

An Interview with Dr. Nancy Wexler



Many of us know someone whose family has been touched by hereditary disease. Dr. Nancy Wexler's creative detective work is helping to solve some of the mysteries of inherited diseases, especially the fatal genetic disorder called Huntington's Disease (HD). Her research blends the high technology of the molecular biology laboratory with the classical approach of tracing genes through family trees. Dr. Wexler is an associate professor at the College of Physicians and Surgeons, at the Columbia University, as well as the president of the Hereditary Disease Foundation in Los Angeles, California. In addition to dividing her time between the West and East coasts, Dr. Wexler spends part of her year in South America studying Venezuelan villagers where many of the inhabitants are afflicted with Huntington's disease. Dr. Wexler's father, Dr. Milton Wexler established the Hereditary Disease Foundation, after his wife was diagnosed as having Huntington's disease. Nancy Wexler, herself at risk for the disease, has worked tirelessly with scientists and patients all over the world to locate the gene responsible for HD and to learn how it causes the disease.

We joined Dr. Wexler in her offices in Los Angeles, where she works with a small staff to administer the Hereditary Disease Foundation. In this interview, Dr. Wexler shares with us the details of her quest to find the fatal HD gene and discusses her recent appointment to the Human Genome Project, perhaps the most ambitious scientific adventure since the Apollo program.

Dr. Wexler, is it true that you arrived at genetics by a rather unconventional route?

Actually, my only formal education in biology, I confess, is exactly the kind of course for which you're writing this textbook. I went to Radcliffe College as an undergraduate and was required to take Introductory Biology. It was a wonderful class. That's the extent of my formal biology training. My PhD is actually in clinical psychology.

Then how did you become involved in genetics?

I started with clinical psychology, but was always very interested in biology and genetics. My mother had a Master's degree in Genetics from Columbia University where I now teach. But I think that I felt (for which I blush) that it was a difficult career for a woman. It was a very stupid feeling. I had a mother who was a geneticist and a father who is a psychoanalyst/clinical psychologist and I chose the psychology route. Then, in 1968, my father started the Hereditary Disease Foundation, and I began meeting scientists of all disciplines, but particularly geneticists and molecular biologists. These people have really been my teachers since then. They've given me a fantastic education on every napkin you could find in restaurants, bars, and workshops. I also read biology texts and go to lectures to try to learn. I've had great friends who have taught me the subject matter as well as the flavour and excitement of their work. It's been a wonderful education, and, of course, no exams. I consider myself, however, still very much a student. I'm definitely still learning.

Would you tell us more about the Hereditary Disease Foundation?

My father started the Foundation when my mother was diagnosed with Huntington's disease. It was our way of preserving hope. At the Hereditary Disease Foundation we are trying to find a cure not only for Huntington's disease, but also for all the hereditary illnesses that afflict people, of which there are many thousands. The Foundation is not for profit. One hundred percent of all public donations go directly to science. Not only do we fund grants and postdoctoral fellowships, but also we sponsor interdisciplinary workshops that focus on an idea or question, such as how do genes express themselves in the brain? How do you find a gene? We try to excite people about the questions that surround hereditary diseases. We want them thinking about the fundamental issues of biology in terms of human diseases. If we understand what goes wrong in Huntington's disease, then we can apply this understanding more widely to unravelling other genetic diseases. These workshops have basic scientists and clinical investigators mixed together, representing all varieties of expertise. We feel it is crucial to show the laboratory scientist what the Huntington's gene looks like in action. To do that, we start every workshop by inviting a patient to meet with the participants, allowing them to really see what a gene can do to a person in all aspects of thinking, feeling, moving, and expressing. The scientists become captivated because the study of genetics is suddenly made more vivid, more than just an intellectual exercise. These unique workshops are one of the most successful new contributions that the Foundation has made to the study of hereditary diseases. From the workshops come suggestions for grants and postdoctoral fellowships, which we fund. In fact, the idea for using DNA markers to find the Huntington's disease gene was born at a Hereditary Disease Foundation workshop.

