Venezuelan Connection

A large and isolated family suffering from Huntington's disease provides the opportunity for scientists to locate the defective gene

By JULIE ANN MILLER

In Laguneta the houses are on stilts in the lake; small, malnourished children paddle plastic wash basins from house to house. There are monkeys on the porches and crocodiles in the water. The men, all fishermen, wear tee shirts from U.S. universities, although they don't know what a college is. The teenagers say they want to leave because life is boring there. But, in fact, almost all of the people do stay in Laguneta or one of a few of the other impoverished communities on Venezuela's Lake Maracaibo. The families of these communities carry an inherited disease that makes them feel like outcasts from the rest of the population and prevents them from improving their lot.

Huntington's disease is translated from formal Spanish as St. Vitus's Dance, because of its symptom of jerking involuntary movements. But in Laguneta and the associated communities it is usually referred to as "el mal," which means simply the disease or the bad thing. Huntington's disease, in addition to the involuntary movements, also often causes such psychological problems as depression and intellectual impairment. Every child of a parent with Huntington's disease has a 50 percent chance of inheriting the disorder, but the symptoms do not usually appear until a person is 35 to 45 years old. By that age a person often already has had children, and in these Venezuela communities, grandchildren. Families there commonly have 14 to 18 children.

"When you compare the sophistication of a biochemistry lab to these little backward towns, it is amazing to me that these people would be the answer in the long search for the Huntington's disease gene," says psychologist Nancy Wexler of the Hereditary Disease Foundation in Beverly Hills, Calif. But these people, who are all linked in a complicated family pedigree with more than 2,000 living members, were crucial in the recent finding of a genetic marker for Huntington's disease (SN: 11/12/83, p. 311).

Scientists in the United States first became aware of this remarkable family in 1972 at a meeting in Ohio marking the centennial of George Huntington's description of the disease. A Venezuelan psychiatrist had filmed members of the family as part of his thesis research. The U.S. researchers were intrigued by the idea of such a community. It seemed that there they might be able to explore how much a different social environment — where Huntington's disease is so common that the patients are not regarded as freaks — influences the course of the disease. Shortly thereafter, physicians from the United States went to Venezuela and confirmed that the disease these people had was indeed Huntington's disease.

Sixteen years earlier a Venezuelan physician named Americo Negrette first met members of the family who were living in San Luis, a suburb made up of shacks outside the large city of Maracaibo. Family members had moved there from the more distant outlying communities in order to look for work or to be nearer to medical care. Negrette wrote a book describing the family and their symptoms. The family members felt that he was the first outsider to take an interest in their plight. Negrette later helped other scientists to make contact with the community.

Successful investigation of a different genetic disease gave U.S. scientists further reason to examine the Venezuelan family. The discovery of the biochemical flaw underlying familial hypercholesterolemia — an inherited disorder causing abnormally high levels of cholesterol in cells and blood — had been achieved only after scientists examined a "double-dose" patient, one who had two defective copies of the gene, one inherited from each parent. Because the gene is dominant, having one copy is sufficient to cause the disease, but the presence of the one normal gene had obscured the biochemical analysis.

Scientists predicted that a double-dose patient with Huntington's disease would aid similarly biochemical analysis of the disorder. Because Huntington's disease is so rare around the world, it had seemed

Photos: R. Stephen Uzzell

Members of the remarkable Venezuelan family with Huntington's disease are predominately impoverished fishermen (above) who live in stilt villages, such as Laguneta (left), or in shacks in San Luis.

unlikely that two people with the disease would pair up to have children. But in the Venezuelan community, with its high frequency of intermarriage, such a family might be found. A 1976 congressionally mandated commission on Huntington's disease recommended an expedition to Venezuela with the search for a double-dose patient as its first priority, and the mapping of the gene behind the disease as a secondary goal.

