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Hereditary Disease FOUNDATION

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Hereditary Disease Foundation Commits Over $20 Million in 2003 to Find New Treatments and a Cure for Huntington's Disease

By Nancy Wexler

Families with Huntington's disease should take heart in our all-out push to find new treatments and a cure for HD!! You will find a complete list of our grantees, their institutions and research topics in this newsletter. We're sure that you—like us—will be extremely gratified and grateful to see so many fabulously gifted and qualified people throughout the world working hard to bring answers rapidly to your doorstep!! The titles of these grants are a bit technical to comprehend precisely what each grantee is doing. In future newsletters we will focus on just a few HDF scientists each time and highlight their work.

There are too many to explain all in one newsletter!! We hope you will take heart and hope that there are so many!!

The Hereditary Disease Foundation has two funding programs: Our Scientific Advisory Board reviews proposals that deal with the fundamental issues of understanding Huntington's disease—what starts it, and how to prevent it, treat it and CURE it. Our Cure HD Initiative (CHDI) is a fast-track program particularly dedicated to constructing cellular and animal models, developing and testing drugs in animals and humans, and catalyzing research aimed at finding new therapeutics.

I hope you will all feel heartened and encouraged by the great work of these fabulous scientists. ■

H. Robert Horvitz, Ph.D., Receives the Nobel Prize

Bob Horvitz—HDF Family Member—Wins the Nobel Prize!

By Nancy Wexler

Congratulations Bob, HDF Scientific Advisory Board member, Cure Committee founding member and close friend!!! **H. Robert Horvitz, Ph.D.** is a professor of biology at MIT and an investigator at the Howard Hughes Medical Institute. The Nobel Committee agrees with our judgment of our spectacular brother! **Bob is sharing the 2002 Nobel Prize in Physiology or Medicine with Sir John Sulston and Sydney Brenner for their work on a tiny roundworm called *Caenorhabditis elegans*.**

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Good News: SAHA Dramatically Improves Motor Function in a Mouse Model of HD!!!

Gillian Bates, M.Sc., Ph.D.

By Gillian Bates

***Gillian Bates, M.Sc., Ph.D.**, is Professor of Neurogenetics, Division of Medical and Molecular Genetics, GKT School of Medicine, King's College, Guy's Hospital, London, UK and **the only two-time recipient of the special HDF Lieberman Award** in both 1994 and 1997, whose research has been featured on **TWO covers of the prestigious science journal** Cell.*

Ever since Leslie Thompson, Larry Marsh and Joan Steffan's research was published last summer which showed that drugs called "histone deacetylase (HDAC) inhibitors" slowed down nerve degeneration on their fruit fly model of HD (see Summer

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RNA TO OUR RESCUE!!

"RNA Modalities of HD Therapy," December 7-8, 2002, Cambridge, MA

By Nancy Wexler

We are all indebted to Gregor Mendel and his garden experiments with pea plants. From him stemmed the basic principles of heredity. James Watson and Francis Crick followed in 1953 with their most amazing discovery of the structure of DNA, which revealed how cells pass on their identity from cell to cell and generation to generation.

Now we are indebted once again to Mendel, Watson and Crick and plant geneticists. Richard Jorgensen, a plant geneticist working in the 1990s in a biotech firm in Oakland, CA, wanted to make his purple petunias a more vivid purple. He fed them extra copies of a purple pigment gene and, much to his amazement, the petunias turned completely white. He speculated that giving the petunia an extra copy of a purple gene shut off its own purple gene and the flower turned white.

At around the same time, geneticists working on tiny roundworms called *Caenorhabditis elegans* began to notice the same bizarre phenomenon. When they gave the worm an extra copy of its own gene—instead of that gene getting stronger as they expected—it seemed to shut down both the native and the new genes! In 1998, Andrew Fire, Ph.D., Scientific Staff, Department of Embryology, Carnegie Institution of Washington, and Craig Mello, Ph.D., Assistant Investigator, University of Massachusetts Medical School, worked out the mystery in worms.

A gene is made of DNA. The order of the "rungs of the ladder of DNA"—or base pairs of DNA—specifies what amino acids go into making up a protein. DNA itself does not directly the making of a protein. Rather, it recruits the help of another molecule called messenger RNA to take the instructions from the DNA in the nucleus of the cell to the protein building factories in the cytoplasm.

Scientists understood RNA's essential role in the protein-manufacturing process. But now, much to everyone's shock and amazement, RNA was turning out to shut down the very gene it was supposed to be making!!! How did that happen? And even more important, would it occur in mammalian cells? When scientists first tried using the same techniques in mammalian cells which had succeeded in worms, the cells died. But fortunately for us, Nobel laureate **Phillip Sharp, Ph.D.**, Institute Professor and Director, The McGovern Institute at MIT, and his former student, Thomas Tuschl, Ph.D., now an associate professor at Rockefeller University, persevered. They finally figured out, building on Fire and Mello's discoveries in the worms, that extremely tiny, highly specific fragments of double-stranded RNA—an abnormal configuration for RNA—could work wonders. In April, 2001, Tuschl and colleagues published in *Nature* how to make "small, interfering RNAs" or "siRNAs" which could work in mammalian cells. They called the process RNA interference (RNAi) or gene silencing.

Phillip Sharp, Ph.D.

The miracle of this new discovery is its fabulous potential for developing new therapies and also for understanding basic biology. It is now possible to shut down selectively every single gene, one by one, in the human genome and in model organisms, and to discover what each gene does and the pathway in which it participates. This knowledge will give us many new leads for new therapeutics because the drug could be aimed at another part of the pathway that might be more accessible to treatment.

Even more critically for us, disruptive genes—like the gene causing Huntington's disease—can be permanently shut down!!

When we first found the HD gene in 1993, we thought perhaps we could just turn it off altogether and that would be a cure for the disease. Maybe people do not need the protein that it makes and could live perfectly well without it.

Unfortunately, when scientists tried this in a mouse—getting rid of the mouse's own version of the HD gene—the mouse died *in utero*. Of course, we don't know for sure if what's true for a prenatal mouse is true in an adult human—but it's a good bet it is.

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Jennifer Jones Simon

Thank You, Jennifer Jones Simon!!!!

By Nancy Wexler

The Jennifer Jones Simon Foundation has pledged $400,000 at the rate of $100,000 per year over the next four years to be used exclusively for our world-renowned Mary Jennifer Selznick Workshop Program, named in honor of Jennifer Jones Simon's late daughter. This generous endowment ensures the continuing success of our unique workshops. These small, informal, free-wheeling workshops foster dialogue among researchers from a variety of fields, who come without prepared lectures or slides to converse across disciplinary borders. Jennifer has been a critical member of the HDF family since she served on the Congressional Commission for the Control of Huntington's Disease and its Consequences in 1976. We appreciate her loyalty and championship of beginning and established scientists worldwide who have, in turn, been graced by her presence at workshops, many in her own home with its stellar art collection.

H. Robert Horvitz Wins Nobel Prize, cont. (pg. 1)

Åt dem som har gjort mänskligheten den största nytta. Nobels testamente

NOBELFÖRSAMLINGEN
KAROLINSKA INSTITUTET
har beslutat att 2003 års
NOBELPRIS
i fysiologi eller medicin
skall tillerkännas
och gemensamt utgå till
H Robert Horvitz
SYDNEY BRENNER
OCH
JOHN E SULSTON
för deras upptäckter
rörande genetisk reglering
av organutveckling och
programmerad cellöd

Bob Horvitz, Allan Tobin and Edward Kravitz organized a Hereditary Disease Foundation workshop in 1979 on cell death. He has been a member of our HDF family ever since. Bob then served for a decade—from 1983 to 1993—as an advisor to the HD Gene Hunters. Bob, Allan Tobin, Richard Mulligan, Mike Conneally and Glen Evens met quarterly with the Gene Hunters to guide and encourage the spectacular collaboration that graced this group and led to finding the HD gene. When we needed sequencing of the top of chromosome 4 to identify the gene, Bob called his good friend John Sulston who began doing sequencing. John then went on to sequence the entire human genome! Bob is now a founding and critical member of our Cure HD Initiative and has been since its inception.

While Bob was advising the Gene Hunters about how to find the HD gene, his own father developed the devastating neurodegenerative disease amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). Bob immediately flew into action to put together a team to find the gene causing ALS. Only about 10% of cases are hereditary, but finding a gene that causes one form can lead to important pathways and clues about all of them. About a month before the HD gene was isolated, Bob called me to say that he and his colleagues had isolated a gene on chromosome 21 that causes ALS in some hereditary cases! Now scientists have used that gene to create mouse models of ALS and to screen for new treatments. Bob still takes an active involvement in that research as well as being a fantastic guide for HD science.

Bob first found genes in *C. elegans* that cause cells to die. When these genes are present, the cell commits suicide (a process known as "apoptosis" or programmed cell death). And when they are absent, the cell lives!!!! Sometimes you want a cell to die—if it has cancer, for instance. But sometimes, cells are dying when you want them to live—like in HD, ALS, Parkinson's disease, and many other disorders. After Bob found these genes, the critical question facing him was: were the genes that controlled life and death in a worm the same as in us?!! Bob searched and searched - and amazingly, the answer is YES, THEY ARE THE SAME!!!

Bob painstakingly and elegantly traced out the pathways of cell life and cell death—which cell talked to which cell and under what circumstances. He found genes in these pathways like railroad switch men who could send the train smoothly down the track or derail the cars in a giant pile up. And he found, over and over, that his minuscule creatures could open the doors to a powerful understanding of new treatment pathways for devastating human diseases.

We are forever indebted to Bob for his friendship, his loyalty, his spectacular mind, his discoveries and the joy he brings us watching his translucent guides wiggle their way toward revelations about health and disease. ■

Good News, cont. (pg. 1)

2002 HDF newsletter online at www.hdfoundation.org/PDF/NewsletterSummer2002.pdf for details), it has been a burning question as to whether these same drugs would work in mice.

We are extremely pleased to report that, indeed, we found administration of SAHA (suberoylanilide hydroxamic acid), an HDAC inhibitor, dramatically improved the movement impairment in one mouse model of HD! This particular mouse was made by my colleagues and me in 1996, the first mouse model of HD. SAHA is in early clinical development for cancer. It has not been approved by the FDA.

Genetically modified mice are the closest models that we have for HD to date. It is extremely exciting that one of these drugs is effective in mice and has provided the green light to develop further HDAC inhibitors for use in the clinic to treat HD. It is also the first time that a drug has been taken through the pipeline from work in cultured cells and yeast cells, to fruit flies and then to mice. This gives us confidence that it is a successful approach for the development of drugs to treat HD!

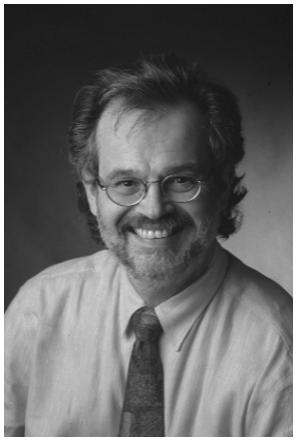
Since the identification of the Huntington's disease gene in 1993, dramatic progress has been made in understanding the molecular events by which this faulty gene causes Huntington's disease. As these steps are uncovered, new targets for drug therapy are revealed. One effect of the faulty gene is that it alters the extent to which other genes, important for the function of brain cells, are switched on. In most cases, the level at which these genes are switched on has been turned down.

