Huntington's Disease: Advocacy Driving Science

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Annu. Rev. Med. 2012. 63:1–22

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-050710-134457

0066-4219/12/0218-0001$20.00

Keywords

Hereditary Disease Foundation, Venezuela, Gene Hunters, kindreds, human genetics, huntingtin

Abstract

My mother, Leonore, was diagnosed with Huntington's disease (HD) in 1968 at age 53. I was 23, my sister Alice 26, and our father, Milton Wexler, 60 years old. The same year, our father created the Hereditary Disease Foundation (HDF), dedicated to finding treatments and cures for HD. HD is an autosomal dominant, neurodegenerative disorder. Alice and I each have a 50% chance of inheriting and dying from the disorder. Over the past 43 years, we have been proud to change the face of science. Through Milton Wexler Interdisciplinary Workshops, judicious funding, and focusing on innovation and creativity, the HDF is an integral partner in key discoveries. The HDF recruited and supported >100 scientists worldwide who worked together as the Huntington's Disease Collaborative Research Group in a successful ten-year search for the HD gene. We found a DNA marker for the HD gene in 1983—the first marker to be found when the chromosomal location was unknown. We isolated the HD gene itself a decade later. These breakthroughs helped launch the Human Genome Project. We supported creating the first mouse model of HD and many other model systems. Currently, we focus on gene silencing, among other approaches, to create new treatments and cures.

MY LIFE

It is rare that a scientific article uses the first person. It is even more unusual for the author to be—in part—the subject of the article. I have the pleasure and gratification of writing about a subject near to my heart. My topic is how advocacy drives science—in particular, how the Hereditary Disease Foundation (HDF) has advanced Huntington's disease research—and the story of the HDF begins with my family.

I was 23 years old and my sister Alice was 26 when our father, Milton Wexler, told us that our mother Leonore had just been diagnosed with a fatal brain disorder called Huntington's disease.

Dad explained to my sister and me that everyone has a Huntington's disease gene. He said, "HD is an autosomal dominant disorder." This means that the gene is not on the X or Y chromosome and that men and women are affected equally. "Dominant" means that the abnormal version of the gene will dominate its normal partner. My mother inherited her abnormal version of the HD gene from her father. She also had inherited a normal version of the HD gene from her mother. Which gene did she pass on to us? Alice and I each have our own 50% chance of inheriting Mom's normal version of the HD gene from her mother or a 50% chance of inheriting her abnormal HD gene from her father. If Alice or I inherit Mom's abnormal version of the HD gene, our children will have a 50% chance of inheriting it as well.

HD is also considered "highly penetrant." Dad explained that if Alice or I inherit the abnormal HD gene from our mother and live a normal lifespan, we will certainly develop HD and die from it. Three generations wiped out simultaneously!

It was appalling and shocking news! It was August 24, 1968. It was Dad's sixtieth birthday. Mom was 53.

When my mother was 15, her father died of Huntington's chorea in a New York State psychiatric hospital. Mistakenly believing that only men were affected, Mom went to Columbia University to study genetics in an effort to save her three older brothers. One horrifying day in 1950, all three of Mom's brothers were diagnosed with varying stages of HD. My uncles each endured 10–20 years of suffering on their odysseys to death. My mother had not told my father of her unwelcome heirloom, thinking that she was safe and hoping that her brothers would escape. In 1950, following my uncles' diagnoses, my parents learned the shocking truth that both men and women can equally develop HD.

One day in 1968, my mother was crossing a street in Los Angeles on her way to jury duty when a policeman yelled at her, "Aren't you ashamed to be drunk—so early in the morning!" My mother's world collapsed. She knew that a common early sign of HD is an unsteady gait. She was diagnosed with HD that afternoon, age 53.

As HD engulfed Mom's body, she suffered from uncontrollable movements of all parts of her body, including her face, toes, fingers, arms, legs, trunk—everywhere. It was as if some mad puppeteer was in control of her body, against her will. These movements distorted and contorted her tiny, emaciated frame. And they were voracious calorie consumers. She needed to eat at least 5,000 calories a day just to maintain her weight. Chorea of her head, mouth, and tongue—her inability to hold her head still and her inability to swallow, once the food was inside her mouth—made eating perilous. Choking was a constant hazard. She suffered from repeated episodes of aspiration pneumonia, a frequent cause of death in HD.

Her abnormal movements also robbed her of her ability to speak and communicate. Her speech slurred and then stopped being intelligible. The frustration and terror of not being able to be understood were an agonizing anguish for all of us. Our only saving grace was that Mom always understood what we were saying. She could nod yes or no, could smile and cry, and she always recognized us. Anything else would have been torture.

Mom attempted suicide. She was gripped by the profound black depression that is part of HD, as well as terror and knowledge of

what she knew lay before her—her certain fate. She worried about my sister and me. Both attempted and actual suicides are frequent in people with HD, and major or bipolar depression is almost universally experienced. Fortunately, Mom never suffered from the panoply of other psychiatric symptoms that can devastate the lives of HD patients and families. Hallucinations and delusions, paranoia, manic spending, obsessive-compulsive behavior, perseveration, irritability, day-night reversal, even violence, and apathy are common.

Mother also never experienced the most severe cognitive symptoms that many people with HD develop. She had gone to UCLA in her forties, possibly already beginning to show symptoms—she got straight As, but it was an effort. As her disease progressed, she lost some of her ability to learn new things and to remember. She lost some of the higher executive skills that had made her a fascinating science teacher. Fortunately, she always knew who she was, where she was, and who we were, and she always retained her sense of humor. This is true of most people with HD, but often others give up trying to make contact.

Mom met each day with unimaginable courage and bravery. She endured ten years of indescribable suffering and agony. She finally succumbed to another bout of aspiration pneumonia on May 14, Mother's Day, 1978.

Our family's trauma would have been unendurable without our father. My sister and I were reeling from the impact of this devastating information.

As Dad told us the awful news on that fateful day in August, 1968, in the same breath, he said that he was creating the Hereditary Disease Foundation. He was going to search for treatments and cures for Mom and everyone with HD (1). Much of what I describe in this article, and much of the story of HD research, is intertwined with the history of the HDF.

Other families struggling with different disorders are increasingly becoming involved in supporting and advocating for research. Families, physicians, and scientists form powerful partnerships that can move mountains. I hope our story can provide useful lessons, inspiration, and guidance on this voyage of discovery.

THE HEREDITARY DISEASE FOUNDATION AND THE BIRTH OF OUR INTERDISCIPLINARY WORKSHOP PROGRAM

Originally, Dad partnered with Marjorie Guthrie, widow of the amazing songwriter and singer Woody Guthrie, who died of HD in 1967. Marjorie created the Committee to Combat Huntington's Disease (now the Huntington's Disease Society of America), which emphasized bringing together HD families and advocating for social services. Dad's passion was for research. He was convinced that without finding and funding scientists—the best and most creative he could attract to this unknown area—we would never make progress. In 1968, very few people had even heard of HD, much less had a research program. Dad felt we would have to start from scratch.

My father met with Seymour Benzer, a *Drosophila* geneticist, and William Dreyer, a biochemist, both at the California Institute of Technology. They advised my father to hold a workshop to bring together talent, assess the "state of the art" of the science, and design a research agenda. The group met for two days. Participants included postdoctoral fellows and graduate students with cutting-edge technologies, expert HD clinicians, and the Nobel Laureate Julius Axelrod from the National Institutes of Health. At the end of two days, they emerged with a research agenda. Dad was ecstatic! He was certain that with such smart people grappling with the problem, a cure was imminent (1, 2).

From our very first workshop in 1968, our Hereditary Disease Foundation Interdisciplinary Workshop Program was born. With good reason, my father was the proudest of creating, nurturing, and maintaining the HDF. The soul of the HDF is its Interdisciplinary Workshop Program, which is now named in his honor (see sidebar, "Comments on the Hereditary Disease Foundation Workshops").

