HIGHLIGHTS OF THE YEAR

The research and education programs at the Laboratory continue their strong momentum. The Watson School of Biological Sciences recruited its second class of students this year, and the DNA Learning Center underwent extensive renovations that will further its educational objectives. The Meetings and Courses program and Banbury Center continue to be invaluable resources for scientific information, and the Cold Spring Harbor Laboratory Press added new projects and properties to its long list of titles. In this, the year of the Human Genome, Cold Spring Harbor Laboratory was a bustling center of scientific activity.

Research

Cancer

Scott Lowe

Malignant melanoma is an aggressive, deadly cancer that does not respond to conventional chemotherapy. Other aggressive, chemoresistant cancers—and approximately half of all cancers—are characterized by mutations in the *p53* tumor suppressor gene. Malignant melanomas, however, do not typically display mutations in the *p53* gene.

To explore alternative explanations for the origins and properties of malignant melanoma, and to identify potential targets and strategies for therapy, Scott Lowe and his colleagues have examined the status of other genes known to function downstream from p53 in a pathway leading to "apoptosis" or "programmed cell death." When intact, this pathway rids the body of abnormal, precancerous cells by triggering a cellular self-destruct mechanism. When this pathway is disrupted (by the loss of p53 function, for example), precancerous cells survive and proliferate, resulting in cancer.

This year, Scott and postdoctoral fellow Marisol Soengas found that malignant melanomas often lose a key trigger of programmed cell death, a protein called Apaf-1 (*ap*optosis *a*ctivation *f*actor-1). They also discovered that the loss of Apaf-1 in melanoma cells is associated with resistance to the chemotherapy drug adriamycin. Most significantly, Scott and Marisol showed that restoring Apaf-1 in melanoma cells rescues the ability of these tumor cells to kill themselves in response to adriamycin. Thus, accurate diagnosis and treatment of malignant melanoma, and perhaps other cancers, should include an assessment of the status of Apaf-1. Scott and Marisol were joined in this work by Yuri Lazebnik, who is examining how Apaf-1 acts in concert with an enzyme called caspase-9 to trigger the cell death machinery.

RNA Splicing and Breast Cancer

In 1977, CSHL scientist Richard Roberts and his colleagues published a paper whose title began "An amazing sequence arrangement…" Rich's use of the adjective "amazing" in a serious scientific article was highly unusual and strangely prescient, because the paper reported a discovery for which he would later win the Nobel prize. A number of papers from Cold Spring Harbor Laboratory and MIT published the discovery that genes are not usually contiguous, but rather occur as blocks of relevant coding sequences (later called exons) that are interspersed with blocks of intervening, noncoding sequences (introns).

Introns are removed at the level of RNA by a splicing mechanism. This year, Adrian Krainer and his colleagues discovered why particular mutations in the *BRCA1* gene alter premessenger RNA splicing and thereby predispose individuals to breast and ovarian cancer.

Adrian Krainer

Although complex in detail, the basic splicing mechanism involves cutting a premessenger RNA molecule at two sites (the splice junctions), discarding the intron thus released, and joining the exons together. This basic splicing mechanism is mediated by the binding of splicing factors to the splice junctions and the action (e.g., cutting and joining) of splicing factors at these sites. Recently, however, additional sites that stimulate splicing have been identified within exons. These sequences are called *e*xonic *s*plicing *e*nhancers or ESEs. Adrian and his CSHL bioinformatics colleague Michael Zhang have developed rules for predicting the presence of ESEs within genes of particular interest. They discovered that a mutation in the *BRCA1* gene—known to alter splicing and predispose individuals to breast and ovarian cancer—disrupts an ESE. In addition, Adrian found that disruption of ESE function may contribute to many other diseases, including cystic fibrosis, neurofibromatosis, Wiskott-Aldrich syndrome, and Menkes disease.

Papillomavirus DNA Replication and Cervical Cancer

DNA contains specialized regions—called origins of replication—that enable the stable "seal" between the two strands of the double helix to be broken. This breaking of the seal between the strands of DNA is the first step in DNA replication, the process that copies DNA. It results from the action of enzymes called DNA helicases that bind to origins of replication and unwind the DNA. Arne Stenlund is investigating how the DNA helicase of papillomavirus binds to the origin of replication in the viral genome and initiates the unwinding of viral DNA prior to DNA replication, a process necessary for the virus to multiply and spread. Papillomaviruses are a family of DNA tumor viruses that infect mammals and cause both benign and malignant epithelial tumors such as polyps and cancer of the cervix. Virtually all human cervical cancer can be attributed to papillomavirus infection. Therefore, the papillomavirus DNA helicase is an attractive target for antiviral drugs and other treatment strategies.

Arne Stenlund

Arne, together with Grace Chen (now at the University of Michigan Medical School), found that a complex mechanism governs how the papillomavirus DNA helicase works. The enzyme, made up of a protein called E1, binds to the viral origin of replication by nestling up to another papillomavirus protein, E2. Together, these proteins bind to adjacent sites at the origin, where E1 then becomes an active DNA helicase and begins to unwind the double helix. Arne and Grace have discovered that E2 acts as a loading factor that deposits E1 on a specific sequence of DNA, the papillomavirus origin of replication.

Leemor Joshua-Tor

Using X-ray crystallography, Leemor Joshua-Tor and postdoctoral fellow Eric Enemark have determined the three-dimensional structure of a part of E1 that binds to DNA and to E2. By obtain-

ing a detailed view of E1's biochemical properties and structure, Arne and Leemor have uncovered interesting clues about how the papillomavirus DNA helicase is put together, how it functions, and what steps might be taken to block the function of this enzyme as a way to prevent cervical cancer.

Neuroscience

Brain Development: How does a single cell—a fertilized egg—become a complex organism composed of billions of cells of thousands of different kinds? How do cells arise at the correct time and place during the development of an organism and adopt the specialized characteristics that make them bone, muscle, or nerve? How is cell number controlled so that tissues, organs, and body parts adopt the correct size? Regulated transitions from cell proliferation to cell differentiation—during which cells stop growing and adopt specialized characteristics—are the key to these phenomena.