What exactly is Huntington's disease?

It's an inherited neurological disorder. It is inherited in what's called an autosomal dominant pattern, which means that the abnormal gene will dominate its normal partner. Each child of a parent with the disease, therefore, has a 50—50 chance of inheriting it. This also means that males and females are affected equally. It usually starts somewhere in mid-life but it can start as early as the age of 2 or as late as the early 80s. It is a slowly progressive disease. The duration can be anywhere from 10 to 20—sometimes even 25 years. The disease is invariably fatal. Unfortunately, the most damaging changes take place fairly early in the disease so that people lose the capacity to work or head a household. The patient becomes impaired relatively early in the illness but lives for a very long time.

What are the symptoms?

The symptoms affect just about everything that makes you human—how you think, move, and feel. It causes different kinds of uncontrollable involuntary movements in all parts of the body. It can also cause severe cognitive problems: loss of memory, loss of judgement, loss of the capacity to organise oneself. In almost all standard school tests, patients with Huntington's Disease do very poorly but they do maintain a social intelligence—an awareness of which they are where they are, their family and friends, and their social setting. The only trauma in this preservation of faculties is that they recognise the loss of their capacities—their ability to do the kinds of simple things that gave them an identity and some sense of satisfaction and self-worth.

The occurrence of depression in people with Huntington's disease is extremely high, partially because of this deterioration that the patient sees happening, but, also, depression seems to be part of the disease itself. Sometimes people will be hospitalised for depression and never know that they have Huntington's in the family. About 1 in 4 patients with Huntington's disease makes a serious suicide attempt. On the other hand, patients also will maintain an impressive sense of humour. And, if allowed, they can be quite active and involved. Aspiration pneumonia and infection are the most frequent causes of death. Due to the loss of motor skills, other ~ causes of death include choking, hematomas that are a result of falling, or other accidental forms of death. Patients lose the capacity to swallow and can sometimes die of malnutrition. They also lose the ability to speak. So even though they understand much of what is going on, they can't communicate. It's a difficult, slow decline.

The onset of the disease is so insidious and long that we tend to think of it as a zone of onset rather than a discrete age of onset. There is a perplexing time when neither the person nor the neurologist can be certain if it's Huntington's disease. Sometimes it takes three to five years before you can definitely say; "This is Huntington's disease." People at risk frequently drive themselves nuts questioning whether or not they dropped something because they have the disease or because they're just klutzy. Even if you do a test for the likely presence of the Huntington's disease gene (a new DNA test that was just developed), it's still hard to say definitely when the disease begins. If the test comes out positive - Indicating that the gene is most likely there - you still don't know if the things you're doing are just garden-variety problems or reactions to the traumatic information or the initial manifestations of the disease, or the disease itself. It's a difficult disease, and until very recently there wasn't any way to tell who was carrying the gene. You just had to wait until the symptoms appeared. People have linked it to a time bomb in a coil of DNA because you just don't know.

How many people have Huntington's disease, and how many people are estimated to be at risk?

The calculation is about 10 patients per 100 000 population which means that in the United States, we have approximately 25 000 patients and 125,000 people who are at risk. People "at risk" are siblings and children of diagnosed patients.

Do you think that HD had a single origin as a genetic mutation, or multiple origins?

I don't really know. I guess I'm a little biased because our own work points to single origin or very few. When we first discovered a genetic marker for the HD gene, our next immediate question was, 'How can we get the most disparate families in the world to give blood samples we can test?' In other words, we wanted to see if the disease gene in distant geographical areas and different racial and ethnic groups was also located in the same place, on chromosome 4. Until we actually have the gene, we won't be able to tell if it's the identical defect in the gene worldwide. At the time there wasn't any

particular reason to think there would be only one genetic location since there's heterogeneity (more than one gene for a disorder in different locations) in so many other genetic diseases. We've now tested about 75 different families from Europe, Venezuela, Peru, Japan, and Papua New Guinea, and have found no indication of heterogeneity at all. The Huntington's disease patients in all those countries seem to have their defective gene on the top of chromosome 4. Once we actually find the gene itself then we can discover if the mutations in these genes from throughout the world are the same. If they are, it may mean that there was one single mutation that spread around the world or the identical mutation more than once. We need to know what the actual change is to know how likely it would be to occur once, a few times, or many times.