The process could be compared to a rail network—if certain trains start to run at a reduced speed, the function of the whole network becomes affected. The precise molecular interactions that lead to genes being turned down is not yet understood, although many clues are emerging. It seems that HDAC inhibitors are drugs that can be used to increase the amount by which genes are switched on which would keep the trains smoothly running on the track!

For the complete article entitled "Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's Disease," see the February 18, 2003 issue of the *Proceedings of the National Academy of Sciences*. ■

Reflections on Three Decades of Progress

(Excerpted from Remarks by Allan Tobin at the August 11, 2002 HDF Meeting, "HD2002—Changes, Advances, and Good News $(CAG)_n$" in Cambridge, MA)



Allan J. Tobin, Ph.D.

***Allan J. Tobin, Ph.D.**, is Scientific Director Emeritus of the Hereditary Disease Foundation, Eleanor Leslie Chair of Neuroscience, and Director of the Brain Research Institute at the University of California, Los Angeles.*

HDF's success has depended on renewal: the turnover of the Scientific Advisory Board may even be the Foundation's most important rule. In that spirit, I have decided to step down as Scientific Director, after nearly 25 years.

A lot has happened in that time. By now, it's been an awfully long time since anyone has asked if I actually meant Hodgkin's disease, since anyone questioned why anyone would work on this orphan disease, and since anyone wondered just what molecular genetics could possibly contribute.

My first introduction to HD, in 1972, featured a late-night conversation, lubricated by Scotch that Milton somehow purchased in defiance of Boston's extant blue laws. Since then, discussions have gone from whiskey-laced speculations about cell death to concrete arguments about apoptotic cascades, from claimed alterations of membrane fluidity to the identification of specific deficits in exocytosis, endocytosis, and autophagy, from misinformation about sex linkage to the systematic search for modifying genes.

Many of these discussions have occurred at HDF workshops. These workshops have included more than 1,500 scientists and clinicians, with nearly every conceivable type of biomedical expertise. More recently, HDF inaugurated larger summer meetings, and the 2002 meeting was the biggest ever.

Why has HD captured the attention of so many talented people? I think it's because—no doubt because of LA's surfer culture—we've always sought to be just in front of the wave crest. For example, in 1979 we brought together clinical geneticists, somatic cell geneticists, population biologists, neurologists, and people who were just beginning to develop DNA-based gene mapping. Locating the HD gene in 1983—the first disease gene mapped with the new techniques—led quickly to HDF's Collaborative Research Group, which found the gene itself in 1993. Some veterans of that consortium—**Gill Bates, Jim Gusella, Bob Horvitz, David Housman, Hans Lehrach, Marcy MacDonald, and Leslie Thompson**—have continued to be at the forefront of HD research.

A great privilege of my work has been meeting some wonderful families. Each HDF workshop begins with a discussion with a family affected by HD, and these conversations have inspired much thought, focus, and urgency. As trustee **Harry Lieberman** puts it, "When is all this work going to help my family?" The question for HD research, then, is not only how to stay in front of the wave but also how to create a new wave—with sufficient force to knock down this disease.

We can think about the three phases of moving from bench to bedside—discovery, development, and delivery. Fortunately, HD has well-organized clinical networks—notably the Huntington Study Group, originally organized by **Ira Shoulson**—which will test, train, and deliver. Similarly, discovery is well in hand: good new ideas about HD almost always find funding. But what about the middle phase—development? Here, the criterion for success cannot be testing of hypotheses but progress toward interventions.

The big news in the last year has been drug screening, both in academic labs and in companies. By the end of 2003, such screens will identify dozens of compounds with therapeutic potential. The next steps will be secondary assays, the synthesis and evaluation of analogs, *in vivo* action, toxicity, and pharmacokinetics. These concerns are mostly new to HD researchers, and we will need new ways of thinking. Systematic assessment of mouse models, for example, will be increasingly important, as will attempts to find biomarkers—biochemical, imaging, or behavioral—that will allow us to study disease progression. Development can now go on in a scientifically engaging manner, and we'll soon begin to cross the fragile bridge from bench to bedside.

I am grateful to the HDF—and especially to Milton, Alice, and Nancy—for making it possible for me to participate almost from the beginning and, I am confident, almost to the end. ■

A Tribute to Allan J. Tobin

(Excerpted from Remarks by Milton Wexler at the January 11-12, 2003 Albert Parvin Foundation-sponsored HDF Workshop, "Huntington's Disease: From Molecule to Miracle in the Search for a Cure" in Los Angeles, CA)

Nancy Wexler, Ph.D. with Allan J. Tobin, Ph.D.

The year 1978 was a momentous one for the Foundation. The Congressional Commission for the Control of Huntington's Disease and its Consequences, of which Marjorie Guthrie was chair, I was co-chair and Nancy Wexler was executive director, had just finished its work. We submitted our report to President Jimmy Carter and to Congress. As a result of that report, NINCDS (National Institute of Neurological and Communicative Disorders and Stroke—now called NINDS) became increasingly interested in Huntington's. One of the Commission's recommendations was that an international meeting be held focusing on the state of the art of HD research and where we needed to go in the future. So that year, NINDS organized a symposium to be held at the wonderful Del Coronado Hotel on Coronado Island in the bay across from San Diego. By this time, researchers had developed a considerable body of information about HD. There were many eminent scientists who had clinical reports to give, speculations about the origin of the illness, and ideas about how to tackle the problem.

The Hereditary Disease Foundation had organized a small workshop following the meeting to brainstorm about how best to pursue ideas presented at the meeting. One of the individuals who attended the symposium and workshop was a young assistant professor of biology from UCLA who had developed an interest in Huntington's when he attended a Foundation workshop back in 1972, as an assistant professor at Harvard. This young biologist was **Allan J. Tobin**—lively, energetic, forceful, determined, enthusiastic and full of ideas.

Allan had been an undergraduate at MIT and earned his Ph.D. at Harvard. He then went to the Weizmann Institute in Israel for a postdoctoral fellowship, returned to MIT for a second postdoctoral position, and became an assistant professor at Harvard before moving to Los Angeles and UCLA.

The previous science director of the foundation left in 1978 to return to research. Even before the workshop, Alice, Nancy and I—and certainly others around us—realized that our foundation needed an excellent basic scientist who not only knew the biological and genetic problems involved in HD, but who had rich ideas of his own, a real interest in Huntington's, and an awareness of what laboratories around the world were doing. We knew at once that if we could get someone like Allan involved, we would be taking a very significant step forward.

So Nancy and I invited Allan to have dinner with us on the first evening of the symposium at the Del Coronado. We were also thrilled to have with us **Jennifer Jones Simon**, who had been an important member of the Congressional Commission for the Control of HD and its Consequences and was now a great representative of the Foundation in the halls of Congress and at the NINDS. We had a wonderful dinner and were all totally charmed by Allan's enthusiasm, his breadth of knowledge, and his willingness to speculate and theorize. Here was the individual who might lead us to the Promised Land.

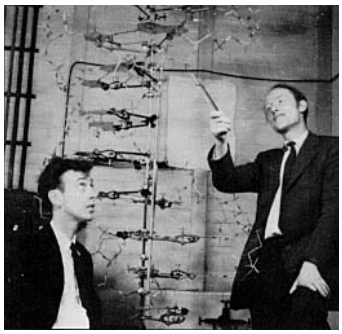
When the dinner was over and Allan went back to the symposium, the first person to speak was Jennifer. She announced very firmly, "There's your man. You've got to hire him. You'll have the answer."

Jennifer's expertise happens to be in the field of acting, in which she is very much a star. We knew that Jennifer—just like us—found Allan delightful and fell under his spell of rapid-fire thought and wit. When Allan is in the room there is a rise in the energy level that is palpable. For the Wexlers at that table, too, there was no question that if we could get Allan to become scientific director for the foundation, it would be a great coup for us, and an extraordinary benefit for HD research through Allan's intelligence and dynamism. The *if* turned to a *yes* and Allan came aboard.

I will put it simply and straightforwardly to you. There has never been an advance, a discovery, a push forward in the direction of finding the gene, the cause of Huntington's and how it manifests itself, and how to treat and prevent it, without the imprint of Allan Tobin. He has been a significant, central, key figure in every advance that we have made; he leaves us with an immensely rich heritage from his efforts. Now, after twenty-three years, Allan is retiring as scientific director of the foundation in order to spend more time in his lab. He continues, of course, as a professor of neuroscience and director of UCLA's famous Brain Research Institute. Allan will also continue to search for a cure for HD as a valued member of the Cure Committee of our Cure HD Initiative.

We are enormously grateful to you, Allan, and we send all our best wishes to your wife Janet Hadda and to your sons, Adam and David, and welcome to your new grandson, Gabriel, to the world. I wish you a glorious sabbatical year, and look forward to many more years of our friendship and shared dedication to science! ■

HDF Plays a Key Role in Celebrating the 50th Anniversary of the Discovery of DNA and the Completion of the Human Genome Project!



James Watson, Ph.D. and Francis Crick, Ph.D. with DNA model

April 2003 marked the 50th anniversary of the most ground-breaking achievement in biology to date: James Watson and Francis Crick's Nobel Prize-winning description of the DNA double helix. To continue the April celebration, we witnessed the momentous culmination of one of the most important scientific journeys in history: the sequencing of the human genome.

To mark these achievements in the history of science and medicine, a month-long series of scientific, educational, cultural and celebratory events sponsored by the National Human Genome Research Institute (NHGRI), parts of the National Institutes of Health (NIH) and the Department of Energy (DOE) were held across the United States. The festivities began with a kick-off event in Washington, D.C., including the scientific symposium "From Double Helix to Human Sequence—and Beyond," as well as various galas and celebrations. The symposium explored the future of science and medicine made possible by breakthroughs in genomic science, and included the unveiling of NHGRI's new vision for the future of genomic research. James Watson, Francis Collins, members of the International Human Genome Sequencing Consortium and Nancy Wexler were among the participants.

There was a celebratory reception on at the **Smithsonian** to launch a big exhibit on DNA and the Human Genome Project called "**GENOME: The Secret of How Life Works" in which the Wexler family and Hereditary Disease Foundation are featured.** The exhibit will be on display through January 4, 2004. Francis Collins, M.D., Ph.D., Director of the National Human Genome Research Institute, NIH, sang a DNA song that even included a verse about Nancy Wexler and the Ethical, Legal and Social Implications working group which she chaired!

There was a gala dinner at the Library of Congress celebrating the completion of the mapping and sequencing of the human genome and the 50th birthday of DNA. News analyst Cokie Roberts, the hostess for the event, asked everyone involved with the Human Genome Project to stand up. Nancy Wexler stood among this impressive group of luminaries. ■

Recent Press

HDF President Nancy Wexler, Ph.D.

HDF President **Nancy Wexler, Ph.D.** has been keeping the press busy lately. To read the complete articles, refer to the HDF website "News" section (www.hdfoundation.org/news.htm).

