

positive mice. The experiments demonstrated conclusively that mice which both *had* the HD gene and *did not have* the gene for caspase-1 lived twenty-five percent *longer* than HD gene-positive mice with the caspase-1 gene intact. Moreover, their symptoms progressed more gradually, giving the animals a longer period of healthy life without the disease.

Because Dr. Friedlander is a neurosurgeon, he decided to test the hypothesis in a surgical way as well. He doused the brains of mice carrying the HD gene with a drug that turned off the action of the deadly caspase-1 enzyme, using a tiny pump inserted into the brains of the mice. These mice showed the same ability to survive longer without the symptoms of chorea. When the symptoms did appear, they advanced more slowly. These mice also lived 25% longer than their untreated comrades.

This is roughly equivalent in human terms to ten years longer without showing symptoms.

Though further research is needed to document precisely the death pathways of caspase-1 in the brain, these findings represent the first evidence of a possible strategy for a drug treatment for Huntington's and related diseases. Indeed, Dr. Anne B. Young, Chief of Neurology at Harvard Medical School, Hereditary Disease Foundation Science Advisory Board Member, and also an author on the paper, immediately flew into action scouting for pharmaceuticals having the same effects.

What makes this work especially exciting is its potential relevance for a broad range of disorders. As the *Nature* article stated, "Caspase-1-mediated pathways appear to be shared in a variety of acute and chronic neurologi-

cal disorders (ischaemia [stroke], Huntington's, Parkinson's and Lou Gehrig's [ALS] disease) as a common mechanism mediating cell dysfunction and cell death. Our findings show that caspase-1 plays an important and specific role in the early stages of Huntington's disease, as demonstrated by the inhibition of both aggregates, blobs of protein inside the cell's nucleus, and the specific neuroreceptor chemical abnormalities found in the disease. Caspase-1 inhibition delays onset and prolongs survival in a transgenic mouse model of Huntington's disease, and is potentially applicable to the human disease." This is the very first time that anything has improved the outlook for Huntington's disease— either for mice or men! ■

September 18 "Hope and Cope" Conference at UCLA

A one-day conference highlighting state-of-the-art research as well as current treatment strategies, genetic testing and consumer resources for families and professionals dealing with Huntington's disease and the ataxias will be held on the UCLA campus Saturday, September 18th.

The University of Southern California's Los Angeles Caregiver Resource Center and UCLA's Department of Neurology and the Brain Research Institute are presenting this event, with co-sponsorship by the Hereditary Disease Foundation, the Greater LA chapter of HDSA, and the National Ataxia Foundation. UCLA researchers and their colleagues will discuss their latest research on these disorders, and will be available for discussion and questions. In addition, the conference will address daily living and management strategies and how to access consumer resources. Here is a great opportunity, for family members and professionals, to hear about the latest research in accessible language, straight from the laboratory bench and from the neurologists' and genetic counselors' offices! Here also is a great chance to ask all those questions for which there may be some new answers. The conference will be wheel-chair accessible, with special meals available. For information about times, location on the UCLA campus and directions, please call the Hope and Cope coordinator at 213-740-8711, or visit the Hereditary Disease Foundation Website at www.hdfoundation.org. ■

Hereditary Disease Foundation

Officers

Milton Wexler, Ph.D.,
Chairman

Nancy S. Wexler, Ph.D.,
President

Frank Gehry,
Vice President

Berta Gehry, *Treasurer*

Susan I. Spivak, *Secretary*

Allan Tobin, Ph.D.,
Scientific Director

Ethan Signer, Ph.D.,
Executive Director, CHDI

Staff

Anita Lee

Judy Lorimer

Julie Porter

Edy Shackell

Robin Underwood

Production

Abby Pardes, *Director*

Hereditary Disease

F O U N D A T I O N

1427 7th Street, #2 • Santa Monica, California • 90401 • 310-458-4183

Fax 310-458-3937 • cures@hdfoundation.org • www.hdfoundation.org



HDF-Supported Scientist, Robert Friedlander, Extends Health in HD Mice While "Darth Vader" Gene Points Toward Possible Treatment for HD

A tour-de-force series of experiments at Harvard Medical School supported by the Hereditary Disease Foundation has shown that a "death gene" called caspase-1 may play a critical role in causing cell destruction in Huntington's and other neurological diseases.