COMMENTS ON THE HEREDITARY DISEASE FOUNDATION WORKSHOPS

"When I first had the experience of observing how many new fresh ideas could come out of a rather unstructured workshop, I began to think seriously about how to organize a workshop program that could maximize accidentals, prove fun for the participants and allow established scientists meeting with other established scientists to become somewhat playful, highly experimental in their ideas. Symposia with a presentation of many scientific papers often prove stuffy and uncreative. I wanted to get rid of the academic and the learned and the established, the constipated, so here is what I came up with finally."

Milton Wexler (1)

"If one examines how marvelous discoveries were made in the neurosciences, in biology and medicine, one often encounters stories of accidental meetings, visits to other laboratories, chance hallway conversations, a telephone tip, a dream . . . . The sudden, almost inspirational connection between two seemingly unrelated facts, the almost romantic development of a thought experiment: these seem to be the hallmarks of what later turn[s] out to be the basis for significant discoveries."

Milton Wexler (1)

"If one looks back in the development of human genetics in our current form, I think the Hereditary Disease Foundation played really the same role that the Rockefeller Foundation played in the 30s and 40s, when it permitted the development of molecular biology. It was a small group of people who weren't waiting around, but were giving money to the right people, with the thought that it was sensible."

James D. Watson (personal communication)

"Everything I know about genomics I learned first at Hereditary Disease Foundation workshops!"

Francis S. Collins (personal communication)

Here are my father's principles for designing and conducting Workshops:

1. There should be no more than 25 participants and preferably fewer. A small size promotes intimacy and willingness to share data and ideas—even confidential research, information, and data just discovered.
2. An interdisciplinary mixture is critical. This interdisciplinary nature includes many different disciplines. It ensures that you have a "critical mass" of people speaking the same language, so that they can understand each other, but not too many of the same discipline, which threatens to overwhelm the conversation.
3. Workshops include both junior and senior scientists. The junior researchers can be graduate students, technicians, or doctoral students. The senior scientists can be very senior, including the Nobel Laureate Max Perutz. Max did us the honor of attending many Hereditary Disease Foundation Milton Wexler Workshops. Max won his Nobel Prize in Chemistry in 1962 for unraveling the structure of hemoglobin, among other proteins. Max was celebrated the same year as James Watson and Francis Crick were awarded the Nobel Prize for discovering the structure of DNA.
4. Workshops include both women and men.
5. Because workshops are interdisciplinary, participants should try to avoid, or at least define, jargon.
6. People from the same institution should not sit next to each other.
7. No slides or other presentation materials are permitted—people can explain their relevant data. This critical point causes a lot of anxiety at first, but is worth implementing.
8. Most important, we begin each Workshop by inviting a family with HD to speak to the researchers. People can see with their own eyes and feel in their hearts how devastating this disease is. They can learn from the real experts—the families themselves. They are motivated to solve this problem for the people—and their children—sitting with them (1).

Over the past 43 years, our HDF has organized and led >200 Workshops all across the United States. The Foundation has dedicated >10,000 intensive hours to the task of curing

HD. The majority of Workshops have been small. In the past decade, we have also developed a biennial three-day international Workshop drawing 400 world leaders in research, working hard to create the science of the future. Our meeting receives accolades as the premier venue for understanding HD and developing treatments and cures (3).

Many of the scientific breakthroughs and much progress have been inspired, shaped, and funded by the Hereditary Disease Foundation. Of all of his many accomplishments, during almost a century of achievements, creating the Hereditary Disease Foundation was my father's greatest pride and joy. Dad died at age 98 on March 16, 2007. He expected to see and celebrate the cure before he died.

THE SEARCH FOR THE HUNTINGTON'S DISEASE GENE

We knew that HD segregates as an autosomal dominant trait. Capturing the HD gene and unraveling the nature of its error were considered the most certain routes to discovering treatments and cures. New breakthroughs in recombinant DNA techniques began making this seemingly science-fiction endeavor feasible.

In October 1979, we held an HDF Workshop focusing on how to use the newly discovered restriction fragment length polymorphism (RFLP) technology to find the HD gene (4). Organized and chaired by David Housman, a young molecular biologist from MIT, this Workshop proved historic. David Botstein, Ray White, and many of the other luminaries of the subsequent genome revolution attended (1, 2, 4). A fierce debate broke out over the best strategy for pursuing the HD gene. In 1979, to find a disease gene, many things were required. We needed RFLPs or DNA markers. By the time of our Workshop in 1979, only a small number of RFLPs had even been created. Each RFLP was hand-crafted with laborious difficulty. We needed to discover the chromosomal locale of these markers. Mostly, this was accomplished by equally hard somatic cell techniques. And we needed families, who served multiple purposes. The position of a marker on a chromosome was determined by genetic linkage. How close was your RFLP to another gene or DNA marker already discovered to be on that chromosome—preferably nearby? Large families helped since we needed to observe many transmissions through the family to determine if markers are neighbors on the chromosomes.

To everyone at the Workshop, designing new markers and positioning them on chromosomes were the highest priorities. There were calculations about how many postdoctoral decades would be required to find sufficient numbers of new markers and position them on chromosomes to map fully the human genome. Once the map was accomplished, the DNA of a family with HD could be run against this map to search for the chromosomal location of the HD gene. Time estimates for finding the HD gene ranged from 10 to 50 to 100 years (2, 4).

The best families for positioning markers on chromosomes are very large, with all four grandparents, both parents, and many children living to provide DNA. Often families with a genetic disease are tiny—with many members already dead from the illness. It was considered almost impossible to find a family large enough to accomplish all these requirements for positioning genes and still carry a disease gene. David Housman advised us to search for the biggest family with HD.

Housman made a brilliant suggestion: As each new DNA marker is created, see if the marker "cosegregates" or "travels together" with the appearance of the disease in an HD family. It might still take 100 years, but we might get lucky and find a linked marker early on. For Housman's strategy to work, it was critical to use the DNA of the largest family with HD we could find.

The HDF gave David Housman the first grant in the world to use DNA markers to find the HD gene.

But where would we find this extraordinary family?

Restriction fragment length polymorphism (RFLP): a laboratory technique that breaks sections of DNA into smaller fragments using restriction enzymes. These remaining fragments are then separated by weight using gel electrophoresis and can be followed as they are passed on to other cells by measuring recombination rates. This technology was used for gene mapping and paternity testing

DNA markers: genes or DNA sequences whose location in the genome is known. Markers can be used to map the chromosomal locations of genes, as was the case with the HD gene

Genetic linkage: pattern of genetic inheritance whereby genes that are located close together on the same chromosome tend to remain together during recombination. The Huntington's disease marker was found using linkage

THE VENEZUELA PROJECT

In July 1979, just months before our October 1979 Workshop, I traveled to the Lake Maracaibo region of the state of Zulia, Venezuela. My original goal was to look for HD homozygotes. Michael Brown and Joseph Goldstein had been studying homozygotes for familial hypercholesterolemia; insights from such individuals were essential in formulating their understanding of that disease (5). We did not yet know if homozygotes for HD would be viable.

In March 1972, the World Federation of Neurology's Research Group on Huntington's Chorea had celebrated the centennial anniversary of George Huntington's historic paper (6). Drs. Americo Negrette, Jorge Avila de Giron and Ernesto Bonilla presented their work on families with HD in Venezuela (7). Due to the dense family structure and intermarriages, it was possible that homozygotes might live in Venezuela.

As we traveled in the Lake Maracaibo region, it became clear that the families were very large—sufficiently large so that we could look for homozygotes and the HD gene simultaneously.

