist appointment at Phylos, Inc., in Lexington, Massachusetts.

Mireya Marin (Van Aelst lab) is taking some time off to be with her family.

Vivek Mittal (Hernandez lab) moved over to Mike Wigler's lab here at CSHL as a research investigator.

Naoki Nakaya (Enikolopov lab) was appointed assistant professor at Okayama University Medical School in Okayama, Japan. He returned to CSHL shortly thereafter to work as a visiting scientist back in the Enikolopov lab.

Laurence Parnell (McCombie lab) moved to a job at Cereon Genomics, a subsidiary of Monsanto located in Cambridge, Massachusetts.

Jean-Christopher Poncer (Malinow lab) has accepted an assistant professorship at the Pasteur Institute in Paris, France.

Baskar Ramamurthy (Grossniklaus lab) will continue his postdoctoral studies with Ueli at Friedrich Miescher Institute in Basel, Switzerland.

Minoru Saito (Tully lab) became an assistant professor at the Tokyo Metropolitan Institute of Neuroscience in Tokyo, Japan.

Kaetrin Simpson (Stillman lab) moved over to the CSHL Press as a project editor in October and was to be the managing editor of this volume. Much to the deep sorrow of all of us, Kate lost her battle with a malignant brain tumor on January 21, 2000.

Charles Spillane (Grossniklaus lab) will continue his postdoctoral studies with Ueli at Friedrich Miescher Institute in Basel, Switzerland.

Peiqing Sun (Beach lab) accepted an appointment to an assistant professorship at Scripps Research Institute in San Diego, California.

Jack Tabaska (M. Zhang lab) is now a bioinformatics scientist at Monsanto in St. Louis, Missouri.

Daan Van Aalten (Joshua-Tor lab) is now a staff scientist at the University of Dundee in Dundee, Scotland.

Jean-Philippe Vielle-Calzada (Grossniklaus lab) is now a professor at the Center of Investigation and Studies in Avangados, Mexico.

Tomoki Yokochi (Hirano lab) is continuing his postdoctoral research in Alan Wolffe's lab at the National Institute of Child Health and Human Development (NICHD) at the NIH in Bethesda, Maryland.

Shahid Zaman (Malinow lab) is now a staff scientist at the University of Bristol in Bristol, England.

Shao-Hui Zhang (Tonks lab) is now a scientist with Tanabe Research Laboratories in San Diego, California.

Dong-Jing Zou (Cline lab) is continuing postdoctoral research in Stuart Firestein's lab at Columbia University in New York City.

Graduate Students Departures

Robert Babb completed his Ph.D. in Winship Herr's lab and has accepted a postdoctoral position at Novartis Pharmaceuticals Corp. in Livingston, New Jersey.

Grace Chen completed the Ph.D. portion of her M.D./Ph.D. degree in Arne Stenlund's lab and moved to the University of Michigan to complete her medical degree.

Jianzhong Jiang completed his Ph.D. with Rui-Ming Xu and is now a postdoctoral researcher in Rui-Ming's lab at CSHL.

Tracy Kuhlman completed her Ph.D. with Nouria Hernandez and went to work for CSHL Press as a developmental editor based in her Seattle, Washington home.

Qiong Liu completed her Ph.D. with Michael Hengartner and is now considering new positions.

Paul Mintz completed his Ph.D. in David Spector's lab and has gone on to do postdoctoral research in Renata Pasqualini's lab at M.D. Anderson Cancer Center in Houston, Texas.

James Moore went with Ueli Grossniklaus to the Friedrich Miecher Institute in Basel, Switzerland, where he will continue his graduate studies.

Ahmed Samatar left after receiving his Ph.D.

Andrew Mark Settles completed his Ph.D. in Rob Martienssen's lab and went on to a post-doctoral position at theUniversity of Florida, Gainesville.

Tzu-Ling Tseng completed his Ph.D. in Adrian Krainer's lab and has moved on to a post-doctoral position in the lab of Jeff Struewing and Ken Beutow at the Laboratory of Population Genetics at the National Cancer Institute in Bethesda, Maryland.

Concluding Remarks

As we rapidly move into the next century and indeed into the next millennium, it is clear that the opportunities for future discovery in biology and medicine are enormous. The past century of biology will be remembered as a golden era that witnessed a renaissance in science that will have an impact for many years to come. The early years of the new century will be the age when biology will be only limited by our imagination. There is a distinct sense of excitement in the air; a feeling that we must endeavor to transmit to the broader communities that will ultimately benefit from this research.

As the pace of modern science continues to accelerate, the resources of academic institutions will be considerably strained, particularly when compared to biotechnology and pharmaceutical companies which have access to technologies that are far beyond the financial capabilities of academia. This is particularly the case in the genomic era.

Cold Spring Harbor Laboratory and institutions like us will need considerable financial resources to remain at the forefront of biology, particularly when increases in federal funding of research abate. But leanness might have a positive benefit in the long run, since academic researchers will be forced to think carefully about how these precious resources are utilized, performing the type of basic research that the more remunerative institutions will find increasingly hard to justify. Ideally there will remain a synergism between industry and academia that will be for the benefit of all.

To me, our mission is as clear as it has ever been. We must continue to pursue basic science at the highest possible level, we must make sure that we continue to grow our strong educational programs, making them even more accessible to scientists and students, and we must encourage public support and participation in these exciting ventures at all levels. For together we are entering what will perhaps be the most exciting phase of biology.

March 2000 **Bruce Stillman**