Gregori Enikolopov

Since 1992, Grigori (Grisha) Enikolopov has made a series of important discoveries concerning how the biochemical messenger nitric oxide (NO) instructs the cells in a developing organism to stop dividing, enabling them to differentiate into specialized cell types. Building on that research, Natalia (Natasha) Peunova, Hollis Cline, and Grisha found that experimentally altering NO levels in the developing brain of tadpoles significantly affects brain volume and the number of brain cells. When they artificially decreased NO levels in the brains of developing tadpoles, brain cell proliferation increased, leading to larger than normal brains (too little NO, too many brain cells). Conversely, when they artificially increased NO levels, brain cell proliferation decreased, and the resulting brains were smaller than normal (too much NO, too few brain cells).

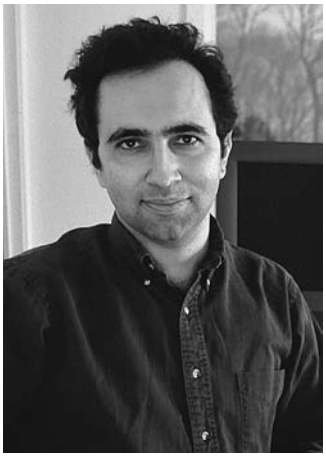
This experiment enabled Natasha, Grisha, and Holly to provide the first definitive demonstration of the essential role of NO as an inhibitor of nerve cell proliferation during vertebrate brain development. Fruit flies, frogs, mice, and humans all have similar sets of enzymes that produce NO. Thus, Grisha and his colleagues are uncovering universal principles concerning the antiproliferative power of NO and how this power is harnessed to create everything from diverse blood cell types, to correctly proportioned body parts, to the complex anatomy of the brain.

Hollis Cline

Brain Imaging: Forget gigabytes. Even the most powerful computers available today are no match for the complexity, efficiency, and information-processing capacity of the human brain. Underlying the brain's far superior design are the billion-million or so connections between brain cells—called synapses—that form vast neural networks in which brain cells, or neurons, are connected to thousands of other neurons. These networks—and their ability to be shaped by experience—enable us to receive, process, store, and retrieve all manner of information about our world. Unfortunately, the extremely tiny size of synapses and the limitations of conventional experimental techniques have hampered detailed studies of these essential structures. (One trillion synaptic compartments, or "dendritic spines," could fit into a thimble.) This year, Karel Svoboda overcame these technical obstacles to gain an extremely close look at the properties of dendritic spines and synapses that govern brain function.

Using “two-photon” microscopy (a high-resolution imaging technique whose application to neuroscience Svoboda pioneered), Karel and postdoctoral fellow Bernardo Sabatini watched calcium flow into single dendritic spines of electrically stimulated brain neurons. These measurements enabled Karel and Bernardo to determine the number and type of “calcium channels” present at synapses in a region of the brain important for learning and memory, the hippocampus. Calcium channels are molecular gates that open in response to electrical stimulation and allow calcium to flow into dendritic spines. Once inside, calcium triggers biochemical events in the spine that modify synaptic strength.

The strengthening of synapses between neurons in response to experience is believed to underlie complex brain functions such learning and memory. Karel, Robert Malinow, and several other CSHL neuroscientists have made a series of significant discoveries about this process. Visualizing how neurons communicate with each other on the most basic level, as Karel has done by imaging calcium, provides important clues for understanding how our brains outperform the most sophisticated computers and, in so doing, enable us to grasp the human experience.



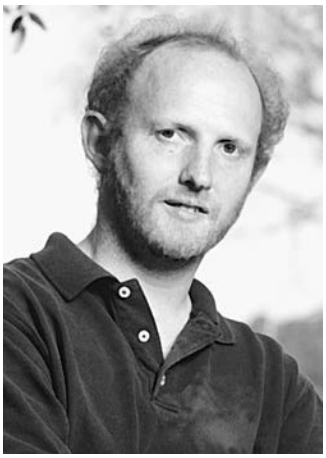
Dmitri Chklovskii

Theoretical and Computational Neuroscience

The discoveries made by traditional neuroscientists result from experiments with living tissue. In contrast, theoretical and computational neuroscientists use mathematics to describe how the brain works. Much of Dmitri (Mitya) Chklovskii’s theoretical neuroscience research is based on the idea that biology and evolution impose several design constraints on the structure of the nervous system. For example, scientists have long believed that neurons are positioned and connected in the brain in such a way as to minimize the length—and hence the volume—of wiring.

Mitya has developed a mathematical formulation of this “wiring economy” principle that enables several predictions to be made about how neurons are connected to each other in the brain. Mitya’s “wire length minimization” model corresponds closely with the observed properties of the mammalian visual cortex, a brain region that processes visual information. The human brain contains approximately 300 million feet of wiring packed into a 1.5-quart volume, but the brain would be much larger if it did not employ the strategy Mitya has uncovered for fitting the necessary wiring into the available, limited space.

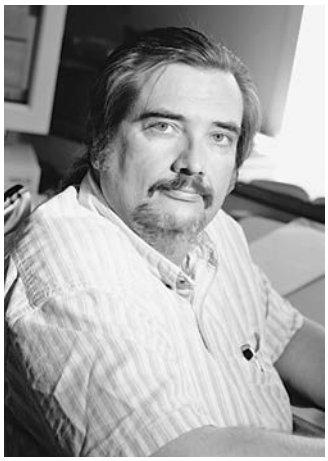
Recently, Mitya has turned his efforts to understanding the neurological basis of optical illusions. By determining what happens when the brain is tricked, e.g., by an optical illusion, Mitya aims to uncover new principles of brain function.



Robert Martienssen

Plant Molecular Biology and Genetics

Owing to its small size and short generation time (~6 weeks from seed to adult), the mustard relative *Arabidopsis thaliana* has



W. Richard McCombie

become a workhorse of plant molecular biology and genetics. In addition to pursuing their specific research interests, W. Richard McCombie and Robert Martienssen helped organize the *Arabidopsis* Genome Initiative, a large-scale international effort established in 1996 to sequence the entire genome of this plant species.

