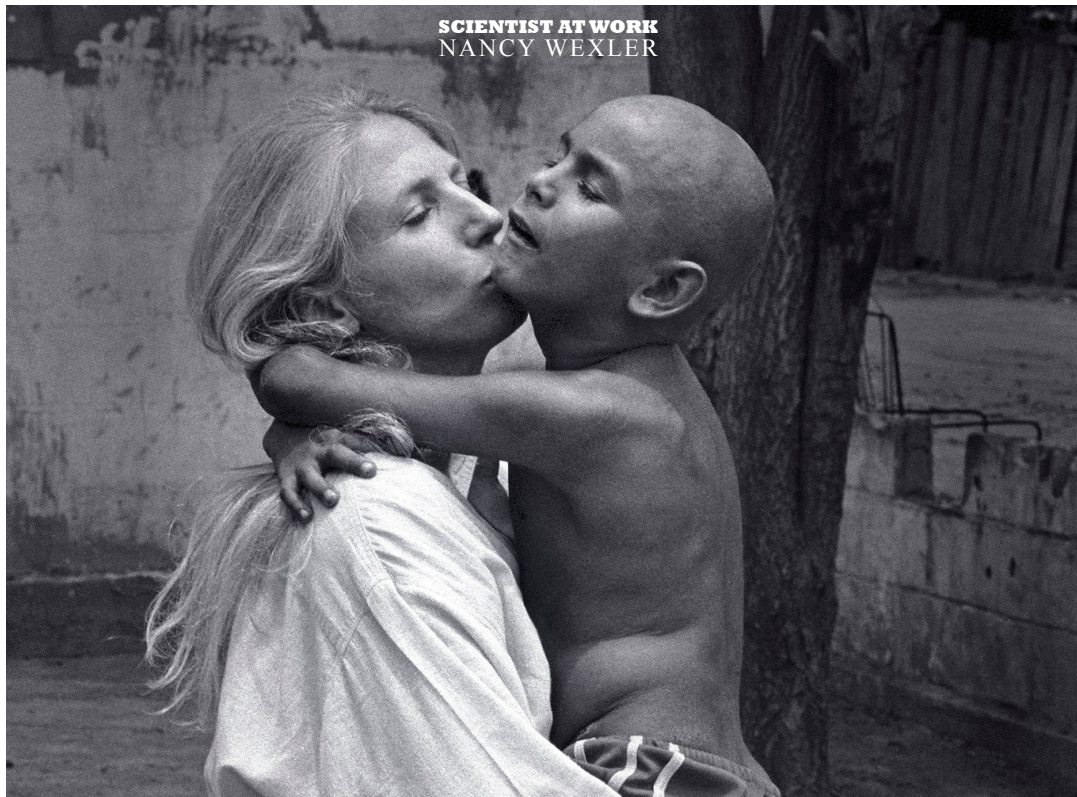


# ScienceTimes

## The New York Times



SCIENTIST AT WORK  
NANCY WEXLER

Dr. Nancy Wexler spent the last 40 years researching Huntington's disease, a gradually debilitating hereditary disease, venturing to remote parts of Venezuela to study large extended families with high rates of the disease.

PETER GINTER

## Haunted by a Gene

For the first time, the biomedical researcher reveals that she inherited the disease she has spent her life studying.

By DENISE GRADY

Year after year for two decades, Nancy Wexler led medical teams into remote villages in Venezuela, where huge extended families lived in stilt houses on Lake Maracaibo and for generations, had suffered from a terrible hereditary disease that causes brain degeneration, disability and death.

Neighbors shunned the sick, fearing they were contagious.

“Doctors wouldn’t treat them,” Dr. Wexler said. “Priests wouldn’t touch them.”

She began to think of the villagers as her family, and started a clinic to care for them.

“They are so gracious, so kind, so loving,” she said.

Over time Dr. Wexler coaxed elite scientists to collaborate rather than compete to find the cause of the disorder, Huntington’s disease, and she raised millions of dollars for research.

