

# Hereditary Disease

## FOUNDATION



1303 Pico Boulevard • Santa Monica, California • 90405 • 310-450-9913

Fax 310-450-9532 • [cures@hdfoundation.org](mailto:cures@hdfoundation.org) • [www.hdfoundation.org](http://www.hdfoundation.org)

### DRUG FOR CANCER MAY TREAT HD!



Leslie Thompson, Joan Steffan,  
Lawrence Marsh

A new class of drugs already in human clinical trials for cancer may also be effective in treating Huntington’s disease (HD) according to a study published in the October 18, 2001 issue of the prestigious British journal *Nature*. Drs. Leslie Thompson, Joan Steffan and Lawrence Marsh, from the University of California, Irvine led the team of scientists who conducted the research with support from the **Hereditary Disease Foundation**.

The Irvine team demonstrated that the drugs, called histone deacetylase (HDAC) inhibitors, reversed the degeneration of neurons and prevented early death in a fruit fly (*Drosophila*) model of HD. Since several drugs in this class have already been approved by the Food and Drug Administration (FDA) for research in human populations, it may be possible to move rapidly into human clinical trials for HD if further animal testing proves successful.

#### HDAC inhibitors counteract genetic mutation in HD

HDAC inhibitors are drugs that interfere with a complex enzymatic pathway that regulates gene expression in cells. In normal cells, two counteracting enzymes (a class of proteins) called HAT (histone acetyltransferase) and HDAC (histone deacetylase) maintain a delicate balance to regulate gene activity. In cells with the HD mutation, however, this balance is destroyed and gene activity is repressed. Researchers believe that this repression of normal gene activity leads to the neuronal damage that is characteristic of Huntington’s disease. Gene activity is similarly disrupted in cancer cells, and researchers had shown that HDAC inhibitors were able to turn on genes that forced transformed cancer cells to revert back to normal.

Thompson and Marsh used fruit flies to study whether the same compounds would similarly restore gene activity in cells with the HD mutation. The flies are genetically modified to carry either a portion of the gene that causes HD or another piece of DNA that resembles the HD gene. Both of these “fly models” suffer from degeneration of the photoreceptors in the eyes and early death. But when the researchers fed the flies HDAC inhibitors during the larval stage of development, the flies lived longer and their eyes remained healthy. “The effect in the eyes was more dramatic than we had dreamed possible,” said Thompson. This finding suggests that HD may be preventable in

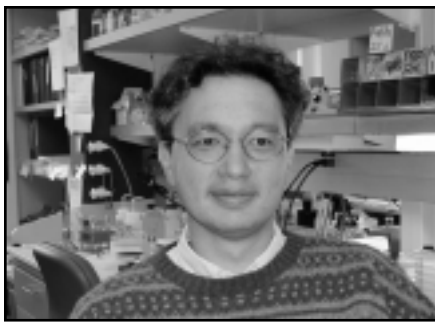
### Two New Huntington’s Disease Treatments Show Promise In Separate Studies

In two separate and unrelated studies, researchers funded by the Hereditary Disease Foundation have identified novel treatment strategies that, in animal models, appear to be effective in treating HD. Since one of these treatments, described in the article on this page, uses a type of drug already approved for use in humans, clinical trials are expected to start soon. The second study, described on page 3, challenges some earlier ideas about the mechanism of the disease and may identify another new therapeutic option. ■

In This Issue	
Drug May Treat HD .....	1–2
Two New Treatments .....	1
HD Mouse.....	3
View From the Chair .....	4
Nobel Prizes .....	4
Trial Drugs .....	5
WFN and IHA .....	5
Brent Stockwell.....	5
SAB News .....	6
Science News .....	7
Foundation News .....	8–9
Workshop Reports.....	10
Trustee News .....	11
Foxes .....	12
Wonderfully Different Life.....	13

individuals even before they show symptoms.

In a subsequent experiment, the scientists showed that HDAC inhibitors also halted progression of neurodegeneration in adult HD flies. These results raise hopes that HDAC inhibitors may be able to diminish significantly the neurodegeneration caused by the HD mutation. In addition, the research provides additional clues about the pathway from mutation to nerve damage, and may well lead to more precisely targeted strategies to combat the disease.



*Robert Hughes*

“I have high hopes that HDAC inhibitors may work as a treatment for HD,” said Thompson. “We know that they are used clinically in cancer, so there is precedence for use in humans. While I am optimistic, I am also cautious. It is not yet time to start providing this as a treatment before extensive mouse studies and human clinical trials.”

### **More evidence for role of HDAC inhibitors in HD**

One of the keys to understanding how HDAC inhibitors can reverse nerve damage in HD will be to demonstrate similar results in other organisms. **The Foundation is supporting other scientists who are doing just that. Dr. Robert Hughes** of the University of Washington uses a yeast model that has a portion of the abnormal HD gene inserted into its DNA. These yeast cells grow more slowly than normal and also develop clumps of protein in their nuclei, similar to the clumps found in the neurons of animal models of HD as well as individuals with the disease. These characteristics, and the fact that

yeast is fast and easy to grow, make yeast a good model for scientists studying HD.

In collaboration with Dr. James Olson of the Fred Hutchinson Cancer Research Center and Dr. Stanley Fields of the University of Washington, Hughes studied gene expression in his yeast cells using DNA microarrays, or “gene chips.” These small glass slides contain portions of all 6000 yeast genes, and allow investigators to measure the expression of each gene. Then, by comparing the expression pattern of yeast cells containing either an expanded or unexpanded piece of the human huntingtin protein, the scientists deduce which genes are activated and which are repressed.

This analysis revealed that in cells with the mutated HD gene, the pattern of gene expression differed strikingly from the pattern seen in normal cells. Some genes that were turned off in normal cells were turned on in cells with the mutation, while other genes that were normally turned on were turned off. Hughes found that the pattern of gene repression accompanying the HD gene resembled that seen in other mutations involved in histone acetylase function.

“So that was a fairly tantalizing coincidence perhaps, or an indication that what these cells were experiencing was a defect in histone acetylase function,” he said. To further test this hypothesis, he grew the yeast cells in a medium containing a compound known to inhibit HDAC. These cells grew normally, suggesting that the HDAC inhibitor “rescued” the cells from the effects of the HD gene, further supporting the use of HDAC inhibitors as a treatment for HD. In addition, the results point to a possible method for quickly screening other agents that might reverse the poisonous effects of the HD mutation.