- *U.S. News & World Report* ran a story in the February 24-March 3, 2003 issue, "Triumph of the Helix," celebrating DNA's 50th anniversary. Included was a detailed timeline of the history of genetics, beginning in 1866 with Gregor Mendel's pea plant experiments and ending with the death of Dolly, the first mammal to be cloned from an adult cell. "**The identification of the HD marker in 1983 by Nancy Wexler and a team of researchers using DNA from the Venezuelan family" was also one of the notable events to be listed on the timeline.**
- *The New York Times* on February 25, 2003, also joined in on the celebration of DNA's 50th anniversary. In one article, *The Times* asked the experts how DNA's discovery, and the decades of genetic research that followed, affected their work and lives. Nancy Wexler spoke of the stigmatization faced by individuals with Huntington's disease: "They can't tell their friends. They can't tell their employers. They can't tell their insurers. They become damaged DNA, mutant DNA. In the beginning, when there wasn't any way of knowing, [the majority] of all at-risk people worldwide said they wanted to know [if they carry a normal or abnormal version of the HD gene]. Now, in the United States less than 3 percent have been [gene] tested." (www.hdfoundation.org/news/20030225-NYTa.htm)

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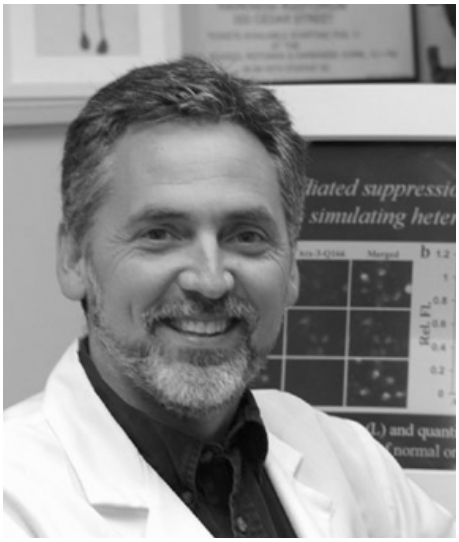
RNA to Our Rescue, cont. (pg. 2)

The best cure for HD would be just to turn off the gene that produces an abnormal protein and leave the normal protein intact. But how, since they are almost identical except for a few extra CAGs at one end, do you do that?

Scientists supported by the Hereditary Disease Foundation have just published results in *Proceedings of the National Academy of Sciences (PNAS)* that they were able to selectively turn off the gene making a protein called ataxin. Too many CAGs in the ataxin gene lead to a disease called spinal cerebellar ataxia type 3 (Machado-Joseph disease). The disease and the mistake in the gene are very similar to HD. The RNA—an abnormal configuration for RNA—could work wonders. In April, 2001, Tuschl and colleagues published in *Nature* how to make "small, interfering RNAs" or "siRNAs" which could work in mammalian cells. They called the process RNA interference (RNAi) or gene silencing.

The miracle of this new discovery is its fabulous potential for developing new therapies and also for understanding basic biology. It is now possible to shut down selectively every single gene, one by one, in the human genome and in model organisms, and to discover what each gene does and the pathway in which it participates. This knowledge will give us many new leads for new therapeutics because the drug could be aimed at another part of the pathway that might be more accessible to treatment.

The challenge is the same—how to shut down the abnormal protein and leave the normal one intact? **Beverly Davidson, Ph.D.**, Roy J. Carver Associate Professor in Internal Medicine, and **Henry Paulson, Ph.D.**, Assistant Professor, Department of Neurology, both from the University of Iowa, first tried targeting the CAG repeat itself and were unsuccessful. They then looked for some tiny genetic difference in the rest of the gene that they could target—something that differed between the normal and the abnormal gene. Fortunately, our DNA has many scattered changes peppered throughout it—about one change in every 1,000 base pairs. These normal variations are referred to as "Single Nucleotide Polymorphisms" or SNPs. An example of a SNP is when some people have an "A" in a certain spot in their gene and other people have a "G" in that same spot. These changes do not cause disease, for the most part, but are essential in differentiating one gene from the next.



Henry Paulson, Ph.D.

Beverly Davidson, Ph.D.

Paulson and Davidson found that a certain SNP characterized 70% of the ataxin genes with an expanded repeat compared to the normal gene. They then fashioned siRNA or RNA interference specifically to target the SNP associated with the abnormal gene. Lo and Behold!! Almost all of the abnormal protein vanished in the cell!!!! And the normal protein was left intact!!! Paulson and Davidson are now trying this on the HD gene and first reports look very promising!!!

There is no doubt about it!!! In the test tube or the cell—RNAi is a cure for Huntington's disease and other expanded repeat diseases!!! But there are many challenges ahead!!

Delivery, Delivery, Delivery!! How do you get the RNAi to stay stable in a cell? How do you get the RNAi into the brain and into enough cells in the brain to correct the problem? How many cells in the brain do you need to target to be therapeutic? Do you need to target cells outside of the brain, even if we think HD is purely a brain disorder? When in a life span do you need to begin the therapeutic process? What are the best delivery mechanisms—viruses? Are they safe?

The gene therapy world is confronted with the most tantalizing challenge ever—here we have a phenomenon that actually seems to work to treat a very wide variety of diseases, from HD to AIDS to cancer to autoimmune problems to essentially all disorders in which scientists want to turn off or turn down an abnormal protein—without effective ways to get these therapeutic agents into the necessary areas!

Continued on page 8

RNA to Our Rescue, cont. (pg. 7)

The Hereditary Disease Foundation is very fortunate to have among its friends and advisors many of the scientists who began this revolution. In December, 2002, we had a workshop in Cambridge that was co-organized by Phillip Sharp and **Richard Mulligan, Ph.D.,** Mallinckrodt Professor of Genetics, Harvard Medical School, a long-standing

Richard Mulligan, Ph.D.

member of the HDF Advisory Committee to the Gene Hunters and now a founding member of the Cure Committee. Richard won a MacArthur Genius Award many years ago for being among the first to design gene therapy vectors and has been an important innovator as well as a voice of caution, warning that gene therapy was not yet ready for prime time. Richard moderated the two-day workshop.

Workshop participants included Beverly Davidson and Henry Paulson, mentioned above. Phillip Zamore, from Phillip Sharp's company Alnylam, specializing in RNAi therapeutics, attended. John Wolff represented both academic and commercial interest and expertise in RNAi—he is a professor at the University of Wisconsin-Madison and Chief Scientific Officer and co-founder of Mirus Corporation. Many at the workshop were working on different aspects of RNAi and others on a variety of ingenious delivery systems. Some of the participants were being funded by the Hereditary Disease Foundation before the workshop. And even more are being funded since new collaborations were formed at the workshop itself. We are planning another RNAi workshop in the fall especially focused on the question of delivery. Stay tuned!

"The Elixir of Life: Special Report: The discovery of DNA unlocked the mystery of existence. But within its coils, science has discovered a prize beyond our wildest dreams"—so read the cover of the *Sunday Magazine of the London Times* on May 23, 2003.

The article entitled "Unlocking the Secrets of RNA Interference" goes on: "As the fight against genetic disease continues, scientists believe that disrupting the RNA message system is the safest way to eradicate harmful proteins in the body"

The text begins:

"As Leonore Wexler staggered along a sidewalk in Los Angeles one morning, muttering to herself with slurred speech, a policeman outside the courthouse rebuked her for drunken and disorderly behavior. But this well-educated, well-dressed 53-year-old mother, with two daughters in their twenties, had not been drinking. She was suffering the onset of a genetic illness of the brain and central nervous system that had already killed several members of her family. She was beginning to experience the symptoms of Huntington's disease (HD), the prognosis of which is devastating and, in the long term, fatal. First, sufferers lose control of their limbs and speech; then they descend into emotional and intellectual fragmentation, ending in death.

"Despite billions of dollars spent on research in the past two decades, despite the sequencing of the human genome and the hype and high hopes for genetic-engineering therapy, no safe treatment for HD has been found. In fact, no safe genetic treatments have been discovered for a galaxy of other illnesses caused by faulty genes. In the past three years, three young people have died worldwide as a result of attempted genetic therapy, leaving the clinical strategy in disarray.

"But recently, patients suffering from Huntington's disease and other genetic diseases were given hope by Professor Beverly Davidson at the University of Iowa [funded by the Hereditary Disease Foundation]. It takes the form of a novel method, already successful in animals, exploiting a fundamental mechanism of all life, which goes by the forbidding title of RNA interference (RNAi). Also known as "gene silencing," RNAi is being greeted as the next quantum leap in medicine by scientists the world over.

"For once, the prospects match the hype. Sir Paul Nurse, Britain's whiz-kid Nobel-prize winner, is this country's leading RNAi enthusiast. The head of Cancer Research UK, who is soon to depart for New York to run the Rockefeller University, where he will have 22 Nobel winners as colleagues, Nurse, 54, sees the technique as a 'fantastic new tool' for discovering how each of the 35,000 human genes contribute to cancer. 'Thanks to the incredible discovery of RNA interference, we think we should be able to crack the problem.'"

The article describes RNAi and how it works in an elegant, cogent and understandable way. The author compares the process of making proteins to a symphony orchestra. If one instrument is playing out of tune, the very precise and delicate process of RNA interference can selectively silence just that instrument and let the rest of the symphony proceed uninterrupted by dissonance.

According to the *London Times*, RNAi is hailed as the greatest breakthrough of this year by the prestigious journal *Science* and is one area where hype is equal to hope. Enthusiasm over RNAi has even sparked a mini-resurgence in the faltering biotech industry.

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RNA to Our Rescue, cont. (pg. 8)

The London Times article continues:

"The diseases that stand to benefit from RNAi therapy include Alzheimer's, breast cancer, leukemia, schizophrenia and many, many more. But it looks as if Huntington's disease will be one of the illnesses tackled earliest by the RNAi process. Leonore Wexler's tragic case history, with which we began our story (she died 30 years ago), became famous in the annals of medicine because Nancy Wexler, one of her two daughters, made a search for HD her life's work. Today she is the President of the Hereditary Disease Foundation in New York and a professor at Columbia University medical school. Nancy Wexler, who herself has a 50-50 chance of contracting the disease, began studying a community on the shores of Lake Maracaibo, Venezuela, where there is an unusual incidence of Huntington's disease. She returned year after year, assiduously collecting DNA samples and carefully tracing family histories.

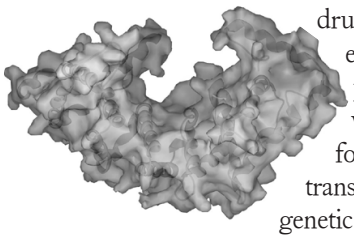
"Finally, she joined forces with [three researchers, David Housman from Massachusetts Institute of Technology, James Gusella from Harvard University, and P. Michael Conneally, from Indiana University. Searching for the HD gene began with a large family from Iowa, which was inconclusive. Adding the DNA and information from the gigantic extended families from Venezuela were absolutely conclusive and in 1983, the team discovered the locale of the gene on the top of chromosome 4.] But it was to take 150 researchers another 10 years to isolate the gene for detailed analysis. Eventually they found that the disease is caused by mutations in the Huntington's gene that generate a protein that destroys parts of the brain. To attempt to knock out the gene entirely would deprive the patient of other important proteins necessary to life. But RNAi works to isolate and reduce or switch off the precise processes that build the [damaged protein, while leaving the normal gene which makes the normal protein intact.] 'When I heard of this work,' said Nancy Wexler recently, 'it just took my breath away.'