I hope that it is one gene. To me, that's a very poetic idea. I remember when we were collecting blood samples in China and I was trying to explain to a little girl what we were doing. So I said to her, "You know, your mother has Huntington's and my mother has Huntington's. If we look way back, you and I are cousins." She looked at me in such horror that she could be related to this Western devil! But I thought that it was a great notion.

In the Papua New Guinea case, we were trying to figure out where the disease originated. It turns out that the Boston whalers used to come to nearby islands. The whalers were afraid to go ashore because the Papua New Guinea people were cannibals. But the Papua New Guineans weren't afraid to go out to the whalers. The books of the whalers were found to say, "Today the natives came aboard, naked and friendly" There's a lot of Huntington's disease in the whole northern New England area, and it is recorded that some of the whalers had Huntington's disease. So, presumably that's how the gene came to Papua New Guinea. This Huntington's disease gene has probably been spread around the world by a lot of friendly whalers, sailors and other folks going from country to country. To me, this is the really interesting part about genetic work. It combines everything that you could possibly be interested in. It's anthropology it's ethnology. It's mystery stories. It's the most fantastic detective story in the entire world. Now that the gene marker is allowing us to trace Huntington's disease in various populations, the next question for us to address as scientists and a Foundation is, "How do you get to the gene itself and find out what's wrong with it?"

The Huntington's disease gene was initially localised by Drs. James Gusella at Harvard University, P. Michael Conneally at Indiana University, myself, and a number of others working closely together. After the marker was found linked to the gene, the Hereditary Disease Foundation naturally wanted to support research seeking the gene itself. We formed a collaboration of six pioneering scientists in laboratories around the country and in Europe who generously agreed to co-operate with each other instead of competing. This collaboration is unfortunately too rare in science, but it certainly has sped up the work and been extremely productive and fun.

Which brings us to your research. Tell us about your work in Venezuela. How did you find out about these fishing villages in South America where the prevalence of Huntington's disease is so high?

I found out about them in 1972 through a film shown at a meeting of the World Federation of Neurology Research Group on Huntington's Disease. A very smart physician in Venezuela named Dr. Americo Negrette documented the disease in small villages along the shores of Lake Maracaibo, Venezuela, in 1955. At first, he thought that all the villagers were drunk all the time. When it was explained to him that they were sick, he began taking careful pedigrees and searched the world literature to identify the illness. He finally determined that this disease was Huntington's chorea, as it was named in those days (chorea is what the abnormal "dance-like" movements that patients have are called — chorea and choreography have the same root in Greek). Dr. Negrette was very dedicated and he began working with families. He wrote a beautiful monograph in 1962 and then got some other scientists involved. Interest in this disease is inherited, as is the disease itself. His students have carried on his work. In 1976, the U.S. Congress mandated a Commission for the Control of Huntington's Disease and its consequences.

We remembered the Venezuelan communities and conducted a workshop with some-of the Venezuelan scientists to determine how best to study their extraordinary kindred (a kindred is a large, extended family) with Huntington's disease.

At that workshop, we discussed the idea of finding a person who is a homozygote among the population in Venezuela. A homozygote is a person who inherits two copies of the HD gene, one from

each parent. The problem with a heterozygote, which is what most patients are, is that you have one normal gene and one HD gene. The normal gene can mask what the defective gene is doing. We thought that if we could just find a homozygote with two HD genes, then the defect would be much more obvious, without the normal gene to confuse things.