In 1979 Wexler, who was then at the National Institutes of Neurological and Communicative Disorders and Stroke in Bethesda, Md., and Thomas N. Chase of NINCDS went to Venezuela, but found it more difficult than expected to find a double-dose family. They had started their investigation in San Luis, but it was only at the end of their visit when they traveled to Laguneta, a 5-hour boat journey on Lake Maracaibo, that they found a promising family group. Both parents had Huntington's disease, and there were 14 living children and 56 grandchildren and great-grandchildren. But there was nothing clinically unusual about the symptoms in that family, and Wexler and Chase were unable to determine if any of the children had a double dose of the defective gene.

Advances in molecular biology soon changed the direction of the investigation. Locating a gene on the set of human chromosomes had been a tedious matter of comparing within families the inheritance of the disorder with that of the limited number of other characteristics for which the gene location was already known. But recombinant DNA techniques, with the use of enzymes that cut DNA in characteristic patterns, suddenly provided researchers with the possibility of an unlimited number of markers for linkage studies to locate genes on chromosomes. The technique has been applied to a variety of diseases (SN: 8/6/83, p. 90; 11/26/83, p. 342). It works best when there is a large family where some members have the disorder and others do not.

"I suddenly began to think we would be missing the boat if we didn't do a linkage study in Venezuela," Wexler says.

In 1981 Wexler returned to Venezuela with a team that included neurologists, a geneticist and a nurse. With their Venezuelan associates, they focused on gene linkage research.

"We used an unusual strategy for deciding which people to study in detail," Wexler says. "It caused problems with those trained in the old methods." Instead of trying to include all the relatives, Wexler and collaborators concentrated on groups of sisters and brothers within a family who were old enough to show the symptoms of Huntington's disease and other older relatives on the side of the family of the parent with Huntington's disease. Younger people who were at risk for the disease, but did not yet show signs, could not give the investigators useful genetic information, because it was not known which of them carried the defective gene.

This man in his 40's suffers from Huntington's disease. His daughter has a 50 percent chance of developing the disorder.

On this and two later expeditions, a pedigree of 3,000 people was compiled. The group also performed medical examinations and took tissue samples from hundreds of members of the pedigree. Getting the tissue samples to the U.S. laboratories where they were analyzed and stored turned out to be a strategic tour de force. The tissue samples had to reach their destinations within 48 hours, so the investigators scheduled collection days to coincide with trips of researchers returning to the United States, who dropped off sets of samples in different cities.

The major difficulty of the project was assembling so large a pedigree, even with computer aid by P. Michael Conneally of Indiana University in Bloomington. "The whole thing ballooned," Wexler says. "It broke the computer program, which had to be redesigned." She says the computer printout of the Venezuelan family tree could paper a wall 100 feet long.

Besides the mass of the data, there were other difficulties. Determining the familial interconnections between people was often a frustrating task. For example, the family tended to use a limited number of given names. "There were Carmen Marias and Carmen Rosas and Rosa Carmens," Wexler says.

In addition, women might change their last names when they married, which didn't necessarily coincide with when they began to have children. Sometimes in the middle of a set of sisters and brothers the last name they were given would be changed. It was said to be because the father does not "recognize" the later children, although he admits biologically he is their father.

The confusing aspect of collecting names was epitomized, Wexler says, by one encounter where a mother firmly reported her son's name was Jose, while standing at her side the son insisted that his name was Eduardo. Within the community people often used family relationships to identify specific members — Carmen Maria, daughter of Carmen Rosa. But the researchers eventually took instant photographs of everyone they interviewed and used those pictures for identification.

A boon for the geneticists was the accuracy with which people reported who was a child's father. Parents generally had stable unions, whether they were married or not. And in the rare cases where a child was not the offspring of the mother's mate, people were candid about it, Wexler says.

