

Huntington's Disease: Historical and Contemporary Connections

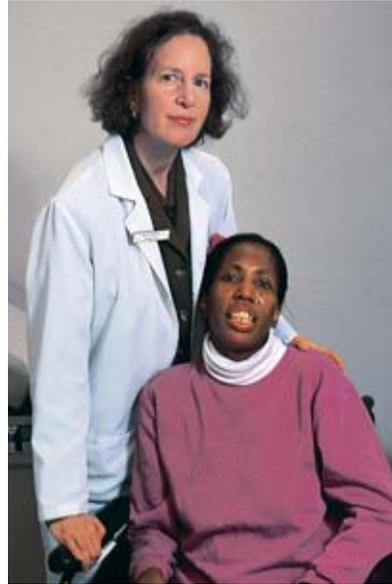
BY ELZY KOLB

In the 10 years that have passed since the discovery of the gene that causes Huntington's disease—the degenerative neurological disorder characterized by cognitive, motor, and behavioral impairments—Columbia has remained in the vanguard.

Columbia has been talking and thinking about Huntington's since the very beginning, when George Huntington, an 1871 P&S graduate, published his groundbreaking paper on the subject a year later. Today, researchers continue to seek a cure and effective treatments for this fatal hereditary disease.

Research done in Venezuela by Dr. Nancy Wexler, the Higgins Professor of Neuropsychology in the departments of neurology and psychiatry, and an international team of top researchers including neurologists, geneticists, and neuropsychologists was instrumental in isolating the HD gene in 1993. Dr. Wexler, who has been at Columbia since 1984, has familial connections to the school and to HD. Her father, Dr. Milton Wexler, received his Ph.D. in clinical psychology from Columbia in 1948. Her mother, Leonore Sabin Wexler, received her master's degree in biology from Columbia in 1936. Leonore Wexler, whose father and three brothers had Huntington's disease, died of the disease in 1978. With his two daughters at risk for HD (Nancy Wexler's sister, Alice Wexler, is an author and historian), Dr. Milton Wexler founded the Hereditary Disease Foundation in 1968, now the essential catalyst for stimulating and funding HD research internationally.

Dr. Nancy Wexler is president of the foundation, which will be moving into Columbia's Audubon Research Park this winter. The foundation is a major funding source for HD research, offering research grants and postdoctoral fellowships, as well as sponsoring the Cure Huntington's



FACING PAGE: This Venezuelan boy, diagnosed with Huntington's disease at age 2, was key to identifying the Huntington's gene.
LEFT: Dr. Karen Marder with Tracy Reed, 39, who was diagnosed with Huntington's disease at age 25.

Disease Initiative. "This program focuses on the high impact of developing new therapeutics," Dr. Wexler explains. Applications are accepted at any time instead of being solicited on a firm deadline cycle. "Whenever you have an idea, write to us, tell us what you're thinking about," she says. "It's a fast-track, catalytic program to develop new treatments."

Such a program would not have been possible before the gene was discovered. In 1979, Dr. Nancy Wexler took her original steps in the journey to discovery, when she first studied the world's largest known HD family. She learned from Dr. Americo Negrette, a Venezuelan physician and biochemist who had discovered and described an extended family with HD, living along the shores of Lake Maracaibo, Venezuela, in which numerous people are afflicted with the disease. The proximity of the families made it unlikely that variations in symptoms would be caused by environmental differences. And it seemed likely that the disease would be traced to a single shared ancestor.

Dr. Wexler said it was meaningful for the Lake Maracaibo HD families to find out that she was also at risk for the disease. During her earliest days in Venezuela she showed patients her skin biopsy scar. The people were impressed by her sincerity, which helped to enlist their cooperation.

Since then, she and her team have spent six to eight weeks in the area annually, collecting blood samples and building a pedigree of more than 18,000 people. The



Nancy Wexler in Venezuela, 1999

disease was traced back to an ancestor who lived in the early 19th century. Each year, the researchers perform neurological and neuropsychological evaluations on approximately 1,000 individuals.