So, when we first went to Venezuela in 1979, our original intent was to find a homozygote. Once we began fieldwork in 1981, however, the recombinant DNA revolution had begun and we changed our plans to do genetic linkage studies with these families. We collected extensive pedigrees—which is related to whom—data that were necessary to map the location of the HD gene on a chromosome. We now have a family tree of almost 10,000 people, which is many more than we ever envisioned. The Venezuelan Pedigree has proved spectacular, not only for research on Huntington's disease, but for understanding inheritance in general. The family trees we've collected are perfectly structured for doing genetic linkage studies. They are huge, interconnected families with many children. One man has 29 children by two wives, and the two wives are first cousins. So we not only have these large nuclear families, but they're all related to each other.

The data that we've collected have been used for studying a whole array of genetic diseases. Studying the Venezuelan families can make normal "maps" of the locations of genes and markers on chromosomes. These normal maps are then used to study other families with diseases of interest, families that are often too small to do any mapping. The Venezuelan samples have been used to help find the gene for familial Alzheimer's disease, for manic-depressive disease, for two different types of neurofibromatosis, myotonic dystrophy and others. Other than having the HD gene on one chromosome, these Venezuelan people have perfectly normal chromosomes. So, if you just want to see how markers and genes are inherited from generation to generation, it's the perfect huge family to study

Earlier you mentioned that it's now possible to detect the presence of the HD gene through the use of genetic markers. What exactly is a genetic marker?

A marker is a way of holding your place in the chromosome. It's really just what it sounds like; it just sits like a landmark and marks a spot. Consider a situation in which you're looking for one person in the United States—without any boundaries or cities or towns marked off. You know that the person is in the country but you don't know where. It would be a hopeless task to try to find him or her like that. So the first order of business is to divide the territory into states. Once that is done, you can say, "This person is in California," and you know where to focus. But California is still a huge state. Where would you go next?

You begin dividing the state into little towns and cities. It turns out that the person you're looking for lives in San Francisco. That's still pretty huge. So then you narrow it down to an area near a ferry terminal. But it turns out that there are three ferry terminals in San Francisco. So you're still in trouble. You must specify that it's the ferry terminal on a particular street. Those street, city, and state demarcations are all markers. They just tell you where you are relative to the object that you're trying to locate. And that's exactly what a DNA marker is. It's a tiny variant in the DNA itself that has a specific home in a chromosome and is inherited from generation to generation, exactly like a gene. Sometimes markers are genes or are in the run of genes. You can follow the inheritance of that chromosome by following the marker. Genes near the marker or the chromosome are usually inherited along with the marker.

Now those good markers for the HD gene have been found, a test to determine whether or not a person has the gene is available. What fraction of individuals who know that they are at risk based on family history are opting to be tested?

Well, the fraction has been small, but then the test has been available to on a very few people. Of the people to whom the test has been available, however, only a fraction of those who could use it have actually requested it. The availability of the test has provoked people to consider in earnest what it would be like to know that they are inevitably going to die, at some unspecified time, of a degenerative disease of the brain. You want to know -that you don't have the disease, but you don't necessarily want to know that you do have the disease. You can't have the opportunity of hearing one answer-without the risk of hearing the other. -Think that most people who has lived their lives at risk has built certain defences with respect to having the disease. Knowing, in fact, that you are carrying the gene and will develop.

The disease is a very different psychological experience from knowing that there is a possibility of developing the disease. Many people have decided not to take the test until there is a treatment. However, there are understandable, pressing reasons for taking the test. People may want to have children free of disease or to clarify the risk for children already born by testing themselves. (The child of a person with a 50% risk has a 25% risk of inheriting HD.) And some people may just want to resolve that ambiguity.

I think that all people should live their lives, to some extent, as though they are in jeopardy because all of us are at risk for something. I think it puts a little edge to your life to be at risk, but to actually know that you will have a disease may be more of a push than a person needs. Counselling prior to the test is absolutely essential for people to know what they're doing when they take this test because you can't erase the results once you've heard them. For a disease like Huntington's, has no treatment, the major value of finding the gene is in advancing basic research, not just diagnosis where the defective gene is. If we can progress from having found the marker that is near the gene to finding the gene itself, then we can find out how the gene works, and what goes wrong, and attempt to fix it. We may be able to develop rational treatments based on knowing the mistake in the gene. But for now we can just predict we can't prevent.