Meanwhile, **Dr. Kurt Fischbeck’s** group at the National Institute of Neurological Disorders and Stroke (NINDS) has been investigating the use of HDAC inhibitors in Kennedy’s disease, a degenerative disease of motor neurons that is caused by a mutation



*Kenneth Fischbeck*

similar to the one that causes HD. Unlike people with HD, individuals with Kennedy’s disease experience mainly motor and some sensory losses, but no cognitive impairment. A graduate student working in the lab, Alex McCampbell, demonstrated that the toxic effects of the Kennedy’s disease mutation could be prevented by treating the cells with certain HDAC inhibitors. Now he is continuing the same type of research, using a fruit fly model of Kennedy’s disease.

### **Collaboration key to advances**

According to Dr. Thompson, interaction with Hughes, Fischbeck, and other scientists has been critical in this research effort. “I cannot emphasize enough how important this has been,” she said. “Beginning with the collaboration to isolate the HD gene, the Hereditary Disease Foundation has nurtured and supported collaborations on every level. None of this work would have been possible without these collaborations and without HDF support.” Fischbeck concurred, noting that his lab’s interaction with Leslie Thompson and Bob Hughes has been entirely mediated by the Foundation. In fact, it was at an HDF workshop less than a year ago that Fischbeck mentioned to Thompson the HDAC effect they had seen in cell culture. Thompson’s lab found a similar effect in their system. There are also ongoing collaborations between these labs and the lab of Gillian Bates, who is studying the effect of HDAC inhibitors in the HD mouse models she developed several years ago. ■

# Drug Lessens Symptoms and Prolongs Life in HD Mouse



*Lawrence Steinman*

The Huntington's disease mice developed by Gillian Bates several years ago mimic the human disease in that they suffer from uncontrollable tremors and weight loss and die at a young age—just three months of age. This is in marked contrast to the more than two-year life-span of a normal mouse. These characteristics make the model invaluable for studying the effectiveness of various treatment strategies. Now a research team, headed by Lawrence Steinman at Stanford Medical Center and funded by the Hereditary Disease Foundation, has identified a treatment that alleviates these disease symptoms and prolongs the lives of these mice. The finding suggests that a similar treatment strategy may be effective in humans with the disease. The study was published in the February, 2002 issue of the journal *Nature Medicine*.

Earlier research had shown that nerve cells in the brains of people with HD become clogged with clumps, or aggregates, of abnormal huntingtin protein.

An enzyme called transglutaminase has been implicated as essential in the formation of these aggregates. If the aggregates are the cause of the disease, Steinman reasoned, then perhaps the disease could be controlled by blocking the action of transglutaminase and thus preventing the formation of the aggregates. Steinman knew of a compound, cystamine, that blocks the action of transglutaminase.

His former graduate student, Marcela Karpuj, Ph.D., now a postdoctoral fellow at the University of California, San Francisco, studied whether injections of cystamine into the sick mice would have any effect on their symptoms. In fact, the treated mice did show signs of improvement; the tremors and abnormal movements became less severe and the lifespan of these mice increased by an average of twenty percent.

Surprisingly, though, the aggregates themselves did not disappear. "We expected [the treatment] to inhibit the aggregations," said Steinman. "But Professor Mark Becher [of the University of New Mexico Health Sciences Center] examined the brains of these mice and found aggregations were the same after treatment." This observation suggested that cystamine might protect the brain by some mechanism other than inhibiting aggregates.

Investigating whether cystamine affected the expression of certain genes in the HD mice, the team found that in mice treated with cystamine, the expression of three particularly interesting genes was elevated. All three of these genes code for proteins that play a protective role in the brain. Increased levels of these same neuroprotective proteins are also seen in the brains of HD patients, suggesting that the brain makes an unsuccessful attempt to protect itself against the disease.

Though these findings suggest that cystamine could someday offer hope to patients with HD, Steinman said the quest for other, potentially better neuroprotective compounds will continue. In recent years other compounds have also been reported to extend the lives of HD mice. Perhaps combinations of these agents will prove to have even greater benefits, Steinman said. ■

## Max Perutz

With sadness, we note the passing of Max F. Perutz on February 6, 2002 at the age of 87. The Nobel Prize-winning molecular biologist was a long-time friend of the HDF and had been working to understand the disease mechanisms underlying HD since the mid-1990s. We will have more about the life and work of Dr. Perutz in the next issue of the HDF Newsletter.



June 1, 2002

## View From the Chair

by Milton Wexler, Ph.D.

Dear Friends:

For the past thirty years we have been fighting the scourge of genetic disease. We feel encouraged that we have made real progress—in mapping the gene for Huntington's disease, in pioneering new technologies for studying genes, and screening drugs that we hope will soon lead to effective treatments for HD and related illnesses. But now the world faces a new scourge of heightened terror and hatred. Aside from the fear and sadness which afflicts us all, I have no doubt that some of you associated with the Hereditary Disease Foundation—trustees, scientists and staff members—

were touched in a personal way by the criminal acts of September 11. To those of you who have lost loved ones, friends, colleagues and coworkers, our hearts are with you in this time of sorrow. The Hereditary Disease Foundation was established to make this world a little better and a little safer. Let us hope that the creativity of science over the past decades will be matched in the coming months by social and political creativity, to stop such crimes against humanity and open new paths toward justice and toward peace.

## Nobel Prizes to Two Friends and Grantees of the HDF

Two scientists whose work has special significance to the HDF have been awarded 2001 Nobel Prizes. **Dr. K. Barry Sharpless**, W.M. Keck Professor of Chemistry at The Scripps Research Institute, won the prize in chemistry. **Dr. Lee Hartwell**, president and director of the Fred Hutchinson Cancer Center and professor of genetics and medicine at the University of Washington, won the prize in physiology or medicine.

Sharpless was awarded this year's prize in chemistry for his discovery of "chiral catalysts"—molecules that enable researchers to selectively control chemical reactions. "Dr. Sharpless' creativity has helped the entire field of chemistry produce extremely useful molecules,

including many different therapeutics, that continue to improve the health and enhance the lives of all Americans," said Dr. Ruth L. Kirschstein, acting director of the NIH. Dr. Sharpless shared the prize with William S. Knowles, formerly of Monsanto, and Ryoji Noyori of Nagoya University in Japan. Dr. Sharpless has been funded by the HDF to create a library of compounds for drug screening efforts.

Dr. Hartwell was honored for his discovery of the genes that control cell division in all eukaryotic (nucleated) organisms, from yeast to frogs to humans. Working with yeast, Dr. Hartwell was the first to harness the tools of genetics to identify and study the genes that cause cells to divide. Hartwell shared the

prize with Paul Nurse and Timothy Hunt, both of the Imperial Cancer Research Fund in London, England.