By turning off caspase-1 in mice carrying a version of the Huntington's disease gene, Dr. Robert Friedlander and his group at Harvard Medical School succeeded in delaying the onset of symptoms in the animals, and in slowing down the progression of the disease. These findings, published May 20 in the prestigious science journal *Nature*, represent the first persuasive evidence of a possible strategy for treating human Huntington's disease. They also demonstrate the power of the new genetically engineered mouse models of neurological disease to come up with treatments in people. New York *Newsday* featured an article (May 20: see our Website) on the work, noting that these experiments represent hope more concretely than ever before.

The Hereditary Disease Foundation's Dr. Ethan Signer, Executive Director of the Cure HD Initiative, learned of this promising research strategy—he liked what he heard. He wasted no time in contacting Dr. Friedlander, who was looking for additional funding to carry out the work. "While most funding

agencies require complex applications and long evaluation times," said Dr. Friedlander, "Ethan fired off an e-mail asking 'What do you need?' Within days, the check was in the mail!" Friedlander later told us, "If it was not for the financial help provided to me by the HDF, this work would have taken at least 2 or 3 years to complete. With the backing of HDF in this early period of my career, we were able to complete the project in less than 12 months."

The research used an ingenious strategy. Friedlander's group mated a series of mice carrying part of the HD gene which were developed by Dr. Gillian Bates, twice a winner of the prestigious Lieberman Award from the Hereditary Disease Foundation, with another set of special mice. These mice *lacked* the gene for caspase-1, a so-called "Darth Vader" gene because it sets into motion the process known as *apoptosis*, or programmed cell death. Apoptosis can be beneficial at the right time and place, getting damaged cells out of the way, and preventing the excessive proliferation of cells which occurs in cancer. In diseases such as Huntington's, however, this uncontrolled cell death turns parts of the brain into killing fields, attacking neurons that are desperately needed for healthy function.

Dr. Friedlander knew that Gill's mice with the human HD gene would



Dr. Robert Friedlander

eventually develop symptoms of the disease. But he did not know what would happen if he could turn off the caspase-1 gene in these same gene-

Continued on page 12

In This Issue

"Darth Vader" Gene	1
View From The Chair	2
"Casa Hogar" in Venezuela	3
Inaugural Speech for "Casa Hogar"	5
Red Hot Chili Peppers Benefit	9
Cells in the Brain	9
Dr. John B. Penney, Jr. Memorial	10
Trustee and SAB Happenings	11
"Hope and Cope"	12

Insert: HD and the Arts—featuring Tiger Tunes, Woody Guthrie, and S-T-R-E-T-C-H-I-N-G

View From The Chair

by Milton Wexler, Ph.D.



Dr. Milton Wexler, Chairman of the Board

Some time back, I had the great pleasure of meeting Michael Balzary—Flea of the Red Hot Chili Peppers. I found him intelligent, sophisticated, and very committed to helping in the search for a cure for Huntington's Disease. The whole band shared his admirable feelings. On June 25th, the Palladium rocked and rolled to a very full house. It blew my mind that the Chili Peppers had only to announce, without even advertising, the concert and it was sold out in the blink of an eye. If we could package that fame into scientific knowledge, we would undoubtedly cure every ailment afflicting mankind.

Our new trustee, Australian actress Marissa Pouw, was on hand to enjoy the event and even to take a look-see at the scientific workshop we held that same weekend. Marissa was accompanied by her sister Saskia and their mother. What a charming, intelligent, thoughtful and beautiful group they made. Our Foundation now has wonderful representation in that great island continent, Australia.

Allan Tobin, Ethan Signer, and Nancy Wexler, the troika that regularly meets with the Cure HD Initiative Advisory Committee in Boston, tell me that we now have a greatly enriched number of excellent research proposals with fruitful ideas leading to a cure for HD.