This year, and well-ahead of schedule, the *Arabidopsis* Genome Initiative reached its goal of sequencing the entire *Arabidopsis* genome and thus obtained the first-ever complete genome sequence from a plant. This achievement has profound implications for biology, medicine, agriculture, and the environment because it will enable detailed studies of the entire genetic structure of plants to be carried out. Such studies will yield a great deal of new information about plant growth; crop yields; disease and drought resistance; ripening and spoilage; pharmaceutical, vitamin, and "edible vaccine" production; and many other aspects of plant biology.

Symposium LXV

From May 31 to June 5, biologists from a number of research fields gathered for the 65th annual CSHL Symposium, this year titled "Biological Responses to DNA Damage." On Sunday, June 4, meeting attendee Jan H.J. Hoeijmakers of Erasmus University in Rotterdam delivered the annual Dorcas Cummings Memorial Lecture to a scientific and public audience, a very successful annual event hosted by the CSHL Association. Hoeijmakers' talk, "Maintaining Nature's Perfection: Cancer and Aging and the Condition of Our Genes," was timely because of its relevance to cancer, but also fascinating because we must inherit and maintain our DNA in as best shape as we can to avoid acquired genetic diseases. The lecture, Symposium, and program were an unparalleled success.

Jan H.J. Hoeijmakers

Cancer Center Designation Renewed

Cold Spring Harbor Laboratory has been a National Cancer Institute (NCI)-designated basic cancer center since 1987. After a recent review and site visit, CSHL's cancer center status was renewed by the NCI, which rated the Laboratory's overall program in cancer research as "outstanding." CSHL was one of only a handful of NCI designees to receive this distinction. Designated cancer centers receive a Cancer Center Support Grant from the NCI, which helps fund the scientific infrastructure of the cancer research program. Funds from the NCI enable cancer centers to take advantage of new research opportunities, state-of-the-art technologies, and other NCI-supported resources to advance cancer research.

Scott Lowe, a CSHL Professor since 1995, has been named Deputy Director of the CSHL Cancer Center. Scott has made leading contributions to the identification and characterization of genetic pathways that suppress tumor development and, when disrupted, make tumors resistant to cancer therapy. As Deputy Director, Scott will help me lead the Cancer Center in new directions and ensure that its resources continue to flourish. Scott's

appointment follows Winship Herr's seven-year role as an energetic and very effective Deputy Director. Winship has stepped down to focus on the development of the Watson School (for which he serves as Dean) and his other duties as Assistant Director of the Laboratory.

Denise Roberts, the Laboratory's new Research Administrator, has also assumed the administrative duties for the Cancer Center.

Watson School of Biological Sciences

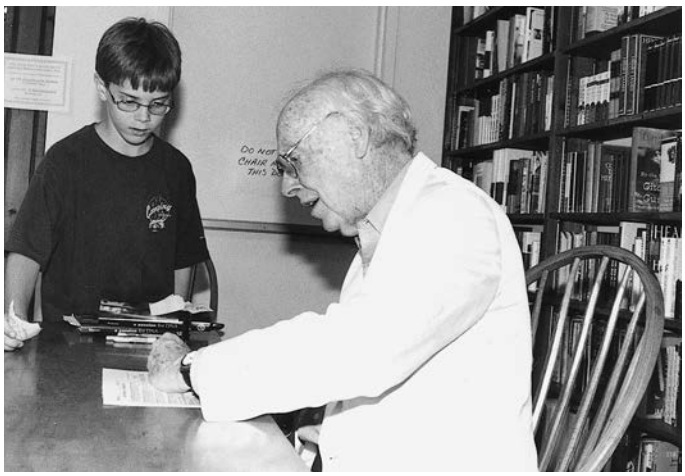
CSHL's graduate school—the Watson School of Biological Sciences—welcomed its second class of students this fall. On August 28, nine new students joined the Watson School's ranks, the second class to enter the program. Hailing from across the country and around the world, the students dove quickly into their rigorous programs, enrolling in the core courses and beginning the laboratory rotations that mark their first year of study.

Honorary Board of Trustees member David L. Luke III continues to lead the fund-raising efforts to fully fund the Watson School programs. This year, nearly $7 million was raised to support the Watson School, its graduate program, and its students.

Presidential Events

James D. Watson, president of CSHL, has had another busy year, most recently promoting his newest book, *A Passion for DNA: Genes, Genomes, and Society*. The collection of essays, published by the CSHL Press, was nationally publicized through an exhausting 4-month book tour. Locally, Jim was a big hit at Huntington's Book Revue, where hordes of fans lined up for the Nobel Laureate's autograph. Jim was also honored on July 4 with the prestigious Philadelphia Liberty Medal. Jim received the award, together with Francis H.C. Crick, for the "tremendous impact of their science on our lives and public policies."

Lewis Miller, an Australian artist and winner of the prestigious Archibald Prize—Australia's premier award for portraiture—returned to CSHL for a month this summer. Miller, who visited the Laboratory during the 1998 Symposium to sketch attendees and Laboratory personnel, has many works exhibited throughout Blackford Hall. His mission this summer was more specific: I commissioned Miller to paint a full-sized portrait of James D. Watson.



James Watson meets young fans while promoting *A Passion for DNA.*

Miller's efforts were a success: A seven-foot representation of CSHL's President now hangs in a place of honor inside Grace Auditorium, where Jim has spent countless hours lecturing to public and scientific audiences. While at the Laboratory, Miller also completed several other portraits, including sketches of Charles and Helen Dolan, long-time supporters of the Laboratory. Mrs. Dolan, who currently serves on the Laboratory's Board of Trustees, was particularly pleased with the charcoal drawings Miller presented to the couple. In all, Miller completed more than 15 portraits while at the Laboratory, and each was framed for display around the Laboratory campuses.

Helen Dolan

Charles Dolan

30th Anniversary Reunion of Yeast Course

Since the inception of CSHL's Yeast Genetics Course 30 years ago, nearly 500 scientists from around the world have traveled to Cold Spring Harbor to learn more about this relatively simple organism. Although simple in structure, yeast undergoes many of the complex biological processes of higher-order organisms, making it a model system for the study of molecular biology. CSHL's Yeast Genetics Course has helped to elevate yeast to its present "stardom," and most of the outstanding yeast geneticists/molecular biologists of the past half-century have either taken the course, taught the course, or both.