From 1979 to 2002, I was fortunate to travel to Venezuela annually with an extraordinary group of amazingly talented, intelligent, dedicated and creative interdisciplinary scientists—including Anne B. Young, her husband, the late John B. Penney, Robert Snodgrass, and many others who played essential roles in all of the discoveries we made and are continuing to make.

The Venezuelan HD families live scattered along the shores of Lake Maracaibo, mostly in fishing villages, some of which are on stilts. Whether in urban or rural settings, most families face extreme poverty and stigmatization in addition to the trauma of their illness. Our team traveled to each village, gathering oral pedigree information from family members, as there were no written records. We created the Venezuelan Huntington's Disease Rating Scale, adopted worldwide as the Unified Huntington's Disease Rating Scale (UHDRS) (8–10). We developed a cognitive assessment battery that was adapted to their cross-cultural needs and sensitive to the lack of literacy in most families. We identified families at highest genetic risk based on their pedigree structure. From those families, we took blood samples from all consenting family members. DNA was extracted and transformed lymphocyte lines were created by James Gusella at Massachusetts General Hospital. We also collected skin biopsies and created skin fibroblast lines. Gusella was Housman's former graduate student. Gusella, Housman, and P. Michael Conneally, a population geneticist at Indiana University, each reviewed the results of our ongoing linkage analyses.

Each DNA was tested with a RFLP. Astonishingly, on the twelfth RFLP tested, we had a hit! Eureka! Our LOD score was 6.42—more than a million to one odds in favor of genetic linkage, or that it did not occur by chance. Our HD gene was near the top of chromosome 4p16.3, very near—or closely linked to—the DNA marker G8 (11). We were the first to find a DNA marker tightly linked to any gene for which the chromosomal location was unknown. Our discovery was the launching pad of the Human Genome Project. Finding the HD gene proved it could be done! Our success demonstrated that these strategies could work to find any gene (12).

GOING FROM THE DNA MARKER TO THE HD GENE

The HDF, together with the National Institute of Neurological Disorders and Stroke, NIH, had funded and intellectually guided the research to find the DNA marker. Now we were confronted with identifying and isolating the HD gene itself. The gene was located in what turned out to be very inhospitable territory, with few genes or markers, near the telomere (or tip) of chromosome 4.

The Hereditary Disease Foundation held a Workshop in January 1984 for investigators who wanted to go after the HD gene itself. David Housman, James Gusella, the late

Unified Huntington's Disease Rating Scale (UHDRS): a clinical rating scale used by neurologists to assess four domains of clinical performance and capacity in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity

LOD score: logarithm of the odds (to base 10). A statistical estimate of whether two genetic loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A LOD score of 3 or higher is generally taken to indicate that two gene loci are close to each other on the chromosome. A LOD score of 3 means the odds are a thousand to one in favor of genetic linkage

John Wasmuth, Hans Lehrach, Francis Collins, Peter Harper, Leslie Thompson, Gillian Bates, Marcy McDonald, Alan Buckler, Russell Snell, Danilo Tagle, P. Michael Conneally, Richard Mulligan, Nobel Laureate H. Robert Horvitz, and I were the key group of Principal Investigators, students, and advisors making up the core of the team known colloquially as the "Gene Hunters." The HDF convened four formal workshops annually of the Gene Hunters and we had many other frequent interactions as well. At our first meeting, we decided to publish the discovery of the HD gene as "The Huntington's Disease Collaborative Research Group"—with no authors specified for credit. The authors were listed in the front only by their addresses. We all were motivated to share quickly and collaboratively when all the Gene Hunters received shared credit.

The Gene Hunters invented many techniques as we went along and ultimately included almost 100 investigators. Even with the dedication and brilliance of this group—advised, funded, and encouraged by the HDF—it took a full decade of hard work to capture the Huntington's disease gene itself (13). The *New York Times* described our discovery as "the most coveted treasure in molecular biology" (14).

THE VENEZUELAN KINDREDS AND THE HUNTINGTON'S DISEASE GENE

Through studying the Venezuelan HD kindreds, we discovered that the HD mutation is an unstable triplet repeat (CAG), acting with a dominant gene action. The HD gene encodes a protein, huntingtin. The HD mutation leads to the expression of an expanded polyglutamine repeat in the huntingtin protein. Alleles with <34 CAGs do not produce symptoms. Alleles with 35–39 CAGs produce incomplete penetrance. Alleles with ≥40 CAGs are fully penetrant. Alleles with 60 CAGs or more result in juvenile onset. These children can be as old as 20 years of age—by most definitions the oldest age for juvenile onset—or as young as 2 years (13).

The Venezuelan kindreds represent the largest and best characterized HD population in the world. Twenty-three years of prospective studies—genetic, neurological, and cognitive—have been carried out with kindred members (15). The Venezuelan kindreds are quite genetically heterogeneous. The majority are Hispanic. Their genetic and phenotypic heterogeneity results from admixtures of Europeans and indigenous populations (9–11, 13, 15). The Venezuelan HD kindreds encompass 18,149 individuals spanning 10 generations, of whom 15,409 are living and 78% are younger than age 40. There are 9,162 males, 8,256 females, and 731 individuals for whom we do not have gender information. There are 83 unique kindreds. The majority of individuals, 14,761, belong to the main kindred, tracing their origin to a single founder, appropriately named Maria Concepcion, who lived in a stilt village in the early 1800s. The remaining 3,388 form 82 separate kindreds. Of the 4,384 immortalized lymphocyte lines we collected and created, 3,989 at highest genetic risk from their pedigree position were genotyped for their HD allele (15). Of these 3,989 individuals, 2,953 have normal-sized alleles. All are family members who care for their relatives with HD and witness their daily turmoil and struggle. Everyone in an HD family is impacted by the disease. We identified 938 heterozygotes, 80 individuals with variably penetrant alleles, and 18 homozygotes (15). These homozygotes, having been followed from birth to their death from HD, we discovered, have no distinguishing clinical characteristics separating them from heterozygotes. Their lack of dose effect suggests that HD is a true dominant disorder (16).

GENOTYPIC AND PHENOTYPIC VARIABILITY LEADS TO NOVEL FINDINGS

Our research goals since initiating the Venezuela Project are multifold: (*a*) to find the HD gene—which we accomplished (11, 13); (*b*) to search for genetic and environmental modifiers of HD (15, 17–22); and (*c*) to

characterize the natural history of HD, providing historical controls for future clinical trials (9, 10). We developed a large prospective database containing clinical and genetic information, spanning 23 years, on >2,547 people who have been examined almost every year. We performed 20,000 neurological examinations and 8,000 cognitive assessments (9–11, 13, 15). From these examinations, we determined the age of onset of HD for 458 people ranging in age at diagnosis from 2 to 69 years. They have an approximately normal distribution and a mean age of onset of 34.35 (±10.07) years. There were no significant sex differences ($t = 1.13, P = 0.26$). The modal repeat length is 44 (median 45), with 90% of alleles falling between 40 and 50 CAG repeats (15).

Modifiers of Age of Onset of HD in the Venezuelan Kindreds

Through studying the Venezuelan kindreds, we showed that the length of the CAG triplet repeat is the most important factor in determining age of onset of HD (13, 17, 20, 22). We wished to discover if other factors, in addition to the size of the CAG repeat, play a role in determining age of onset. We discovered that, after controlling for the effect of the repeat length, substantial variability remains. Analysis of the 83 kindreds demonstrates that the residual variability in age of onset has both genetic and environmental components. We created a residual age-of-onset phenotype from a regression analysis of the log of age of onset on repeat length. Familial correlations (correlation ± SE) were estimated for sibling (0.40 ± 0.09), parent-offspring (0.10 ± 0.11), avuncular (0.07 ± 0.11), and cousin (0.15 ± 0.10) pairs, suggesting a familial origin for the residual variance in onset age. By using a variance-components approach with all available familial relationships, we found that the additive genetic heritability of this residual age-of-onset trait is 38%. A model including shared sibling environmental effects estimated the components of additive genetic (0.37), shared-environment (0.22), and nonshared-environment (0.41) variances, confirming that ~40% of the variance remaining in onset age is attributable to genes other than the HD gene and ~60% is environmental (15).