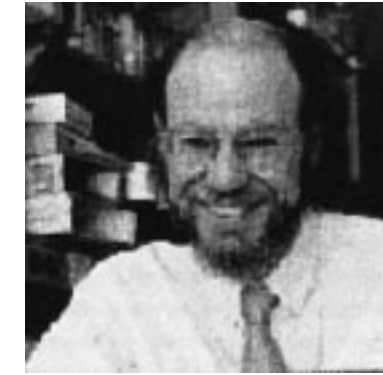
Clearly we are entering a new era with our current knowledge about the HD gene and the protein it produces, particularly how it affects cells. We are now able to make substantial moves in the direction of testing potential treatments for this malignant ailment. In the beginning we had to move slowly because our knowledge was so limited. Now, knowledge accumulates with increasing rapidity and we are able to fund very promising research at a much greater rate.

I had the great pleasure of going to a wonderful party arranged by Marjorie Fasman for her husband Michael to celebrate his 90th birthday. The pleasure included meeting two of Michael's brothers who also enjoy great longevity. On behalf of all of our Trustees, Happy Birthday, Michael Fasman, and we expect you to enjoy many more!

To my delight, I had the pleasure of reconnecting with Dr. John Menkes at the party. In the early period of the Hereditary Disease Foundation, John was chair of Neurology at the UCLA Medical School, and also chair of our Scientific Advisory Board. What a wonderful contributor and inspiration he was. John is now in private practice, but as a creative sideline he is writing mystery novels. He has already been published, and is just completing another novel which will very soon be available for purchase. Given John's creativity and imagination, I believe I can recommend it sight unseen! ■

Trustee and SAB Happenings

Vice President of the Hereditary Disease Foundation and Trustee Frank O. Gehry has been chosen to design the new addition to the famed Corcoran Gallery of Art in Washington D.C. Winning out over the designs of two distinguished competitors, Gehry's addition will go over the roof of the old Corcoran to house the gallery's art school and an expanded children's education center. The President of the Corcoran, David C. Levy, especially liked Frank's approach, which looked at the building as a totality. Said Levy, "In his presentation, instead of saying, 'Here is my building,' he started in the basement and worked his way up. Then he said, 'Here is how we will enclose these spaces.'" The submitted design envisions an exterior with tumbling arcs billowing above the present structure, with interior canyons full of air and light. We can't wait to visit!



Dr. H. Robert Horvitz

Cure Committee and former Science Advisory Board member Dr. H. Robert Horvitz, professor of biology at the Massachusetts Institute of Technology and Howard Hughes Medical Institute Investigator, has been named co-recipient of a 1999 Gairdner Foundation International Award, which recognize outstanding contributions to medical science. Horvitz and a colleague at Cambridge University, Andrew H. Wyllie, were honored "in recognition of their pioneering contribution to our understanding of apoptosis, or programmed cell death," according to the Gairdner Foundation. The Foundation further explained, "Horvitz's work definitively showed that apoptosis is a genetically regulated mechanism and has subsequently led to the discovery of countless novel death-signaling pathways whose dysregulation directly contributes to human disease."

Trustee Alice Wexler has been awarded a Guggenheim Fellowship for the coming year, for her research on the history of Huntington's disease on Eastern Long Island. Dr. George Huntington, who wrote about the disease in 1872, grew up in a medical family in East Hampton, New York, where his grandfather and father had also observed families afflicted with this illness. Huntington's disease, as the *East Hampton Star* once wrote, is in some ways "an East Hampton story" which Alice is trying to unearth in her research. Her book, *Mapping Fate*, was recently selected as a "Great Brain Book" by the Dana Alliance for Brain Initiatives. See their publication, *Cerebrum*, Spring 1999, for a complete listing of "Great Brain Books."

Trustees Arthur Golding and Dewanna Covey have been beaming lately, all on account of a new grandson, Connor Jay Burke, whose birth set off these smiles! Congratulations, Arthur and Dewanna, and also to the new parents, Dr. Ilyssa Golding and Doug Burke.

Memorial for Dr. John B. Penney, Jr. Held in Boston

by Alice Wexler, Ph.D

To the haunting guitar strains of Michael Lorimer, mourning family, friends, students and colleagues of Dr. John B. Penney, Jr. gathered at the historic First and Second Church of Boston on Saturday afternoon, May 22, to remember, to grieve, and to celebrate a remarkable life tragically cut short.

