

Hereditary Disease Foundation

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MILTON WEXLER – 1908-2007



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A VISIONARY WHO LED A GENETIC REVOLUTION

by Elaine Woo, LA Times Staff Writer, Printed on March 22, 2007

When Milton Wexler's ex-wife lurched across a downtown Los Angeles street one day almost 40 years ago, a police officer called out to her, "Aren't you ashamed of drinking so early in the morning?"

But Leonore Wexler was not drunk.

She was showing the signs of Huntington's disease, the rare, incurable genetic disorder that had slowly killed her father and three brothers and several months earlier had claimed the life of folk singer Woody Guthrie.

She had believed the disease only afflicted men, but that afternoon a neurologist's examination confirmed that she had been wrong. Even worse, she knew that her two grown daughters with Milton — Alice and Nancy — had a 50-50 chance of facing the same fate.

The devastating news sent Milton Wexler — a lay psychoanalyst popular with actors and artists, including a then-budding architect named Frank Gehry — on a journey to the edge of a scientific frontier. He would emerge a hero.

Please see Milton Wexler, page 2

40

years

Hereditary
Disease
Foundation

innovation
research
collaboration
community

Thank You from Alice and Nancy

Dear Friends,

We are so touched by the fabulous cards, letters, and notes we have received from all of you regarding the death of our father, Milton. Your generous contributions to the Hereditary Disease Foundation are a wonderful tribute to his life's goal of finding a cure for Huntington's and other genetic diseases, a goal we continue passionately to pursue.

Equally as important, in a personal way for us, were the beautiful thoughts and memories you shared with us. Despite knowing our father for sixty-odd years, we are learning many new things about him from your wonderful words — about his role as a "cornerstone" in many people's lives, his "voice of sanity," and his "elegance and patience."

From the science teachers at Culver City High School here in

Please see Thank You, page 3

Milton Wexler: A Visionary Who Led a Genetic Revolution

continued from page 1

Wexler, 98, who died of respiratory failure Friday at his Santa Monica home, ignored the scientific wisdom of the time and poured his energy into unlocking the mysteries of one of the most enigmatic and crippling of diseases, often described as a time bomb because the mental and physical havoc it wreaks typically does not surface until midlife.

In the early 1970s, after starting what is now the Hereditary Disease Foundation, he began to recruit bright young scientists willing to gamble on a longshot to workshops aimed at finding a cure. The freewheeling workshops — structured like the group therapy sessions Wexler ran in his Westside practice — stressed brainstorming and were unlike anything the scientists had ever experienced.

In 1983, after a decade of struggle in laboratories around the country, the scientists nurtured by Wexler — and later also by Nancy, a clinical psychologist — achieved the breakthrough few people believed possible: They found the genetic marker for Huntington's. In 1993, they located the gene itself.

Wife dies of the disease

These milestones in the genetics revolution did not help Leonore Wexler, who died of Huntington's on Mother's Day in 1978 — 10 years after her diagnosis. But they would have a profound impact on others.

Discovering the gene not only represented an enormous step toward finding a cure for Huntington's, but it demonstrated the feasibility of mapping the entire array of 30,000 human genes.

Wexler "proved it could be done," said Dr. Francis Collins, who was a junior professor at the University of Wisconsin when he joined Wexler's

workshops in the mid-1980s. Collins helped develop the methods for identifying the genes responsible not only for Huntington's disease but for cystic fibrosis before leading the successful effort to complete the genome blueprint in 2003.

"The search for the Huntington's gene became the paradigm for all such gene hunts.... That all came out of that wonderful intellectual ferment that Milton and Nancy created," said Collins, now director of the government-supported National Human Genome Research Institute in Bethesda, MD.

Dr. Anne B. Young, a Harvard Medical School professor and chief of neurology at Massachusetts General Hospital, said Wexler was "a visionary.... He was the guru and the glue," who held together a project that many eminent scientists had deemed foolish.

"Today we have the gene. We have an inkling of what the gene does. It wouldn't have happened without Milton," Young said. "He was a catalyst for all of that."

Born in San Francisco but reared in New York City, Wexler entered Syracuse University at 16 and earned a law degree from New York University. But he hated practicing law and abandoned it in 1937 to get a doctorate in psychology at Columbia University. He also studied under Theodor Reik, a Sigmund Freud disciple who helped legitimize the practice of psychoanalysis by non-physicians in the United States.

Wexler followed Reik's path and became one of the country's first lay psychoanalysts. After serving in the Navy during World War II, he



Milton with Carol Burnett and Julie Andrews

joined the staff of the Menninger Foundation, a renowned psychiatric research and treatment center in Topeka, Kan., where his success treating schizophrenics gained attention. He gave his patients round-the-clock care, even taking a small group of them on vacation with his family so their treatment would not be interrupted.

"He was an organizing force in their life. A lot of people got better," Nancy Wexler said.

In 1951, he left Menninger and moved to Los Angeles to begin a more lucrative private practice that would enable him to help support his wife's brothers, who had been diagnosed with Huntington's the year before. He found success treating clients who were well-known in Hollywood. He even shared a screenplay credit with director Blake Edwards, the husband of actress Julie Andrews, for the movie "The Man Who Loved Women."

Wexler also accepted many struggling artists into analysis and by the early 1960s treated them free in groups.

One of his patients was Gehry, who entered therapy because of personal and professional problems. Shy and intimidated by the high-powered movie industry figures, lawyers,

writers and doctors in his group, he went two years without saying a word to them. One night the entire group stunned him with its criticism. They thought his silence meant he was judging them. Afterward, Gehry talked with Wexler and realized that his clients had formed the same impression, which explained his career difficulties.

“It was a defining moment,” Gehry, who would go on to design such iconic buildings as Los Angeles’ Disney Hall, said in an interview this week. “He was brilliant at the moment of truth.”

Transferring the group therapy method of free association to solving the quandary of Huntington’s was, Gehry added, “sheer genius.”

Several principles guided the workshops. The priority was to encourage a free flow of bold ideas, so written lectures and slide presentations were banned because they stifled interaction. The groups were kept small — usually no more than 20 participants — with an emphasis on postdoctoral students and young scientists who were less likely to be bound by orthodoxy.