Especially in the project's early days, the group worked under less than state-of-the-art conditions in the poverty-stricken villages. Even now they are only able to draw blood for testing when one of the researchers is returning to the United States and can act as a courier, delivering samples to labs within 48 hours. Most members of Dr. Wexler's original research team stayed with the Venezuela project for more than two decades.

Just three years into the Venezuela project and thanks to genetic and clinical data from the families, a marker for the HD gene was discovered at the tip of human chromosome 4. It took a decade of arduous, collaborative work to isolate the HD gene itself. The Hereditary Disease Foundation organized and supported the Huntington's Disease Collaborative Research Group of more than 150 investigators from around the world, who published the seminal paper, "A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes," in *Cell* on March 26, 1993.

Information collected from the Venezuelan families continues to be a treasure trove for researchers. "We have incredible amounts to learn from it," Dr. Wexler says. "There is a strong correlation between the number of repeats—polyglutamines—in the gene and the age of onset of Huntington's," for example. The age of onset is typically between 35 and 50. Someone with more than 60 repeats, however, will show symptoms before age 20—even as young as 2 years of age—while a person with fewer repeats may have onset delayed until he or she is age 60 or older.

The Hereditary Disease Foundation has developed a wide range of model systems containing the HD gene, including cells, yeast, *C. elegans*, *drosophila*, and many different mouse models. The Columbia lab of Dr. Argiris Efstratiadis, the Higgins Professor of Genetics and

Development, and Dr. Scott Zeitlin, former assistant professor of clinical pathology, created the first knock-out mouse model for Huntington's disease and proved, since the mouse died in utero, that a normal protein, huntingtin, is essential for life. A mutation that expands the length of a glutamine repeat in the protein, however, causes Huntington's.

A decade after the gene's discovery, Dr. Wexler is hopeful and optimistic about progress in HD research. "There's been a plethora of models, and having the gene in hand has allowed us to look at all of these model systems—mice models, yeast models, cell models, *drosophila* models. Any promising compound, we can try through a wide range of preclinical testing. The best drugs we can test in mice. The most effective of these, we can try in people."

A new brain bank at Columbia should also be a research catalyst. Dr. Jean-Paul Vonsattel, professor of pathology, joined Columbia in 2001 to create and direct Columbia's brain bank, where brain donations are used to study a range of neurodegenerative diseases, including Huntington's disease.

Dr. Wexler cites work done at Columbia by Dr. Ai Yamamoto in the laboratory of Dr. René Hen, supported by the Hereditary Disease Foundation, as "the most exciting piece of research in ages, practically since finding the gene." (See "Graduate School Life," page 29, for more about the research.)

"Ai Yamamoto genetically engineered a mouse so she could turn the Huntington's gene on and off, like putting it on a light switch," Dr. Wexler says. "When she turned the gene off, the brain cured itself, movements got better, cognition got better, memory got better." Dr. Wexler believes the research results gave scientists a new way of looking at the disease and possible treatments. Once the HD-causing gene was turned off, the mice in Dr. Yamamoto's research "got back to a kind of normality that even surprised the most optimistic person! And that was done here at Columbia!"

Columbia's Huntington's Disease Society of America Center for Excellence at the New York State Psychiatric Institute also is busy with HD research, as well as assisting HD patients and people at risk. "We're at the forefront both of clinical trials and of trying to determine how to make people's lives a little bit better," says Dr. Karen Marder, who has been the center's director since 1991.

She is the Sally Kerlin Professor of Neurology (in the Sergievsky Center, the Taub Institute, and Psychiatry), a former member of the Huntington's Study Group's executive committee, and head of the Huntington's Study Group's Clinical Correlates Working Group.

The center is modeled after New York State Psychiatric Institute's Memory Disorder Center. Its staff is a multidisciplinary team of neurologists, psychiatrists, physical therapists, an occupational therapist, a speech therapist, a nurse practitioner, a social worker, a genetic counselor, and others. "A person might spend two or three hours at one of our clinics, held three times a month, and see all of those different disciplines and get an evaluation from all of those professionals at any one time," Dr. Marder says. "We try to offer the best clinical care available and also offer people an opportunity to participate in clinical research. Our professional services are offered free of charge. We're unique. There's nothing like it anywhere in the country."