Ira Shoulson spoke movingly of his professional and personal bonds with



Jack B. Penney in Venezuela

Jack and their work together, including in the barrios and towns around Lake Maracaibo as part of the Venezuela HD research team.

Nancy Wexler followed, recalling Jack's love for his daughters Jessica and Ellen, his wife Anne, for all of his family, and speaking in turn to each one of them in the audience. She played a short video she had made, showing Jack in Venezuela, wearing shorts, a bright blue Bahamian shirt and baseball cap, giving neurological exams to barefoot people with Huntington's in the barrios of San Luis and Barranquitas, joking with the patients and coaxing smiles even from the most anxious and fearful. There wasn't a dry eye in the entire church. Jang-Ho Cha, a former graduate student and post-doc in Jack and

Anne's lab, affectionately recalled Jack's famous New England reserve and his very human foibles, making everyone laugh with his memories of ski trips with Jack in his beloved New Hampshire, when Jack couldn't wait to "mount Blondie" (the name of an especially tough ski slope)!

Most stunning of all was Jack's daughter Jessica Penney, whose story about Jack—not the original story which was packed somewhere in a box, she explained, but her memory of that story, about how she figured he was the ground on which she stood—won a tearful, standing ovation from the entire audience. Jack's sister Janet Cronin and his brother Steve Penney also shared their eloquent recollections of a much admired older brother. And Jack's dad spoke powerfully of his son and his grief at this irreplaceable loss, which echoed the tragic death of his

wife, Jack's mother, from cancer, at the same young age of fifty-one, many years earlier. Finally, Dr. Anne B. Young got up to share her grief at the loss of the man who had been, for nearly thirty years, her best friend, lover, husband, scientific and medical colleague, and part of herself, her universe. When she stopped for a moment, struggling for words, asking the audience to "please bear with me," it was as if the world had come to an end, stopped, here, in this Boston church, no place to go on, yet she did, and we did, and she will, though the world is a poorer place without Jack.

Between all these presentations, the brilliant Michael Lorimer wove a delicate, delicious tapestry of sound echoing in music the mood of the

speakers. Anne had selected quotations from several literary works which were included in the short program for the service, including this one from Robert Louis Stevenson which speaks poignantly to Jack's enduring legacy. "It is better to lose health like a spend-thrift than to waste it like a miser. It is better to live and be done with it, than to die daily in the sickroom. It is not only in finished undertakings that we ought to honor useful labor. A spirit goes out of the man who means execution, which outlives the most untimely ending. All who have meant good work with their whole hearts have done good work although they may die before they have time to sign it. Every heart that has beat strong and cheerfully has left a hopeful impulse behind it in the world, and bettered the tradition of mankind."

"And even if death catch people, like an open pitfall, and in mid-career, laying out vast projects, and planning monstrous foundations, flushed with hope, and their mouths full of boastful language, they should be at once tripped up and silenced: is there not something brave and spirited in such a termination? And does not life go down with a better grace, foaming in full body over a precipice, than miserably straggling to an end in sandy deltas? When the Greeks made their fine saying that those whom the gods love die young, I cannot help believing they had this sort of death also in their eye. For surely, at whatever age it overtake the man, this is to die young. Death has not been suffered to take so much as an illusion from his heart. In the hot-fit of life, a-tiptoe on the highest point of being, he passes at a bound on to the other side. The noise of the mallet and chisel is scarcely quenched, the trumpets are hardly done blowing, when, trailing with him clouds of glory, this happy-starred, full-blooded spirit shoots into the spiritual land.

—From *Aes Triplex*, Robert Louis Stevenson

Unique Pilot Center for Integrated HD Care and Research Inaugurated in Venezuela— Drs. Nancy Wexler, Margot de Young and The Honorable John Maisto, U.S. Ambassador to Venezuela, Attend and Celebrate

by Nancy S. Wexler, Ph.D

June 16, 1999

In 1992, one of the most infamous neighborhood bars in San Luis, Venezuela, "El Toro Rojo" (the Red Bull), was purchased by the Venezuelan government and the Asociacion Amigos Del Enfermos de Corea de Huntington (the Association of Friends of People With Huntington's Disease), a non-profit charity for families, which has title to the property. In 1993, Public Works of the State began construction on a combined research and clinical center for the care and cure of Huntington's disease.