Wexler also invited established scientists — including Nobel laureate and DNA pioneer James Watson — who functioned as living encyclopedias across a wide range of disciplines. Scientists who ordinarily would not be in the same room together — geneticists who studied worms and flies side-by-side with neurologists and psychologists — shared thoughts.

Wexler “had an ability to bring together a room full of disparate people and basically remove the walls. He was a master of the creative,” said David E. Housman, a Massachusetts Institute of Technology biologist who played a crucial role in the collaborative effort that led to the identification of the Huntington’s gene.

As an added perk, Wexler’s celebrity friends hosted parties for the scientists. “Us geek scientists were totally blown away that this was also part of the workshop scene,” said Collins, who remembered Saturday night soirees with Andrews, Carol Burnett, Walter Matthau and Jack Lemmon.

The spirit of cooperation was so strong that when the scientists published their findings, the authorship was given to the Huntington’s Disease Collaborative Research Group.


A family project

By then the effort had become a Wexler family project. Nancy, a professor at Columbia, recruited scientists, led workshops and collected blood samples in a remote village in Venezuela where what was believed to be the world’s largest family with Huntington’s disease lived. She succeeded her father as president of the foundation. Alice, a historian, wrote “Mapping Fate,” a stirring 1995 memoir of her family’s struggle.

When the Wexler daughters learned that they might have inherited their mother’s defective gene, they decided not to have children. When the procedure for detecting the gene was developed, in part through their brave efforts, they chose not to undergo it, believing that testing positive could raise more questions than they could handle.

Their father agreed with their decision. They were the reason he got into the fight in the first place. “I became an activist because I was terribly selfish,” he once said. “I was scared to death that one of my daughters would get it too.”

Now in their 60s, they are his only survivors. So far, they have remained free of the disease.

Reprinted from:  latimes.com

Thank You

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Los Angeles, we learned how “his model for collaboration continues to influence our work,” and how “one person’s vision, your father’s, could turn something bad into something very good.” And from the New Center for Psychoanalysis in Los Angeles we heard that “his innovation, dedication and creativity in dealing with issues considered impossible made him a giant.”

One thing we always knew about our father is that, like his hero Benjamin Franklin, he was drawn to take on difficult challenges. As a young psychotherapist in the 1940s, he tackled the disease of schizophrenia which was then considered impossible to treat. Decades later, he took on Huntington’s, a similarly “impossible” disease. At the age of sixty, when many people are dreaming of retirement, he plunged into an entirely new world of genetics, neurology, and molecular biology, dedicating his time, when he was not seeing patients, to organizing workshops on medicine and basic science. (Perhaps his passion to find a cure for Huntington’s was part of his secret for longevity!)

We are grateful to all of you for sharing in his life and for your support at this difficult time.

Affectionately,

Alice and Nancy Wexler

Please visit our website:
www.hdfoundation.org
to see obituaries from
The New York Times,
The Daily Telegraph and others.

Spurred on by the loss of her mother and four relatives, scientist Nancy Wexler has been tracking a cure for Huntington's disease. **She is among nine being honored by the Franklin Institute.**

When science is personal

By Tom Avril
Inquirer Staff Writer

It might seem hard to convince a roomful of strangers to let you gouge a few skin cells from their arms for genetic testing, especially when you are a foreigner in a poor Venezuelan community ravaged by disease, and you speak very bad Spanish.

So, Nancy Wexler played her ace card. She held out her arm. A bilingual nurse then guided the American scientist through the crowd.

¡Mira! the nurse said, again and again. *Ella tiene la marca.* "Look! She has the mark."

As one of the oldest and most prestigious comprehensive science and technology awards programs in the world, The Franklin Institute Awards Program has honored thousands of scientists, engineers, inventors, and entrepreneurs since its inception in 1824. Previous Franklin Institute Laureates include such luminaries as Alexander Graham Bell, Marie Curie, Thomas Edison, Albert Einstein, Stephen Hawking, Jane Goodall, Gordon Moore, Jonas Salk, and Frank Lloyd Wright.

Wexler had undergone the same skin biopsy that she was asking of the skeptical villagers. The reason, they were astonished to learn, was that she, like them, was at risk for Huntington's disease — a killer that slowly lays waste to the brain, causing its victims to speak as if they are drunk, to jerk uncontrollably, and, finally, to die.

Wexler, a Columbia University neuropsychologist, is in Philadelphia this week as one of nine people being honored by the Franklin Institute for achievement in science and technology. Other winners of the prestigious awards range from a native of Wenonah, Gloucester County, who is the lead scientist on NASA's Mars Rover mission, to an IBM engineer whose work transformed computers.

Yet, none has so personal a connection with his research as Wexler. Her mother, a grandfather and three uncles all were stricken with the genetic disease that would become her life's work.

More than a quarter-century has passed since Wexler and her colleagues started to collect skin and blood samples in northwestern Venezuela, part of a research trail that also winds through Philadelphia. Now 61, she is past the age when most Huntington's sufferers start to display symptoms, so she may



be in the clear - and is thus able to continue the quest for a cure.

One at a time

In this day of the sequenced genome, when every week brings the announcement of a new gene connected to this trait or that disease, it is worth recalling what the field of genetics was like in 1979.

Nancy Wexler, a psychologist by training, had turned gene hunter after her mother's death the year before.

Backed by the Hereditary Disease Foundation, which her father had established upon her mother's diagnosis in 1968, she made the first of two dozen annual trips to Venezuela. Three villages on the shores of Lake Maracaibo are home to the largest concentrations of Huntington's sufferers in the world, a fate passed down for generations.

But the lab tools available to Wexler and her colleagues were primitive by today's standards. And the available genetic road maps were sketchy at best, says Kenneth Fischbeck, a former University of Pennsylvania researcher who went on three of the trips.

"It's kind of like map-making in the days of exploration and discovery

Winners of the 2007 Franklin Institute Awards

The institute has given its prestigious awards in the sciences since 1824. Past recipients include Marie and Pierre Curie, Albert Einstein and Stephen Hawking.

Bower Awards

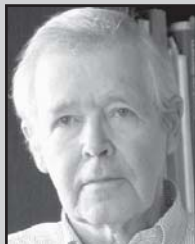


Norman R. Augustine, business leadership, for his outspoken efforts to improve U.S. science education and research and for his stewardship of Lockheed Martin Corp.