Dr. Hartwell is the director of the Fred Hutchinson Cancer Center. He recently hired Dr. James Olson, who organized and runs the HDF's Huntington's Disease Array Group (HDAG). Even though "the Hutch" is a cancer center, Dr. Hartwell has been extremely supportive of Jim's work on HD and his collaborations with the HDF. Jim's clinical trials with Gillian Bates' mice are being carried out at the Hutch with Lee's blessing. We have Lee and his wife, Theresa, to thank for attending the tribute for Trustee Buster Blethen. ■

---

## Trial Drugs for HD Not Statistically of Benefit in Slowing Disease

A large-scale clinical trial that tested the ability of the drugs remacemide and Coenzyme Q10 to slow the progression of Huntington's disease showed that neither drug resulted in any significant improvement for the patients. After one year of treatment, the disease seemed to progress more slowly in patients treated with Coenzyme Q10, investigators of the Huntington Study Group said, but overall results were statistically insignificant as to whether there is a real benefit from this drug. The study was published in the August 14, 2001, issue of *Neurology*.

The "Coenzyme Q10 and Remacemide Evaluation in Huntington's Disease," or CARE-HD trial, involved 347 patients in the early stages of disease. It was conducted over a 30-month period, making it the largest-ever study to investigate treatments for HD. It was funded primarily by the National Institute of Neurological Disorders and Stroke (NINDS). Participants in the trial were randomly assigned to one of four treatment groups in the double-blind study. (Neither the subjects nor their care providers knew to which group the individual had been assigned.) One group received remacemide alone, one Coenzyme Q10 alone, one the two drugs in combination, and one a placebo.

Remacemide is a new investigational drug that blocks a neurotransmitter in the brain (the NMDA-type of glutamate receptor) which has long been suspected of contributing to the death of brain cells in HD. Remacemide was well tolerated by the participants but yielded no improvement in total functional capacity (TFC) although there was a trend toward improvement in the intensity of patients' chorea.

Coenzyme Q10 occurs naturally in the body and is available as a nutritional supplement in health food stores. It plays a role in the function of mitochondria, the energy factories of cells. As an anti-oxidant, it neutralizes potentially injurious oxygen-containing chemicals called free radicals, which may play a role in nerve cell death. In the trial, Coenzyme Q10 was well tolerated yet failed to show a statistically significant improvement in functioning over the duration of the 30-month trial. After the first year, however, the symptoms of participants treated with Coenzyme Q10 worsened at a somewhat slower rate, declining approximately 13% less on the TFC scale than the symptoms of those not receiving it. In addition, on two cognitive scales there was a slower decline in the group receiving Coenzyme Q10.

But again, researchers found that the data were statistically insignificant.

"Despite the fact that the results of this trial are inconclusive, the study does provide the hope that an agent may some day be found which will slow the progression of Huntington's disease and other neurodegenerative disorders," said Eugene J. Oliver, Ph.D., program director at the NINDS.

"CARE-HD is important because it is the first study to show a hopeful trend toward slowing of disease with a particular therapy and gives us some good clues to work with in future studies," said Walter J. Koroshetz, M.D., of Massachusetts General Hospital and co-principal investigator of the study. "We hope that further research will build on the CARE-HD trial and lead to an effective treatment that significantly slows progression of Huntington's disease and eventually a cure for these patients." He added, **"The real heroes of this study were the participants with HD and their families."** ■

*For more information about this and other clinical trials, go to the Huntington Study Group website:*

*[www.huntington-study-group.org](http://www.huntington-study-group.org)*

---

## World Federation of Neurology and International Huntington's Association Pass Articles on Protection of Human Rights

The World Federation of Neurology (WFN), an influential organization of scientists and clinicians, and the International Huntington's Association (IHA), meeting together, went on record as supporting important civil rights legislation in relation to genetic testing and health care at the 19th International Meeting of the World Federation of Neurology Research Group on Huntington's Disease in Copenhagen, Denmark, August 25-28, 2001. The two organizations voted unanimously to endorse several articles from the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Among the articles passed at the WFN/IHA meeting were general provisions recognizing that the interests and welfare of the human being shall prevail over the interests of society or science, and a call for measures to ensure universal access to health care. Articles were also passed prohibiting discrimination against individuals because of their genetic heritage, limiting the use of predictive genetic tests to health purposes or for scientific research linked to health purposes only, and requiring appropriate genetic counseling and informed consent. ■ *For full text, go to [www.hdfoundation.org](http://www.hdfoundation.org)*

Summer 2002

---

## Brent Stockwell Wins Career Award

Brent Stockwell of the Whitehead Institute and HDF grantee has been selected for a 2002 Burroughs Wellcome Fund Career Award at the Scientific Interface. After a rigorous selection process, eight scientists from across the United States were chosen for the scientific excellence and innovation of their proposals. Stockwell will use the award of \$538,000 over five years to conduct high-throughput testing of thousands of small molecules in order to uncover the mechanisms underlying Huntington's disease and identify possible new therapeutic agents. Congratulations, Brent! We hope to hear much more good news from you in the coming months and years. ■



**Dr. H. Robert Horvitz** has been showered with awards over the past few years. Most recently, he was the recipient of the 1<sup>st</sup> annual Wiley Prize in the Biomedical Sciences. In February 2002, he received the 14<sup>th</sup> annual Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research. Horvitz, who is the David H. Koch Professor of Biology at the Massachusetts Institute of Technology and a Howard Hughes Medical Institute investigator, received the \$50,000 award in recognition of his landmark discovery that specific genes control programmed cell death, or “apoptosis.” His discovery revealed that the genetic pathway of apoptosis is a naturally occurring and specific biological process and that it occurs in many organisms including humans. This pathway is involved in a variety of human diseases, including neurological disorders. “By identifying the genes and proteins responsible for cell death, Dr. Horvitz opened the door to the possibility of new interventions in a variety of human diseases,” said Frank D. Yocca, Ph.D., executive director, neuroscience drug discovery at Bristol-Myers Squibb Pharmaceutical Research Institute.

Horvitz was named as one of *Time* magazine’s “America’s Best: Science and Medicine” for his cell death research. Earlier in the year, Horvitz was awarded the Feodor Lynen Medal from the University of Miami; and in 2000, he won several other awards, including the extremely prestigious Louisa Gross Horwitz Prize for Biology or Biochemistry from Columbia University, given annually to recognize exceptional accomplishments in biological and biochemical research and considered by many to be the precursor to the Nobel Prize. Horvitz shared the award with Stanley J. Korsmeyer of Harvard Medical School.

Our own **Dr. P. Michael Conneally**, Distinguished Professor at the Indiana University School of Medicine, a long-time associate of the Foundation, beloved member of the Venezuela team, and key collaborator in the identification of the gene for Huntington’s, has been elected President of the American Society of Human Genetics for the year 2002. He has also been chosen to serve as Secretary General of the World Federation of Neurology for 2002-2003. Congratulations Mike and Mary!