In our field-work expedition this year, we appealed to the Governor, Lieutenant Colonel Francisco Javier



Mayor Saadi Bijani, Gladys de Arias Cardenas (the Governor's wife), Nancy Wexler, Hon. John Maisto, Margot de Young



Casa Hogar Corea de Huntington, Amor y Fe

Arias Cardenas, and his wife, la Licenciada Gladys de Arias Cardenas to complete and equip the clinic. They were very responsive. In addition, we contacted people in all areas of the public and private sector, including Shell Petroleum, whose representatives were extremely cooperative and helpful.

The government poured in the resources to finish and equip the building.

The new edifice is unique in the world. It is the first pilot center anywhere for an integrated program of care and research for families with Huntington's

disease. It is called the "Casa Hogar Corea de Huntington, Amor y Fe," or "Huntington's Chorea Home of Love and Faith"—love because that is the first medicine for patients and faith in God and science to find the cure.

The building has two stories and is built to accommodate both ambulatory and resident patients. The interior spaces are highly flexible and suit multiple uses. On the first floor are four generic consulting rooms which can serve a rotating group of specialists. At a minimum, family medicine will be provided at the clinic daily, with specialists as needed. There is also a unit for minor surgery.

The first floor has a dining room and kitchen, one of the focal points of the Casa Hogar. People with HD need approximately five times the usual number of calories to maintain their weight—a high-caloric diet being an important therapy in HD. The kitchen will serve not only those resident in the facility but will also provide food for people

with HD in the neighboring community. They can come to the Casa Hogar or food can be brought to those bedridden at home.

In addition to ambulatory care and nutritional services, the Casa Hogar has 18 beds for resident care. Some



Hon. John Maisto, U.S. Ambassador to Venezuela, and Nancy Wexler

rooms are for brief hospitalization for infectious disorders, especially pneumonia—a constant threat in HD—dehydration, malnutrition, broken bones, and other maladies. The other rooms accommodate patients in pre-terminal and terminal phases of the illness who have no family to care for them. There is a separate section for children, decorated appropriately. As most children with HD suffer from seizures, their care is especially complex.



Nancy Wexler, Lic. Gladys de Arias Cardenas (wife of Governor of Zulia), Margot de Young

There is a small conference room equipped for workshops. A larger, comfortable day room for families can also be used for educational talks for the community on hygiene, infection control, and genetic counseling as well as to address

visiting foreign scientists. A cupola made of colored glass covers a small enclosed red-brick plaza whose benches, trees, flowers, red clay pottery “ollas” (bowls), and a statue of the Virgin Mary completes the Casa Hogar Corea de Huntington Amor y Fe and makes it a place of respite, renewal and hope.



Dr. Americo Negrette receiving award from Mayor Econ. Saadi Bijani

A large, festive inauguration took place on June 16, 1999 to celebrate the completion of the Casa Hogar. I returned to Venezuela to participate. The Governor’s wife presided. It was attended by luminaries from government and society.

Also in attendance to be honored was Dr. Americo Negrette, the scientist who originally diagnosed Huntington’s Disease in this family and launched the initial research studies. In recognition of our contributions, Dr. Negrette, Dr. Margot de Young and I received the “Pride of The Municipality of San Francisco” Award. This is the highest honor bestowed by the municipality on a citizen and was presented at the inaugural ceremony.

The U.S. Ambassador, Mr. John Maisto,

traveled from Caracas for the event. He immediately grasped the special nature of coupling sophisticated biological research with genuine humanitarian concern for the community. He witnessed love between family members and researchers and between Venezuelan and U.S. professionals.

The Casa Hogar awaits additional funding to become operational. It stands as a symbol of hope and international cooperation and promises when the doors open to begin its work. In the words of United States Ambassador John Maisto, “Through these two professional women—one Venezuelan, one American—we have achieved a marvelous cultural and scientific interchange that will benefit all that are involved in the advancement of science and treatment of persons with Huntington’s.” ■



Thais de Bijani (wife of the Mayor), Nancy Wexler, Gladys de Arias Cardenas (wife of the Governor), Hon. John Maisto, Mayor Saadi Bijani, Margot de Young

Red Hot Chili Peppers Sizzle for Science!