Stuart K. Card, achievement in science, for his study of the psychology of interaction between humans and computers, including work that led to the development of the mouse.

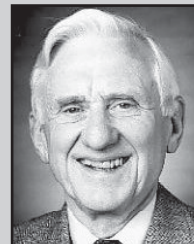
Benjamin Franklin medals



Klaus Biemann, chemistry, who pioneered the use of mass spectrometry to analyze the structure of molecules, especially proteins, which laid the groundwork for the new field of proteomics.



Robert H. Dennard, electrical engineering, who invented the small, inexpensive — and now ubiquitous — computer memory chips called dynamic RAMs.



Merton C. Flemings, materials engineering, for research on how metallic alloys solidify and for the invention of a way to work with metals in a semisolid state, now widely used to make aluminum components in cars.



Steven W. Squyres, earth and environmental science, for his work as lead investigator on NASA's Mars Rover project, which has provided evidence of water on the red planet.



Arthur B. McDonald and Yoji Totsuka, physics, who discovered that the elementary particles called neutrinos have mass and that the three known types of neutrinos can change into one another.



Nancy S. Wexler, life science, for her international crusade to find a cure for Huntington's disease, establishing a model for those seeking the cause of other genetic diseases.

back in the 1500s," says Fischbeck, now at the NIH.

Once they gained the trust of the villagers, recording their family trees and convincing them to give skin and blood samples, the researchers began the laborious hunt for what the sick people had in common. They looked at different genetic markers — small variations in DNA — to find one that might be associated with the disease. They chopped the DNA into bits with bacterial enzymes, looking at the candidates one by one. In comparison, today's robotic machines can do 500,000 such analyses in a single run.

Yet, faster than anyone predicted, the team found a marker in 1983, just two years after testing had begun in earnest. The find was a "major motivator" that helped galvanize support for the Human Genome Project, Fischbeck says.

Still, the marker was only a guidepost for the disease — allowing scientists to narrow their search to a region of Chromosome 4 — not the fatal mutation itself. Scientists proceeded to look on that chromosome for the omission or misspelling of genetic code that they presumed caused the disease.

Not until eight years later did a Philadelphia scientist make a key discovery: A mutation could consist of a mere genetic stutter. Albert La Spada, then a doctoral candidate in Fischbeck's lab at Penn, found a different disease that was caused by an ordinary three-letter sequence of DNA that simply repeated too many times.

Wexler's team then looked to see if Huntington's might follow a similar pattern. It did. (Since then, two dozen more diseases have been found to fit this pattern.)

Please see Nancy Wexler, page 6

Nancy Wexler Receives Franklin Institute Award

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Fellow scientists say her infectious passion was key to moving the work along. Says Penn biologist Nancy Bonini, who has attended one of the energetic workshops sponsored by the Wexlers' foundation: "You feel like you're part of a mission."

Genetic quandary

But now that people could be tested for the disease, Wexler wrestled with a sobering thought: Would they want to find out?

People who learned they had the mutation could see their lives disrupted - perhaps losing the ability to get health insurance or land a job.

"After we found it, I think all of us realized that there was more to knowing than we thought," she says. "As the Human Genome Project goes on, we're all going to be uninsurable. We're all going to have something."

She declines to say whether she has been tested, calling it a "private issue." Her sister, Alice, who wrote about the family's struggle in a 1995 memoir, *Mapping Fate*, says she does not

wish to learn the truth. Because their mother carried the gene, each had a 50 percent chance of developing the disease.

Wexler has garnered numerous awards for her work, but says this one, named for Benjamin Franklin, has special - and bittersweet - meaning. Her father, who joined her for decades in trying to find a remedy for what struck down his wife's family, died last month at 98.

Milton Wexler was "a huge, huge gigantic fan" of the famous inventor, his daughter says. He even wrote a nonfiction book (unpublished) titled *Winning Ways* — based in part on the 13 virtues that Franklin espoused, among them resolution, industry and humility.

As he lay in his hospital bed in March, father and daughter joked about how he, too, had won an award named for Franklin — in high school. She told him how she would have to give a public lecture the week of the award ceremony and asked what she should call it. Exhausted from his bout with

pneumonia, Wexler's father suddenly brightened and said, "The Lucky 13." And, indeed, that is the title of her free talk tomorrow night. Then, she hopes, it is back to Venezuela.

The team has identified nearly 1,500 people who have symptoms of Huntington's or have already died from it, dating to the early 1800s. An additional 1,000 or so are carrying the fatal mutation, and will get the disease at some point. As many as 10,000 more are at very high risk. "It's going to get much worse," Wexler says. The team has not been to Venezuela since 2002, temporarily dissuaded by U.S. officials because of political unrest. But now Wexler is in talks to return. The reason, she says simply: "There's a cure down there."

Find this article at:

http://www.philly.com/philly/health_and_science/20070423_When_science_is_personal.html

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Rave Review of Women's Adventures in Science Series including "Gene Hunter – The Story of Neuropsychologist Nancy Wexler"

The *Women's Adventures in Science* series, featuring "Gene Hunter — The Story of Neuropsychologist Nancy Wexler," has been given a rave review on the National Science Teachers Association "NSTA Recommends" website (<http://www2.nsta.org/recommends>):

"The 10-volume *Women's Adventures in Science* series, co-published by National Academies Press and Scholastic Library Publishing, should be on every middle and high school librarian's 'must buy' list for 2007. The books are, first of all, beautiful. Each is filled with photographs, sidebars, glossaries, timelines, maps, and other graphics that provide key information about the field of science within which each woman has excelled. These text features are so well designed and captivating that they create excitement and interest that draws readers into the book.

"Once inside, the true power of the *Women's Adventures Series* is revealed as eight talented authors weave the very personal story of their journey from girl to scientist. The books begin with an overview chapter of the life and career of the scientist profiled, and then they move into a kind of flashback to her earliest years. The emphasis on adventure will appeal to a wider variety of young women than most biographies.

"The *Women's Adventures in Science* project, supported in part by Sara Lee Schupf and the National Academies of Science, also includes its own website (<http://www.iwaswondering.org>) with additional biographical and scientific information in the form of scrapbooks, activities, web-links, interactive games, and timelines."