Evidence for Genetic and Environmental Modifiers

HD is a devastating, fatal disorder without remission. Notwithstanding its relentless progression, significant variability exists in symptomatology and the age of onset, even within families. Most surprisingly, this variability exists within each repeat length, so that people sharing the identical CAG repeat length in their HD gene may have very different ages of onset. Careful study of this variability should illuminate factors that modify age of onset, symptoms, and even new biological disease mechanisms and therapeutic targets. The Venezuelan kindreds are unique in that they comprise the world's largest genetically related HD community and have already provided a wealth of genetically and phenotypically informative data. The fate of these kindreds is growing even more perilous. The growth of communities at risk, compressed logistically by poverty and stigma, is increasing the number of HD families in which both parents are affected or are at risk. Since all children of homozygotes are destined to inherit the disease, this raises the genetic hazard in these communities to the extreme (15).

An essential component of our Venezuelan HD research is to investigate genotype/phenotype relationships. How does the study of the natural history of HD in these genetically related communities give us evidence of genotypic or environmental modifiers? Age of onset is one component, among many, to search for modifiers. Members of the Venezuelan kindreds manifest a statistically significantly earlier age of onset in comparison to American and Canadian populations. The Venezuelans' average age of onset is 34.35 (±10.07) years in contrast to the mean age of onset for Americans (37.47 ± 13.28) and Canadians (40.36 ± 12.97) (15).

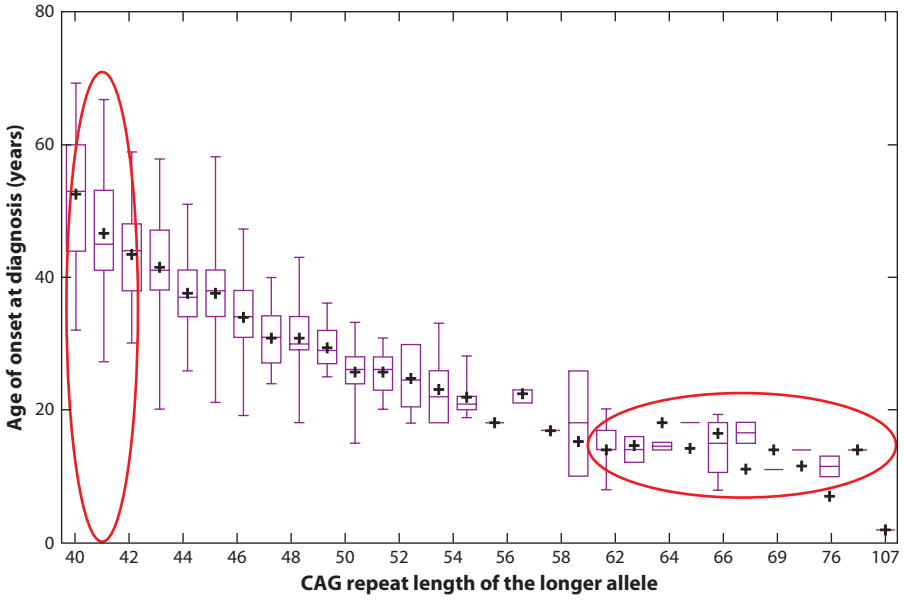

Figure 1

Box plot of age of onset and repeat length of the longer allele. The curvilinear relationship between the two variables can be observed. It also is important to note the large variability of age-of-onset values, even within each repeat length (15). © 2004, National Academy of Sciences, U.S.A.

Other deleterious modifying genes, not associated with the HD gene, may also be segregating in these kindreds. Because kindred members are interrelated, many may inherit both the HD gene and these pernicious modifiers. There also could be shared environmental modifiers that are influencing the age of onset, as mentioned above. Although the families are scattered widely in both urban and rural environments and across all socioeconomic strata, the majority live in extreme poverty and their diet is marginal. Most live near Lake Maracaibo, fish for a living and are exposed to potential pollutants through effluvia from the lake and poor sanitation. They eke out a meager survival (15).

Our analysis of the Venezuelan kindreds confirms a strong, inverse correlation between repeat length and age of onset (**Figure 1**) (15). As this relationship is exponential, the log-transform of age of onset (LAO) was analyzed. This significant negative correlation weakens, however, for individuals with repeat lengths between 40 and 50 CAGs, the majority of individuals in the Venezuelan kindreds and elsewhere. Within this group there is great variability in age of onset, even among those with identical-length repeats. We have demonstrated in our analysis of the Venezuelan kindreds that this variability is attributable to genetic and environmental modifiers acting in concert with the HD gene.

By using variance-components analysis, we have been able to obtain a more precise estimate of the familiality than previous studies have reported (19, 20, 23). Surprisingly, even after controlling for the effect of allele length, our results indicate that fully 59% of the variability in residual age of onset is familial and attributable to either genetic or shared environmental factors (15). The heritability estimate of 38% demonstrates that additive genetic effects importantly influence age of onset, in addition to the HD gene. Our analysis of the Venezuelan kindreds provides the strongest evidence to date for genetic factors influencing age of onset of HD that are statistically independent of the

mutation causing the disease. We also confirmed a role for environmental modifiers in modulating age of onset (15).

With virtually complete penetrance after 40 or more CAG repeats and an invariably fatal course, the HD gene would seem to be the epitome of genetic determinism. And yet our results demonstrate that genetics as well as environmental factors modulate its impact. Identifying these modifiers, particularly those that might lead to postponing age of onset until much later in life and prolonging productive years, would be beneficial (15).

SNP: single-nucleotide polymorphism, a difference of a single nucleotide in a genome that occurs at a given frequency in the population. The primary type of genetic difference between any two humans is due to the SNPs. SNPs are used to assess inheritance patterns

Genomewide Linkage Scan Reveals Novel Loci Modifying Age of Onset

We demonstrated that CAG repeat length accounts for 70% of the variability in HD age of onset. However, 90% of individuals worldwide have expanded alleles between 40 and 50 CAG repeat lengths, and the size of their repeat determines only 44% of the variability in their age of onset. Once the effect of the CAG repeat has been accounted for, the residual variance in age of onset is a heritable trait. Since we demonstrated that there are both genetic and environmental modifiers of age of onset, we wished to find these genetic modifiers (15, 19, 21).

We analyzed the large Venezuelan kindreds, once again, because they offer greater analytic power than standard sib-pair designs. We developed novel pedigree member selection procedures to maximize power. Using a 5,858-SNP marker panel, we performed a genomewide linkage analysis. We discovered two novel loci on chromosome 2. Chromosome 2p25 (LOD = 4.29) and 2q35 (LOD = 3.39) may contain genes that modify age of onset. A third linkage peak on chromosome 6q22 (LOD = 2.48) may also be informative. Two other candidate loci are suggestive on chromosome 5 (LOD = 3.31 at 5p14 and LOD = 3.14 at 5q32). All these regions harbor candidate genes that are potential HD modifier genes. Finding these modifier genes should reveal accessible and promising novel therapeutic pathways and even targets to ameliorate and cure HD (21).

Therapeutic Benefits for the World

The ultimate aim of all of the research supported by the HDF is to develop therapies that are available and accessible to everyone with HD in the world. In our Venezuelan investigations, we have attempted to conduct our research in a manner that is culturally sensitive as well as ethically protective of their specific needs, constraints, and priorities. We hope that the Venezuelans will be able to benefit fully from the results of the research, as they played such a critical role in making everything possible.

Although since 2002 our fieldwork in Venezuela has been interrupted for a variety of reasons, we continue to study every aspect of clinical data and DNA from these families. This includes whole-genome sequencing, RNA sequencing, and other novel strategies to learn everything that these Venezuelan kindreds hold promise to discover.