Michael Balzary (Flea), Bob Forrest, Milton Wexler, Nancy Wexler

The Red Hot Chili Peppers shook the Los Angeles Palladium with a thrilling, sold-out benefit performance on June 25, with proceeds split fifty-fifty between the Hereditary Disease Foundation and the Musicians’ Assistance Program (MAP).

Organized by former Thelonius

Los Angeles-based group, whose spicy new album, *Californication*, on the Warner Brothers label, hit No. 3 on the Charts that week. Appearing also at this unforgettable concert were DJ Perry Farrell, Eddy Vedder, Carla Bozulich, Mike Watt, guitarist Nels Cline, and members of Fishbone.

Monster frontman Bob Forrest, who also performed at the event with his new band, Bicycle Thief, the concert, according to the *Los Angeles Times*, was “long on energetic performances and refreshingly short on proselytizing.” Chili Peppers fans rocked out on old and new songs by this

Many thanks, Chili Peppers, and especially bass guitarist Flea, Michael Balzary, for your red hot gift to genetic research! And particular thanks to our new friend and trustee, Australian actress Marissa Pouw and her family, whose warmth and enthusiasm added a particular glow to this memorable event! ■



Hollywood Palladium

HDF Workshop Finds Stem Cells in the Brain Offer Hopeful New Paths for Research

Ethan Signer, Ph.D., Executive Director, Cure HD Initiative

At a recent Hereditary Disease Foundation workshop held in New York City on July 18 and 19, researchers focused on the striking and unexpected finding of “stem cells” in the adult mammalian brain, a finding with valuable implications for exploring previously inaccessible features of the disease process.

Stem cells are basic, undifferentiated cells that can generate not only more stem cells but a host of different adult cell types as well. Each stem cell is like a baby, with the potential to develop in many different directions. For many years, neurobiologists believed that cells of the adult brain, which normally don’t proliferate further, had permanently lost that special ability. They believed there were no stem cells in the brain. It has recently become clear, however, that a small number of brain cells are, in fact, stem cells. In the proper conditions, these stem cells can

become activated, begin to proliferate, and eventually produce what is essentially the entire range of differentiated brain cells.

Because HD is marked by the loss of neurons in specific brain regions, the striatum and cortex, this finding raises the possibility that stem cells might provide a way of replacing the neurons lost to disease. Although this possibility is quite likely far off, it is certainly real and promising.

More immediately, though, stem cells provide an exceedingly valuable research tool for learning about features of the disease process that as yet we have no other way of approaching. With that in mind, the HDF organized a workshop entitled “Neural Progenitor Cells and Novel Regenerative Strategies for Neurodegenerative Diseases” which was held in mid-July in NYC. Seventeen scientists sat down to discuss how best to exploit the possibilities of stem cells in the brain, using the new

transgenic HD mouse models developed in the last three years, most of them with Hereditary Disease Foundation support. One approach is to graft not only normal stem cells into diseased brain, but also stem cells carrying the HD gene into normal brain, in order to study how the cells interact. Another approach is to uncover the molecular signals that can activate stem cells, so that chemical compounds able to generate such signals can be provided from outside, with drugs for example.

The level of excitement and enthusiasm among the participants was unusually high, and the coming months will likely see more and more stem cell research bearing on HD. This should in turn soon begin to reveal details of disease initiation and progression—formation of intranuclear inclusions (clumps of protein in the nucleus), establishment of connections among neurons, behavioral manifestations and the like—that could prove vital for eventual therapy. ■

complete, I felt total conviction and trust. He is a remarkable man who can move mountains. Drs. Carlos Alberto Cardenas, Juan Carlos Carroz and Ms. Marielis Briceno, with their exquisite expertise in medicine, architecture, and every aspect of health care delivery, breathed functional life into dry blueprints and brought to life a vibrant center better than anything for which we had dreamed.