To celebrate the great science and lifelong friendships that have resulted from the Yeast Genetics Course, the Laboratory held a reunion for course participants on August 11. The event brought together students and instructors of the course—both past and present—for 2 days of reminiscing and sharing of current research. The reunion illustrated the influence that the course has had on its participants, as well as the impact that these investigators have had on science. "It's hard to imagine where we'd be today without yeast," said Jim Watson, who kicked off the reunion celebration. More than 35 alumni of the Yeast Genetics Course attended the reunion, taking part in the 2-day mélange of lectures, reflections, and activities, including the now-famous "plate race."

Jim Hicks, Ira Herskowitz, and Chris Kaiser at the reunion.

Banbury Center

One of the highlights of the Banbury Center year is the annual Executives' Conference. Begun in 1986 to bring top executives in the pharmaceutical and biotechnology industries together to learn about the newest concepts and technologies, the meetings attracted both speakers and invited guests of the highest quality. The 2000 meeting, entitled "Human Consciousness and Intelligence," lived up to this tradition. The keynote speaker was Oliver Sacks, the eminent psychologist and best-selling author. Oliver is the first Banbury Center

visitor to have been immortalized by Hollywood, when he was played by Robin Williams in the film *Awakenings*, based on his book. Howard Gardner spoke on his theory of multiple intelligences, and there was a spirited discussion of human intelligence following a presentation by Charles Murray, coauthor of *The Bell Curve*. Participants were treated to appearances by Alex the African Gray Parrot (by Irene Pepperberg) and, at the other extreme, robots (by Howard Gardner). In between, Stephen Pinker discussed his ideas on language, while Vilayanur Ramachandran reviewed the neuropsychological basis of sensory perception. We are grateful to David Deming of J.P. Morgan for helping us to present such an extraordinary meeting.

Some years ago, the world was astonished and shocked by the cloning of Dolly, the sheep. It seemed to be an extraordinary step in the manipulation of living organisms. However, Dolly herself was the only success of many attempts, and subsequent studies have only achieved limited success. Cloning is very difficult. The Banbury Center meeting "Mammalian Cloning: Biology and Practice" tried to identify those elements of the biology underlying cloning that might be responsible for the low success rate. Almost all of the leading scientists cloning a wide variety of animals participated, including Ian Wilmut, leader of the team that cloned Dolly.

A special feature of the 2000 program at Banbury Center was the large number of meetings on neuroscience, reflecting the increasing research effort in neuroscience at the Laboratory. The topics ranged from the experimental ("Structure, Mechanism, and Function of CaMKII") to the theoretical ("Natural Stimulus Statistics"). Neural Networks and Cognition was particularly noteworthy because neural networks underlie the Palm operating system. The meeting was funded by Jeffrey Hawkins, the developer of the Palm OS and cofounder of Handspring, Inc., who is now a Trustee of the Laboratory. The Swartz Foundation, established by another good friend of the Laboratory, Jerry Swartz, funded a meeting called "Toward Animal Models of Attention and Consciousness," discussing how the brain is able to focus selectively on items of interest in the world around us.

Robertson Research Fund

Since 1973, the Robertson Research Fund has been the primary in-house support for scientists at Cold Spring Harbor Laboratory. The fund has grown from its original 1973 total of $8 million to more than $95 million for the year 2000. This year, Robertson funds supported cancer research in the labs of David Helfman, Michael Hengartner, Tatsuya Hirano, Ryuji Kobayashi, Yuri Lazebnik, Greg Hannon, and Dick McCombie; neurobiology research in the labs of Grigori Enikolopov, Roberto Malinow, Tim Tully, Jerry Yin, and Yi Zhong; and plant research in the lab of Robert Martienssen. Robertson funds also supported several new investigators, including Andrew Reiner, Shivinder Grewal, David Jackson, Zachary Mainen, and Anthony Zador.

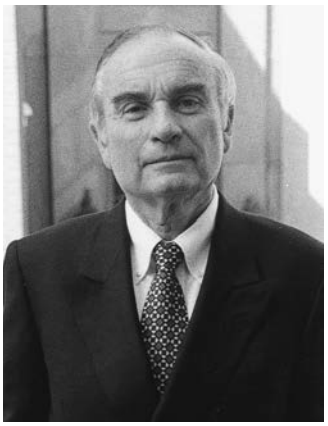
The Marie H. Robertson Memorial Fund, devoted to neuroscience, provided support to Grigori Enikolopov and Zachary Mainen and provided funds for a neurobiology seminar program and a Banbury Center meeting on neuroscience.

Cold Spring Harbor Laboratory Board of Trustees

Cold Spring Harbor Laboratory's Board of Trustees has led the Laboratory through another year. At its two annual meetings, the Board members continued to help shape the vision and

drive of this institution. This year, the Board welcomed the addition of Jacob Goldfield, a private investor.

The Board of Trustees bid a fond farewell to two long-standing Board members, Martha Farish Gerry and John J. Phelan. Mrs. Gerry has served on the Board for more than 10 years, serving on the Banbury Program, Building, DNA Learning Center, and Development Committees; she was also Secretary of the Board from 1997 to 2000. Mr. Phelan, who led the Board's Commercial Relations Committee since 1996, served the Laboratory for more than 8 years and was also represented on the Board's Audit and Executive Committees. Both Trustees were honored at the Board's November 4 meeting for their outstanding service and unwavering loyalty to Cold Spring Harbor Laboratory.



John J. Phelan

CSHL Association

The CSHL Association (CSHLA) held its annual meeting on February 5, 2000. The membership honored its retiring directors, including Mary Ann Charlston and Mary D. Lindsay (who was simultaneously named an Honorary Director). The Association also elected several new directors, including William F. Gerry, Lynn M. Gray, Susan Hollo, and Allen Dulles Jebsen. George W. Cutting, Jr., a former president of the CSHLA and a former honorary director, was reelected and returned as an active director this year.

Martha Farish Gerry

The annual meeting also featured a lecture by Dr. Steven Pinker, Professor of Psychology in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology. His lecture, titled "Words and Rules: The Ingredients of Language," discussed the components and importance of human communication.