Her work led to the discovery in 1993 of the gene that causes Huntington’s, to the identification of other genes that may have moderating effects and, at long last, to experimental treatments that have begun to show promise.

Now, at 74, Dr. Wexler is facing a painful and daunting task that she had long postponed. She has decided it’s time to acknowledge publicly that she has the disease she’s spent her life studying and that killed her mother, uncles and grandfather.

“There is such stigma, and such ostracization,” Dr. Wexler, a professor of neuropsychology at the College of Physicians and Surgeons at Columbia University, said in a lengthy interview. “I think it’s important to destigmatize Huntington’s and make it not as scary. Of course it is scary. Having a fatal disease is scary and I don’t want to trivialize that. But if I can say, I’m not stopping my life, I’m going to work, we’re still trying to find a cure, that would help. If I can do anything to take the onus off having this thing, I want to do it.”

Among her greatest concerns are the thousands of Venezuelans from the families full of the disease, whose willingness to donate blood and skin samples, and the brains of deceased relatives, made it possible to find the gene. But they live in an impoverished region, and, Dr. Wexler said, they are still

outcasts. The clinic that she and her colleagues opened has been shut down by Venezuela's government.

"We share DNA," Dr. Wexler said. "They're part of my family. They are super-stigmatized. So I thought, this is part of my decision to come out, about me — which I still find hard to do without breaking into tears."

If treatments now being tested do pan out, she said in an editorial in *The New England Journal of Medicine*, the Venezuelan patients should get them, for free.

"She's a remarkable human being who's been an incredible leader of a scientific initiative," said Dr. Francis Collins, director of the National Institutes of Health, who was among those she recruited to help find the Huntington's gene.

Although Dr. Wexler has not talked about her diagnosis until now, it is no surprise to friends or colleagues. For at least a decade, her symptoms were noticeable. Her gait is unsteady, her speech is sometimes slurred, her head and limbs move uncontrollably at times. She loses her temper. She needs a walker to get around outside the Manhattan apartment she shares with Dr. Herbert Pardes.

But her mind is sharp and her will is strong, and she has chosen to deal with the disease — or not deal with it — on her own terms and in her own good time.

"We've been close friends for 37 years and it has been very hard to not have this as a topic we can share," Dr. Collins said. "But she's a private person, and I think we all understood she was not ready to go there."

Part of her coming out includes appearing in a new documentary film, "The Gene," produced by Ken Burns and Barak Goodman, to air on PBS this spring. Film shot later, not part of the documentary, shows her exuberantly touring a facility that makes an experimental drug being developed by Roche that she is hoping will work and become available in time to help her. The studies she led made development of the drug possible, but she is too old to qualify for the clinical trials testing it. Results are not expected until 2022.

In the film, a researcher shows her a vial of the drug. She kisses the vial and hugs the researcher. "That's my disease there," she says. "You're curing it!"

The specter of the disease has been hanging over Dr. Wexler since 1968, when she was 22. One morning, a police officer accused her mother, Leonore, of being drunk as she crossed a street in Los Angeles on the way to jury duty. She had not realized she was staggering.

Leonore Wexler's father and all three of her brothers had died from Huntington's. She was a geneticist, a field she had chosen in hopes of finding a way to save her brothers, Dr. Wexler said.

Huntington's is caused by a dominant gene: If one parent has the disease, every child has a 50/50 chance of having it, too. The disease is rare. About 30,000 people in the United States have it, and another 200,000 are at risk. It is the disease that killed the folk singer Woody Guthrie in 1967.

At the time of Leonore's diagnosis, there was no test for the gene. People who knew they were at risk could only wait to see whether they fell ill. The symptoms usually appear when patients are in their 30s or 40s — after they've already had children. Leonore was 53 at her diagnosis, past the average.

Depression, irritability and other psychological problems can occur, along with the uncontrolled movements. Patients lose the ability to speak, but remain painfully aware of their decline.