- Dr. Alejandro Avila, Professor, University of Zulia:** colleague, companion and contributor. His experience and total dedication have already brought significant scientific discoveries to the world.



Dra Margot de Young at Podium

- Shell Petroleum Corporation, Venezuela:** It is difficult to have sufficient words to thank fellow companions in the struggle to improve the lives of families. Particularly to Donal O'Neill, Vice President of Exploration and Production; Mauricio Perez Badell, Vice President; Moises Abreu, Engineer and Head of Public Affairs and Community Relations; Bernard Wheelahan, former President; Heinz Rothermund, Managing Director of Shell International; and Attorney Jesus Leal.
- To Engineer Nabil Zaharan,** for his indefatigable efforts, quality requirements, tender heart and creative vision which produced a Home of warmth and excellence.

In 1993, we stood in this very spot to announce the isolation of the HD gene. Back then it was the infamous but newly purchased bar El Toro Rojo. Thanks to this magnificent Casa Hogar and most especially thanks to the continued cooperation and collaboration of our families and friends, we can look forward, God willing, to a reunion here once again in the near future. We look forward to celebrating right here the CURE OF MAL DE SAN VITO.

—by Nancy S. Wexler, Ph.D.



Hospital Room for Adult Residents

Homage to Venezuelan Family and Friends: Inaugural Speech for Casa Hogar

Twenty years ago, I first walked these streets of San Luis arm in arm with Drs. Americo Negrette, Ramon Avila Giron and Ernesto Bonilla. From those initial moments in the Ciudad de Fuego, to use the evocative description of my friend, poet, artist, physician and scientist Dr. Negrette, my heart melted. And since that time my heart, soul, body and mind has been molten together with the hearts and minds of these extraordinary families and my professional colleagues.

For two decades, the struggles of these families have been my struggles; their grief and losses, my sorrow and tears; their affectionate smiles, my joy; their courage, my inspiration; their compassion, my model; their willingness to participate, my sustaining energy; their sense of humor, my daily enjoyment; their endurance, my strength; their dignity, my constant admiration and respect; their medical and humanitarian necessities, my defining mission in life. Anyone who has spent time with these families, who has been welcomed into their lives, has received such a precious gift that it can never be adequately recompensed. It has changed our perspectives on what matters in life.



Hon. John Maisto, Mayor Saadi Bijani, Dra Margot de Young



Casa Hogar Corea de Huntington, Amor y Fe

The entire world owes a debt of gratitude to Dr. Americo Negrette. He is the pioneer who for the first time correctly diagnosed the existence of Huntington's disease—or as it is popularly known, *mal de San Vito*—in these families with their strange movements and shy smiles. He initiated the family tree that we continued, which today comprises 16,000 individuals, originating in the early 1800's. He was the first to recognize that powerful new scientific tools could potentially benefit these families. His vision, his prescience, made all the subsequent work possible.

Because the families love and trust Dr. Negrette and his students and later colleagues, Dr. Ramon Avila Giron and Dr. Ernesto Bonilla, when we all three walked the streets together, the doors opened and we have been well received ever since. Dr. Ernesto Bonilla in particular deserves special thanks for being such a stalwart and dedicated colleague and friend for the last two decades.

For the first decade of our work, it was agony for our team to leave the families unattended each year. In 1991, we had the extraordinary good fortune to

encounter the miracle worker and angel, Dra. Margot Mejia de Young. In her professionalism, her intelligence, her compassion, her devotion, her courage, her expertise as a physician, her wisdom of the heart, her ferocity to defend the defenseless and her tenderness with those in pain—there is no equal.

I would also like to pay tribute to two special members of our team, Dra. Anne B. Young, Julieanne Dorn Professor and Chief of Neurology, Harvard University, and her husband, the late Dr. John B. Penney, Professor of Neurology, Harvard University. Both have accompanied me each year since 1981 and both serve vital roles here in Venezuela and in international science. Jack died tragically of a heart attack several months ago at the age of 51.

I would also like to welcome a new member of our team who is here today. Dr. Roberto Friedlander is a Venezuelan neurosurgeon/scientist who, in his studies at Harvard University, has made important discoveries leading toward new clues for developing therapies.