On April 15, 2000, the Association hosted *Jazz at the Lab 2000*, its second jazz benefit. The performance featured The Harold Betters Quartet, with Harold Betters on trombone, Kevin Moore on piano, Charles Ramsey on bass, and Cecil Brooks III on drums. Kenny Blake, a saxophonist, and Eric Johnson, a guitarist, were also featured in the performance.

The annual major donors' cocktail party was held in the Lloyd Harbor home of Mrs. John W.B. (Robin) Hadley. The event, held November 11, 2000, provided an elegant and enjoyable setting in which the Laboratory's scientists were able to personally thank the generous individuals who help to support their work.

DNA Learning Center

During the year, the DNA Learning Center (DNALC) multimedia group opened a major new Internet site, *Image Archive on the American Eugenics Movement*. The site provides students, teachers, scholars, and the interested public with an extraordinary window into a "hidden" chapter of history and a cautionary tale for our current rush to exploit the human genome. Through more than 1500 images and documents, most never publicly released before, the archive traces the rise and fall of this ill-guided experiment to protect the "American germ plasm from pollution by 'bad genes.'" With the support of many prominent geneticists and public citizens, eugenicists successfully lobbied for coercive social legislation to restrict European immi-

DNALC Internet site, *Image Archive on the American Eugenics Movement.*

gration, to prevent race mixing, and to sterilize "hereditary defectives." The *Eugenics Archive* makes no attempt to lead users to a "correct" interpretation of the materials; however, contextual narratives remind users that the vast majority of scientific "facts" presented by eugenicists were fundamentally flawed and have been discredited by modern research standards. It is especially appropriate that the Laboratory should sponsor this effort, because from 1910 to 1940, the Eugenics Record Office at Cold Spring Harbor was an epicenter of the American movement.

By far, the most exciting event at the DNALC was the completion of the BioMedia Addition. Construction began on April 18, 2000, and included the addition of a suite of administrative offices, an additional teaching lab, a computer lab, a lunchroom, and additional exhibition space. Through the generosity of The Dolan Family Foundation, established by CSHL Trustees Charles and Helen Dolan, the DNALC also gained a state-of-the-art facility for multimedia production, now called the "multitorium." The facility includes high-tech equipment and the latest technology, which will enhance the DNALC's mission to educate the students of Long Island. In June, 2001, the site will be dedicated and renamed *The Dolan DNA Learning Center*.

CSHL Press

The Cold Spring Harbor Laboratory Press had a very successful year. One highlight was the eagerly anticipated December appearance of the celebrated laboratory manual *Molecular Cloning*, in a new edition by Joe Sambrook and David Russell that is already a best-seller. Eleven other new titles were published, including three manuals, a monograph on translational control, the annual symposium volume, an elegant book on embryonic development, and a compendium of classic papers in cell biology. A memorial volume for Alfred Hershey was also released. Several of the new titles were aimed at nonspecialist readers, most notably Jim Watson's essay collection *A Passion for DNA*, which was particularly popular. Altogether, 220 books are in print and are available at the attractively redesigned Web Site CSHLPress.com. The book program's sales support was strengthened through contracts with major booksellers and distributors in the U.S. and the creation of a European sales team centered in Oxford.

In the textbook division, four major projects were initiated and discussion of co-publishing contracts initiated with three major textbook marketing firms. Particularly satisfying was the agreement reached with Benjamin Cummings for a fifth edition of Jim Watson's classic text *Molecular Biology of the Gene*.

The journal program continued to advance. Subscriptions increased, advertising sales rose, and the measurable impact of all three journals was either maintained or strengthened. The on-line editions were enhanced with new features such as freely accessible back issue archives. The Protein Society's journal *Protein Science*, acquired from another publisher, was redesigned both in print and on-line and relaunched under the CSH banner in December.

Major Gifts

2000 was an exciting year for fund-raising. Several major campaigns continue to be successful: the campaign to fund the new Genome Research Center; the BioMedia Addition to the DNA Learning Center; and a continuing campaign for the Watson School of Biological Sciences. Results for all were astounding, and we are very fortunate to have such generous and supportive friends at Cold Spring Harbor Laboratory.

The Genome Research Center

As the Genome Research Center in nearby Woodbury nears completion, the fund-raising effort to support this new facility is already under way. A pledge of support was made by Mrs. Joy Levy, wife of the late Senator Norman J. Levy, who has offered to make the Genome Research Center the beneficiary of the efforts of the Norman J. Levy Foundation. To start the process, Mrs. Levy has pledged $250,000; her brother and sister-in-law, Jerry and Linda Saslow, have pledged $50,000 as well. The William & Maude Pritchard Charitable Trust has made a gift of $280,500 to support the Genome Research Center, and Arrow Internet Business Group and the Irving A. Hansen Memorial Foundation pledged $30,000 each. Other major gifts were received from Mr. Lawrence Flinn, who donated $50,000; Nathan E. Saint-Amand, M.D., who made a gift of $50,000; and the Mary G. Turner Charitable Lead Unitrust, which made a gift of $20,000 to the project. The Seraph Foundation, Inc., also gave a leadership gift of $100,000 to support the new facility.

Architectural rendering of the Genome Research Center.

The BioMedia Addition to the DNA Learning Center

The DNA Learning Center facility was updated and expanded this year, brought to the cutting-edge of technology with a new BioMedia Addition. The campaign was anchored by a generous donation from The Dolan Family Foundation, which made a total commitment of $3,000,000 to finance the renovations, build the new facilities, and equip the new lab areas.

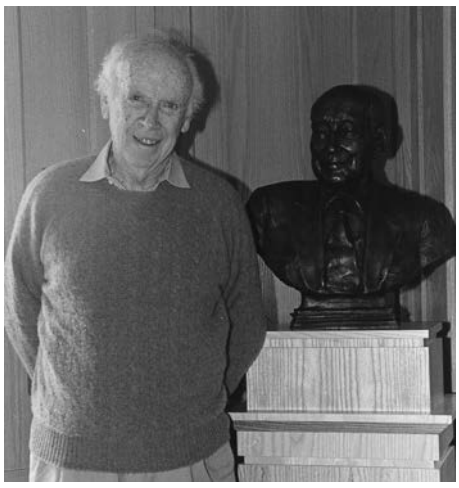
PE Biosystems made a gift-in-kind of $130,570 to furnish the addition with equipment, and Mr. and Mrs. Denis J. O'Kane made a generous gift of $35,000 to further fund the facility. The New York Stock Exchange also made a gift of $10,000 to the project.