"...In the meantime, scientists such as Nancy Wexler would be happy to see a breakthrough in the disease that threatens her own life and that killed her mother. If RNAi can prove successful in just one genetic disease, it will offer hope for sufferers in many others. Sir Paul Nurse, as he prepares to go to Rockefeller University, has his eyes and his own continuing research set steadily on cures for cancer, but he does not blench at dropping hints about wider comparisons between animal research and human applications. 'Through RNAi research we are discovering what gives animals big brains, or makes them fat, or makes them stupid, and making adjustments. It is more difficult, of course, but there is no reason why we will not one day do the same thing in humans.'"

Please also see an excellent article "Biotech's Billion Dollar Breakthrough" in the May 26, 2003 issue of *Fortune*, where HD research is also featured—www.fortune.com/fortune/technology/articles/0,15114,450721,00.html. ■

Max Perutz Protein Purification Project *By Marina Chicurel, Michael Sauder, and Julie Porter*

HDF and **Structural GenomiX, Inc. (SGX)** announced in December 2002 a collaboration agreement to investigate the structure of huntingtin, the protein responsible for Huntington's disease. SGX is a drug discovery company, which focuses on translating genetic information—such as proteins—into structural models for drug development. Determining huntingtin's structure should help reveal the protein's normal function and how it causes disease when it is mutated. It should also provide key insights for the design of new therapies.



Ever since the huntingtin gene was discovered in 1993, investigators have been eager for information on the protein's shape, predicting it would allow them to make important strides towards understanding Huntington's disease. Indeed, some of the most prestigious scientists who have tackled Huntington's disease were frustrated by the lack of this information. The late Nobel laureate Max Perutz, for example, repeatedly stressed how much the field could move forward if only we had more data on huntingtin's structure and how it is altered in disease.

"Max Perutz was always saying, 'Where's the structure? We need the structure!'" recalls **Nancy Wexler**, president of the Hereditary Disease Foundation. She also notes that the Foundation is carrying out this new collaborative partnership in his honor. **Max was a good friend to the Hereditary Disease Foundation family and made critical contributions to HD research.**

The structure of huntingtin has remained obscure because it is a difficult protein to work with. Unlike most proteins, huntingtin is extremely large and unwieldy. Researchers have met with many obstacles when trying to obtain large amounts of it in pure form, a key requirement for unambiguously deciphering its three-dimensional shape.

"It's huge," says Wexler. "We haven't been able to get our arms around it."

SGX will use a high-tech X-ray technology to understand how the huntingtin protein functions, both in its healthy and unhealthy forms.

Meanwhile, clues can already be gained from modeling the protein by comparison to other structures, using computational simulation. SGX's ability to rapidly generate high-quality structural data will help HDF identify potential drug leads. We can learn of pockets in the protein's structure that might be accessible for targeting a drug.

Wielding such cutting-edge tools, HDF and SGX hope to get a first-ever view of three-dimensional huntingtin. This new vista should provide important clues about the functions huntingtin normally performs in cells and the proteins with which it interacts. By comparing the shapes of normal and mutated huntingtin, the researchers also hope to better understand what goes wrong in Huntington's disease. "Working side-by-side with an organization like SGX and tapping into their extensive knowledge of protein crystallography brings us many steps closer to uncovering the molecular pathology of Huntington's disease," says Wexler.

The study of normal and mutated huntingtin structures is also expected to help researchers design drugs that uniquely target the diseased form of huntingtin. If a promising structure is identified, SGX's expertise in analyzing structural interactions between small molecules and proteins could greatly accelerate the development of new drug candidates. "The HDF collaboration exemplifies the importance of SGX's gene-to-structure technology platform in aiding the fight against debilitating diseases like Huntington's disease," says Stephen K. Burley, chief scientific officer of SGX. ■

With a Little Help From Our Partners...HDF Featured in the *New England Journal of Medicine*

By Apoorva Mandavilli

The Hereditary Disease Foundation's efforts in finding drugs to treat Huntington's disease recently received acclaim from the vanguard of the scientific community. The *New England Journal of Medicine* explored the pitfalls of public-private partnerships in drug discovery in "Collaborating with Industry—Choices for the Academic Medical Center" in the October 24, 2002 issue. One alliance that works, according to the article, is a collaborative effort between HDF, Aurora Biosciences—a drug discovery company now known as Vertex Pharmaceuticals Incorporated—and academic researchers from the Huntington Study Group. Drug development is the ultimate goal for all involved.

"The Foundation provides funding and an organizational structure," the authors say, "and Aurora provides capability in screening of compounds against targets that are identified by the academic researchers."

In public-private-academic partnerships, each participant brings unique capabilities to a shared problem, and all of them together solve obstacles that face them. Whereas most attempts to forge such partnerships have failed because they did not lay firm ground rules for their cooperation, the article praises HDF's alliance as one of few that "overcame critical questions of mutual respect and governance...support the dissemination of new findings, and yet remain compatible with eventual commercialization." ■

Dye Delivers Death Blow to Huntington's Disease Symptoms

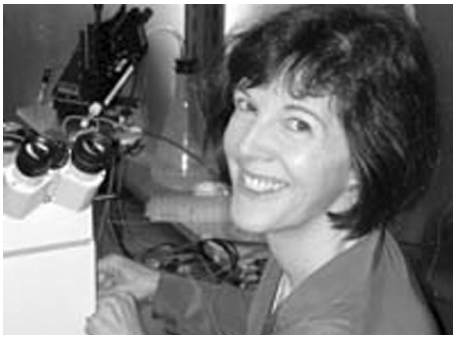
By Apoorva Mandavilli

The results of Hereditary Disease Foundation-supported researchers **Junying Yuan, Ph.D.**, Professor of Cell Biology, Harvard Medical School; **Ivelisse Sanchez, Ph.D.**, Assistant Professor of Anatomy and Neurobiology, Boston University; and colleagues were reported in the leading journal *Nature* on January 23, 2003. They showed that, at least in mice, disrupting clumped proteins in the brain can dramatically lessen the symptoms of Huntington's disease and may suggest important possibilities for therapy. The clusters—also called aggregates—are a hallmark of several neurodegenerative disorders, including Huntington's disease. In most cases, scientists have shown that the proteins form clusters when a repeated sequence of amino acids—CAG in their letter code—grows too long.

The scientists used a dye called Congo red, which selectively binds to the protein aggregates. In a mouse model of HD, the dye disrupted existing clumps and prevented more clumps from forming, the scientists found. Perhaps as a direct result of the change in the clump formation, Congo red also prevented brain cells from dying, decreased the high blood glucose levels and severe weight loss associated with Huntington's and improved limb movement in the mice. With the aggregates breaking down or never forming in the first place, researchers may be able to determine if it is the clumps themselves which cause the symptoms of HD or if something else causes the symptoms to begin and clusters to develop. Congo red is not a drug humans can take but its success does give us important leads about compounds that might have a similar effect. ■

HDF SPECIAL AWARDS

Lieberman Award Presented to Lynn Raymond from University of British Columbia



Lynn Raymond, M.D., Ph.D.

Lynn Raymond, M.D., Ph.D., Associate Professor of Psychiatry from the University of British Columbia, Vancouver, Canada, is this year's special **Lieberman Award** recipient. Lynn's work focuses on a kind of receptor called NMDA receptors. Receptors are like doors into a cell. The door can be open too long and let in thieves that rob the house blind or be stuck shut and unable to open when the family arrives home. We have good evidence that NMDA receptors are altered in HD. Because the NMDA receptor plays a central role in producing stroke and other diseases, these clues can lead us to new therapeutics as many pharmaceutical companies feel that this receptor is a hot topic. We could potentially use medicines developed for other disorders. Lynn has been a key player in learning how these receptors are altered. *The Lieberman Award was initiated by longtime HDF trustee* ***Harry Lieberman*** *to catalyze innovative proposals leading to the treatment and cure of Huntington's disease.*

Milton Wexler Postdoctoral Fellowship Award to Edoardo Marcora—Mentored by Mary Kennedy of Cal Tech

Edoardo Marcora, Ph.D., a research fellow from the lab of **Mary Kennedy, Ph.D.**, Professor of Biology at the California Institute of Technology, received this year's **Milton Wexler postdoctoral fellowship**, a special award for promising young investigators. Mary Kennedy has been a critical contributor to our Scientific Advisory Board for the past four years and during previous terms. The Kennedy laboratory is studying synapses—the connections between neurons in the brain—and investigating the ways these synapses change their strength to encode memories. They are also developing computer simulations of synaptic signaling to aid in the understanding of how a large number of signaling molecules present at the synapse may work together. ■

For a complete list of workshops and workshop reports, go to www.hdfoundation.org/workshop.htm

"Changes, Advances, and Good News $(CAG)_n$"

August 8–11, 2002
Cambridge, MA

Over 350 HDF-funded researchers from around the world attended this HDF-supported biannual meeting. **Allan J. Tobin**, Scientific Advisory Board Director Emeritus, issued this challenge to the participants at the opening session: "How can this community not only stay in front of the wave of contemporary science but also create our own wave; a wave with sufficient force to knock down this disease?" This wave, he said, will carry the HD research community forward towards a cure. "So in addition to the outstanding work we will hear that connects huntingtin action to the latest discoveries in cell and molecular biology; in addition to the creating and testing of mouse models of HD; in addition to the unraveling of cellular and neural pathology, we basic scientists need to focus still more strongly on interventions."

In response to the swelling attendance, a new meeting format was invented. An impressive fifty-eight presentations were grouped into six "data blitzes," sandwiched between panel discussions on a related topic. Investigators presented a total of 157 oral presentations and posters.

The data blitzes were limited to three slides and the panel presenters had none. This kept the discussion fresh and dynamic. ONLY UNPUBLISHED DATA WERE PRESENTED—a great tribute to the trust and loyalty the group feels for each other that unpublished data will be respected and not shared outside the group until it is published. The participants have a strong sense of perspective and priorities to get on with the job of finding a cure having met families with HD and realizing how large the stakes are.

Participants represented academic labs as well as government and industry, with significant collaborations among these arenas. Research advances included findings in drug screening in model systems, cell death, clinical trials and possible new therapeutic approaches to treating the disease. While presentations covered a wide variety of topics, the focus on finding effective interventions pervaded the entire conference.

In wrapping up the meeting, Allan Tobin likened the three phases of moving from bench to bedside—discovery, development, and delivery—to a "fragile bridge." "I think we've got the discovery phase pretty well under control and things could not be better," he said.