The center participated in CARE-HD, the largest and longest HD clinical trial, involving 340 patients participating for 31 months, and is now completing a trial to see if creatine improves motor function.

Dr. Marder finds two current observational studies particularly exciting. One follows people who are at risk for HD, don't know their genetic status, and don't plan to have genetic testing. These healthy participants will be evaluated over five years. Researchers hope the study will pinpoint the very earliest signs of HD; the information may eventually be used to design a presymptomatic trial. The second study will document the earliest signs of the disease in people known to have the HD gene. Dr. Marder says, "These studies are being done because we think we're going to be at a point where we will have agents to offer people at risk that will prevent symptoms."

Dr. Marder's involvement with HD research goes back to 1987. She describes herself as being hooked on the disease. "As a neurologist, it's an unusual opportunity to be more like a family practitioner," she explains. "As a specialist, you usually don't get to take care of whole families, and I do. I might know somebody, know the kids, know the grandchildren. Families are so invested, everyone has a lot at stake."

Dr. Marder has been to Venezuela with Dr. Wexler as part of the Venezuela project. "The Venezuela project is a



Two P&S George Huntingtons

George Huntington, for whom Huntington's disease is named, graduated from P&S in 1871. He had been interested in the disorder since childhood, when he was exposed to HD patients through his father's medical practice on Long Island. In 1872, just a year after graduation, Dr. Huntington published the definitive paper on the malady he found horrifying but intriguing. In addition to his own research, he drew on work done by his father and grandfather for the paper. He concluded from astute observation that children of just one parent affected by the disease had a high likelihood of developing it as well. On the other hand, if a person never develops the illness, it will not be passed down to future generations. George Huntington's appreciation and perception of hereditary patterns were made independent of Gregor Mendel and his famous pea plants.

More than one P&S alumnus named George Huntington has made a notable contribution. Though each George Huntington made his mark in different areas of research, the shared name has led to more

than a century of confusion, with George Sumner Huntington often incorrectly credited with writing the groundbreaking paper describing Huntington's disease and its symptoms and hereditary nature.

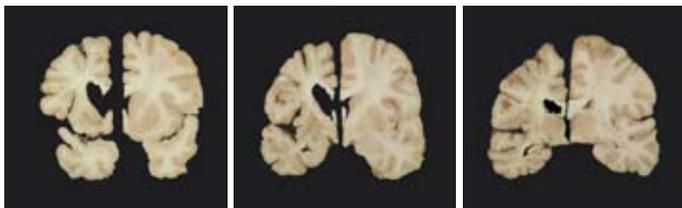
George Sumner Huntington graduated from P&S in 1884 and became a full-time professor of anatomy five years later. He revolutionized the study of anatomy during his 35 years on the P&S faculty and was instrumental in having anatomy recognized as a science separate from surgery.

Perhaps the mix-up is inevitable, as both doctors practiced medicine in the state of New York in the late 19th and early 20th centuries. The two Doctors Huntington were distant cousins; they shared at least three generations of common ancestors, the earliest known of whom sailed from England to Boston, arriving in 1633.

The Dr. Huntington for whom the disease is named spent the majority of his career as a rural physician. He published several other papers and had many interests outside medicine. "George Huntington was so multitasked. He was an artist, quite serious about it," says Nancy Wexler. "Ironically, his family remembered him primarily as a painter. Thanks to so many recent discoveries, the full ramifications of George Huntington's medical genius is coming increasingly to the public attention it deserves."

good cross-pollination for training neurologists how to recognize Huntington's disease, seeing people at all stages of the disease, living with the disease. It gave me a tremendous appreciation for what it is to live with Huntington's. A lot of neurologists have volunteered over the years. It's made us much better neurologists and better able to take care of people with Huntington's."