Reviewer: Kari Augustine

Thank You, Julie, for Over 30 Years of Leadership with Hereditary Disease Foundation!

Reprinted from *Neurology Now*, March/April 2007

JULIE ANDREWS

Our Fair Lady

Hollywood icon Julie Andrews plays a starring role in the fight against Huntington's disease.

BY LINDA CHILDERS

She's a Hollywood legend, a Dame of the British Empire, and one of the most beloved actresses in the world. During the course of a career spanning more than 50 years, Julie Andrews has been a star of the stage and screen, mesmerizing audiences in *My Fair Lady*, *The Sound of Music*, *Mary Poppins*—the list goes on. This year, Andrews is also the recipient of a number of special accolades. She was presented with a Lifetime Achievement Award by the Screen Actor's Guild in January, and in May, she will accept the 2007 Public Leadership in Neurology Award from the American Academy of Neurology.

The Academy is honoring Andrews, 71, for being a stalwart advocate in the fight against Huntington's disease. She has served on the board of trustees of the Hereditary Disease Foundation with her husband, film director Blake Edwards, for over 30 years. The HDF funds cutting-edge research and is committed to finding treatments and cures for Huntington's disease and other hereditary illnesses. Andrews was first approached to serve as a board member by Milton Wexler, Ph.D., the chairman and founder of the Foundation, and his daughter, Nancy S. Wexler, Ph.D., who became the Foundation's President in 1983. Milton, who died on March 16 at 98, created the HDF in 1968 after learning that his wife, Leonore Wexler, had Huntington's disease. Leonore died from complications of Huntington's in 1978.

PASSION FOR COMPASSION
"Huntington's disease is a devastating inherited condition," Andrews says.



THE SOUNDS OF JULIE: Although her grandchildren think of her as Queen Lillian in the *Shrek* movies, Andrews' most memorable film roles were in (top, left to right) *My Fair Lady* (1964), *The Sound of Music* (1965) and *Mary Poppins* (1964). Left, with husband (and fellow HDF board member) Blake Edwards on the set of *Victor/Victoria* (1982); right, at a 2006 book signing for *The Great American Mousical*, one of the more than 20 children's books she has penned with daughter Emma Walton Hamilton, seen here (far right) when Andrews received the Order of Dame Commander of the Order of the British Empire from Queen Elizabeth in 2000.

FIGHTING A DEBILITATING DISEASE

This is a devastating inherited condition that often waits until mid-life to strike," Andrews says. "Huntington's is also a 'marker disease,' which means that if a cure is found, researchers will also gain insight on how to cure hereditary forms of Alzheimer's disease, Parkinson's disease, Lou Gehrig's disease, other genetic diseases—even cancer."

In her work with the Hereditary Disease Foundation, Andrews has found that many people are still unfamiliar with this fatal neurological illness that causes involuntary movements, severe emotional disturbance, and cognitive decline. Huntington's disease usually strikes people in their thirties and forties, although it can also attack children and the elderly. There is no treatment yet to halt the inexorable progression of Huntington's, which leads to death after 10 to 25 years.

Because it is an autosomal-dominant disorder, each child of a parent with Huntington's disease has a 50-percent risk of inheriting the illness. In the United States, the prevalence of the disease is approximately 10 cases per 100,000 people—about 30,000 people in all. There are another 150,000 individuals at risk.

While Andrews and Edwards could lend their celebrity status to any number of charitable causes, they are committed to helping the Hereditary Disease Foundation.

"Blake and I were thrilled when the Wexlers asked us to serve on the board," Andrews says. "We primarily serve as spokespeople for the organization and assist with fundrais-

ing. This is a cause that both Blake and I feel strongly about, and we see how the HDF's work has the potential to impact a variety of diseases."

In spite of her high-profile position within the foundation, Andrews is modest in describing her own role. And her appreciation of the work that the Wexlers have done is palpable. "It's impossible to talk about Huntington's disease," Andrews says, "without heralding the accomplishments of the Wexler family and their commitment to neurological research."

"The work the Wexlers do on behalf on Huntington's is truly remarkable," she continues. "Both Nancy and Milton are brilliant, and they have put together a team of the best and brightest scientists and other staff—people who are truly committed to finding a cure. I would love to see them win a Nobel Prize for their work."

Indeed, a Nobel Prize might be in Nancy Wexler's future. In April, Nancy will receive the Benjamin Franklin Award in Life Science from the Franklin Institute for leading the combined efforts to identify the gene responsible for Huntington's disease and establishing a model used to investigate the genetic basis of other inherited diseases. Many winners of the Franklin Institute Award have gone on to receive the Nobel Prize.

FROM VAUDEVILLE TO VICTOR/VICTORIA

Andrews, who is in the process of writing her autobiography to be published later this year, began her career as a vaudeville performer in London.

CLOCKWISE FROM TOP RIGHT: PHOTOFEST; TWENTIETH-CENTURY FOX FILM CORP./PHOTOFEST; BETTMANN/CORBIS; REUTERS/CORBIS; RINE HELSTAD/CORBIS; MGM/PHOTOFEST



DAME JULIE
Julie Andrews
with daughter
Emma Walton
Hamilton

“I would love to see [the Wexlers] win a **Nobel Prize** for their work,” says Andrews.

Whangdoodles, *Dumpy’s Friends on the Farm*, and *Dumpy at School*. Their most recent book, *The Great American Mousical* (Harper Collins, 2006) gives young readers a behind-the-scenes peek at the theater world through the eyes of a mouse. Andrews is a staunch believer in promoting literacy among children and likes to read stories to her own grandchildren when they come to visit.

“Reading meant so much to me as a child,” she says. “So many children today rely on television and electronic media for entertainment, but they don’t require a child to use their imagination. It’s not a substitute for reading.”

Andrews says she is intrigued by the idea of writing a children’s book on how children can cope with a family member who has a neurological disease such as Huntington’s.

“I would love to write a book that could engage children and talk to them about family illness,” she says. “I know there aren’t a lot of books for children that deal with illness and loss.”