Focusing on the development phase is something new for the HDF, but we recently received a tremendous boost from the National Institute of Neurological Disorders and Stroke (NINDS). NINDS is developing a new program for supporting translational research—a venture almost entirely new for them as well and, in part, in response to encouragement and input from Allan Tobin when he chaired a committee for NINDS on neurodegenerative diseases. NIH is now looking at the NINDS as an exemplar of how the drug pipeline can be pushed along. Tobin highlighted work in multiple areas, including pharmacology, behavioral testing, biomarkers, gene arrays, and imaging. These all give us handles for following the disease in humans and mouse models.

"We're at a very ripe time," said Tobin. "We're able to do these experiments in a scientifically engaging way and in a way that will allow us to traverse the fragile bridge from bench to bedside."

"Transcriptional Dysregulation in Huntington's Disease"

December 21–22, 2002
Berkeley, CA

By Jang-Ho Cha and Nancy Wexler

Just as each musician in an orchestra has access to the complete score of a symphony, each cell in the body contains the same DNA sequences. But just as each musician plays only his or her portion of the score, each cell must only read specific parts of the genome. The process by which cells selectively read the genome is highly controlled and is known as "transcription." During transcription, DNA converts to RNA. The RNA then undergoes a process called "translation" in which it is converted into protein. Scientists are increasingly realizing that disturbances in the transcription process may play an important role in causing Huntington's disease.

Intellectual sparks flew in Berkeley, California last December when transcription and HD mavens met. The HDF-supported workshop was organized by **Robert Tjian, Ph.D.**, a Howard Hughes Medical Institute investigator at the University of California and a world

Robert Tjian, Ph.D.

authority on transcription, and **Jang-Ho Cha, M.D., Ph.D.**, Associate Professor of Neurology, Harvard Medical School,

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an HD researcher based at Massachusetts General Hospital and **a new member of HDF's Scientific Advisory Board**.

As always, the workshop began with the family perspective. A young woman and man, both of whom had recently been diagnosed with HD and are also girlfriend and boyfriend, gave us an added perspective on the challenges facing two people with this disease who can share their problems and also support each other in unique ways. Another woman spoke movingly of how she discovered that her husband, from whom she had been long separated because of his disturbed behavior, turned out to have had HD. He passed the gene to both their children, one of whom is living in a nursing home contending with many severe difficulties. His mother fought so hard to acquire a source of Coenzyme Q10 for her family and others with HD who could not afford it that she now distributes it herself at a reduced cost from her own home (www.escoq10.com/).

Over the next two days, transcription experts and HD researchers educated each other. The scientific conversations were animated, particularly as it became increasingly clear to everyone that the mutant huntingtin protein is a culprit in disrupting transcription. The normal HD protein usually lives in the cytoplasm and does not get into the nucleus of the cell where transcription occurs. But the abnormal HD protein gets cut and a tiny piece enters the nucleus—the heartland of the cell. Unfortunately, that piece carries the abnormal number of CAG repeats. There are molecules in the nucleus called "transcription factors" which help the cell with the transcription process. Oddly enough, a number of these transcription factors also have long strings of CAGs similar to the HD gene, but not quite as long. It could be that the HD fragment masquerades as a transcription factor—but actual ly gums up the works! We do know from research done by workshop participants that the abnormal protein definitely intrudes itself into the delicate transcription machinery and interferes with making proteins. By adding additional molecules to the cell's nucleus we possibly could compensate for the damage already done. Or perhaps we can learn ways to keep the wayward HD fragment out of the nucleus altogether where it cannot wreak havoc on the cell and waylay the critical process of making proteins.

At the workshop, people discussed very exciting unpublished findings and formed new collaborations and research projects which the Foundation is now funding. It is immensely gratifying to welcome a new cadre of superb scientists to understanding the very soul of the disease—in its most fundamental aspects.

Albert Parvin Foundation-Sponsored HDF Workshop "Huntington's Disease: From Molecule to Miracle: Searching for the Cure"

January 11-12, 2003
Los Angeles, CA

Excerpts from the Workshop Report Prepared by Marina Chicurel

We were extraordinarily honored to receive a grant from the **Albert Parvin Foundation** to support this critically important HDF Workshop. The Albert Parvin Foundation Workshop took place at the home of **Jennifer Jones Simon** in Los Angeles. Support from the Albert Parvin Foundation was especially gratifying as it was through the excellent representation of Hereditary Disease Foundation trustee **Mary Carol Rudin** to Mrs. Parvin and her Board that the grant was made possible. The Albert Parvin Foundation specializes in giving to projects that improve health. Many thanks to the Albert Parvin Foundation and to Mary Carol Rudin for facilitating a catalytic effort!!

HD's Far-Reaching Consequences

The generous participation of three women from a family suffering from HD greatly helped workshop attendees grasp this disease's far-reaching and complex consequences. By sharing their experiences coping with the myriad ways in which their lives and those of the people they love have been disrupted, the women highlighted the multi-faceted nature of the damage caused by HD.

Describing their affected family members, the women recounted their experiences witnessing the loss of motor and cognitive abilities in their loved ones and the heartbreaking end-stages of the disease in which these individuals have difficulty even eating. Inextricably linked to this suffering was the pain of associated family members. One woman, whose mother is bed-ridden due to HD, for example, noted that her father is completely dedicated to caring for his wife, a once intelligent, talented and independent woman. Indeed, he has been unable to get a seriously needed knee replacement because of the all-absorbing nature of his role as caregiver.

The women also noted the extremely difficult considerations they have had to face in deciding whether to be tested for the HD mutation. One of the women said she did not want to know her personal fate, but had wanted to make sure that her children wouldn't have the disease.

There is a procedure called "non-disclosing prenatal testing" that permits a person to test a fetus without revealing either parent's own genetic destiny by examining an area very close by the HD gene on chromosome 4 and not the gene itself. This test will check which chromosome 4 a fetus inherits—one from an unaffected grandparent or one from an affected

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grandparent. The HD gene lives close to the top of chromosome 4. A person "at risk" for Huntington's disease inherits two chromosome 4s—one from the affected parent and one from the parent who carries a normal version of the HD gene. If the at-risk person passes on this normal gene to his or her fetus, then that child will never have HD and can never pass it on to subsequent children.

However, if an at-risk parent passes on the chromosome 4 he or she inherits from an affected parent, the fetus has a fifty percent risk of receiving the abnormal copy of the gene, the same risk as the at-risk parent. This is because the affected grandparent also had two chromosome 4s—one with the abnormal version of the gene and one with the normal. Some people decide to terminate pregnancies with 50% risk and keep pregnancies with virtually no risk.

One of the women at the workshop terminated two pregnancies with a 50% risk, exerting incredibly heroic efforts to donate the tissue for research. This was just too psychologically and physically devastating. She then decided to proceed with two subsequent pregnancies without testing. Now she lives with the fear that she and her two small children may be carriers of the mutation. As noted by **Nancy Wexler**, a major difficulty for families afflicted with HD is balancing their desire to protect their children with their aversion to learning their own fate.

One woman described how she had always been fearful of suffering her mother's fate and had even been preoccupied with finding traits in herself that resembled her mother's, even if they were unrelated to the disease. Yet she had avoided thinking about the possibility of getting tested. It wasn't until a counselor suggested the idea to her, while she was visiting her mother in the hospital, that she decided to get tested.

She tested positive and has begun experiencing early symptoms of the disease. In addition to the fears she harbors for her own health, she is now intensely worried about her husband, who will probably have to become her caregiver, as well as her young children, who may suffer from her failing health and may be carriers of the mutation.

The family has also had to face tough economic issues, such as keeping their jobs and trying to secure suitable medical and life insurance. The woman who recently tested positive, for example, has not yet notified her employer for fear of losing her job. And the whole family is uncertain about how to obtain the insurance they need. As noted by **Alice Wexler, Ph.D.**, Nancy's sister and a trustee of HDF—HD families confront a highly complex web of social, psychological, and financial challenges.

The women's personal and highly articulate presentation of their family's experiences made a strong impression on workshop participants. Shaken by the terrible and wide-ranging effects that HD has wreaked on this family, participants were inspired to help develop strategies to understand the biology of HD and to accelerate the search for a cure.

Meeting Synopsis

One of the most striking features of Huntington's disease is its multiple faces, its varied effects on behavior, anatomy, biochemistry, and electrophysiology. Although the disease has its roots in a single, well-defined dominant mutation—a CAG expansion in the huntingtin gene—its consequences have proved complex and multi-faceted.

Participants at the Albert Parvin workshop suggested that HD is a multi-hit disease, in which an accumulation of cellular and molecular dysfunctions ultimately leads to the lack of motor control, cognitive impairment, and death. They emphasized that elucidating the timing of these dysfunctions, particularly identifying the earliest alterations, will be critical, not only for understanding the disease, but for developing therapies. They also highlighted the importance of resolving the question of whether the primary source of pathology lies in the direct effects of the abnormal huntingtin protein on striatal cells in the basal ganglia—the part of the brain most obviously affected—or on huntingtin's effects on other cells which interact with them. In this context, participants discussed huntingtin's disruptive effects on cellular transport, neurotransmitter receptor signaling, and the functionality of connections between the cortex and the striatum.

Several methods for screening candidate drugs were also discussed. An increased emphasis on assays that closely reflect the disease process in humans was proposed, as well as the establishment of criteria to select therapeutic candidates for clinical trials. In addition, participants reviewed the status of therapeutic candidates, including regulators of chaperone protein function, minocycline, and coenzyme Q10. Of particular interest was the discussion of histone deacetylase inhibitors, which have recently provided encouraging results in a mouse model of the disease. (See page 1—*Bates–Good News*)

(See the full report at www.hdfoundation.org/workshop/200301Report.htm)

Huntington's Disease Drug Discovery Working Group

March 18–20, 2003
New York, NY

By Nancy Wexler

The purpose of the working group was to bring HD researchers together with top-ranked medicinal chemists to discuss possible treatments and drug screening for

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HD. There was chemistry in action everywhere—from the HD investigators, most of whom had been collaborating for years, to the medicinal chemists and informatics specialist who, by virtue of their extraordinary expertise, could merely look at a chemical structure lying two-dimensionally on the page and know if it would produce cancer, birth defects, or a possible treatment for HD! It was exhilarating and mesmerizing to watch!!

The biologists presented how they had built "model systems" to look for drugs for promising treatments for HD. These are literally fly traps, mouse traps, as well as worm, cell, yeast and test tube traps with pieces of the HD gene in them. If, in a model, a drug made the HD abnormal protein better, we sprung the trap to see what drug had this beneficial effect. This is where the medicinal chemists exerted their magic. They perused each structure for class of drug, for the likelihood that it could cross the blood-brain barrier, and for other analogs or drugs with similar core structure that might be more potent or less toxic. They rank ordered compounds based on their promise to be turned into a drug.

It was a love fest in action. The biologists watched in awe as the compounds were assessed one by one in a language that seemed completely foreign. And the chemists were impressed by the sophistication of the model systems built by the biologists to find new drugs, saying they were even better than many constructed by big pharmaceutical companies.

We look forward to working closely with this group towards a cure.

The focus of this working group was on "preclinical testing." Over the last ten years since we helped discover the HD gene, the Hereditary Disease Foundation has spent millions of dollars to develop tools to search for new drugs to treat and cure HD. These tools are cells, yeast, flies, worms and mice that all have some or all of the HD gene in them in various different combinations.