**Dr. Gillian Bates**, of Guy’s Hospital Medical School in London, UK, received the Klaus Joachim Zulch Prize for basic neurological research from the Gertrud Reemtsma Foundation, a research organization affiliated with the Max-Planck Society. Dr. Bates shared the award with Dr. Jean-Louis Mandel of the University of Strasbourg in France. The prize, awarded September 7, 2001, honored Dr. Bates for her development of transgenic mice now widely used in Huntington’s disease research. In bestowing the prize, the Foundation noted that Bates’ discovery “brought unity into an entire group of neurodegenerative diseases, all of which now appear to be due to aggregation of

proteolytic fragments and their deposition in neurons.” These diseases include, in addition to HD, Alzheimer’s disease, Creutzfeldt-Jakob disease (CJD), Bovine Spongiform Encephalopathy (BSE, commonly known as Mad Cow Disease), and Parkinson’s disease.

**Dr. Fred H. (“Rusty”) Gage**, professor of biology and director of the Laboratory of Genetics at the Salk Institute for Biological Studies at UC San Diego, has been making headlines with his stunning discoveries of the ways that adult brains can grow new nerve cells. Challenging the received wisdom that nerve cells (neurons) cannot regenerate, Rusty has shown that stem cells in the brain can morph into new brain cells, depending upon the chemical signals they receive as they grow. His work suggests that such capacities for regeneration may eventually be harnessed therapeutically with drugs which promote new cell production, thereby opening new possibilities for the treatment of neurological disease. *Time* magazine featured Rusty as one of their top 100 “The Next Wave: Science on the Edge” Innovators. Gage’s discovery forced scientists to rethink some of their most basic ideas about how the brain works. ■

## Drugs on the Shelf May Treat HD!

For the past year, some 30 investigators have been screening a library of approved drugs for agents that are effective against neurodegenerative diseases, thanks to a joint program of drug discovery sponsored by the National Institute of Neurological Diseases and Stroke (NINDS), the Hereditary Disease Foundation (HDF), the Huntington's Disease Society of America (HDSA), and the Amyotrophic Lateral Sclerosis Association (ALSA). Of the 30 investigators funded, 15 are working on Huntington's disease.

This unusual collaborative research initiative, announced on May 8, 2001, was developed in response to recommendations of the NINDS Strategic Planning Panel on Neurodegeneration, which was chaired by HDF Scientific Director Allan Tobin and with HDF President Nancy Wexler as a member. The initiative provided supplemental funding for scientists already funded by NINDS grants or grants from one of the three voluntary groups. Up to \$1.3 million was committed by the four organizations for this

program. Dr. Jill Heemskerk, program director of neurodegeneration at NINDS, said it was "tremendously valuable" to have the voluntary agencies participating in this program, not only because they contributed additional funds but also because they permitted the participation of investigators not currently funded by NIH grants. These supplemental grants facilitated the testing of a pre-defined set of compounds in models of Huntington's disease, ALS, and other neurodegenerative diseases.

One of the unique aspects of this initiative was a requirement that scientists share their results. Data are being entered into a database maintained by NINDS. A workshop held in April, 2002 enabled investigators to compare their results with those obtained using other models and assays and to evaluate and prioritize the effectiveness of tested compounds for eventual inclusion in clinical trials. An article about the workshop can be found in the May 9, 2002 issue of the journal *Nature* (417, 109, 2002) [online at <http://www.nature.com>].

NINDS has been excited by the positive response of investigators to this aspect of the program, said Heemskerk. "Hereditary Disease Foundation has a good history of getting people to share information, and we are pleased to see that this spirit is shared by the broader community."

Approximately 1,000 drugs were tested, about three-quarters of which are already approved by the US Food and Drug Administration (FDA). The others were chosen because they showed some influence on brain activity. A number of drug leads have arisen from this collaboration and, according to Heemskerk, "some [compounds] are already being prepared for follow-up studies in mice."

The goal of this collaboration is to move therapies into clinical trials based on the hits from this screen. Once this happens, the trial should move quickly as many of the drugs are already FDA-approved. "We would like to push that through clinical trials in an active way, and see that it gets put into patients as soon as possible," added Heemskerk. ■

## First International Gordon Conference on CAG Triplet Repeat Disorders

Huntington's disease and other neurodegenerative diseases caused by CAG triplet repeat expansions were the focus of a Gordon Research Conference (GRC) held at Mount Holyoke College on July 15-20, 2001. Gordon Research Conferences, started in 1931, are considered among the most prestigious scientific meetings worldwide. They provide an international forum for the presentation and discussion of frontier research in the biological, chemical, and physical sciences, and their related technologies. The conferences emphasize the free exchange of information and presentation of cutting-edge research.

Participants must apply and are selected by the Chair based on their interest and

contribution to the field. This was the first conference on triplet repeat diseases and many applicants had to be turned away.

The decision of the GRC organization to focus on triplet repeat diseases reflects the importance of these diseases on the map of molecular genetics research. The conference, chaired by HDF grantee Dr. Patrik Brundin, with Scientific Advisory Board member Dr. Marie-Francoise Chesselet as vice-chair, brought together many of the world's leading scientists in the field to discuss recent advances in understanding the mechanisms operating in these diseases and efforts toward the development of effective treatments. Participants includ-

ed researchers in the early stages of their careers as well as veteran investigators. One of the highlights of the program was a dialog between graduate student Ai Yamamoto (an HDF grantee) and the late 87-year-old Nobel prize winner, Max Perutz.

Participants gave the conference very high marks. We, at HDF, are exceedingly proud to announce that the second Gordon Conference on CAG Triplet Repeat Disorders will be held May 4th-9th, 2003 at Il Ciocco, Barga in Italy. Gillian Bates will chair the conference and Michael Levine will be vice chair. Both are also grantees and members of the Scientific Advisory Board of the HDF. Congratulations! ■

## A Tribute to Ethan Signer *By Allan Tobin*

During the last four years, a single man has had an extraordinary effect on Triplet Repeat Disorders. I want to acknowledge his many contributions.

I refer, of course, to Ethan Signer, who, since March 1997, has been the founding Executive Director of the HDF's Cure HD Initiative. Ethan has recruited dozens of scientists, suggested scores of experiments, instigated hundreds of creative discussions, and directed the flow of millions of new dollars into HD research. He helped focus the field's attention on the possibilities of drug development, and he has set into motion more than 15 screens—both in academia and in biotechnology companies—for compounds that act upon HD-relevant targets.

The hallmark of Ethan's science is his critical focus on the unappreciated detail—the unnoticed and sometimes ugly fact that strengthens or weakens the case of its possessor. His favorite phrase—one I have come to dread—is “I don't understand.” By this he means, “How in the world can you possibly

think that?” The whole field has profited.