THE CASA HOGAR AMOR Y FE (HOUSE OF LOVE AND HOPE)

Huntington's disease is devastating in almost all respects around the world. Striking between the ages of 30 and 40 years, it pummels people in the prime of their lives. As an autosomal dominant disease, it kills in almost every generation. But as bad as this disease is throughout the world, every aspect of its devastation is magnified in Venezuela.

HD is financially catastrophic because it strikes during people's most productive years. For the Lake Maracaibo families, this means that the fishermen are no longer able to fish and the women cannot learn a trade since they are caring for so many family members. In the later stages, everyone requires a tremendous amount of assistance for care. People lose the ability to walk, talk, and feed themselves, but are still conscious and aware.

Our pioneering collaboration with the Venezuelan HD families has led to critical breakthroughs in understanding genetic disease and medical science. But in stark contrast to all

these families have given the world, they suffer from extreme poverty, deprivation, and duress. They are subject to all the diseases and disasters of small, impoverished fishing villages. In some villages, the lake frequently inundates the "ranchos" or shacks where people live in dirt homes. Streets and alleyways are impassable. The children play in ditches that are covered with green fluorescent scum, dead fish, and barbed wire. In addition, in almost every home, there are many people in every stage of HD, from the initial aberrant movements to the prolonged bed-ridden agonal years when they are wracked by unceasing motion but aware and conscious.

The family sizes in general are very large in Venezuela. These means that families are coping with many family members who are dying simultaneously. Childhood onset tends to run in families. In one family, seven of the nine were affected as children, one as young as two years old. Children usually have complex seizure disorders to care for—which is virtually impossible at home. One mother cared for and buried 11 of her 13 children. Another family is coping with HD's lethal impact on 10 of their 14 children. The children do not go to school because they must care for the many relatives incapacitated and dying all at the same time. The six-year-olds must earn a living. By age 13, they are parents themselves. Owing to the density of this illness, it is not unusual for children to have two parents with HD. The genetic risk to those children is three chances in four. If one parent is a homozygote for the HD gene, all of his or her children will die. Some families of homozygotes are very large—as many as 10 children who will all die of HD.

Our research and collaboration with these exceptional families have been essential to solving many of the scientific puzzles of HD. They have helped in defining the natural progression of the illness from a neurological and neuropsychological perspective. They were absolutely critical to finding the DNA marker in 1983 and capturing the gene itself in 1993. Their DNA, their clinical information, and their cooperation were key for this breakthrough. The largest American family we were studying at this time was too small to demonstrate genetic linkage.

In gratitude for the families' contributions, the HDF worked with local Venezuelan authorities to build the Casa Hogar Amor Y Fe (House of Love and Hope) over a ten-year period (3). Opened in 1999, the clinic is now home to over 65 people and provides treatment, food, care, and an integrated nursing home to thousands of family members with HD who live along the shores of Lake Maracaibo. The patients are treated with dignity, cleanliness, exquisite medical attention, hope, and love.

The Director of the Casa Hogar is Dr. Margot de Young, a Venezuelan physician who, since 1991, has been working full-time with the HDF. She is the Director of Research and Treatment for our Project in Venezuela. She has devoted herself whole-heartedly to helping these families.

The Casa Hogar provides the community with a wide range of medical attention, from antiparasitics to antipsychotics. For more than a decade, the HDF has continued to support the costs of medicine, supplies, salaries, and other expenses.

One unique and exceptional feature of the Casa Hogar is its extraordinary 30-member staff. Our requirement is that only HD family members can do this job. All work is reserved for them. They have the most skill and experience taking care of many HD family members in their homes. Their homes often have bare concrete or sometimes dirt floors with leaking tin roofs. Living and working at the Casa Hogar gives family members training, salary, dignity, and a sense of purpose in their lives. All of this feeds back into the community since they live locally.

The Casa Hogar is an exemplar to the world of the resilience of the Venezuelan professionals and these extraordinary family members suffering from HD. The Casa Hogar currently is a model for best care practices, even though the patients, families, and caregivers are living in the most extreme circumstances of poverty and duress. The clinic also serves as a potential clinical trial location and a home for genetic

and neurological research that may impact the future of HD discoveries.

The families living along the shores of Lake Maracaibo have revolutionized HD research and the lives of people living with HD around the world. The Casa Hogar exists as a way to say thank you to the patients and families who donated their precious tissues, time, energy, and blood to find the HD gene. The Casa Hogar enables them to continue to live in dignity and peace.

STRATEGIES TO FIND TREATMENTS AND CURES

Genetic Models of Huntington's Disease

Following our 1993 discovery that the expanded CAG repeat in the HD gene causes the disease (11, 13), the HDF turned to understanding mechanisms of pathogenesis. In the years since, the Hereditary Disease Foundation, its advisors and leading scientists worldwide have carried on a near constant dialogue around hypotheses of HD pathogenesis. They are fueled by data on the phenotype of HD in humans and by results from research on HD models. Through a series of Milton Wexler Interdisciplinary Workshops and selective funding of grants and postdoctoral fellowships, the HDF has stimulated and encouraged the critical research needed to facilitate finding and developing new treatments and cures (3).

The discovery of the genetic change that causes HD was followed quickly by the development of many disease models. The HD gene mutation was inserted into well-studied model organisms including yeast, the nematode *C. elegans*, the fruit fly *Drosophila*, and a variety of mammalian cell lines—mice, rats, and more recently sheep, monkeys and minipigs.

Gillian Bates was a critical member of the "Gene Hunters" and she continues to create breakthrough scientific discoveries. Funded by the HDF, Bates took the gene she had helped discover and created the first transgenic HD mice. The best known of the many she created is R6/2, which expresses an N-terminal fragment of the human HD gene with a CAG repeat encoding ~150 glutamines. Bates and the world were surprised to find that the R6/2 mice rapidly developed HD-like symptoms—clasping difficulties, choreiform-like movements, involuntary stereotyped movements, tremor, sometimes seizures, and severe weight loss. R6/2 mice become symptomatic at four weeks, progress rapidly, and require euthanasia by 12 weeks due to severe emaciation (24).

In 1997, the following year, Bates and her team made an even more startling, remarkable and paradigm-shifting discovery (25). Using antibodies against the N-terminus of huntingtin, she identified unusual nuclear inclusions in the brains of R6/2 mice. In her article, she also identified these same "neuronal intranuclear inclusions" in human biopsy tissue removed from the brains of HD patients in 1974 (25)! Studies subsequently have demonstrated these same aggregates, containing N-terminal fragments of huntingtin, in autopsy tissues from brains of people with HD. These data led to a "toxic fragment hypothesis," which proposes that the pathogenesis of HD is triggered by the toxicity of N-terminal fragments of huntingtin, perhaps as a consequence of aggregate formation.

Huntingtin Aggregation, Degradation, and Clearance

The discovery of huntingtin aggregates and the formulation of the toxic fragment hypothesis led to an explosion of studies on the folding properties of polyglutamine and N-terminal fragments of huntingtin carrying different glutamine stretches. This effort, which continues actively today, seeks to distinguish and characterize different types of oligomers and aggregates, elucidate the molecular pathways that lead to their formation, and determine which, if any, cause toxicities that contribute to the pathogenesis of HD and which might be protective. Our goal is to design therapies that prevent toxicity or enhance neuroprotection. In

this respect, HD research parallels other neurodegenerative diseases—Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), and the prion diseases—also characterized by abnormal protein aggregates. Similar mechanisms of pathology in these diseases may one day yield to common therapeutic approaches (3).