We supported the analysis of all the approximately 2,000 FDA-approved compounds which were tested in these tools or model systems to see if any of these drugs can be helpful in treating HD (see the Summer 2002 HDF newsletter online at www.hdfoundation.org/PDF/NewsletterSummer2002.pdf for details).

The first step in testing the FDA drugs and other compounds is to use tools that could screen thousands of different drugs at a time extremely rapidly. These are tools or model systems like chemicals in a test tube, cells, or yeast. Worms, flies, and mice take longer to test. This first step is called **"high-throughput screening"** or **"primary screening."** If any drug seems to help in this first primary screening—by saving a cell or dissolving a clump in a test tube—it is looked at more carefully. This is called a **"hit."** Hits from primary screening are selected and these chemical compounds then go through a process called **"secondary screening."** The hits are retested in the same primary screens to see if we get the same result. But this time they are also tested in model systems that take longer to run. At this point the worms and flies play a key role as the hits from primary screening are applied to them. Again, we hope for "hits" in secondary screening. **The hits that survive this more rigorous screen are then given to mice with the HD gene—the closest animal model we have to ourselves.** Testing in mice is the most time-consuming and most expensive.

Our Drug Discovery Working Group has the mission to review all the primary hits, assign them for secondary screening and also, in some cases, select those further enough along to test directly in mice. It was exciting and gratifying to include "hits" that resulted from our collaboration with Aurora Biosciences (since acquired by Vertex), as well as hits from other programs around the world.

Our next "Of Mice and Men Working Group" meeting in July will include the scientists who created mouse models as well as other experts to decide which promising new compounds to test. The drugs which successfully helped the HD mice will help us then assess which, if any, should be brought to the FDA to be tried in humans suffering from HD.

This is a very exciting prospect—one we are all anticipating enthusiastically and can even see on the horizon!!!!

Mechanisms of Neurodegeneration: From Triplet Repeat Expansions to Protein Toxicity

May 2–4, 2003

Milan, Italy

The focus of this meeting was on the mechanisms of neurodegeneration in hereditary diseases, aimed at stimulating new and productive interactions among basic and clinical research groups involved in this exciting area of human genetics. **Elena Cattaneo, Ph.D.**, Professor of Pharmacology, Department of Pharmacological Sciences and Center of Excellence on Neurodegenerative Diseases, University of Milano, one of the meeting's organizers, **is a new member of the HDF Scientific Advisory Board.**

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Gordon Research Conference on CAG Triplet Repeat Disorders

May 4–9, 2003
Barga, Italy

Promoting the understanding of the molecular mechanisms operating in CAG triplet repeat disorders, such as Huntington's disease, and developing treatments or cures were the primary goals of this meeting. Although the genetic defects of various triplet disorders are established, it remains to be elucidated how the abnormal gene in each case generates the specific pathogenic process and how this leads to a characteristic anatomical pattern of changes.

The Gordon Research Conferences follow a format similar to that used by the Hereditary Disease Foundation, to establish good, direct communication between scientists working in the same subject area or in interdisciplinary research. The Gordon Research Conferences promote discussions and free exchange of ideas at the research frontiers of the biological, chemical and physical sciences. Scientists with common professional interests come together for a full week of intense examination of the most advanced aspects of their field discussing unpublished work!

The conferences provide a valuable means of disseminating unpublished information and ideas that cannot be achieved through the usual channels of communication—publications and presentations at large scientific meetings.

Information presented at a Gordon Research Conference, whether in a formal talk, poster session, or discussion, is a private communication offered with the restriction that such information is not for public use. ■

The World Congress on Huntington's Disease August 16–19, 2003 and the International Huntington Association Meeting August 20–21, 2003 in Toronto

The World Congress on Huntington's Disease is a newly-structured conference of the World Federation of Neurology Research Group on Huntington's Disease and the International Huntington Association traditionally held every two years. Unlike many scientific meetings that are often incomprehensible to the non-scientist, this year's scientific program is meant for both researchers and HD organizations alike.

The first part of the meeting from August 16-19—traditionally the meeting of the World Federation of Neurology—includes a scientific program with presentations on genetics, drug discovery and development, pathogenesis, the latest advances in therapeutic areas, clinical trial results, future clinical trials, public policy and education.

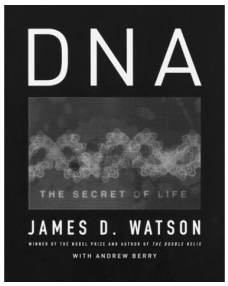
After the main scientific sessions, the IHA will meet for two additional days, from August 20-21. The IHA is a federation of national voluntary health agencies involved in HD—on the clinical research front as well as for support services needed by families affected with HD. The meeting will feature updates and reports on the work of IHA member organizations, its annual general meeting, as well as featured presentations from IHA members.

This meeting is an opportunity for Huntington's disease scientists, activists, and family members to share and exchange ideas to shape the future of the disease. For more information about the program and schedule, go to www.hsc-ca.org/english/congress/index2.htm. The World Congress on Huntington's Disease is supported by the World Federation of Neurology, the International Huntington's Association, the Hereditary Disease Foundation, the Huntington's Disease Society of America, the Huntington Study Group and the Huntington Society of Canada.

Recent Press, cont. (pg. 6)

- On February 17, 2003, *Time Magazine* published a special report on the 50th anniversary of Watson and Crick's historic discovery of DNA. Included in this issue is a short profile on **Nancy Wexler** as one of "The Pioneers of Molecular Biology." Nancy discusses the difficult decisions surrounding testing for HD, "Even if you think you've thought about something inside out and backwards, there is still something that lets you say that if you don't know [your results], you're still somehow protected." (www.hdfoundation.org/news/20030209-Time.htm)
- The *Time for Kids* March 14, 2003 issue featured a bio on **Nancy Wexler** in the "Profiles in Women's History" section. Nancy, ever trusting and confident in the HD researchers, says, "We shouldn't sit around and say, 'This is impossible.' We should say, 'It's possible,' and figure out how to do it." Barbara McClintock—the grandmother of genetics—was featured on the same page. She was the first American woman to receive an individual Nobel Prize. Her work, which began in 1921, focused on how genes were inherited. (www.timeforkids.com/TFK/magazines/story/0,6277,431021,00.html)
- In January 2003, **Nancy Wexler** appeared in *Our Genes/Our Choices*, a three-part series on PBS, produced by Fred Friendly Seminars, which examined the impact of genetic advances on the right to privacy, reproductive choices, and personal responsibility. Nancy shared the stage with impressive figures such as U. S. Supreme Court Justice Stephen Breyer; Representative Louise Slaughter from New York whose legislative efforts are directed at protecting individuals from discrimination by health insurance providers based on their genetic makeup; and others who focus on health care-related policy issues. (www.pbs.org/fredfriendly/ourgenes/)
- "Huntington's Disease: Historical and Contemporary Connections," written to commemorate the ten-year anniversary of finding the HD marker, was featured in the *College of Physicians & Surgeons of Columbia Magazine*, Winter 2003. **Nancy Wexler** praises the collaborative efforts of everyone involved in HD research, "The group of scientists who are working on this devastating disorder and the group of Huntington's families are so extraordinary. They are all generous, enthusiastic, collaborative, they aren't egotistical...There's a lot of hope on the horizon. Families and scientists are sharing in the hope—and in the celebration when we have a cure." (www.hdfoundation.org/news/winter2003.pdf)

Book Reviews



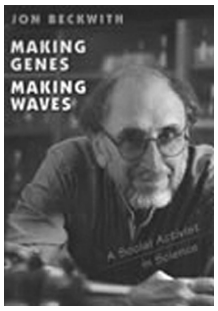
DNA: The Secret of Life *by James Watson with Andrew Berry*

DNA, a beautiful new hardcover book was published in April, 2003 by Knopf. Chapter 11, "Gene Hunting: The Genetics of Human Disease," opens with the story of HD and the Wexler family, and continues with the Venezuela Project and the identification of the HD gene. This is the celebration of the very first gene found using new recombinant DNA technology. In the last chapter, Jim Watson also discusses the Wexler family and the dilemmas we all face about knowing our genetic futures.

"*DNA* is a mesmerizing romp through the ladder of life. Accessible, acerbic—Jim's vision and accomplishments will change this millennium as he did the last."
—Nancy Wexler, Hereditary Disease Foundation President and Higgins Professor of Neuropsychology, Columbia University

"A remarkable alignment of the planets is occurring in 2003, the fiftieth anniversary of the double helix and the completion of the sequence of the human genome. As a defining figure in both landmark events, no other human being on the planet is positioned to write as authoritatively about all this as Jim Watson. In *DNA*, he does so with characteristic clarity, style, and wit. If you really want to know what happened in the most important half-century of biology since the world began, read this!"
—Francis Collins, Director, National Human Genome Research Institute, National Institutes of Health

"This is the story of DNA and therefore the story of life, history, sex (lots of sex!), money, drugs, and still-to-be-revealed secrets. DNA is quite a molecule—she's been around a long time and played a lot of roles. At last, she has a truly worthy biographer."*—Mary-Claire King, American Cancer Society Professor, University of Washington School of Medicine*



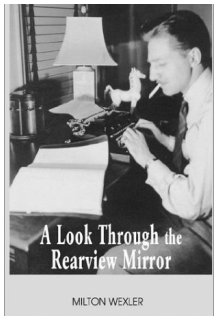
Making Genes, Making Waves *by Jonathan Beckwith*

Jonathan Beckwith was a critical first member of the Joint National Institutes of Health/Department of Energy Ethical, Legal and Social Issues Working Group of the Human Genome Project, chaired by Nancy Wexler. In his memoir, *Making Genes, Making Waves*, released in October, 2002, Jonathan writes with verve and elegance about science—particularly genetic science—and its potential for harm if misappropriated by political agendas.

"It is rare to find an honest man describing how he became a first-rate scientist while his mixed feelings about the role and function of science turned him into an effective

Continued on page 24

Our Multi-Talented Board of Trustees Continues to Amaze and Delight Us—BRAVO TO THEM!!!



A Century of Originality—the Path of HDF Founder and Chairman Milton Wexler

At age 94, we finally get to hear the complete story of HDF founder and chairman **Milton Wexler's** exciting journey from attorney to psychoanalysis to starting the Hereditary Disease Foundation. In his memoir, *A Look Through the Rearview Mirror*, released in July, 2002 by Xlibris, Milton describes his quest to understand and heal some of our most intractable illnesses, while also revealing the human and sometimes humorous side of a psychoanalyst's life. The book is available for order on *www.xlibris.com* in hardcover or paperback. **All proceeds go to the Hereditary Disease Foundation!**

Gehry on the Hudson—Accolades for an Architectural and Acoustic Triumph for HDF Vice-President Frank O. Gehry!