The Watson School of Biological Sciences

Cold Spring Harbor Laboratory Trustee David L. Luke III continues to lead the campaign to fund the Watson School of Biological Sciences. This year was a particularly fruitful year for the fund-raising effort. Bristol Myers Squibb, The Charles A. Dana Foundation, and The Florence Gould Foundation each pledged $1,000,000 to support the Watson School. Mr. Alan Goldberg pledged $500,000 to support the School, and Lazard Freres & Company, LLC, and The Koshland Foundation each gave $100,000 to the campaign. Laboratory Trustee Robert D. Lindsay and his wife pledged $500,000, and CSHLA President David H. Deming and his wife pledged $50,000. Mr. and Mrs. Charles E. Harris made a gift of $103,075 to the Watson School Campaign, and The Rathmann Family Foundation made a commitment of $300,000. The Lita Annenberg Hazen Foundation, a long-time Laboratory supporter, made a pledge of $825,000 to continue the School's educational programs. Dr. Michael Wigler, a CSHL professor, made a pledge of $55,000 to support the School, and Mrs. John H. Livingston and the Fairchild Martindale Foundation each gave $50,000 to the Campaign. Among many other donations made, significant commitments and gifts of support were made by the Alan B. Slifka Foundation; Biogen, Inc.; Mrs. Gertrude W. Conner; Mrs. Frances Elder; Mr. and Mrs. Edward Giles; Dr. and Mrs. Walter C. Meier; Mrs. Wendy Vander Poel Russel; and Karen and Mark J. Zoller, Ph.D. All told, nearly $7 million was raised this year to support the Watson School, and we continue to be grateful to our many donors and friends.

Research Support

We have received the following generous gifts in support of research in the year 2000: The Arthur and Barbara Crocker Charitable Trust gave $200,000 to the Young Incoming Scientists Endowment; the Goldring Family Foundation gave $60,000 to support postdoctoral fellowships; and Mr. and Mrs. Edmond J. Nouri gave $84,551.70 to support the work of Dr. Tim Tully, part of a 3-year pledge of more than $130,000.



James Watson standing beside a bust of Arnold O. Beckman, CSHL benefactor.

The Arnold O. and Mabel M. Beckman Foundation

The Arnold O. and Mabel M. Beckman Foundation, a long-time Laboratory supporter, continued its generous support in 2000. The Foundation pledged $1,000,000 to support the students of the Watson School of Biological Sciences, and pledged $250,000 for Core Course support in the School.

Members of 1 in 9: The Long Island Breast Cancer Coalition present a gift to Michael Wigler to fund breast cancer research.

Breast Cancer Support

A new decade did nothing to hamper the efforts of the numerous breast cancer groups who support the Laboratory's cancer program.

1 in 9: The Long Island Breast Cancer Action Coalition—which celebrated 10 years of support to the Laboratory in 2000—presented a check in the amount of $240,000, its largest single gift in the organization's history. To date, the support from 1 in 9 has surpassed $650,000.

Several other groups continued their support of breast cancer research, including The Breast Cancer Research Foundation, The Huntington Breast Cancer Action Coalition, The Long Island Foundation for the Elimination of Breast Cancer, and Breast Cancer Awareness Day in Memory of Elizabeth McFarland. The West Islip Breast Cancer Coalition also made a generous donation to support the work of Dr. Michael Wigler, the first time the group has made a donation to the Laboratory.

We were also pleased to welcome the members of Long Islanders Against Breast Cancer (L.I.A.B.C.). The group announced with its formation that it would raise funds to benefit Cold Spring Harbor Laboratory, and its 2000 gifts—since its October formation—already total more than $65,000.

President's Council

This year's President's Council meeting was on "The Dog and Its Genetics: Breeds, Evolution & Behavior," an unbeatable combination of cutting-edge genetic research and humanity's closest friend. An eminent roster of speakers began with Roger Caras, internationally known for his encyclopedic knowledge of dogs and as Master of Ceremonies at the annual Westminster Club Show. Mr. Caras talked on the special relationship between human beings and animals. Elaine Ostrander (University of Washington) and Greg Acland (Cornell University) then described the dog genome project, and how the dog is afflicted by genetic

disorders that may have a genetic basis identical to disorders of human beings. But perhaps the most fascinating feature of dogs is their behavior. Raymond Coppinger (Hampshire College) has specialized in studies of the behavior of working dogs, and he described the differing characteristics of the sheepdogs that guard flocks and those that herd flocks. All-in-all, the speakers introduced us to a wonderful blend of science and our everyday experiences of the animal that has been associated with human beings for at least 14,000 years.

Gavin Borden Visiting Fellow

Douglas A. Melton, Ph.D., of the Howard Hughes Medical Institute and the Department of Molecular and Cellular Biology at Harvard University was the Laboratory's sixth Gavin Borden Visiting Fellow. Dr. Melton's lecture, titled "Construction of the Pancreas," was held on October 2 in Grace Auditorium. The Lecture series was named in memory of Gavin Borden, a science writer whose work on *Molecular Biology of the Cell* and several other books made a lasting impression on the Laboratory.

Douglas A. Melton, Ph.D.

Building Projects

The historic landscape of Cold Spring Harbor Laboratory changed again this year, with the completion of three new building projects. On May 3, the Laboratory dedicated the Samuel Freeman Building, located adjacent to Urey Cottage. The Freeman Building—part of the Laboratory's neuroscience program—is a state-of-the-art facility for neuroscientists who use computer technologies to aid in the study of the brain. The building was made possible through a generous gift from the Samuel Freeman Charitable Trust, led by CSHL Trustee Bill

Samuel Freeman Building dedication.

Townsend J. Knight (second from right) joins his family at the building that bears his name.