Ethan is allergic to bombast, dismissive of cant, and insistent on logic. My favorite example of his satiric style and wry humor is his “Precepts of Right Living,” which may apply to some of the discussion at this conference: “(1) Everything is everything; (2) Nothing is anything; (3) All is one.”

Most of you know that Ethan was a professor of biology at MIT until he took early retirement, first to found a biotechnology company and then to join and help create the Cure HD Initiative. You may not know, however, that Ethan never allowed his career to reach a steady state that balanced synthesis and degradation. Ethan has moved from field to field, ranging from *lac* operon to nitrogen fixation, from antiwar activism to a successful music group, the Charles River Valley Boys.

I became worried about the possibility of Ethan's withdrawal when he moved from the intellectual hothouse of Cambridge to the pastoral vacuity of

Manhattan. As I have calculated, however, the periodicity of his phase changes is about three years; so we have had a big bonus in having him for four.

I cannot predict where Ethan's road will now take him, but I know it will move in some marvelous ways and that sometime in 2005 we will see a flare of new energy in his next field of endeavor. Please join me in thanking Ethan for his many contributions and in wishing him well in his new wanderings.

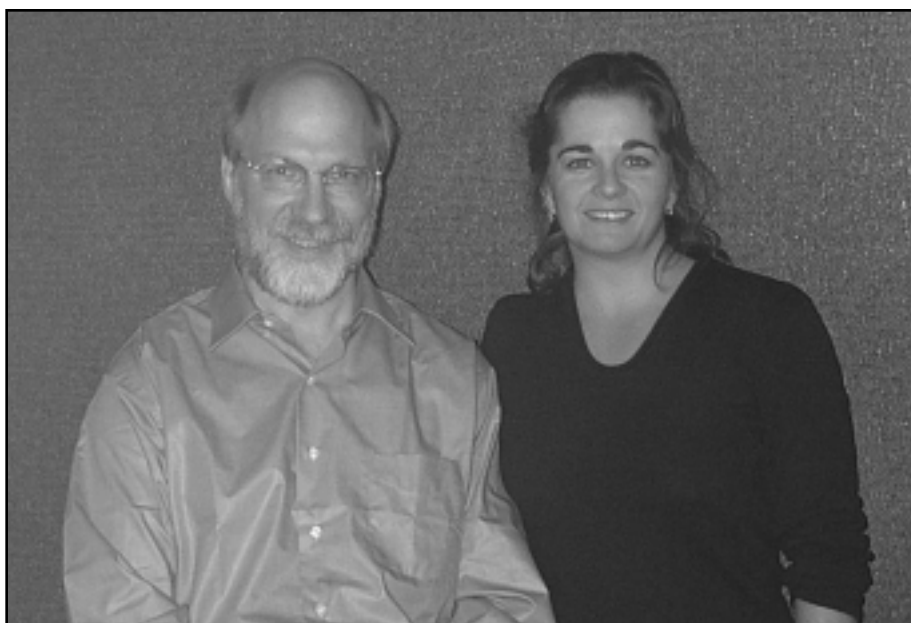
*Editor's note: This tribute was delivered at the Gordon Research Conference on CAG Triplet Repeat Disorders, July 15-20, 2001. Ethan had decided to retire from scientific pursuits. Fortunately for us, his retirement was short-lived! Recently, finding that he could not stop searching for a cure for Huntington's disease, Ethan joined a new foundation called the High Q Foundation. This foundation, which focuses on polyglutamine diseases including HD, will work closely with the HDF.*

## Cure Huntington's Disease Initiative's Focus on Drug Discovery

### New Directors

With a renewed focus on drug discovery, the Cure Huntington's Disease Initiative (CHDI) announced the appointments of Dr. Carl Johnson to the post of Executive Director and Minka vanBeuzekom as the new Managing Director. Both bring to their posts extensive experience in the biotechnology and pharmaceutical industries as well as the zeal to leave no stone unturned in the search for effective therapies against HD.

Dr. Johnson, an accomplished neurobiologist, has worked in the biotechnology industry for nearly 15 years, most recently as Vice President, Research at



*Carl Johnson and Minka vanBeuzekom*

*Continued on next page*



Trustees Debbie and Buster Blethen, surrounded by their daughters Courtney (left) and Kerry (right), after the Buster Blethen Tributes (see *TRUSTEE NEWS* - page11)

Axys Pharmaceuticals, Inc. He was Director of Genetics at Cambridge NeuroScience, Inc. from 1987 to 1990. In 1990, he and board member Bob Horvitz founded NemaPharm, Inc., the first functional genomics company focused exclusively on the discovery of human therapeutics based on technologies using a well-studied model animal, the nematode (or roundworm) *Caenorhabditis elegans*.

NemaPharm was acquired by Sequana Therapeutics in 1996 and subsequently merged with Arris Pharmaceutical in 1998 to form Axys Pharmaceuticals. Carl holds a B.S. in Chemistry from the University of Chicago and a Ph.D. in Biology from the California Institute of Technology.

Ms. vanBeuzekom was most recently Associate Director of Business Development at Axys Pharmaceuticals. Prior to that she was Director of Operations for the NemaPharm Division of Sequana Therapeutics and Vice President and Treasurer of NemaPharm, Inc. Before joining NemaPharm, Ms. vanBeuzekom was the Senior Director of AIDS Epidemiology for the

Massachusetts Department of Public Health. She holds a B.A. in Molecular Biology from Wellesley College and an M.P.H. from Boston University School of Medicine.

### What is CHDI?

Thanks to a substantial anonymous gift to the HDF in 1997, the CHDI was founded with a specific mission to accelerate progress from research to therapy. Several generous contributions since then have ensured continuity of CHDI goals. Using a goal-oriented, task-force strategy aimed at stimulating and coordinating research in academia and private industry, the CHDI approaches HD as a problem in practical drug discovery. The Initiative proactively solicits research proposals, making grants to numerous investigators studying potential new drugs, developing screening methods for quickly assessing the effectiveness of new drugs, and studying the mechanism of disease and potential drug targets.