Once the gene was discovered, genetic testing for HD became possible. Less than 3 percent of people at risk for HD—who are over age 18 and eligible for testing—have been tested. "It's a big issue," Dr. Marder says. "We have a genetic testing program here, and we spend a huge amount of time—instead of just sending out a lab test—discussing what they might do or not do if they had that knowledge," Dr. Wexler and Dr. Marder agree. "Once an individual knows this information, you can't take it away."



The images on the left in this series show the brain of a 48-year-old with Huntington's disease. The images on the right are from the brain of a 34-year-old without the disease.

Carol Moskowitz has been involved in caring for HD families since 1984 and is a former member of the executive committee of the Huntington Study Group. A nurse practitioner at the center, she says her view on genetic testing was changed dramatically by Dr. Wexler. "You can't not be influenced by Nancy's take on things," she says. "I ask people: Why do you want to know if you carry the gene? What will you do differently as a result of this information?" She recalls talking to family doctors who were unaware of the potentially devastating implications of genetic testing, such as individuals—who were not offered pre-test genetic counseling—committing suicide after learning they carried the HD gene.

With a high level of caring evident in her voice, Ms. Moskowitz describes talking to a suicidal Huntington's patient, verbally walking him through his life, mentioning his doctor, listing the people who would miss him, the negative effect his act would have on his at-risk children, weeping with him, and finally asking him to consider partic-

Wanted: Researchers

The Hereditary Disease Foundation wants to recruit more researchers into Huntington's disease investigation. Below are resources for researchers interested in learning more:

HUNTINGTON'S DISEASE INFORMATION, INCLUDING RESOURCES FOR RESEARCH:
The Hereditary Disease Foundation,
(310) 450-9913 (until its move to Audubon Research Park this winter)
<http://www.hdfoundation.org>
RESOURCES FOR RESEARCH:
Cure Huntington's Disease Initiative, Hereditary

Disease Foundation,
Dr. Carl Johnson at
carl_johnson@hdfoundation.org
(608) 767-2193
<http://www.hdfoundation.org/cureinit.htm>
HUNTINGTON'S DISEASE CARE AND RESEARCH AT COLUMBIA/NEW YORK STATE PSYCHIATRIC INSTITUTE:
Huntington's Disease Society of America Center for Excellence
(212) 305-9172
<http://www.hdny.org>
ADDITIONAL HUNTINGTON'S DISEASE INFORMATION:
Huntington's Disease Society of America
(800) 345-HDSA
<http://www.hdsa.org>

icipating in a research study. "I often sit down with someone like this and give them the whole history from the gene discovery up until now and tell them they have to hang in there. People want us to put up a big wall right now—put up a huge wall and stop the disease. I tell them: We have to make each brick by hand, we have to build the information to prevent the disease from beginning, and we need your help. This is not the time to kill yourself. The only real hope is based on solid research," she says, "but it's one brick at a time, and it's never fast enough for anybody."

Since HD was the first neurological disorder for which the gene was identified, Dr. Marder calls it a "vanguard disease. Today we have the gene for Huntington's, tomorrow it will be another disease. We have to think of issues, in terms of risk, genetic testing, symptomatic treatment, and eventually prevention. These are issues that are going to come up all the time." Since the onset of Huntington's is typically in midlife, "people are diagnosed after they've made certain life decisions," Dr. Marder says. "They've had children, and sometimes there's a lot of guilt involved, though it is not warranted. With this disease there's lots of interplay of complex ethical and medical issues that make it very, very challenging."

The challenge of finding a cure and treatment for Huntington's disease is a collaborative international team effort, and Dr. Wexler is effusive in her praise for all involved. "The group of scientists who are working on this devastating disorder and the group of Huntington's families are so extraordinary. They are all generous, enthusiastic, collaborative, they aren't egotistical. They're willing to share. It's just astonishing. The attitude, the ethos, is so warm and friendly, accepting. The families want the scientists to have the most fabulously exciting intellectual time while they're finding the cure for Huntington's. And the scientists want the families to feel, genuinely, that things are changing. There's a lot of hope on the horizon. Families and scientists are sharing in the hope—and in the celebration when we have a cure."