The willingness of people to participate

Both parents in one Laguneta family (only partly represented in front of their house, in photograph at far left) have Huntington's disease. Some of the 14 children already have the disease, and the 56 grandchildren and great-grandchildren are at risk. In near photo, nurse Fidela Gomez and Nancy Wexler talk to a patient about her illness.

in such an extensive study by predominately foreign scientists was not a problem. "We usually had no trouble getting people to cooperate," Wexler says. One factor in their cooperation was the initial introduction by Negrette, whom they already had reason to trust. Another factor was that they respected Wexler, who explained to them that her mother had had Huntington's disease and therefore she, like many of them, was at risk. Some people said they participated simply because the researchers seemed so serious about it.

Because of the frequency of intermarriage, the people in the Venezuelan community did not know how the disease was inherited. The children of parents who did not get Huntington's disease did not think of themselves as free of the disease, but still as part of the Huntington's disease family. Therefore they, like the others, felt a vested interest in participating in research that they hoped would find a treatment for the disease. Because the people realized each contribution became more valuable as more people became involved, community members also pressured each other to participate.

Although Huntington's disease is so common in this community, each case is regarded as a "great sadness." Almost everyone there is involved in the care of an affected parent or sibling. The people are very good diagnosticians, Wexler says. They will recognize the disease in themselves and their relatives — by noticing small movements, objects dropping from the hands, dispositions becoming gloomy or short-tempered — before Huntington's disease would be discovered in a general medical examination.

Wexler tells of a picture in a home she was visiting. It showed the hostess as a stout woman, when at the time of the visit she was thin. "It's just because of the disease that comes," the woman said matter-of-factly. However, other members of the community get so depressed over even the uncertain prospect of Huntington's disease that they cannot work and many attempt suicide.

Neurologist Anne Young examines a boy with the juvenile form of Huntington's disease and his brother in the visiting researchers' temporary clinic.

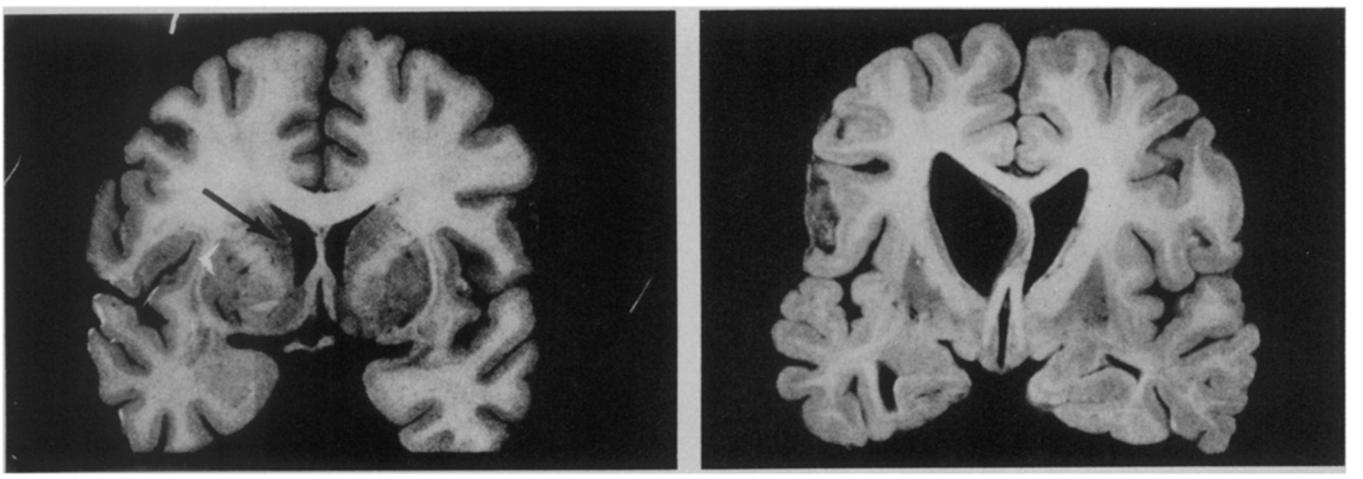
The pedigree now assembled goes back to a mother who died of Huntington's disease more than a century ago after having many children. The original source of the Huntington's disease gene in this community is uncertain. It is likely to have been brought to the area by a 19th century trader; the family members say the gene probably came from a Spanish sailor who jumped ship from a German vessel. Recently historian Alice Wexler (Nancy Wexler's sister) found death and birth records of this sailor's immediate family. But they did not fit with the Huntington's disease pedigree. So the sailor was not a myth, but he cannot be held responsible for the disease.