The Cure HD Initiative receives further advice and support from a Cure Committee comprised of **Dr. Nancy Wexler**, President, Hereditary Disease

Foundation and Higgins Professor of Neuropsychology, Columbia University; **Dr. Allan Tobin**, Scientific Director, Hereditary Disease Foundation and Eleanor Leslie Chair in Neuroscience, Director, Brain Research Institute and Professor of Neurology and Physiological Science, University of California, Los Angeles; **Dr. Kenneth Fischbeck**, Chief, Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health; **Dr. H. Robert Horvitz**, Investigator, Howard Hughes Medical Institute, David H. Koch Professor of Biology, Massachusetts Institute of Technology; **Dr. David Housman**, Ludwig Professor of Biology, Center for Cancer Research, Massachusetts Institute of Technology; **Dr. Richard Mulligan**, Investigator, Howard Hughes Medical Institute, Children's Hospital, Boston, Mallinckrodt Professor of Genetics, Harvard Medical School; **Dr. Anne Young**, Julieanne Dorn Professor of Neurology, Harvard Medical School, Chief, Neurology Service, Massachusetts General Hospital; and **Dr. Ethan Signer**.

Further information about the Cure Huntington's Disease Initiative and programs of the Hereditary Disease Foundation can be obtained at the Foundation's web site: <http://www.hdfoundation.org>. Inquiries regarding Cure Huntington's Disease Initiative research and funding should be addressed to Dr. Carl Johnson at [carl\\_johnson@hdfoundation.org](mailto:carl_johnson@hdfoundation.org) or (608) 767-2193. Inquiries regarding other HDF research programs should be addressed to Dr. Allan Tobin at [ATobin@mednet.ucla.edu](mailto:ATobin@mednet.ucla.edu) or (310) 825-5061. ■

## Creative Crosstalk Leads to New Directions for HD Research

For the past 34 years, workshops have been an essential component of the Hereditary Disease Foundation's efforts to find treatments and cures for Huntington's disease. Milton Wexler imbued these workshops with a psychoanalyst's mindset: release creativity by encouraging free association. Cooperation and trust are important ingredients, as participants are encouraged to share incomplete and unpublished results, comment constructively on the research presented by others, and think "outside the box." Complete reports from all the workshops are available to read or download at the Foundation's website: <http://www.hdfoundation.org>. Recent workshops include the following:

**Fast Tracks to Lead Compounds**, held in Los Angeles on January 6th and 7th, 2001, attracted some 35 HD researchers to discuss the necessary steps and potential bottlenecks faced in developing drugs to treat the disease. While researchers understand little about how expanded CAG repeats in the *huntingtin* gene lead to cellular dysfunction and cell death in selective regions of the brain, participants agreed that focusing efforts on a few of the molecular clues now available might yield candidates for drug therapy. They presented strategies for screening compounds that disrupt long stretches of polyglutamine repeats or interfere with the well-known tendency of the mutant HD protein to form clumps, or aggregates, in the nucleus. Participants also explored other approaches, such as inhibiting production of mutant huntingtin protein and interfering with the cutting and movement of the protein into the nucleus, which appears to be a necessary condition for toxicity. Participants predicted that hundreds of candidate compounds are likely to emerge. The challenge will be to screen these compounds to determine which are promising enough to study in animal models and ultimately in human clinical trials. In order to speed up this process, participants suggested outsourcing toxicological and pharmacokinetic studies. And to increase the power and efficiency of clinical trials, they stressed the need to identify appropriate genetic, pathological, and behavioral markers of disease.

**Microarrays, Models and Mechanisms** used videoconferencing to link 34 members of the Hereditary Disease Array Group (HDAG) who

gathered in Seattle and Boston on January 26<sup>th</sup> and 27<sup>th</sup>, 2001. The HDAG is a consortium of approximately 50 scientists from 18 laboratories around the world, all of whom are conducting research using microarray technology, or "gene chips," to understand better how the mutant huntingtin gene affects expression of other genes in cellular and animal models of HD, as well as in humans with the disease. Gene chips are glass slides onto which small segments of genes are placed in an orderly array. They allow scientists to analyze changes in the expression of thousands of genes in a single experiment. Within an individual model system of HD, researchers have demonstrated a consistent pattern of changes in gene expression, yet they do not know which of these changes contribute to pathology and which are simply markers of cells that are damaged. Among different models, patterns of gene expression varied, pointing to the need for consistent methods and clearly defined protocols that link pathogenic or behavioral changes in animals with changes in gene expression. Some of the observed patterns suggested that critical cellular pathways were not working properly. Further study of these pathways may point to possible therapeutic targets. In addition, gene array experiments may lead to the identification of markers of disease progression, which could be useful in determining whether a potential therapeutic agent is working.

As the search for Huntington's disease therapies heats up, better methods are needed for quickly evaluating whether a drug is working. At the **Biomarkers for Huntington's Disease** work-

shop, held in Playa Del Rey, California in June, 2001, seventeen scientists focused on the search for easily measurable markers of the disease. Such markers would not only facilitate accurate evaluation of the effectiveness of new therapies, they would also improve the safety and efficiency of clinical trials. The ideal biomarker should be measurable in a sample that is easy to obtain, such as blood or urine, and the level of the marker should correlate with disease progression and response to treatment. At the present time, no such biochemical marker for HD has been identified. However, imaging techniques, such as magnetic resonance imaging (MRI), another magnetic resonance technique called NMRS (nuclear magnetic resonance spectroscopy), which measures chemical components in the tissues, and positron emission tomography (PET), are showing promise in the monitoring of disease progression and response to treatment. Results of cognitive and behavioral testing may also provide information about disease state.

Other techniques discussed, which are currently used to study mechanisms of disease but may one day be useful in identifying markers, included gene microarray analysis and the emerging field of proteomics, in which levels of hundreds to thousands of proteins can be identified and measured in a single experiment. Participants at the workshop stressed the need to run animal and human studies of biomarkers in parallel, in order that the advances being made in animal models to understand the mechanisms of disease will be relevant to humans. ■

Our deepest sympathies to trustee **Carol Burnett** on the loss of her daughter, Carrie Hamilton. Hamilton, an accomplished actress, musician, and writer, died of cancer on January 20, 2002. Her play, "Hollywood Arms," based on her mother's memoir about growing up in Hollywood in the 1940s and co-written with her mother, premiered at Chicago's Goodman Theater in late April, 2002, directed by Harold Prince.

In the late 1970s, Hamilton made headlines when she and her parents went public with the revelation of her drug addiction. By speaking openly about their daughter's addiction, Burnett and Carrie's father, the late producer Joe Hamilton, hoped they could help other families cope with their own drug problems. After rehabilitation, Hamilton went on to join her parents in the entertainment industry, appearing in many popular television series and feature films. She also wrote and directed short films and won the Women in Film Award at the 2001 Latino Film Festival.

Carrie Hamilton is survived by her mother and two sisters. Her tragic death strengthens our dedication to finding cures for these devastating diseases.