Murray. The building, designed by Jim Childress of Centerbrook architects, is an Adirondack-style structure, accented by dark wood siding and a gabled roof of copper-foil-coated shingles. The Freeman Building—which will house three faculty in the field of computational neuroscience—is reminiscent of the cabins that formerly occupied the site.

On June 10, the Laboratory dedicated the newly renovated Knight House, across Cold Spring Harbor from CSHL's main campus. The 190-year-old structure was an original home of the Jones Family, the Laboratory's earliest benefactors. Named for CSHL Honorary Trustee Townsend J. Knight—a descendant of the Jones family—the historic, two-story white structure is a beacon of the Cold Spring Harbor shoreline. Following extensive renovations, the Knight House is now being used as a residence for students of the Watson School of Biological Sciences. The interior contains six bedrooms, a living area, television room, kitchen, and laundry facilities.

Renovations continue on the Genome Research Center in nearby Woodbury. The building, now near completion, is a 72,000-square-foot facility that houses four research components: a Bioinformatics Center, a Cancer Research Center, a Genome Sequencing Center, and a Plant Genomics Center, as well as new space for the CSHL Press, and other administrative departments. A campaign is under way to fully fund the complex. Its first tenants—CSHL's Purchasing Department and the CSHL Press—are expected to occupy the building in Spring 2001.

Undergraduate Research Program

The 2000 summer Undergraduate Research Program (URP) consisted of 27 students—14 men and 13 women—from 8 countries. They were chosen from among 546 applicants from more than 59 nations.

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 the top scientists who visit CSHL.

The program received financial support in 2000 from the C. Bliss Memorial Fund, the Burroughs Wellcome Fund, Robert Cummings, Dr. Ira Herskowitz, the Jephson Educational Trust, the JM Foundation, the National Science Foundation, and the URP Endowment Fund (composed of the Emanual Ax Fund, the Garfield Fund, the Glass Fund, the Libby Fund, the Olney Fund, the Read Fund, the Shakespeare Fund, and the Von Stade Fund).

Partners for the Future

The CSHL Partners for the Future program was established in 1990 to give young students a taste of the real world of biomedical research. Each year, six or eight Long Island high school students entering their senior year are chosen from a large pool of nominees to participate in the program. The selected students spend a minimum of 10 hours per week, October through March, doing original research under the guidance of a Cold Spring Harbor Laboratory scientist. At the conclusion of the program, students present their research project to an audience of scientific mentors, high school teachers, friends, and relatives.

The program, now in its 11th year, is an overwhelming success. To date, 53 students have completed the program, and all of them are now or have been enrolled in top-ranked colleges and universities.

Back row: Maria Reimels, Brian Mohr, Daniel McAlvin, Owen Martin
Front row: Eric Van Nostrand, Jacqueline Rho, Deborah Yom, Allison Brincat

Community Outreach

Grateful for the overwhelming support that CSHL receives, a number of employees set out this year to "give back" to the Long Island community.

- CSHL "road-runners" were on-hand at the Cigna 5K Walk/Run, to support 1 in 9: The Long Island Breast Cancer Action Coalition, held at Eisenhower Park in East Meadow on August 24. The CSHL group is grateful for more than 10 years of support from 1 in 9. Lynn Cannon, Administrative Assistant in the Development Office, came in third for her age group in the run. In all, the event raised more than $100,000.
- Members of the W. Richard McCombie lab made a generous contribution to the North Shore Pediatric Oncology Unit to purchase holiday gifts for the patients. In their certificate of appreciation, administrators at North Shore noted how the gifts really touched the children.

Special Events

Neuroscience Lecture Series

This year, the Laboratory continued a series of public education lectures by hosting its first Neuroscience Lecture Series. The three public lectures attracted more than 900 visitors to Grace Auditorium. The first lecture was given by Dr. Michael Merzenich on November 14, titled "Training Strategies for Brain Illnesses and Disabilities in Children." Dr. Merzenich is the Francis A. Sooy Professor of Otolaryngology at the Keck Center for Integrative Neurosciences at the University of California, San Francisco. The second lecture, held November 21, was given by Dr. Charles F. Stevens, a professor from The Salk Institute for Biological Sciences. Dr. Stevens' lecture was titled "Synapses: The Neural Information Highway." The final lecture in the series was given by Dr. Larry Squire, Professor of Psychiatry and Neurosciences at the University of California School of Medicine in San Diego. Dr. Squire's lecture, held November 28, was titled "Memory Systems of the Brain."

Dr. Michael Merzenich

Other Lectures

Cold Spring Harbor Laboratory continued to host the Huntington Hospital Lecture Series, which ran from February to June. This year's topic was "Keeping Your Heart Healthy," part of Huntington Hospital's Heart Health Lecture program.

On June 26, the Laboratory welcomed Viviana Risca, the 2000 winner of the Intel Science Talent Search, and Laura F. Landweber, an assistant professor at Princeton University, for a special public lecture on "DNA Games: From Computing to Espionage." The event attracted a large group of teens and adults interested in DNA and the human genome.

On October 28, Phillip Valentine Tobias, Professor Emeritus at the University of the Witwatersrand in Johannesburg, presented a special public lecture titled "Humanity's Cradle: 75 Years of Evolutionary Studies in Africa." As part of a special Halloween program, "Bones and Strings," Dr. Tobias lectured on his research of the human biology of the peoples of Southern Africa. A special public concert by famed violinist Viviane Hagner followed the lecture.