Through your work on hereditary disease, you have become involved in the Human Genome Project. Could you us about the project?

The Human Genome Project is probably the most ambitious, imaginative, daring effort for humanity to know itself that has ever been attempted. It has extraordinary potential! The Human Genome Project literally sets out to locate every gene on all human & chromosomes and to map each one in increasing detail. Eventually we hope actually to determine the nucleotide sequence for the entire human genome - all of our DNA - all 3 billion base pairs! The real hope is that by learning where these genes are, we will understand what they do. I think this will have profound implications for our understanding of how we function, how we're put together, how diseases originate, how genes interact with each other, and how our genes interact with our environment. At the moment, I think there are less than 100 major laboratu round the world working in a concentrated way on the mapping effort.

How long will the project take?

The hope is to have quite a good detailed map in 15 years. In the next five years, we should have a genetic map that will have markers spaced approximately a million base pairs apart - So every mill ion base pairs - rungs of DNA double helix ladder. We will have a marker. And then People will begin filling in the intervals between markers.

What is your role in the Project?

I think that the Project is fantastic, and I am overjoyed that they asked me to be a part of it. It's not only excellent science, it's the best human adventure in the world. I'm the chairperson of the Ethics Working Group within the Project. The ethical, social, and legal questions that might be raised as the work is progressing need to be investigated. We cannot afford to wait until after problems arise to consider the ethical ramifications.

Other than the problem of telling someone that he or she has a gene for a disease that we're unable to prevent or cure, what are some of the other ethical, social, and legal issues attached to the Genome Project?

A very big question is the problem of possible discrimination and stigmatisation. An insurance company could refuse coverage or an employer could refuse a job if a person was found to carry the gene for a particular disease. People might also be coerced into taking a test that they wouldn't want in order to be considered for a job or an insurance policy, maybe when the public really understands that each of us has four to ten potentially lethal genes, it will realise that you can't single out any particular patient group as a target for discrimination. But this issue is complex. The question could be asked, "Do you want people who have genetic susceptibility in positions in which they could have a major impact on other individuals?" For example, do you want an airline pilot with a genetic predisposition toward heart attack? My own feeling is that all of us have genes for something that may be quiescent

for a major part of our lives. If you start kicking out everybody who has some genetic susceptibility, then you're going to be in tough shape because there won't be anyone left. It's better to provide excellent medical care and preventive measures or early treatment for problems as they arise. Another interesting aspect of identifying susceptibility genes is what we are learning about the interaction of genes and the environment. Take, for example, manic depression. A gene was found on the X-chromosome in some Israeli families that appears to predispose toward this disease. The penetrance rate for this gene is not 100%, which means that even though you may have the gene, you might not necessarily develop the disease. Well, what spares some people? What other influences were brought to bear on the expression of the gene? It could have been another gene or a couple of genes. It could have been the environment. It could have been the fact that you had terrific parents.

Or it could have been what you ate. Who knows? There's a very complicated interaction between our genes and our environment. You're never going to say that the environment has no impact, no matter how sophisticated our genetic information gets.

And, in fact, I think we'll have a better appreciation of the environment in light of this new information because I think we'll be able to see better how inheritance and environmental influences mesh. You actually spend a lot of your time and considerable energy explaining these things to non-scientists. Is educating the general public an important responsibility for scientists? Oh, yes. Definitely! This is very important when you consider that the Genome Project is going to put a massive amount of information in our hands, and we must choose what to do with it. The myths need to be dispelled because people are going to have to be making policy and medical decisions about how the information is used.

The Genome Project is funded by taxpayers' dollars, so I think that we are obliged to teach people what it is all about. College students are a critical audience because they're the people who will shape the future. They're the people who are going to process this information—whether they're working on it as scientists or not. When people go to college, they begin to make the kinds of decisions that shape their own lives, and eventually the country and the world. If we can just get the students and the public interested in wanting to learn, that education will be reflected in their awareness, their actions, their policies and laws, and in the vitality of the nation. We just have to open our books and get started.