“Many of my fans don’t realize that I began my career in vaudeville,” Andrews says. “Those were wonderful years touring around England. I met some of the most amazing people, many of whom had a profound impact on my singing career.”

She made her Broadway debut in 1954 at the age of 19 and went on to star in many popular musicals, including *Camelot* and *My Fair Lady*. Andrews was later cast in a multitude of stage, TV, and movie roles, including her Oscar-winning role in *Mary Poppins*. She has also starred in theatrical films such as *The Sound of Music*, *Victor/Victoria*, *10*, *Thoroughly Modern Millie*, and *The Princess Diaries*.

Forty-three years after the release of *Mary Poppins*, Andrews continues to be a favorite actress of children around the world. In May, she will once again provide the voice of Queen Lillian in *Shrek 3*, much to the delight of her seven grandchildren.

“Knowing their grandma as *Mary Poppins* and a star of *Shrek* rates me very highly in their eyes,” says Andrews with a laugh. “I think they are more impressed by my role in the *Shrek* films than in the body of work behind it.”

THE PEN IS MIGHTIER THAN THE VOICE

Collaborating with her daughter Emma Walton Hamilton, Andrews has also penned over 20 children’s books, including *Mandy*, *The Last of the Really Great*

EMBRACING THE FUTURE

Not surprisingly, another one of Andrews’ great loves is the theater. Two years ago, her daughter, Emma, one of her five grown children, persuaded her to return to the theater to direct a production of *The Boyfriend*, the musical that first brought Andrews to Broadway in 1954.

“I think the transition from actor to director is a natural progression,” Andrews says. “It’s also a lovely way to pass along many of the acting techniques I’ve learned along the way.”

For someone who has performed in front of audiences for years, Andrews is refreshingly honest about her nervousness over accepting the American Academy of Neurology Public Leadership Award.

“It’s a little intimidating to think about addressing a roomful of neurologists and other medical experts who know far more about the disease than I do,” she says with a smile. “But I’m happy to help the Wexlers spread the word on their important organization, and I wouldn’t be surprised if the Hereditary Disease Foundation discovers a cure for Huntington’s in the near future.”

To find out more, contact:
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Linda Childers is a health writer whose work has appeared in More and ePregnancy.

Workshop Updates

Pipelines and Pathogenesis: New Horizons

January 20-21, 2007
Santa Monica, California
By Marina Chicurel, Ph.D.

The Hereditary Disease Foundation's annual January workshop, "Pipelines and Pathogenesis: New Horizons," brought renewed hope to the fight against Huntington's disease. The goal of the meeting was to survey the status of Huntington's disease research, with a focus on areas with particular therapeutic promise. A wealth of strategies to attack the devastating illness was discussed. With so many options emerging, treatments for Huntington's disease seem to be closer at hand than ever before. Participants analyzed ways to block the production of mutant huntingtin, the harmful protein that causes Huntington's disease, ways to



Participants at the January 20-21, 2007 Workshop

prevent it from causing damage, and ways to help the body defend itself against the troublesome protein.

For example, participants discussed the steps that would be necessary to start testing compounds designed to reduce the production of mutant huntingtin. They also considered enlisting the aid of proteins in the body that help destroy or re-fold misshapen proteins like mutant

huntingtin. Participants also examined the possibility of boosting a natural compound known as brain-derived neurotrophic factor (BDNF) that helps keep nerve cells alive and healthy in the brain. Other therapeutic avenues discussed included strategies to preserve and normalize communications between nerve cells which become disrupted

*Please see **Workshop Updates**, page 11*

Thank You, Elaine!

The Hereditary Disease Foundation held its annual research update workshop, "Pipelines and Pathogenesis: New Horizons," January 20-21, 2007 in Santa Monica, California. On Saturday night, the workshop attendees, members of the Scientific Advisory Board, as well as numerous HDF Leadership members attended a fantastic party, full of love and warmth, hosted by longtime friend and Lifetime Director Elaine

Attias. Word spread quickly that Milton Wexler would be attending the event, so many people made the extra effort to join in the festivities. Some notable individuals in attendance were Carol Burnett, Marie-Francoise Chesselet, Jodie Evans and Max Palevsky, Berta and Frank Gehry, David Housman, Zaven



Khachaturian, Arnie Klein, John Mazziotta, Phyllis Parvin, Claire Pollack, Mary Carol Rudin and Anne Young. Many of these individuals have been involved with HDF since its inception 40 years ago.

We want to express our appreciation to all of you for playing such a special role in the life of the Hereditary

Disease Foundation. Many of you were in the home of Elaine Attias and friends back in 1968 when we began this odyssey. We've accomplished far more than anyone anticipated! And we are on track to change history once again!

We were so thrilled you all could be there! Thank you, Elaine, for opening your home and your heart to us. ■



Workshop Updates

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Participants at the January 20-21, 2007 Workshop

in Huntington's disease, as well as approaches to harness the anti-aging capabilities of genes that might help reduce deterioration associated with both Huntington's disease and aging.

The list of potential treatments for Huntington's disease is growing so fast that participants agreed it will be important to prioritize them so that time and resources are allocated to the most promising candidates first. In addition, because so many candidates are emerging from laboratories conducting experiments with animals, guidelines for translating these results into clinical procedures will be needed. New markers to follow the progression of the disease and its changes in response to candidate treatments will also be required.

Although Huntington's disease presents a formidable challenge for scientists trying to understand its pathology and develop therapies, these new results and approaches suggest effective treatments may emerge in the not-so-distant future. In addition, the lessons learned from this research may help develop treatments for other devastating brain disorders, such as Parkinson's disease and Alzheimer's disease.

For a more detailed report, visit our website - www.hdfoundation.org. ■

Sirtuins as Targets for HD Treatment

January 27-28, 2007

Massachusetts Institute of Technology, Cambridge, MA

By Lianna R. Orlando, Ph.D.

In January 2007, the Hereditary Disease Foundation brought together scientists from various disciplines to discuss the potential of treating Huntington's disease by targeting Sirt1, an enzyme linked to longer life span and healthier aging in several model organisms.

It is well known that many organisms, including humans, can increase their lifespan by restricting the amount of calories they consume. Scientists have shown that these low-calorie diets boost the activity of Sirt1, suggesting this enzyme may be responsible for the link between metabolism and aging. Furthermore, resveratrol, a compound found in red wine that extends lifespan and promotes healthy aging in model organisms, also activates Sirt1.