Shortly after Bates' discovery, Ai Yamamoto was funded as a graduate student by the HDF. With our encouragement and guidance, she also made a path-breaking discovery. She generated a mouse that expressed a transgene encoding an N-terminal fragment of huntingtin with 94 glutamines. The transgene was controlled by a promoter that could be turned off by treatment with the antibiotic doxycycline. These mice developed behavioral symptoms and intracellular aggregates similar to those of R6/2. However, if, after behavioral phenotypes had developed, Yamamoto turned the HD transgene off by feeding the mice doxycycline, they recovered from their behavioral symptoms. Even more amazing, the aggregates that punctuated their brains vanished! This "reversible mouse" was another landmark in our understanding because it suggests a degree of plasticity and reversibility that could be engaged therapeutically (26).

Yamamoto's discovery began a continuing fruitful search to understand how cells degrade huntingtin and its aggregates. Research efforts designed to discover ways to enhance the degradation of mutant huntingtin are a promising—albeit complex—active area of investigation. Capturing and boosting the cells' own clearance mechanisms can be a valuable therapeutic strategy. The research agenda required to develop such therapies was the topic of a number of recent HDF Workshops. We also fund many promising research projects in this area (3).

Intrabodies and Post-Translational Modifications

While the huntingtin protein, with an expanded stretch of glutamines, is considered by most investigators to cause the pathogenesis of HD, the mechanism by which it does so remains to be established and validated. One potential way to block the toxicity of mutant huntingtin might be to use proteins that bind to amino acid sequences that flank the glutamine stretch. Paul Patterson and Anne Messer, with encouragement and funding from the HDF, have created "intrabodies," proteins derived from antibody fragments, that bind these sequences. Expressed in HD cells and model organisms including HD mice, these intrabodies can significantly reduce toxic symptoms (27, 28). Judith Frydman has focused on the heterotrimeric chaperonin TRiC, which binds tightly to the N-terminus of huntingtin. TRiC is also a potent suppressor of mutant huntingtin aggregation and toxicity in cell and model-organism models of HD (29).

Recent HDF Workshops have focused on helping scientists validate mechanisms that could be responsible for causing toxicities (3). A bewildering array of pathways and factors are changed in cells expressing mutant huntingtin. These changes impact cell function and dysfunction, survival and death. Determining which factors are causative and which are only correlated is critical. The combined investigations of Leslie Thompson, Joan Steffan, Ronald Wetzel, and X. William Yang, all funded by the HDF, have been ground-breaking in this respect. Thompson and Steffan and colleagues, working with *Drosophila* and cell-based models, demonstrated that secondary modification, via phosphorylation of the amino acid serine at positions 13 and 16 of huntingtin, changes the toxicity of N-terminal fragments (30).

Yang has created many transgenic BAC (Bacterial Artificial Chromosome) mouse models, including fragment and full-length, to capture and elucidate different aspects of the HD phenotype. One model, a full-length BAC, with 97 glutamines, developed significant abnormalities in movement, behavior, and cognition. Additionally, these mice developed aggregates and cell death (31). In order to test the impact of differential phosphorylation, Yang created two new BAC transgenic mice. Both were full-length, with 97 glutamines. In one set, Yang converted serines 13 and 16 to alanines, which

rendered them incapable of being phosphorylated. These mice also developed motoric, cognitive, and psychiatric symptoms, as well as cell loss and aggregates. Phenotypically, they resembled Yang's original BAC mice. Amazingly, when Yang converted serines 13 and 16 to aspartate, an amino acid that serves as a phosphomimetic, the animals were virtually cured. They had no disturbance in gait and no cognitive or behavioral symptoms. Even more striking, they had no aggregates or cell loss (32).

The implication of these discoveries is that phosphorylation of serines 13 and 16 protects against the toxicity of the expanded glutamine stretch. Efforts are accordingly under way to develop therapies that enhance or mimic the phosphorylation of serines 13 and 16. We also seek to elucidate the protective mechanism engaged by this modification as a potential target for HD therapy. The HDF is strongly encouraging and facilitating work in these promising therapeutic avenues. **Figure 2** provides an explanation of the effects of the abnormal huntingtin protein on neuronal function.

Gene Silencing

We discovered, by studying the Venezuelan kindreds, that the CAG repeat expansion causes HD. Perhaps even more surprising was our confirmation that the same CAG expansion causes HD in virtually everyone worldwide. This contrasts with other major neurodegenerative diseases, where only a small percentage of people with the disease have a known genetic change. In Alzheimer's disease and amyotrophic lateral sclerosis (ALS), only a few causative mutations have been identified,

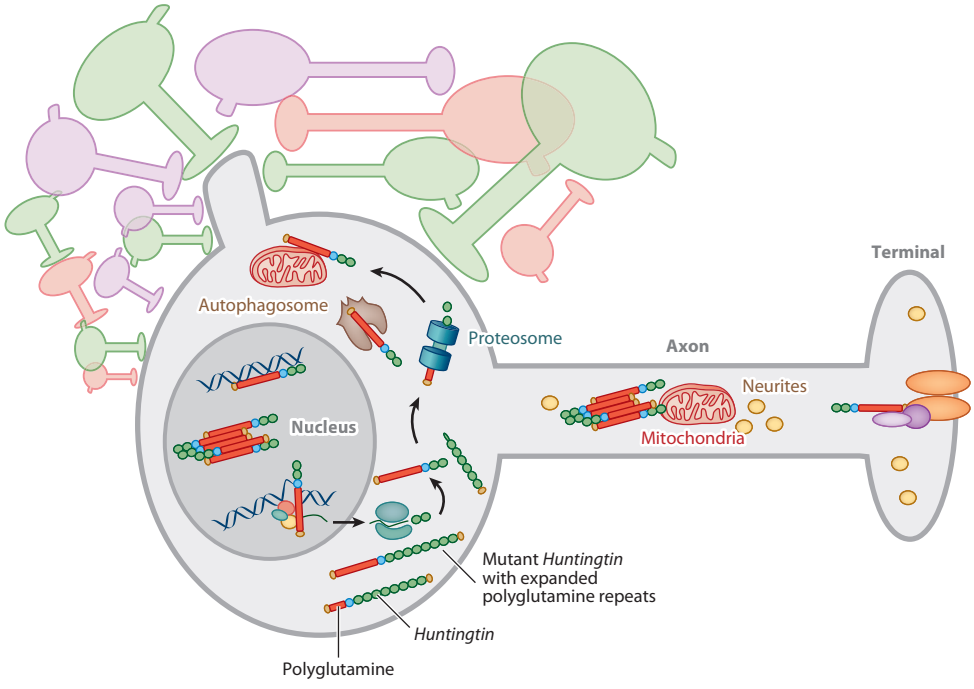

Figure 2

Schematic diagram of an HD neuron. The nucleus is in dark gray and an axon and terminal are also shown. Huntingtin is depicted as a string of green beads, interrupted at one end by a stretch of red that symbolizes the polyglutamine tract. The mutant protein is cleaved into pieces and these are metabolized through the proteasome and autophagasome. Fragments also affect the mitochondria and aggregate in the nucleus and in the neurites, interrupting transport. Mutant huntingtin directly and indirectly alters gene transcription. Courtesy of Anne B. Young.

while in Parkinson's, there are more than a dozen. The single-gene nature of HD makes the prospect of "gene silencing," to decrease the amount of huntingtin produced, an attractive therapeutic option. As the HD gene is the same worldwide, this treatment for HD should be successful for all patients.

Gene silencing is accomplished by a number of nucleic acid–based approaches. Two types of gene-silencing technologies have gained prominence for being potentially efficacious and safe—antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). Both siRNAs and ASOs suppress the translation of mRNAs that are complementary in sequence. The result of an ASO or siRNA that is complementary to the HD gene is the production of less huntingtin.