Graduate School Life

Professor René Hen and graduate student

Ai Yamamoto's insight into Huntington's disease

Is Huntington's Disease Reversible?

BY RICHARD KESSIN, PH.D. ASSOCIATE DEAN FOR GRADUATE AFFAIRS

HUNTINGTON'S DISEASE IS A DEVASTATING NEURODEGENERATIVE disorder characterized by progressive motor disturbances, cognitive deterioration, and personality changes. It is inherited as an autosomal dominant. In humans it usually appears at about age 40. For the past eight years we have known the cause of Huntington's disease—a protein called huntingtin sometimes has a large number of glutamines at one end. When a patient has more than 40 of these repeated

amino acids incorporated in their huntingtin, insoluble inclusions in the brain result and these appear to lead to the disease. Although many people have studied this disease, including Columbia's own Nancy Wexler, questions remain. Are neurons killed when inclusions form? Why are these inclusions not dealt with by normal cellular protein degradation mechanisms? Is the disease reversible?

In the face of such neuropathology, it might be natural to assume that the effects are irreversible and that

even if, by some miracle, the excess huntingtin found in the inclusions could be degraded, the patient would be beyond recuperation. That may be so, but recent experiments by René Hen and his graduate student Ai Yamamoto give us reason to think that irreversible damage should not be assumed.

The human disease is difficult to study so researchers have created a mouse model. In this lengthy, but now standard, procedure, a gene coding for huntingtin (plus extra glutamines) was inserted into a mouse oocyte, which was then re-implanted into a mouse. This manipulation resulted in transgenic mice that overexpressed the defective form of huntingtin. Did the mice develop Huntington's disease? Yes. The mice are normal at first, but then acquire the staggering gait, loss of activity, and brain neuropathology that occur in human patients. In fact, the huntingtin protein is

GENE ON means that the toxic mutant huntingtin is expressed in the brain and forms aggregates (pink, in left panel). When these mice are suspended by their tails they clasp their limbs and arch their back.

GENE OFF means that the same mice have been treated with tetracycline, which shuts down expression of the mutant huntingtin. The aggregates disappear and the mice recover a normal posture.



not needed to produce the disease—only 96 repeated glutamines expressed in all tissues of the body are required. But these earlier experiments had a limitation. One could not turn off the huntingtin gene and it was expressed in all parts of the body. Affected mice deteriorated and died.

What Yamamoto and Hen decided to ask was whether the damage observed in the brains of Huntington's patients and in the mice was irreversible. To do this they fused a huntingtin gene (with extra glutamines) to a promoter that could be regulated. A promoter is a piece of DNA that does not code for a protein but controls the expression of a particular gene. Yamamoto and Hen judiciously chose a promoter that was expressed exclusively in the brain and that could be regulated—turned off and on by regulating the diet of the mice. Give them a normal diet and the gene is expressed, the defective form of huntingtin is made, and, predictably, the mice develop the disease. The promoter turns off when the experimenter adds tetracycline to the diet. The gene is silenced and no new defective huntingtin is made.

By this time, Ai Yamamoto was several years into the process. She had fused the regulated promoter to huntingtin and inserted this piece of engineered DNA into transgenic mice. When the pups were born, there was another wait—to see if they developed the disease. Summaries such as this one tend to make experiments sound easy, but this series of experiments could have failed at any step, leaving Ai without a thesis.

Now imagine a small group of affected mice, each sickening with the staggered gate of Huntington's disease. Half of them are fed tetracycline. They recover over a period of weeks—they cease to stagger and on subsequent neuropathological examination, the inclusions in their brains have disappeared. The untreated controls continue to sicken and die. The results suggest that as long as no new defective huntingtin is made, the brain can recover—a constant assault of new protein is necessary to maintain the symptoms. While a complete extrapolation to human brains is unwarranted, Ai and René's results are the first indication that this devastating disease can be reversed.



Ai Yamamoto received her Ph.D. degree in May 2002. She received the dean's award for the best thesis of the year for this work. René Hen is associate professor of pharmacology in the Center for Neurobiology and Behavior. His lab specializes in animal models of neurological and psychiatric disorders.