HD scientists are interested in Sirt1 for a number of reasons. First, if activating Sirt1 can slow the aging process, perhaps it can also delay the onset and progression of age-related diseases like HD. This line of reasoning has also been applied to other neurodegenerative disorders, and published reports show that

activation of Sirt1 can reduce the neuropathology seen in Alzheimer's disease models. Moreover, since aging and metabolism appear to be linked via Sirt1, activating it may also be beneficial in alleviating some of the metabolic symptoms of HD, such as severe weight loss and diabetes.

Evidence from various animal models indicates that targeting Sirt1 in HD is likely to be beneficial. Resveratrol treatment reduced neuronal damage and increased lifespan in both worms and flies that have an abnormal huntingtin protein, and at the workshop it was reported that improvements are also seen in HD mice. Resveratrol-treated HD mice lived longer and with better motor function, and they experienced less weight loss and brain pathology.

Preliminary results indicate that HD mice with enhanced Sirt1 live longer, and current studies are examining whether they experience less weight loss, memory impairment and motor dysfunction. These measures are good indicators of whether enhancing Sirt1 activity is likely to improve these symptoms in HD patients as well.

The workshop at MIT was a great success! It was widely agreed that Sirt1 is a promising target for therapy in HD, though more research is needed. The good news is that several Phase I clinical trials are already underway to assess the safety of resveratrol, and biotechnology companies are in the process of making more stable, selective and potent compounds targeting Sirt1. Scientists are also examining six other related enzymes, called sirtuins, which may be relevant in the treatment of disease. Investigators at the workshop were optimistic that continued work in this area could lead to effective therapies for HD in the not-too-distant future. ■

HDF Welcomes New Members of Scientific Advisory Board

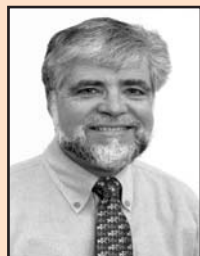
The Hereditary Disease Foundation's Scientific Advisory Board is composed of distinguished scientists from around the world. At the January Scientific Advisory Board meeting, the following individuals were voted in as its newest members:



Yvette M. Bordelon, M.D., Ph.D.
Assistant Professor
Department of Neurology
David Geffen School of Medicine at UCLA



Dennis W. Choi, M.D., Ph.D.
Professor
Department of Pharmacology and
Experimental Therapeutics
Boston University School of Medicine



Michael S. Levine, Ph.D.
Chair
Interdepartmental Neuroscience
Ph.D. Program
Professor
Department of Psychiatry and
Biobehavioral Sciences
Associate Director
Mental Retardation Research Center
Associate Director
Education, Brain Research Institute
Jane and Terry Semel Institute for
Neuroscience and Human Behavior
David Geffen School of Medicine at UCLA



Diane E. Merry, Ph.D.
Associate Professor
Department of Biochemistry and
Molecular Biology
Thomas Jefferson University



Paul J. Muchowski, Ph.D.
Associate Investigator
Gladstone Institute of Neurological Disease
Associate Professor
Biochemistry and Biophysics, and
Neurology
University of California, San Francisco



Joan Sawyer Steffan, Ph.D.
Assistant Professor in Residence
Department of Psychiatry and
Human Behavior
University of California Irvine



Ai Yamamoto, Ph.D.
Associate Research Scientist
Columbia University

Fundraising News Blethen Family Campaigns



Kerry (Blethen) Quinn,
Trustee Debbie Blethen,
and Courtney Blethen

When Debbie Blethen, HDF Lifetime Director and longtime friend, and her family and friends set up a fund

to find treatments and cures for Huntington's disease — as soon as possible — they intended to honor the memory of HDF Lifetime Director Alden "Buster" Blethen. However, when Debbie and Buster's daughter, Courtney, recently underwent genetic testing and was found to carry the gene which will cause HD in the future, everyone instantly realized the urgency of what we are doing right NOW for Courtney's future!! The fund is now **Courtney's Hope Fund**. So far, they have raised over \$187,000 and this is just the beginning! Know that time is of the essence and every penny helps! We look forward to celebrating the CURE with the Blethen family and friends!

*Please make checks payable to **Hereditary Disease Foundation** and specify that they're for the **Courtney's Hope Fund**. Send donations to: Hereditary Disease Foundation, 3960 Broadway, 6th Floor, New York, NY 10032. To donate by credit card, please visit the HDF web site at www.hdfoundation.org. ■*

Update on O'Brien Drive

When Mike and Chris O'Brien set out two years ago to climb Mt. Everest and bring awareness to Huntington's disease and the Hereditary Disease Foundation, they had a objective of raising \$100,000. The current total for the O'Brien Fund is an impressive \$140,488! And the total continues to grow! We're so appreciative of everyone's hard work to make — and exceed! — Mike and Chris's goal! ■

Scientific Advisory Board News

Our Own Gill Bates – Longtime HDF Researcher and Scientific Advisory Board Member Elected to the Fellowship of the Royal Society – Bravo, bravo, Gill!!!!!!



Gillian Patricia Bates, Professor of Neurogenetics at King's College London, is hobnobbing with the ghosts of Sir Isaac

Newton, Charles Darwin, Albert Einstein, Francis Crick and Max Perutz. Current compatriots include James Watson, Stephen Hawking and many of the world's most prominent scientists. She was just elected to the Fellowship of the Royal Society — the world's oldest scientific academy in continuous existence, on the forefront of inquiry and discovery since its foundation in 1660. Each year, 44 Fellows are elected in recognition of their exceptional contributions to science, engineering and medicine.

Gillian Bates is a member of an even further elite as one of only the five percent of female Fellows. Gill served a critical role as an inestimable member of the Gene Hunters in our decade-long struggle to isolate the HD gene. For many workshops a year — including on the Islamorada Keys, FL, where Gill was discovered to be a great dancer! — to hard slogging through genetic data, Gill played a key part. In fact, DNA fashioned by her hands went to Sir John Sulston, a fellow Fellow of the Royal Society and Nobel Laureate, who used the top of chromosome 4, as edited and arranged by Gill Bates, when he began sequencing the human genome.