Trustee **Julie Andrews** was saluted as one of the world's most talented artists when she was recognized as one of the 2001 Kennedy Center Honorees. Kennedy Center Chairman James A. Johnson said, "We honor a beloved actress whose performances in films and the musical theater are treasured by millions of Americans." The 2001 Honorees were saluted by stars from the world of the performing arts at a gala performance on December 2, 2001, attended by President and Mrs. Bush, and by artists from around the world. Also recognized was another supporter of the HDF, **Quincy Jones**, whom Johnson cited as "a musician who has had a spectacular influence on all facets of American popular music for more than 50 years."

Trustee **Carol Burnett** has once again donated her proceeds—\$100,000—from an April 2001 "Toys 'R Us" benefit to the Hereditary Disease Foundation. Later in the year, she celebrated her marriage to Brian Miller. In April, 2002, a play based on her best-selling memoir "One More Time," co-written with her late daughter Carrie Hamilton,

premiered at Chicago's Goodman Theater. Congratulations, Carol, and many thanks for your beautiful generosity, which is helping to cure genetic and neurological disease.

**Buster Blethen**, a long-time Trustee, along with his wife Debbie Blethen, was honored at a fund-raising dinner in Seattle on January 26, 2001. Buster was diagnosed with Huntington's disease thirteen years ago when he was just forty-five years old. He is the father of two beautiful young daughters, and a publisher at the *Seattle Times*, which is owned by his family. The celebration of Buster's life drew many outstanding women and men from the Seattle community, some of them Buster's friends from childhood. At the dinner, Debbie described a history familiar to many families with Huntington's disease: "Twenty-eight years ago, when Buster and I had our beautiful wedding reception here at the Sunset club, I never dreamed that I would hold an event here to raise money for Huntington's research, with Buster so severely afflicted in a wheelchair. I also never dreamt that we'd have two outstanding daughters,

Kerry and Courtney, who would each have a 50% chance of dying of this disease. On the positive side, I didn't know the outpouring of love and support we would receive from our friends and family. Here you are, and we thank you from the bottom of our hearts. I pray that my next event here will be a big dance to celebrate the cure for Huntington's!"

Trustee **Frank O. Gehry's** magnificent retrospective at the Solomon R. Guggenheim museums in New York and Bilbao, have once again sent critics and public alike into paroxysms of ecstatic praise. "You want the best? Here it is," writes architecture critic Herbert Muschamp in *The New York Times* (May 18, 2001). This exhibition presented forty of Gehry's projects, and included the multiple models that form the heart of this architect's creative process. "One is free to appreciate these projects on purely formal terms," writes Muschamp. "Mr. Gehry's sculptural gifts are unmatched." For Muschamp, Gehry is also "an architect of democracy. Freedom and equality, and the tensions between that Tocqueville analyzed, are everywhere at play." Gehry was bestowed the Gold Medal for Architecture, from the American Academy of Arts & Letters, in a ceremony in New York held on May 15, 2002. Hooray, Frank!

Trustee **Marjorie Fasman** has completed another novel. Her first book, *The Diary of Henry Fitzwilliam Darcy* (New Leaf Press, 1997, available from Amazon.com), drew on Jane Austen's *Pride and Prejudice* to tell the story of Darcy, tracing the love of Darcy and Elizabeth Bennett from Darcy's point of view. Fasman's new book, *Waltzing the Whirlwind*, is also a romance, set in Paris in 1925, with characters from the Grand Guignol theater as actors in the drama. We look forward to a great read. ■

**“Full Speed to a Cure”  
Biennial meeting on Huntington’s Disease  
August 9th to August 11th, Cambridge, MA**

Three full days of data blitzes, panel discussions and posters covering the latest developments in HD research— from pathogenesis and drug screens to clinical trials and diagnostics. We are planning a fantastic meeting full of exciting information and opportunities to exchanges of ideas. Investigators who receive HDF funds are expected to attend and present a poster summarizing recent results. Our venue is the newly renovated Sonesta Hotel, on the banks of the Charles River, in Cambridge, Massachusetts. Check the website <http://www.hdfoundation.org> for registration details. Abstracts will be due by June 15th.



*“I have a great deal of hope that these scientists will change the future for my kids and maybe for me. I know that they are already making a positive impact.”*

—Bill Fox

**Foxes Sprinting for a Cure**

As he approached the age of 50, Philadelphia real estate executive Bill Fox began to notice the telltale signs of Huntington’s disease: dropping things, losing his balance, and forgetting. Having watched his mother’s health deteriorate from the time she was diagnosed with HD at the age of 40 until she died at the age of 78, Bill knew what was ahead for himself, his wife Sandy, and their four now at-risk children. Finding a cure became a top priority, and Bill and Sandy backed up their concern with financial support for the Hereditary Disease Foundation’s top-notch team of scientists. They became personally involved as well. At one of the

recent scientific workshops, they and their daughter, Tacie, met with the assembled group of scientists, including one whose lab they had funded. The Foxes learned about the progress being made in the search for treatments, while the scientists learned about the human impact of this puzzling and devastating disease. The Fox’s generosity and courage injected a renewed sense of urgency into the research being discussed.

Recently, Nancy Wexler told the Foxes that HDF needed funds to test some promising new drug therapies. In December, the Fox family came through with a significant donation, which will provide matching funds that will enable the HDF to begin a Phase I trial of the promising new drug SAHA (see article on page 1). This drug is already FDA-approved and has been through many successful trials on non-HD afflicted cancer patients. Provided the Phase I trials go well, clinicians can quickly move into Phase II and Phase III trials. And the Foxes have not stopped there. They are turning to their network of friends and business associates to spread the word about these promising new drugs, stressing the need for additional funds for a Phase II trial. “Time is of the essence,” said Tacie.

For Tacie’s recent birthday she requested all her many friends to donate to the Hereditary Disease Foundation. This gift not only celebrates Tacie and her generosity—it also saves lives around the world!! Thank you Tacie! ■

**Hereditary Disease  
Foundation**

**Officers**

Milton Wexler, Ph.D.  
*Chairman*

Nancy S. Wexler, Ph.D.  
*President*

Frank O. Gehry  
*Vice-President*

Susan I. Spivak  
*Secretary*

Berta A. Gehry  
*Treasurer*

Jodie Evans  
*Chair, Development Program*

Allan J. Tobin, Ph.D.  
*Scientific Director*

Carl D. Johnson, Ph.D.  
*Executive Director,  
Cure HD Initiative*

Minka van Beuzekom  
*Managing Director,  
Cure HD Initiative*

Ethan R. Signer, Ph.D.  
*Executive Director Emeritus,  
Cure HD Initiative*

**Staff**

*New York Office*  
Judith Lorimer  
Julie Porter  
Evgenia Lipkina

*Los Angeles Office*  
Edith Shackell  
Tamar Shackell  
Dietrich Blade-Freitag

*Editor*

Lisa J. Bain

*Production*  
Abby Pardes

## “It’s a Wonderfully Different Life” by *Carlos A. Urrutia*

**I**t is Thanksgiving evening and I find myself uncomfortably full and lounging in my home... I am relaxed, but not tired. My mind is reeling with so many thoughts, so many things to be thankful for, that I am too overwhelmed to sleep...