Concerts

As part of the Laboratory's Millennium Cultural Series, several concerts were held this year. Attended by the participants of CSHL's Meetings program and the public, the free concert series was a huge success. The concerts included:

May 6	Karen Gomyo, violinist
May 20	Adam Neiman, pianist; Stefan Malenkovich, violinist; Ani Aznavoorian, cellist
May 27	Margarita Shevchenko, pianist
August 19	Julia and Irina Elkina, duo piano
August 26	Randall Scarlata, baritone and accompanist
September 9	Makoto Nakura, marimbist
September 16	Eric Johnson, jazz guitarist, with band
October 28	Viviane Hagner, violinist
November 11	Mark Ptashne (CSHL Board of Trustee Member), violinist

Millennium Cultural Series

In addition to the concert series, the Millennium Cultural Series brought several art events to the Laboratory for the year. Dale Chihuly, famed glass sculptor, presented a lecture on May 2 titled "Chihuly on Chihuly: The Jerusalem Project." The lecture, cohosted by the Hecksher Museum of Art, examined the sculptor's year of work in Israel. The Laboratory's second outdoor art show, *Sculpture by the Sea,* ran from May 28 through October 31 and featured 17 original works. On August 31, sculptor Charles Jencks unveiled his sculpture *Spirals Time-Time Spirals* and lectured on his work, particularly how the structure of DNA had inspired this latest piece. On November 4, the Laboratory hosted *Labscapes 2000*, a painting show which featured 25 pieces depicting the beautiful grounds and historic buildings of the Laboratory's property. Many of the exhibits were possible due to the generosity of Jim and Liz Watson.

Stefan Malenkovich, violinist; Ani Aznavoorian, cellist; Adam Neiman, pianist

Viviane Hagner

Sculpture by the Sea

Margarita Shevchenko

First Row (top): Bruce Stillman, James Watson, Harry Wozniak, Frank Carberry
Second Row: Michael Riggs, G. Morgan Browne, Madeline Wisnowksi, David Spector
Third Row: Steven Tang, Linda Rodgers, Marlene Rubino, Patricia Hinton-Stenko
Fourth Row: Andrea Stephenson, Lisa Manche, Bruce Fahlbusch

Laboratory Employees

Long-term Service

On June 29th, employees celebrating milestone anniversaries with the Laboratory were honored at a special poolside dinner at Robertson House, on the Banbury Center property. Congratulations to all! Honorees included:

30 Years	Madeline Wisnewski
20 Years	Bruce Fahlbusch, Michael Riggs, Linda Rodgers, Marlene Rubino and Andrea Stephenson
15 Years	G. Morgan Browne, Frank Carberry, Patricia Hinton-Stenko, Lisa Manche, David Spector, Wanda Stolen, Steven Tang and Harry Wozniak

Awards and Honors

I was honored to be elected to the National Academy of Sciences (NAS) in May, 2000. Membership in the Academy is one of the highest honors a scientist can receive from an American organization.

Changes in Administrative Staff

Annette Gangitano joined us this year as the Executive Director of the Cold Spring Harbor Laboratory Association. Annette came to the Laboratory from a position with the firm of J&W Seligman.

Jeff Picarello joined us as the Director of Public Affairs. Jeff formerly worked at the C.W. Post Campus of Long Island University, where he was Director of Media Affairs.

Charles Prizzi joined the Laboratory staff as Director of Special Events. Charlie was formerly Director of Special Events for Long Island University.

New Faculty and Staff

Z. Josh Huang joined the Laboratory this year as an assistant professor and Bhubaneswar Mishra, as an adjunct professor. Other new hires included Gilbert (Lee) Henry and Terence Strick, who joined the Laboratory as Cold Spring Harbor Laboratory Fellows.

Promotions

Scott Lowe was promoted to professor and deputy director of the CSHL Cancer Center. Greg Hannon, Lincoln Stein, Karel Svoboda, Rui-Ming Xu, and Jerry Yin were each appointed associate professor, and Robert Lucito and Vivek Mittal were promoted to assistant professors.

Departures

After many years of association with Cold Spring Harbor Laboratory, David Beach, an adjunct professor, left the Laboratory to focus on his role as president of Genetica. Bruce Futcher, an associate professor, left Cold Spring Harbor for a position at the State University of New York at Stony Brook.

Visiting Scientists

Five visiting scientists joined us this year: Vincent Colot will spend his sabbatical year in the lab of Robert Martienssen; Anna Giulini joined the lab of David Jackson; Edith Heard will spend her sabbatical year in the lab of David Spector; Jacqueline Vitali joined the lab of Rui-Ming Xu; and Ying-hua Zhu joined the lab of Yi Zhong. Five scientists also wrapped up their stays at Cold Spring Harbor Laboratory: Christine Berthier, Daniel Bogenhagen, Hilde Grasmo-Wendler, Nathalie Pavy, and Fumio Shiobara.

Postdoctoral Departures

The following postdoctoral researchers left Cold Spring Harbor Laboratory in 2000:

Guy Birkenmeier
James Chong
James Dezazzo
Nicholas Edgington
Ludwig Englemeier
Francisco Ferrezuelo
Andrew Groover
Mariko Hayashi
Yasunori Hayashi
Daniel Hoeppner
Jianzhong Jiang
Keiji Kimura
Zhixin Lin
Hong Liu
Tohru Mizushima
Michael Murray
Jairaj Puthenveettil
Keiichi Shibahara
Javor Stolarov
Suzanne Tharin
Venugopal Valmeekam
Daniel Vaughn
Michael Weinreich
Herman Wijnen
Jianlong Zhou
Jian Zhu

Graduate Student Departures

The following graduate students left Cold Spring Harbor Laboratory in 2000:

Eric Gillitzer
Tina Gumienny
Susan Harrington
Shirly Pinto
Julia Polyakova
Alex Rai
Bjorn Schumacher
Setareh Sepehri
Beth Trumbull
Helena (Xiaohong) Yang
Lee Zou

Concluding Remarks

Constant change has been the theme at Cold Spring Harbor for much of its history, and this past year has been no exception. This dynamism, coupled with results emerging from the various genome projects, has opened new doors and revealed tremendous opportunities for biology and biomedicine, possibilities that were unheard of when I first came to Cold Spring Harbor Laboratory 21 years ago. It is time once again for this institution to rise to the challenges before us, enjoying, but not resting on, our significant past achievements.

Cold Spring Harbor Laboratory is a unique research and educational institution, more like an advanced research university now than ever before. More than many other universities, we have the flexibility to rapidly adapt to the fast pace of modern science. However, to remain at the leading edge of research in areas such as cancer and neuroscience, we will require major new infrastructure, significant new funding, dedication, and much energy from our already efficient and busy staff. This institution has never shied away from a challenge, and I am confident that with the right help, we will go on to an even brighter future.

April 2001 **Bruce Stillman**