When this tour de force occurred, Gill was completing finding the HD gene as her postdoctoral stint with mentor Hans Lehrach at ICRF in London. Gill could have chosen

to bask on her laurels. Instead, she went to Guy's Hospital of King's College and worked on putting her newly discovered gene into a mouse. Gill understood how crucial it was to study her gene in a mouse — as mice are very similar to humans in how they behave. Gill made a mouse, astonishingly enough, with a very dramatic illness — after a huge amount of effort, in the early days, when making mice with genetic diseases was incredibly painstaking!! Her mouse gets sick after about a month and dies after three months. Gill's mouse is incredibly standardized, reliable and a superb tool to unravel the nature of HD and develop new treatments. Through Gill's generosity and collaborativeness, her mouse has been distributed throughout the world. This mouse has been used for many hundreds of studies and has already taught us a tremendous amount about human Huntington's disease. It promises to make miracles for the future.

The Hereditary Disease Foundation was honored to TWICE award Gill the prestigious Lieberman Award for the development of her mouse and for further therapeutic studies. Again, bravo, bravo, bravo, Gill — we love you!!!!!!!!!!!!

According to the Royal Society's citation: "Professor Gill Bates is distinguished for her significant contributions to the understanding of Huntington's disease. She played a key role in the cloning of the Huntington's disease gene. She generated the first mouse model of Huntington's disease, which has been pivotal in uncovering previously unknown aspects of the disease's pathogenesis. In recognition of her achievements Professor Bates was

awarded the Royal Society Glaxo Wellcome Award in 1998."

"This is an unexpected honour and I am absolutely thrilled and delighted. It reflects a 20 year endeavour to understand and develop disease modifying treatments for Huntington's disease that I have shared with many talented and exceptional people," says Professor Bates.

Gillian Bates is head of the neurogenetics research group at King's within the Division of Genetics and Molecular Medicine. Since her postdoctoral work when she was part of the collaboration which cloned the Huntington's disease gene, Gill has conducted pioneering research to further our understanding of this degenerative disease. Her group currently explores early molecular events that occur in HD with the aim of exploiting these as potential targets for therapies.

The Royal Society is the UK's national academy of science, supporting the country's top scientists and influencing science policy. A fellowship is the highest accolade for scientists, short of receiving a Nobel Prize.

Lord Rees, President of the Royal Society, says: "These new Fellows are at the cutting edge of science in the UK and beyond. Their achievements represent the enormous contribution science makes to society."



Research News

Research Study Identifies Many Proteins Implicated in HD — May Lead to New Avenues for Treatment

HD researchers have identified more than 200 new proteins that bind to normal and mutant forms of the protein that causes Huntington's disease. The research was led by Hereditary Disease Foundation's Scientific Advisory Board member and HD researcher Robert E. Hughes of the Buck Institute for Age Research, in Novato, CA.

Results of the study, which may facilitate the discovery of an effective treatment for HD, were published in the May 11, 2007 edition of PLoS Genetics, an online, open-source journal, enabling scientists from around the world to take advantage of the findings immediately. Joining Hughes as co-authors of the paper are Buck Institute scientists Cameron Torcassi and Lisa Ellerby; along with Eliana Romero and Juan Botas from the Baylor College of Medicine in Houston; Andrew Strand and James Olson from the Fred Hutchinson Cancer Research Center in Seattle; and Linda Kaltenbach, Sudhir Sahasrabudhe, Cornelia Kurschner, and John M. Peltier of Prolexys Pharmaceuticals in Salt Lake City. The work was supported by grants from the HDE, High Q, and the NIH.

Although the mutation responsible for Huntington's disease was identified over a decade ago, how this mutation leads to disease is still not clearly understood. The neuronal toxicity that is seen in HD is thought to be due, at least in part, to abnormal protein interactions involving the mutant protein.

This current study, which involved high-tech screening of the human genome and proteome, was unprecedented both in terms of its scale and in the way the protein interactions were validated in a genetic model of the disease.

By conducting additional experiments in fruit flies genetically altered to express features of human HD, scientists showed that changing the expression levels of these interacting proteins affected the degree of damage seen in the flies.

Of the over 200 proteins that interact with the huntingtin protein, the researchers identified over 25 proteins that, when present in higher or lower levels, were able to modify the Huntington's disease phenotype to make it better or worse. The proteins identified in this study represent proteins that can be targeted for therapeutic intervention to treat, cure or prevent some of the devastating symptoms of Huntington's disease. They may also hold clues to the variances in age of onset that cannot be attributed to longer or shorter CAG repeat lengths. It is the hope of the researchers that more in-depth studies of these individual proteins and their effects on HD will lead to a better understanding of the disease and, ultimately, to a cure.

Now that researchers have discovered the interacting proteins using human libraries and human protein extracts and tested them in the fly, Hughes says the next step is to bring the research back into the mammalian world. The new genes and proteins discovered in this study are being screened and analyzed in cultured mammalian cells; the ones that show activity in ongoing experiments will be tested in mouse models of HD.

"Here at the Buck Institute, we're going to be focusing on a few dozen proteins," said Hughes. "Effective follow-up on any target protein depends, in large part, on how much expertise a scientist has with that target. We are hoping that researchers will look at this study and that those with specific expertise in a particular protein will move forward with their own inquiries." ■

HSG and Euro-HD Report Results of Two Phase III Studies of Miraxion in HD: No Effect

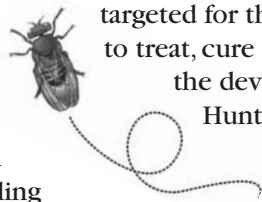
LONDON, United Kingdom—

Amarin Corporation announced on April 24, 2007 results from its two Phase III clinical trials of Miraxion (also known as LAX-101, eicosapentaenoic acid [EPA], or "fish oil") to treat Huntington's disease (HD). The Company conducted two Phase III double-blind, placebo-controlled studies in which HD patients were randomized to receive either placebo or 2 grams (1 gram twice daily) of Miraxion daily for six months. Study data showed no statistically significant difference in either study between Miraxion and placebo with regard to the primary and secondary endpoints.