How does the course of Huntington's disease in the Venezuelan community compare with that in the United States, where it is far less common? The range of symptoms shown is the same. The Venezuelan community has the rare juvenile Huntington's disease, as well as the adult form. Patients may be stable or decline rapidly; they may have tremors, depression, hallucinations and delusions. These observations demonstrate that a single gene defect can cause all forms of Huntington's disease. Previously, physicians had suspected that the variability of disease characteristics might reflect different genetic defects or environmental factors.

But there are differences in the fate of the patient with Huntington's disease in Venezuela and in the United States. In the United States, the family is usually reluctant to have a Huntington's disease patient go about in public. But in Venezuela, patients remain part of the daily stream of life, walking around town and, even in late stages, feeding themselves. Because the disease is so common, no one is startled or frightened by the patients. Nancy Wexler also attributes the difference in part to the impoverished life style. In a one-room shack there is no place to sequester a patient, and eating rice and fish with a spoon is simpler for someone with jerking movements than is manipulating fork and knife at a more elaborate dinner.

The lack of medication in the Venezuelan community also may be responsible for some of the differences between patients there and in the United States.

In Huntington's disease, cell death hits hardest the area of the brain called the basal ganglia. This area (arrow) is almost completely missing in the brain of a Huntington's patient (right) compared to a normal brain (left). In the Huntington's patient's brain, the space normally occupied by the basal ganglia is filled with an expansion of the fluid-filled ventricle.



The medication used to control the abnormal movements can immobilize a patient and have psychological effects. In Venezuela the patients remain mobile and psychologically active although the uncontrolled movements may be severe.

Venezuelan patients on the average do not live as long as U.S. patients do. The Venezuelan patients become malnourished and also succumb to infections for which a U.S. patient would receive antibiotic treatment. The patients in the stilt villages risk falling in the lake and drowning.

A treatment for the disease appears still to be only a distant possibility. Prenatal diagnosis coupled with abortion may soon be feasible, but it is not clear whether members of this community would use such a procedure. Previous attempts to convince persons at risk not to reproduce were poorly received. In a community where families often have more than 10 children, being childless would be more foreign than having Huntington's disease.

In addition to childlessness being considered "unnatural," parents count on their children to support them if they become ill. "Children are my life and my workers," a family member told Nancy Wexler.

The public health problem imposed by Huntington's disease on this community is staggering. Currently there are approximately 1,100 children who have either a 50 percent or a 25 percent risk of developing the disease, and the community doesn't have the resources to handle it. "If there is no medical intervention devised, the projection of what is going to happen there is dim," Wexler says.

In March Wexler and colleagues plan to return to Venezuela to continue their analysis in the hope of learning the distance on the chromosome between the marker recently identified and the actual Huntington's disease gene. And they plan to continue adding to the pedigree.

Since their first expedition to Venezuela, the strategy of using recombinant DNA and restriction enzymes to map genes has proven feasible and is being applied to many genes. Linkage studies are best done on large families, and it is difficult today to find U.S. families with as many as 10 children, let alone 18.

The tissue samples collected from the Venezuelan family, remarkable in both the size of nuclear families and of the extended pedigree, are expected to be useful for analyzing other genetic traits if the gaps in the pedigree are filled. Then the family could become a "standard reference pedigree." The pedigree of a Mormon family is also being assembled to serve geneticists in this way.

"The Venezuelan pedigree is not saturated," Wexler says. "We still could easily add 300 informative people. But we're hoping not to add another thousand. With newborns and collateral relatives, we could make it grow forever." □