Congratulations to HDF vice-president and internationally-acclaimed architect **Frank O. Gehry** on the opening of the Richard B. Fisher Center for the Performing Arts at Bard College in Annandale-on-Hudson, New York this past April. Frank's design of interconnected and overlapping canopies of brushed stainless steel—now a trademark signature of his buildings—magnificently reflects the light and colors of the sky and the slopes of the surrounding landscape. Nicholas Adams, a professor of architectural history at Vassar College, who authored an article about the Fisher Center for the May issue of the Italian design magazine *Casabella*, hailed the building as the region's first important work of architecture in decades and predicted it would become a "classic Hudson Valley view." "His buildings are really actively involved in their environment, they don't simply mimic the surrounding landscape but actually engage it," Adams said in a phone interview for the *Poughkeepsie Journal*. In this way, he added, the Fisher Center is characteristic Gehry: "This is a building that doesn't slink into itself. It stands up."

Another original marvel is Frank's Peter B. Lewis Building, the new home of the Weatherhead School of Management at Case Western Reserve University in Cleveland, Ohio. The building's design is

Frank Gehry's Weatherhead School of Management at Case Western Reserve University

intended to reflect Weatherhead's international reputation for innovative management education. On the building's exterior, flowing ribbons of shining stainless steel cascade over and down the surface, while inside, fluid, curved walls defy convention. Gehry's design effectively eliminates the traditional, top-down relationship between teacher and student. "The future of business belongs to those who constantly embrace change, risk and explore new ideas," said the building's lead donor Peter B. Lewis, chairman of the Progressive Corporation, who understands Frank's aesthetic. "The building is a place where people cannot help but think differently. It challenges the students, the University and the City of Cleveland to break boundaries. The status quo is not acceptable here."

Trustee Carol Burnett is With Us for *One More Time*

Carol Burnett

A more poignant tribute to the extraordinarily special relationship between **Carol Burnett** and her daughter Carrie Hamilton could not be found than their collaboration on the play *Hollywood Arms*. Carol and Carrie had toured around the world teaching others the lessons they learned beating drug addiction. The seeds of working together bore fruit again when they created the play *Hollywood Arms*, based on Carol's prize-winning memoir, *One More Time*—published by Random House in 1986. Directed by the famous Harold Prince and starring Linda Lavin as Carol's grandmother who raised her, Michelle Pawk as Carol's mother and Frank Wood as her alcoholic father, the play opened on Broadway last fall to rave reviews. And Carrie and Carol just won top honors at the June, 2003 Tony Awards when Michelle Pawk won best featured actress in a play and thanked Carol and Carrie for giving her the performance of a lifetime.

The play's success has been bittersweet for Carol after Carrie died in her arms of lung cancer in January, 2002.

Carol's own candid, funny, beautifully written love song to her batty, unique family is coming around one more time. In fall, 2003, Random House will be reissuing Carol's memoir *One More Time*. Started as a letter to Carol's three daughters, Carrie, Erin and Jody, about her early life, and growing up in poverty and insecurity in Hollywood, Carol's memoir topped the bestseller list for many months. Let's hope *One More Time* does it one more time—but this time, for years!!! because the book is terrific and a must read for everyone!!!

Trustee Julie Andrews Minds Eloise at the Plaza

Julie Andrews

From the Banks family to the von Trapps to Eloise, HDF trustee **Julie Andrews** adds yet another kudo to her list of accolades!!! *Eloise at the Plaza* aired on ABC on April 27, with Julie playing the nanny—the intrepid British guardian to Eloise. The show is based on the best-selling Eloise books by Kay Thompson about a six-year-old girl who lives at New York's Plaza Hotel and is in constant search for adventure.

Julie made her Broadway debut on September 30, 1954 in the musical *The Boy Friend*. She now makes her directorial debut in *The Boy Friend*, set to open at the Bay Street Theater on August 5 in Sag Harbor, New York. The Bay Street Theater is the thriving dream realized by Julie's daughter, Emma Walton. Julie's 1954 performance in *The Boy Friend* led to perhaps her most notable stage role ever—that of Eliza Doolittle in *My Fair Lady*.

Rock and Roll Hall of Fame and HDF Salute Trustee Morris Ostin!

Congratulations to founding HDF trustee **Morris Ostin** who was recently inducted into the Rock and Roll Hall of Fame with a lifetime achievement award. With Ostin as chief, Warner Bros. Records became the most commercially successful record company in history. Ostin put the creative needs of his artists ahead of the bottom line and created an atmosphere where executives could develop their talents, as well as build a nurturing corporate environment that has been a model for businesses ever since. Ostin has worked with a vast and varied group of artists including Frank Sinatra, Neil Young, Ry Cooder, Jimi Hendrix, Joni Mitchell, Van Morrison and the Kinks. He is currently the principal executive at DreamWorks Records, the music division of DreamWorks SKG, formed in 1994 by Steven Spielberg, Jeffrey Katzenberg and David Geffen.

Mo Ostin with Paul Simon as Neil Young and Lorne Michaels look on.

Savoring the Precious Moments

Joyce Ostin

HDF trustee **Joyce Ostin**, daughter-in-law of **Evelyn and Mo Ostin**, teamed up with Eastman Kodak to create a calendar featuring celebrities and breast-cancer survivors enjoying valuable, everyday moments shared between loved ones and friends. Ostin, a breast-cancer survivor and professional photographer, says, "My battle with cancer taught me many things, one of which is to savor every precious moment."

Adult Entertainment Returns to New York... Off-Broadway

Elaine May

Adult Entertainment, the clever new comedy by HDF trustee **Elaine May** and Stanley Donen made its Off-Broadway debut last December. True to Elaine's original, off-beat sense of humor and eclectic take on the world, the play features six porn stars who decide to go independent and make their own film. Starring Elaine's talented daughter Jeannie Berlin along with Danny Aiello, the play within the play shows what happens when "Porn Culture" and "True Culture" collide.

Elaine May is best known for her improvisation stage comedy with Mike Nichols and for screenplays including "Heaven Can Wait," "The Birdcage" and "Primary Colors." Stanley Donen directed "Singing in the Rain" and "Funny Face" among many other stellar movies.

Welcome to the World!

In January, 2003, trustees **Kelly Posner Gerstenhaber, Ph.D.** and **David Gerstenhaber** welcomed in a new member to the HDF family—Alexander Jacob Gerstenhaber—who weighed in at 7 pounds, 13 ounces and is stunningly beautiful like his parents. Kelly is a research scientist and Director of Clinical Services of the Research Unit for Pediatric Psychopharmacology, at New York State Psychiatric Institute, Columbia University. David founded Argonaut Capital Management, a hedge fund, and is also active as an investor in both real estate and private equity. David is widely recognized as one of the world's leading macro-strategists. Congratulations!! ■

HDF Scientific Advisory Board Welcomes Newest Members

We are pleased to announce the election of five new members to our Scientific Advisory Board, each for a four-year term. These scientists were selected for their individual expertise as well as their passion for collaborative research. Some have been funded by us or were previous members of the Board; others are new to the foundation and offer important insight into research akin to ours. We extend a warm welcome to:

Elena Cattaneo, Ph.D.
Professor of Pharmacology
Department of Pharmacological Sciences Center of Excellence on Neurodegenerative Diseases
University of Milano

Jang-Ho Cha, M.D., Ph.D.
Associate Professor of Neurology
Harvard Medical School
Massachusetts General Hospital

Ira Shoulson, M.D.
Louis C. Lasagna Professor of Experimental Therapeutics
Professor of Neurology, Medicine and Pharmacology
University of Rochester

Stephen J. Tapscott, M.D., Ph.D.
Member, Division of Human Biology
Fred Hutchinson Cancer Research Center
Professor, Department of Neurology
University of Washington Medical Center

Christopher Walsh, M.D., Ph.D.
Investigator, Howard Hughes Medical Institute
Beth Israel Deaconess Medical Center
Bullard Professor of Neurology

Ann M. Graybiel, Ph.D. with President George W. Bush

Ann Graybiel Receives National Medal of Science

Congratulations to HDF Scientific Advisory Board member **Ann M. Graybiel, Ph.D.**, Walter A. Rosenblith Professor of Neuroscience and Investigator at the McGovern Institute for Brain Research at MIT, who received the National Medal of Science—the nation's most prestigious science and technology honor—from President George W. Bush. To add further accolades, Ann was the only woman medalist of the fourteen National Medals of Science and five National Medals of Technology awarded in June 2002! The Medals recognize individuals in a variety of fields for pioneering scientific research and for their lifetime achievements. Ann's research focuses on the neurophysiology of the basal ganglia, a region in the brain implicated in the control of movement and cognition, and commonly associated with Huntington's, Parkinson's and other diseases.

Leslie Thompson—Distinguished Assistant Professor Award, University of California, Irvine

Congratulations to **Leslie Thompson, Ph.D.**, who received the Distinguished Assistant Professor Award for Research from UC Irvine in February, 2003. Leslie is an HDF Scientific Advisory Board member, a **Lieberman Award recipient in 1998** and assistant professor in the Department of Biological Chemistry at UC Irvine College of Medicine. She has developed cell culture and fruit fly models, all containing the HD gene. The fruit fly work is in collaboration with **J. Lawrence Marsh, Ph.D.**, professor in the Department of Developmental and Cell Biology at UC Irvine's School of Biological Sciences, and **Joan Steffan, Ph.D.**, an associate professor in the Thompson Lab.

These extraordinary living test tubes have enabled Leslie and her colleagues to screen all kinds of drugs for promising ones. And her work has paid off, particularly in finding a new class of drugs called HDAC inhibitors which protect against the lethal effects of the HD gene. Her research continues to focus on the therapeutic promise of these compounds as well as on others that suppress the formation of clumps of protein accumulating in HD brains. ■

OBITUARIES

Eppie Lederer [1918-2002]

We trustees knew her as Eppie. More than 90 million readers of 1,200 newspapers around the world knew her as **Ann Landers**. We personally knew and loved her for twenty years as a fount of practical wisdom, a champion of the distressed and a grand combatant for social justice. The tragic illness that deprived us of her presence is close to being an unbearable loss.

Others may choose to write about her virtues, talents and accomplishments. We wish to speak of one part of her work that made her profoundly important to thousands of families around the world suffering from Huntington's disease and related disorders.

For nearly a quarter of a century, Eppie devoted thought, interest and concern toward the discovery of a cause and cure for HD. She joined the Hereditary Disease Foundation because she was impressed with our fiscal responsibility, especially the fact that all publicly collected funds support our science programs while trustees pay for our low administrative costs. When Eppie praised the foundation in her column and called us trustworthy—in response to a reader's question about charitable organizations—we received innumerable bequests: that's how much people trusted Eppie's judgment!

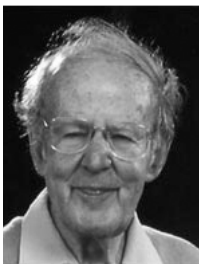
Eppie's inimitable presence, her enthusiasm and her wit graced many HDF dinners and workshops. Scientists flocked around her to soak up her extraordinary qualities; many asked her for advice—which she generously gave. They were also awed by her championship of issues critical to their work. Through her column, Eppie championed the need for animal research and supported AIDS research, for example. When Nixon hesitated to sign an important piece of legislation allowing the National Institutes of Health to fund cancer research, she exhorted her readers to clip her column and send it to Washington. The deluge that ensued forced the government to hire extra staffers just to handle the mail; Nixon capitulated, picked up his pen and created the National Cancer Institute.