Developing gene silencing as a treatment for HD is an area of research in which the HDF plays a very significant role. In December 2002, we held the first workshop ever on RNA modalities and gene silencing in HD therapy. The Workshop focused on the use of gene-silencing techniques as one of the most promising strategies for developing new therapies and even cures (3). We continue to play a critical role in funding, guiding and shaping the field. In 2005, a proof-of-concept study by HDF grantee Beverly Davidson and her team demonstrated that silencing the HD transgene in an HD mouse, using siRNAs delivered with an adeno-associated virus (AAV), ameliorates disease phenotypes and neuropathology (33). Davidson is now using siRNAs in an artificial microRNA context. These microRNAs are expressed at much lower levels and have fewer off-target silencing toxicities while remaining efficacious at silencing expression of the HD gene. Davidson is targeting a sequence found in all HD genes sequenced to date, so treatment should work for everyone.

Most attempts to develop gene silencing for HD, including Davidson's, are non-allele-specific. They reduce the expression of both the disease-causing and the normal alleles. Additional efforts, initiated by Neil Aronin and colleagues (34), and adopted by other groups as well, including Davidson, are exploring a variety of approaches to selective silencing of only the disease-causing allele, leaving the normal allele unaffected. Accomplishing allele-specific silencing is more complex, for a variety of reasons. It will also not be universally applicable to all HD patients.

The delivery and distribution of silencing agents still pose some challenges. We need to identify the relevant cells to target therapies. HDF grantee Yang developed a transgenic mosaic mouse in which some cells express the HD transgene while others do not. His results suggest that multiple cell types play a role in HD pathogenesis—including some cells that degenerate and others that do not (35, 36).

How to deliver therapies to the relevant cells raises some questions. Delivery of non-viral silencing constructs, either antisense oligonucleotides or siRNAs, into the CNS using implanted continuous-delivery pumps appears capable of spreading fairly widely within the brain. Advances in brain-injection technologies, such as convection-enhanced delivery, permit silencing viruses, such as AAV, to reach the entire human caudate and putamen.

The promise and potential of gene-silencing therapy for HD remain high, despite some impediments. At present, nearly a dozen gene-silencing approaches for HD treatment are in development. Through follow-up Workshops, as well as frequent consultations, the HDF is guiding these research efforts and designing plans for clinical testing in HD patients (3).

THERAPEUTIC OPTIONS IN HUNTINGTON'S DISEASE

The treatments for HD today are not so different from those available to my mother in the 1960s. They were inadequate then and are even more so today. Apart from tetrabenazine for chorea, most of the new drugs approved since then have been palliative treatments for psychiatric symptoms. These treatments are marginal, at best, and no cure for HD is on the horizon.

People with HD have symptoms in most areas that make us human: mood, mentation, and

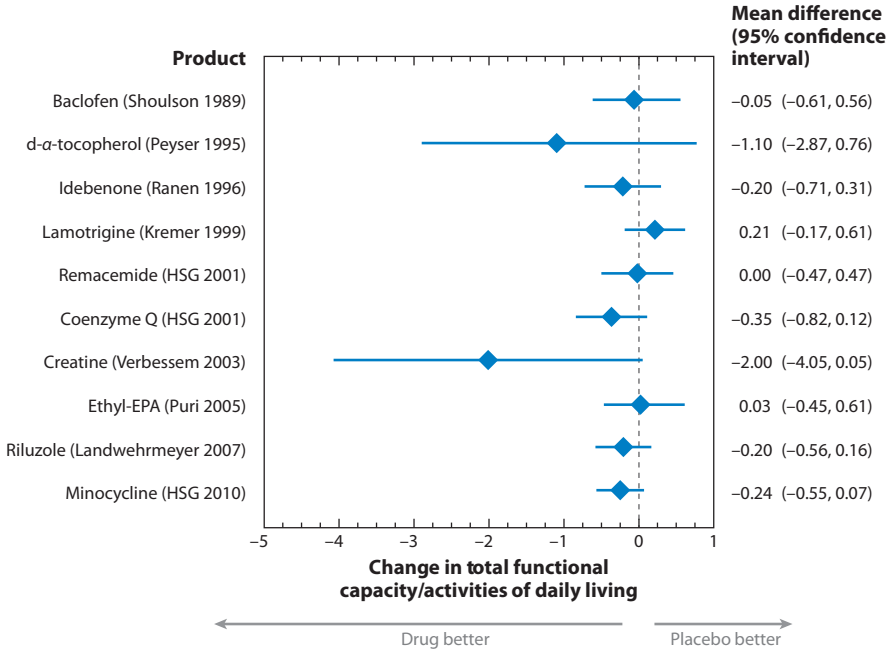

Figure 3

Forest plot of the results of randomized placebo-controlled trials assessing effects of drugs on progression of Huntington's disease. Courtesy of Michael D. Rawlins.

movement. All symptoms are progressive over potentially 20 years, which makes treatment especially challenging.

There are two types of research priorities for developing HD therapeutics. The first priority focuses on disease-modifying treatments, which slow the progression of the disease or prevent it. The second priority is research on symptomatic treatments. **Figure 3** is a forest plot of the results of 10 studies of putative disease-modifying drugs (37–45). None shows any statistically significant benefit. Because there is a suggestion of some effect for coenzyme Q10 and creatine, larger independent trials are currently under way to evaluate their potential (46). Some disease-modifying therapies might also benefit symptoms.

Treatment of Movement Disorders in HD

Chorea responds to treatments that reduce the actions of dopamine in the basal ganglia. Conventional dopamine antagonists, such as haloperidol, have been shown to reduce the intensity of chorea but are associated with significant adverse effects—including Parkinsonian signs and symptoms—as well as tardive dyskinesia after long-term use. By treating HD patients with haloperidol, we may cause other movement disorders. Tetrabenazine is a better alternative (47). It is less likely to produce Parkinsonian symptoms and does not cause tardive dyskinesia. It is the only treatment specifically indicated by the U.S. Food and Drug Administration (FDA) to treat chorea caused by HD. Tetrabenazine has been available in Europe since 1962 and has been widely used to treat a variety of movement disorders, including HD. It was finally approved by the FDA in 2008.

Bradykinesia and tremors, rather than chorea, are common features of juvenile HD. These patients also suffer from convulsions, which respond to anticonvulsants. Bradykinesia can also be severe in late-stage HD.

Dystonia can appear at any time in the course of the illness and is difficult to treat.

Treatment of Cognitive and Psychiatric Symptoms

There are no adequate treatments for the cognitive symptoms of HD: a decline in the ability to do complex tasks or carry out executive skills; a decline in memory, especially working memory; and loss of ability to speak and be understood. This loss of articulation makes it difficult to communicate. Nevertheless, those with HD can usually recognize family and friends and maintain knowledge of where they are. People with HD also suffer from a complex array of difficult-to-treat psychiatric symptoms. Bipolar and major depression are extremely common (48), with a high suicide rate (49). Actual suicides among HD patients are as high as 13%, 7–12 times the national average. Suicidal ideation, in people either at risk for or diagnosed with HD, is as high as 23%. Other symptoms include hallucinations and delusions, especially paranoid delusions; obsessive-compulsive disorders; irritability, sometimes leading to aggressive, violent outbursts; apathy, with failure or inability to initiate activities or follow through; and day-night reversal. This broad panoply of diverse psychiatric symptoms is difficult to treat adequately and often changes over time. Treatments may appear to lose effectiveness, so continued monitoring and modification are required. Treatments for the movement disorders in HD may make cognitive or psychiatric symptoms better or worse. Depression, anxiety, and obsessive-compulsive disorders are often treated with selective serotonin reuptake inhibitors (SSRIs), despite the lack of evidence from formal clinical trials in HD patients. Psychotic symptoms sometimes appear to respond to conventional or atypical antipsychotics, although, again, there are no trials to support such use.