After Leonore's diagnosis, her ex-husband, Milton Wexler, told their daughters, Nancy and her older sister, Alice, about the disease and that they were at risk of getting it, too. Despite the odds, he insisted that they would be spared.

But looking back at that day, Dr. Wexler said she felt that, in an instant, three generations had been wiped out: Her mother, herself and the children she had hoped to have. She and her sister decided that they would not have children. To this day, Dr. Wexler said it is a decision that she very much regrets.

Determined to find a cause and cure, or at least a treatment, Milton Wexler started the Hereditary Disease Foundation to



Dr. Wexler at home last month.

JACKIE MOLLOY FOR THE NEW YORK TIMES



raise money and recruit researchers. Nancy, who received a doctorate in psychology, nonetheless decided to devote her career to Huntington's and its genetics.

Leonore Wexler's condition worsened. She tried to commit suicide, but Milton Wexler saved her by calling an ambulance. Dr. Wexler said she thought her father later regretted that decision, because her mother suffered for years afterward, in nursing homes.

"As she became increasingly ill, I dressed her, carried her, helped her brush her teeth and go to the bathroom, fed her and, mostly, held her and kissed her," Dr. Wexler wrote in an essay published in 1991. "Her eyes still haunt me with their sadness and fear."

Leonore Wexler died on Mother's Day in 1978, 10 years after the diagnosis.

The following year, Nancy Wexler made her first trip to Venezuela to study a large extended family, first described in 1955 by a Venezuelan doctor, Americo Negrette. The family was thought to have the world's highest prevalence of Huntington's disease. She knew that to find the gene, scientists would need DNA samples from as many affected people and their healthy relatives as possible.

The scientists, arriving by boat, found patients everywhere, some of them children, with the classic writhing and flailing signs of the disease, which was known locally as "el mal."

Dr. Wexler told them that she and they were related, that her family had the disease, too. She showed them a tiny scar on her arm where she'd had a skin sample taken, as she was asking them to do.

"I fell in love with them," she said.

For 20 years, she returned with teams that ultimately collected 4,000 blood samples. They traced the path of the disease through 10 generations in a family tree that included more than 18,000 people.

"Working with Nancy in Venezuela was a real testament to how an individual can take a team and get absolutely water out of a brick," said Dr. Anne B. Young, a professor and former chief of neurology at the Massachusetts General Hospital, who made 22 trips to Venezuela with Dr. Wexler. "She was able to take all of us and drive us, 16-hour days out in the field where it was 96 degrees and 90 percent humidity."

Dr. Wexler was a powerful presence.

"She was just totally charismatic, and when you walked into the room she would hug you and look you in the eye and listen to everything you said," Dr. Young said. "She never thought about herself. She was always thinking about what she could learn from the other person. People just became totally devoted to her. Everybody felt they'd take a bullet for her."

In 1983, just four years after the first trip, the team found a marker, a stretch of DNA that was not the gene itself but nearby. It took a half dozen high-powered research groups — handpicked by Dr. Wexler and her father — 10 more years to find the gene itself, on chromosome 4, one of the 23 pairs of chromosomes found in most cells in the body.

The discovery was a landmark in genetics, one that scientists say would never have happened without Dr. Wexler.



WEXLER FAMILY PHOTO

Dr. Wexler, left, with her father, Milton, her sister, Alice, and her mother, Leonore, in the late 1940s.

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## **'Biomedical research wasn't a team sport in the 1980s, not until Nancy got involved, and then it had to be.'**

*DR. FRANCIS COLLINS  
NATIONAL INSTITUTES  
OF HEALTH*

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"Biomedical research wasn't a team sport in the 1980s, not until Nancy got involved, and then it had to be," Dr. Collins said.

Dr. Wexler and her father were "relentless," he said, by insisting the research groups work together.