Eppie was a humanist to the core: she opposed the death penalty, favored a woman's right to choose to continue a pregnancy, supported gun control and pleaded for tolerance in sexual preference, religion and ethnicity. Eppie's support of research at the HDF was critical to sparking the Human Genome Project. She also pleaded for an end to genetic discrimination in employment and insurance.

Eppie's effervescence, her kindness and her delight in people in all their complexity make her a unique person in our hearts. When the full story is written of her life and of this past century—which we both had the privilege of witnessing almost fully—the world will acknowledge Eppie's true role as a significant contributor to the advancement of the neurosciences and the treatment of hereditary illness.

Our sympathies go to members of Eppie's family, to her daughter Margo Howard and to her grandchildren, and to her sister Pauline and her family. We also send our condolences to the Chicago Tribune, Eppie's home-base and great supporter of the woman known worldwide as Ann Landers. Margo Howard said that Eppie wanted the world to know her life had been "a simply wonderful ride." Dearest Eppie, we are grateful to have shared the ride.

Milton Wexler, Ph.D., chairman, and Nancy Wexler, Ph.D., president



Max Perutz [1914-2002]

Missing Max

By Nancy Wexler

Max came into our lives in 1993 by way of a short letter which arrived at the Hereditary Disease Foundation. In his inimitable, almost indecipherable handwriting, Max explained that he had been reading about the discovery of the gene causing Huntington's disease and he had some ideas—were we interested?!!! With this letter, coming almost casually across the ocean, began our near decade of discovery, and most importantly, my admiration, respect and love for Max.

Reading an article on the train which described the isolation of the gene by the Hereditary Disease Foundation's Huntington's Disease Collaborative Research Group, Max told us in his letter that his attention was riveted by the explanation of the abnormality in the gene.

HD focused his extraordinary knowledge and intuition on the stretch of excess amino acids which comprised the gene's mutation. There are too many glutamines in a row. With 39 consecutive glutamines, you can live a normal life span—add one more glutamine and you certainly will die of a catastrophic, autosomal dominant, neurodegenerative disorder. To Max, the existence of that threshold spoke structural change. Before his eyes, those amino acids lifted themselves off the page and formed a polar zipper, an insoluble structure. Before he had even left the train, Max had the relevant experiments figured out to test this hypothesis. He was "new to this field," he said with his customary modesty, but he had some ideas and he wondered, were we interested?

Absolutely! We were not just interested, we were enthralled by his gracious genius and generosity to become involved. His entry marked a critical milestone in the path-like locating and cloning the gene—toward finding treatments and cures.

Over the past decade, Max attended numerous small, interdisciplinary workshops held by the Foundation. On one rare occasion when we had slides, and a presenter was regaling us with a profusion of jargon—letters, abbreviations, etc.—Max stood up and asked, "What ARE you talking about? Don't use jargon that none of us can understand!" He made the young man explain every term in his slide. When we finally got through that slide, the next was even worse! And everyone burst out laughing. From then on, Max persuaded everyone to speak clear English, be comprehensible and make sense. He was so sure of himself, so comfortable and self-confident, so candid, direct and straightforward, that he encouraged all the rest of us to be so as well. We all relaxed, exchanged ideas and information freely and collaboratively, and had a good time—thanks to him.

At the first Gordon Conference on Triplet Repeat Disorders, Max was in a dialogue with Ai Yamamoto, a graduate student presenting her work on the "reversible HD mouse model," a mouse that "cures itself" when the genetically engineered gene is switched off. As the eldest at the meeting, Max was talking with Ai, who was the youngest there, as an equal, with respect, kindness and interest, as a full partner in the stunning mystery of scientific discovery.

Max possessed an encyclopedic grasp of science—and music and art as well. He had lived through, participated in personally and created most of the scientific advances in biology and chemistry of the past century.

With his extraordinary memory, he would always know to whom to give credit, who had already done the work you think you are doing that is unique.

Max was never afraid to be bold, daring and imaginative in his ideas. His courage to enter an entirely new scientific realm, his tenacity in developing and testing new models, his zest and enthusiasm for all aspects of life—but particularly science—and his determination to proceed, despite obstacles, were breathtaking. From the polar zipper to the elegant, delicate structure of the nanotube, Max discovered, described, tested and published the most innovative structures. He grappled with the essence of the problem with an iron will, despite suffering from heart disease, celiac disease, spleen problems and finally cancer. Such was his determination that he sent his two last papers to the *Proceedings of the National Academy of Sciences* only hours before going to the hospital for his final siege. And then, in those last weeks, with a continued zest for life till the end, he filled his days with grace, courage, humor, gravity, science, friends, family and love.

Max changed the world scientifically, and also politically and psychologically, by where he chose to shine the brilliance of his scientific beam. His championship of young scientists, his enormous generosity of spirit in encouraging their ideas, research, collaborations and in advancing their careers, is legendary. **Gillian Bates** and **Steven Davies** of Guy's College, and **Erich Wanker** of the Max-Planck Institute of Molecular Genetics, are three among scores who have benefited over the years. And Max's scientific interest also brought a very healing corrective to the field of Huntington's disease research which had not yet come into its own. He was among the first to recognize that disorders leading to abnormal protein aggregation create a common pathology in Huntington's disease, Parkinson's, ALS and Alzheimer's disease.

One of my biggest frustrations and disappointments is that we were not able to provide Max with purified, crystallized huntingtin—the protein made by the gene

Continued on page 23

Max Perutz, cont. (pg. 22)

causing Huntington's disease. I so wanted Max to look at the X-ray diffraction pattern and see its shape materialize before his eyes. I promised him - and we tried in many different laboratories—but this enormous protein of more than 3,000 amino acids, like hemoglobin before it, is recalcitrant.

"Where is the crystal, Nancy?" Max would ask me in his low, soft but insistent voice. "I want to see that structure!" So now the Hereditary Disease Foundation has launched an all-out attack to purify and crystallize the protein. The scientific endeavor is called the **Max Perutz Protein Purification Project** and is being conducted in his honor (See Max Perutz Protein Purification Project story, page 10)

To my mind, Max is the Michelangelo of Molecules. He takes featureless elements of the protein and carves beautiful and precise structures of hemoglobin and huntingtin like Michelangelo took a block of marble and created David. In his mind's eye, Max saw and described the structures of these proteins. But all the same, one day, when we get the crystal and diffraction pattern, I'm going to show them to Max and he's going to say, "Ah ha, so that's what it is! I thought so all along!"

My last letter from Max:

"Cambridge, 23/12/2001

Dearest Nancy,

I have some good and some bad news; the good news is that I have solved the structure of amyloid fibres, which include poly-L-glutamine. I have been working and thinking of nothing else for the last 3 months, but it was all finished last Monday and I was able to send off two papers to PNAS. I hope that they will appear in March. I am enormously pleased to have done this, which would never have happened if the discovery of the gene for Huntington's disease had not given me the idea for the polar zippers leading to aggregation of the proteins. The idea for the structure just floated in from nowhere one day last summer.

The bad news is that I have a rare cancer that started with a lump in my cheek and all attempts to contain it have failed. It is caused by "Merkel cells." The oncologists will try a drug that slows it down, but success is uncertain...

...I have had 65 years of fantastically productive research and a happy marriage, delightful children and grand children surrounding me with affection, and finally I have enjoyed the friendship of so many wonderful people like yourself. I should have liked a few more years, but am lucky to have had so many...

Yours,

Max

Recollections of Max

By Gill Bates

My first encounter with Max was around 1994-1995 after he had published his *PNAS* paper on polar zippers. He invited me to visit him in Cambridge. On that first encounter, I felt overwhelmed whilst we discussed recent publications and our very different approaches to understanding Huntington's disease. However, I never felt like that again. I soon found that Max's genuine desire to discover one's thoughts and experimental approach, and to find out if one might happen to know anything new, meant that he always talked to everyone as an equal.

Because he was so approachable, it was only after I read his obituaries that I was reminded of his true stature. He had an insatiable curiosity for science and a determination to participate, even when in recent years he suffered bouts of serious ill-health. I could never quite work out how he managed to achieve so much and was left to wonder at his schedule and diverse productivity.

Max was a champion for young scientists and a defender of fair play. He was an energetic fighter and never gave up a cause that he thought was important. I saw this demonstrated in his defense of scientific values, and in defense of Steve Davies and myself when he felt that we were being judged on issues that were not important. He was extremely enthusiastic about the research that Erich Wanker, Steve Davies and I published in 1997, describing the nuclear inclusions in mouse brains and the formation of the *in vitro* amyloid fibrils, and went out of his way to promote our work. He nominated Steve and me for two very prestigious awards, the Royal Society Glaxo Wellcome Award and the Pius XI Medal from the Vatican, both of which were awarded in 1998.

Max's support and promotion of my work has certainly helped to advance my career and for this I thank him dearly. But just have known him and to have gained a sense of his personal and scientific integrity is equally valuable and will be a lasting legacy. ■

Donna O'Neill

We are saddened by the loss of our dear friend and founding trustee Donna O'Neill who passed away on July 18, 2002 at the age of 73. We will have more about the life and work of Donna in the next issue of the HDF Newsletter.

The New York Brain Bank

Many neurodegenerative disorders are unique to human beings. Therefore, brains from other species are of limited value for research. Human brain donation is crucial! It is a priceless gift leading to new understanding and cures. Moreover, the definite diagnosis of neurodegenerative diseases depends on a postmortem examination of the brain (i.e. brain autopsy).

Brain autopsy is a type of surgical procedure done after death, which does not disfigure and does not interfere with funeral plans. Some neurodegenerative disorders, including Huntington's disease and subtypes of Alzheimer's or Parkinson's disease, are related to gene dysfunction. Brain autopsy may help to identify the genetic dysfunction causing the disease.

Postmortem brains from individuals without neurological or neuropsychiatric disorders are also important for research to determine the differences between functional and dysfunctional brains. To facilitate this research, the Taub Institute at Columbia University established the New York Brain Bank. The NYBB is the link between the family, caregiver, donor, clinician and basic scientist. If you are healthy or have a disorder, donating your brain will greatly contribute to the progress towards understanding why and how these diseases occur, and how they can be prevented or treated.

To learn more about brain donation, please call Arlene Lawton, R.N. at (212) 305-9086 or Carol B. Moskowitz, R.N. at (212) 305-5779 or for information about the New York Brain Bank at Columbia University visit www.nybb.hs.columbia.edu/. ■

Book Reviews, cont. (pg. 17)

social activist. *Making Genes, Making Waves* is an excellent account, by a participant, of the debates about science and society that occurred in the last 30 or 40 years. It is especially interesting that the same man who was engaged in social activism was producing the best of the science that generated so much passion."—*François Jacob, winner of the 1965 Nobel Prize for Physiology or Medicine and the author's postdoctoral professor*

"*Making Genes, Making Waves* has special credibility coming from one of America's most distinguished microbiologists. It is a must read for any young scientist who is concerned by the tension between the beautiful rationality of science and the sometimes disconcerting outcomes of its applications."—*David Baltimore, President of California Institute of Technology and winner of the 1975 Nobel Prize for Physiology or Medicine* ■

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