Treatment for Dysphagia

Weight loss is almost universal in people with HD. Due partially to the calorific demands from abnormal movements, it is compounded by dysphagia. Swallowing therapy as well as percutaneous enterogastrostomies can help. Inhalation of food, leading to aspiration pneumonia, is one of the most frequent causes of death in people with HD.

UNDERSTANDING THE PAST TO CHANGE THE FUTURE

Through the last century, families with HD often had to cope with discrimination, stigmatization, and ostracism. In the United States, Charles Davenport was one of the first individuals to draw up pedigrees and conduct large-scale genetic studies of HD families. In 1910, he founded the U.S. Eugenics Record Office at Cold Spring Harbor (50, 51). The Supreme Court ruled in 1927 that compulsory sterilization was lawful under the U.S. Constitution (50, 51), and by 1935, most states permitted compulsory sterilization of people with certain conditions. The 1927 ruling was reversed only as recently as 1974. In 33 states, as many as 65,000 compulsory sterilizations took place (52). We do not know if any of these individuals had HD or were at risk for it. This harsh and punitive attitude would most likely make it onerous for HD patients and their families to get the help they needed and deserved.

This policy was strongly influenced by the work of Charles Davenport and Elizabeth Muncey, a fieldworker at the Eugenics Record Office, Cold Spring Harbor. They published a paper in 1916 entitled "Huntington's Chorea in Relation to Heredity and Eugenics" in the *American Journal of Psychiatry* (53). Their paper stated:

> These half-dozen immigrants are not the only ancestral sources of Huntington's chorea in the United States to-day. From the records of hospitals it is clear that new choreic stock has come in with the immense immigration of recent years. It requires little imagination to picture what the consequences of this new blood—these new centers of weakness—will mean to the population of this country three

> or four generations hence. It would be a work of far-seeing philanthropy to sterilize all those in which chronic chorea has already developed and to secure that such of their offspring as show prematurely its symptoms shall not reproduce. It is for the state to investigate every case of Huntington's chorea that appears and to concern itself with all of the progeny of such. That is the least the state can do to fulfil its duty toward the as yet unborn. A state that knows who are its choreics and knows that half of the children of every one of such will (on the average) become choreic and does not do the obvious thing to prevent the spread of this dire inheritable disease is impotent, stupid and blind and invites disaster. We think only of personal liberty and forget the rights and liberties of the unborn, of whom the state is the sole protector. Unfortunate the nation when the state declines to fulfil this duty!

This eugenic fever was felt throughout the world. In Nazi concentration camps, families with HD were euthanized by directive.

Particularly distressing to me, because I knew him personally, were the words of Macdonald Critchley, President of the World Federation of Neurology, which has a Working Group on Huntington's Chorea (now called the World Congress on Huntington's Disease). In 1934, in the United Kingdom's *Journal of State Medicine*, he wrote (54):

> "[M]embers of the family who are themselves free from the disease are nevertheless liable to bear the marks of a grossly psychopathic taint, and the story of feeblemindedness, insanity, suicide, criminality, alcoholism and drug addiction, becomes unfolded over and over again."

Huntington's disease symptoms are obvious. Most people are easy to spot. Clearly, medical knowledge did not prevent others from using it to target more carefully, stigmatize, and ostracize families. Medical knowledge did not protect families from vilification or harsh treatments. It was used, instead, like a radar beam, to home in on families more precisely. Having discovered the gene but no treatments or cures, I am afraid for families with HD worldwide. We are in a limbo that I dreaded when we discovered the gene—and this limbo has persisted for far too long. We cannot ethically encourage HD families to participate in research or clinical trials or any aspect of visibility, unless we can guarantee that they will be safe, secure, and protected from discrimination.

RECOMMENDATIONS AND LESSONS LEARNED

Since the Hereditary Disease Foundation was created 43 years ago, other advocacy organizations have been founded aiming to participate more fully in the search for new treatments and cures. We have enjoyed being full partners in these efforts to accelerate discoveries. Here are lessons learned on this sojourn:

1. You need money to fund research. Adequate funding is critical to accomplishing anything.
2. The HDF plays an indispensable role as a convener and shaper of ideas through our Milton Wexler Interdisciplinary Workshop Program.
3. It is essential to fund research ideas generated at Workshops. Combining funding with good ideas generated at Milton Wexler Interdisciplinary Workshops is important synergy.
4. Workshops, by themselves, play an elemental role—even if funding research is not possible. Catalyzing ideas in the HDF Workshops and funding them immediately is best, if possible.
5. Money alone cannot buy cures. One business model of funding assumes that if you push sufficient funding at the problem, treatments and cures can be purchased.
6. Funding is essential to find treatments and cures but you need to spend it on the right people with the right ideas at the right time. Frank Gehry's Guggenheim Museum in Bilbao and Michelangelo's *David* are works of genius and inspiration, like scientific creativity. Watson

and Crick discovering DNA, Einstein's theories—all these fundamental paradigm shifts in our elucidation of the world—changed almost every aspect of it. Genius cannot be prescribed or dictated. It can be permitted to flower, to be nourished and enhance our world.

7. We direct funding by the HDF to scientists doing high risk–high reward research. This cutting-edge research is often difficult for the National Institutes of Health (NIH) to fund.
8. We try to be flexible in our funding, "light on our feet" and able to pursue new leads wherever they go. The NIH and other government sources of funding tend to be ponderous, less flexible, and more conservative in their funding—especially when funds are scarce.
9. The NIH and other major organizations are usually the only ones capable of investing the large sums of money required to carry through projects. We work synergistically with them.
10. We fund pilot studies that enable investigators to apply to the NIH, or other sources of funding, to continue the project.
11. We leverage our funding so that an initial small investment benefits a lot. This increases the overall resources in a field.
12. We collaborate with investigators assiduously to create the best possible projects.
13. We usually fund young investigators beginning their careers and postdoctoral students. Often, a passion for research and for finding cures accompanies them forever.
14. We preferentially fund women and minorities.
15. We actively advocate for increased funding for the NIH and other research organizations. Since cures may come from many sources, it is vital for all aspects of research to receive increased funding. We work collaboratively with other advocacy organizations since there is power in numbers. Educating and advocating can be very effective.
16. We feel that it is critical to be involved with every aspect of patients' and families' lives. To accomplish this end, we testified before the FDA on behalf of tetrabenazine and influenced the FDA's approval of the only medicine specifically indicated for treating the chorea HD causes. We advocated for the successful passage of the Genetic Information Nondiscrimination Act of 2008 (Public Law 110-233).
17. We work with biotech and pharmaceutical companies—Novartis International AG, GlaxoSmithKline, and Lundbeck, Incorporated, among others. Pharmaceutical companies play key roles in developing and delivering new treatments and cures.

CONCLUDING THOUGHTS

Since 1968, the HDF has funded >$60 million in pioneering biomedical research, producing results that reach far beyond the HD community. The scientific collaborations and groundbreaking research developed through the HDF model are providing a blueprint for other illnesses, including Alzheimer's disease, Parkinson's disease, ALS, schizophrenia, bipolar disorder, and even cancer.

When we began the HDF, we had no idea that it would take so long or be so difficult to understand, treat, prevent, cure, or eradicate HD. Human biology is vastly more complex to unravel and elucidate than we thought. We discovered the gene that causes HD almost 20 years ago—but we still do not have our therapeutic magic bullet. Finding the gene was vital and has changed research forever, especially in creating and testing model systems. But it is not an instant cure. The problem is orders of magnitude more difficult than we anticipated.

The HDF is fortunate to work with an extremely gifted, innovative, and dedicated Scientific Advisory Board and Board of Directors. We continue to have Milton Wexler

Interdisciplinary Workshops in key areas. We continue to hone and work collaboratively with the investigators whose critical work we fund. We are confident that novel treatments and cures for HD will come soon. We would all like to be there to celebrate!

DISCLOSURE STATEMENT

The author is the nonpaid president of the Hereditary Disease Foundation.

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