The primary endpoint of the trials was a change in the Total Motor Score 4 (TMS-4) component of the Unified Huntington's Disease Rating Scale (UHDRS). TMS-4 has been shown to be a sensitive measure of movement disorder in patients with HD. In addition, secondary endpoints included cognition and Total Functional Capacity outcomes.

The first study, TREND-HD, was conducted in 42 sites in the U.S. and Canada by the Huntington Study Group (HSG) based at the University of Rochester Medical School in Rochester, N.Y. This study, led by Principal Investigator Ira Shoulson, enrolled 316 patients with HD. The TREND-EU Phase III study was conducted in 27 sites in six countries across Europe and in conjunction with the European HD Network. This study was led by Principal Investigator Bernhard Landwehrmeyer, and enrolled 290 patients with HD.

Miraxion for HD has Fast Track designation by the FDA and Orphan Drug designation in both the U.S. and in Europe. ■



2007 Science Funding

Hereditary Disease Foundation grants, postdoctoral fellowships and research contracts are helping identify routes to the development of cures and treatments for Huntington's disease and other similar hereditary disorders. With your support, the HDF's Scientific Advisory Board, comprised of world-renowned experts in genetics, neurology, neuroscience, and therapy development, has funded groundbreaking research. The following projects were funded recently:

Research Grants

2007 Lieberman Award recipient:

Albert La Spada, University of Washington, Seattle WA: Elucidating the mechanism of energy disruption in Huntington's disease.

Karine Merienne, IGBMC, Strasbourg, France: Role of the DNA damage response in Huntington's disease.

Anton Reiner, University of Tennessee, Memphis: Role of striatal parvalbuminergic neurons in dystonia in Huntington's disease.

Paul Rosenberg, Harvard Medical School: The role of glutamate transport in the pathogenesis of Huntington's disease.

Doda Rudnicki, Johns Hopkins University: Clues to HD pathogenesis from HDL2: protein aggregates and the muscleblind-like pathway.

Postdoctoral Fellowships

2007 Milton Wexler Postdoctoral Fellowship Recipient:

Jeremy Van Raamsdonk, McGill University, Montreal, Canada (Mentor: Siegfried Hekimi): The role of aging genes in Huntington disease.

Yun-Sik Choi, Ohio State University (Mentors: Karl Obrietan, Kari Hoyt): Neuroprotection by CREB/CRE transcriptional pathway in Huntington's disease.

Kim Holloway, Cornell University (Mentor: Paula Cohen): Mechanisms of mismatch repair protein function in the pathogenesis of Huntington's disease.

Katherine Steinkraus, University of Washington (Mentor: Matthew Kaeberlein): Suppression of polyglutamine proteotoxicity by dietary restriction in *Caenorhabditis elegans*.

Andrey Tsvetkov, Gladstone Institute, University of California, San Francisco (Mentor: Steven Finkbeiner): Metabolism of huntingtin in health and disease.

Vietminh Paz Villgran, University of Bordeaux, France (Mentor: Yoon Cho): Habit memory coding by striatal cells in HD transgenic mice.

Research Contracts

Beverly Davidson, University of Iowa: Preclinical development of a gene therapy for Huntington's disease via RNA interference.

Stephen Dunnett and **Lesley Jones**, Cardiff University, UK: A comparison of behavioral and gene expression changes in rodent models of HD.

Paul Patterson, California Institute of Technology: Intrabodies as therapeutics for HD.

Alfred Stracher and **Leo Kesner**, State University of New York Downstate Medical Center; **Lisa Ellerby**, Buck Institute for Age Research: Testing calpain inhibitors in HD mice.

Leslie Thompson and **J. Lawrence Marsh**, University of California, Irvine: The role of secondary modification of huntingtin protein in the pathogenesis of HD.

A Note from the Board



It was a sad time for all of us when Milton Wexler passed away in March. Milton was a guiding force in my life. He was my Guide, Guru, good friend and Elder of our tribe. It was he who piqued my curiosity about neuroscience and led me to the Hereditary Disease Foundation. It was his inspiration that has allowed and encouraged my design style to take shape.

Because of Milton's influence, I focus my buildings not only on design, but also on how design affects an individual's neurobiology — how space influences the function of the brain. I take into account the impact of architecture on emotion, thought, creativity and personal interactions, because — within and without a building — architecture can either push people together or separate them. Milton's philosophy influenced me when I was designing the Stata Center at MIT, the Peter B. Lewis Building at Case Western Reserve, the Lou Ruvo Brain Institute in Las Vegas and the Walt Disney Concert Hall in Los Angeles, among others.

Forty years ago, when Milton started the Hereditary Disease Foundation, I had no idea where this road would take all of us. Today, I welcome the opportunity to shape tomorrow.

Thanks, Milton. We miss you!

Frank Gehry

**Save the Date for a Benefit celebrating
The Hereditary Disease Foundation
with a special tribute to its founder, Milton Wexler
Thursday, January 24, 2008
Casa del Mar
Santa Monica, CA**

Memories of Milton

Dear Friends,

We would like to hear any memories, stories, recollections, commentaries about Milton Wexler that you would care to share, whether they are connected with Huntington's disease or the Hereditary Disease Foundation or anything else. We are especially eager to hear stories about specific incidents or episodes. We would also appreciate receiving copies of letters he wrote.

Please send to Alice Wexler at arwexler@ucla.edu, or to the Hereditary Disease Foundation, 3960 Broadway, 6th Floor, New York, NY 10032, cures@hdfoundation.org. ■

Your Legacy Today Advances the Science of Tomorrow

There are many creative ways of giving to the Hereditary Disease Foundation to help us find treatments and cures for Huntington's disease and other hereditary illnesses. Your gift is a vote of confidence that serves as a catalyst for other donors to contribute, and helps ensure the financial security and continued success of the Foundation.

Your gift of cash or appreciated securities, or including the HDF in your estate planning, can help ensure that the progress of today will lead to a cure. You can make a bequest to HDF simply by asking your attorney to include HDF in your will or codicil.

For more information about making a donation or how your legacy gift today can fund the discoveries of tomorrow, call Karen Dean at 212.928.0420 or e-mail her at karendean@hdfoundation.org.

For more information about Ways of Giving, please visit our website - www.hdfoundation.org. ■



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