Let me go back to the beginning. I had an idyllic childhood, almost the stuff you see in after-school specials. My parents were very much in love and showered my two younger brothers and me with an abundance of love, caring and support. I was a very outgoing kid and did quite well in school. I particularly enjoyed reading books, talking to people, making and playing with friends and engaging in sport.

After my father’s death from a brain tumor when I was 13, my mother did everything she could to provide us with as normal a family life as possible, all the while hiding her grief from my brothers and me. We had extended family in close proximity, so they acted as an additional source of support. However, my mom’s mother (Grandmother, to me) was also sick. I remember being at various relatives’ houses and hearing them say in hushed tones how sad things were for my grandmother. You see, my grandmother had Huntington’s disease and, for the past several years, had been living in a state hospital.

My mother began exhibiting some unusual behavior, particularly concerning my grandmother and her illness. For example, my mother would not acknowledge that it was Huntington’s disease. In fact, she would not even say Huntington’s, much less allow anyone else to discuss Huntington’s in her presence. The irony here was that she was a nurse, and knew exactly what Huntington’s was and knew

better than most what it could do to one’s life. She had watched her own mother progressively lose both mental and physical capabilities and witnessed the toll it took on the whole family.

My mother went to doctors for help in treating the symptoms she noticed in herself. She endured poking and prodding of every kind and received diagnoses ranging from manic depressive disorder to paranoid schizophrenia. She was even subjected to shock treatments. Year after year, hospital after hospital, no two doctors could agree on a diagnosis, course of treatment or a safe place for us. Unfortunately, there was no way, or test, available at that time to confirm any suspicions.

My brothers and I were affected by my mother’s illness as well. I remember constant headaches and never being able to sleep. I had to bear most of the responsibility around the house for chores and for my younger brothers. My mom ended up in an institution. In fact, she was sent to the same state hospital as my grandmother. I went away to college deciding that I could only worry about things that I could control.

I was very angry with my mother, even after finding out about Huntington’s disease, because of how she treated us. My mother had a twin brother, her only sibling. He had six children. As it turned out, my mother’s twin brother also inherited the Huntington’s gene. He started showing signs of onset close in time to my mother and died 16 years later. Four of my six cousins have HD. It still amazes me how one gene can devastate an entire family. After being institutionalized for several years, my mother passed away in 1986, thus ending twenty long years of suffering through the disease and all its ramifications.

I made a conscious effort to learn more about HD for my own sake. I became a member of the Huntington's Disease Society of America, as well as the Hereditary Disease Foundation. I decided, then and there, that if HD was going to be in my future, I was not going to let it control me and my life as it had so many others. And, most importantly, I would not let what happened to my mom happen to me.

During this time, a very important encounter took place: I met my wife, Karen. Karen helped me to see life in a whole new way. Being with her brought back the same types of feelings I remember having as a young child—feeling safe, warm and loved. Before we wed, we went to a genetic counselor in New York. I wanted Karen to know everything she was getting into by marrying someone like me. If I had inherited the expanded form of the gene, it was a death sentence. Worse yet, a death sentence that I could pass along to any children we might want to have together. I was not surprised to learn that the counselor had to read about HD. After a careful review of the known literature of the disease, she offered Karen her “professional” advice. I will never forget the exact words that she said to Karen, “... this was a horrific disease ...” and “....to run as far away as fast as you can from him...” Despite the genetic counselor’s best efforts to discourage her, Karen stuck with me. We were married soon thereafter and planned a wonderful life together.

My wife and I dearly wanted children. I wanted the opportunity to be the kind of father my father was to me. However, I knew I could not take the chance of passing the Huntington’s gene on to a child. Karen and I agreed to adopt. Both my wife and I have created a really great environment for our two children.

As you can probably imagine, I did not hold medical practitioners in high esteem or regard. My experiences with Dr. Nancy Wexler, President of the Hereditary Disease Foundation, and her team have worked to greatly improve my view of the medical community and restore my hope that there may one day be a cure for HD. To assist in the research and educate others about HD, I volunteer for anything I can with HD-related medical issues.

A tremendous breakthrough occurred in the early 1990’s when a determined group of scientists found the HD gene. They also developed a genetic test to determine if someone had inherited it. They could tell you if you had the gene, but could not yet deter-

mine when the progression would start. With my wife’s support, I took the test. I can’t begin to describe the emotions that I felt prior to deciding to take the test and, then after taking the test, awaiting the results. Up until this point, I knew that I might have the gene. But then again, I might not. Not knowing allowed me some comfort and allowed me to continue to live my life as I had. What kind of quality of life would I have if I knew I had the gene, and I was merely waiting for life as I knew it to fall apart? This test was going to remove all wondering and doubt. The test results made it official—I did, in fact, carry the gene for Huntington’s disease. There was no more wondering. My anxiety shifted from the question of “what if...?” to “when...?” That question was answered in 1992, when I first started noticing that something wasn’t quite right.

After everything that has transpired in my life, I consider myself a very lucky man. I honestly feel that having this disease has not only made me who I am, but has helped me to really appreciate life. I feel especially blessed that I found God. He is a source of amazing strength that I draw upon daily to help keep me positive and focused on the right things in my life. I try to live in the day and not worry about things out of my control. I’ve become more able to express myself emotionally. I laugh often and am not embarrassed to cry when I am moved to. My sense of humor helps me to make others feel at ease around me, especially when my symptoms are unusually pronounced.

I do have one more dream that I would dearly love to have realized in my lifetime. I really want to live to see my two children get married. I want to be able to give my daughter away at her wedding and to see her in a beautiful wedding gown. I want to be at my son’s side to give him last minute advice and to see the look on his face when his bride-to-be walks down the aisle. To help them transition into the next phase of their life would be confirmation for me that I did my job as a father. My daughter is eleven years old today, my son only nine, which means I have a while to wait. Until then, I hope for a cure for HD, or, in lieu of a cure, new and better medicines that will extend my life a little longer. I also keep very active mentally, spiritually, and physically. I am forty-four years old today and am committed to making this dream a reality. ■

*We welcome Carlos’s inspiring piece which reflects his point of view.*

---

*This essay is excerpted from a longer one, which is available upon request. Carlos welcomes feedback, questions, and comments.  
Contact Carlos Urrutia at 1526 Olcott St., Wantagh, NY 11793; 516-781-6085;  
Carlos.Urrutia@Chase.com.*