"Each group was driven by a strong-egoed principal investigator," Dr. Collins said. "You can imagine things didn't always go smoothly. But there was no way you could go to Nancy and say, 'I can't work with this person.'"

Milton Wexler had been a psychotherapist to the stars, and tapped some of his celebrity clients to help his cause.

"During the annual meetings in Santa Monica, there might be a dinner at Julie Andrews' house or Carol Burnett's house," Dr. Collins said. "We were all starry-eyed. It was quite a perk for us nerds."

Dr. Wexler brought people with Huntington's and their family members to the research meetings, to describe what life was like with the disease. Many of the scientists had never seen Huntington's up close.

"You couldn't listen to that as a researcher and not be impressed by the seriousness of the task," Dr. Collins said. "This was not some academic exercise."

Concern for Dr. Wexler herself also drove the teams.

"We knew the clock was ticking for her and for Alice," Dr. Collins said. "It was a matter of watching Nancy all the time and wondering if she's escaped the curse or is it going to fall on her, too."

The gene contains the blueprint for a protein that the researchers named Huntingtin. Its role in the brain is not understood. But in people with the disease, a series of three DNA building blocks — represented by the letters CAG — is repeated too many times. The repeats lead to an abnormal form of Huntingtin, which poisons nerve cells in the brain.

Finding the gene made it possible to develop a test that could tell people at risk whether they would develop the disease. The discovery posed a wrenching ethical and emotional quandary that persists to this day.

Do people really want to know that a disabling and fatal disease lies in wait for them, when there is no cure, not even a treatment that can slow it down?

Researchers feared that the information would make people hopeless and depressed, and even drive some to suicide.

A breakthrough therapy, making testing worthwhile so that treatment could start early to head off the disease, has yet to arrive.

Given her drive for knowledge, many people assumed that Dr. Wexler would be among the first to take the test. But she never did. Nor has her sister.



SUZANNE DECHILLO/THE NEW YORK TIMES

Dr. Wexler with her sister, Alice, left, at a convention of the Huntington's Disease Society of America in Milwaukee in 2006.

"I don't think I could have lived with that knowledge," Dr. Wexler said. "I think I assumed I wouldn't get it, because I was fine."

It was easier to live with ambiguity, she said, adding, "Denial is important."

As she moved through middle age, she felt all eyes were on her and resented it.

"Everybody watched me like a hawk," she said.

Gradually, the symptoms appeared. She became aware of them only when she saw herself on video or even in the mirror, and would think, "Oh gee, why am I moving?" There was no single moment of realization; there were many. It is not uncommon for people to recognize they have the disease only when they see photos or videos of themselves, Dr. Young said.

"Every time I saw myself on video, I looked a little bit worse," Dr. Wexler said.

Others noticed the movements, the spilled drinks, the wobbly handwriting.

"I love her so much that I had trouble convincing myself that she had it," said Dr. Young, who is an expert on the disease. "I would try to make it go away in my mind. And I think a lot of people did."

But some colleagues bluntly asked Dr. Wexler if she had the disease. A few went so far as to tell her she did. She would say she did not, only to be told that denial was a symptom. If she happened to cross her legs, some accused her of trying to hide tremors. She found it infuriating.

Dr. Pardes warned the meddlers to back off. People learned to avoid the subject.

"It was always the big elephant in the room," Dr. Young said. "It made everything uncomfortable for all her best friends, who just withdraw a little bit because they don't want to hurt her."

Her sister encouraged her to open up.

"I think that one thing her coming out about it will show is that getting a diagnosis of Huntington's disease is not a death sentence," Alice Wexler said. "It's something people can live with for a long time, if they have the right medical care and social services. She has been living her life in a productive way, and still will."

And so she is, reviewing grant applications, raising money for research and attending scientific conferences. Dr. Wexler holds out hope for the work on new drugs. There is still much to be learned, she says, and she still has a great deal of work to do.

"Enjoy life while you can," she advises. "Find what gives you some pleasure and go for it. Don't get kidnapped by this."

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