The families from the State of Zulia are extremely well known throughout the

world, perhaps even better known than they are here in their own land. They have appeared in *Time Magazine*, “60 Minutes,” and in other press, as well as in almost every genetics textbook worldwide. Their contribution cannot be overestimated. Let me tell you some of their accomplishments and you will immediately appreciate why the world is grateful to them and why we stand here today in their honor.

First, let me describe the disease from which they suffer. HD or “mal de San Vito,” as it is known popularly here, has been called one of the worst diseases known to mankind. It affects all aspects of mind and body. HD can attack children as young as two and the elderly as old as 80. Here in Zulia, the average age of onset is 34 years old. Symptoms are uncontrollable movements in all parts of the body, certain difficulties in thinking and often profound, suicidal depression. All symptoms are insidious at first but inevitably and implacably lead toward death in 10 to 20 years. There are no remissions, no treatments except for antidepressants and the usual cause of death is starvation or pneumo-



Dining Room

nia. The disease strikes all peoples throughout the world, and hits males and females equally. It is caused by a mistake in a single gene—or unit of heredity—and each child of a parent with the disorder has a one in two chance of inheriting it.

Zulia is the world capital of Huntington’s disease. In the state of



Day Room

Zulia, several thousand people are currently affected and 3,000 children are destined to develop the disease in the future.

It is difficult enough to be poor and hungry. But HD makes every aspect of poverty and starvation worse. Because the disease attacks in mid-life when people should be at their peak earning capacity, they have nothing to feed their families. If the men are sick, the women must tend to them and have no earning ability. Outside of the barrios, family members are stigmatized and ostracized when they attempt to find work. One young man told me, “We are the last to be hired and the first to be fired.” Children as young as 8 years old must go fishing to earn a living because they are the only ones able to go. Almost none of the children go to school because sometimes there are as many as 11 family members sick in one household for whom they must care. People

with HD need 5 or more food than someone without HD and instead they are starving and have parasites. HD affects all aspects of life and makes it worse.

And what have these families given the world? Twenty years ago, some extremely novel scientific ideas were proposed regarding how to find genes.

The theory was that if you can find a defective gene, you can figure out what is wrong with it and fix it or develop new treatments. DNA is the chemical that makes up a gene—the most powerful chemical on earth. The idea was to use small variations in DNA to search for our HD gene, like detectives following clues. When we began our research, this had never been done before and many wise people told us it was impossible or would take hundreds of years. The secret of success was to be able to work with large families.

Because the families were so collaborative, gracious and participated so fully, much to everyone’s shock!—we located the gene in scarcely 3 years!! There were celebrations all around the world—in Venezuela, the U.S., Europe, India and Japan, everywhere—because Huntington’s disease was the first disease gene to be found using these novel techniques—due to

the strength of these families. It meant that the same strategies could be used to find all genes—and so it has been! Scientists who have discovered genes for breast cancer and other cancers, heart disease, Alzheimer’s disease, Lou Gehrig’s disease, dwarfism and all other genes owe a debt of gratitude to these families. These very same families around us helped launch the Human Genome Project, an international effort



Consultation Room

which will find all of our genes by the year 2003!

Again, thanks to the help of these families in the State of Zulia, and an additional decade of arduous work, we finally isolated the actual Huntington’s disease gene itself, and discovered its tiny but lethal mistake. Now we know the abnormal protein it produces. We can even put the human gene into animals and cells so we can understand its effects better and test new treatments as they are developed. The Hereditary Disease Foundation, for which I have the privilege of serving as President, has recently launched the Cure HD Initiative, a major effort to accelerate the search for treatments and cures for this devastating disease.

The gap between the enormous gifts these families have given the world and

their tremendous needs was painful to contemplate. As Margot has described, the odyssey began almost a decade ago to build the Casa Hogar which has now been so joyously and efficiently completed, thanks to all the people assembled here.

Yesterday I had one of the best experiences of my life! I had the privilege of walking with the First Lady of the State of Zulia through the Casa Hogar. It is magnificent—as you will see! And the Sra. Gladys de Arias Cardenas is personally responsible for finishing the construction in record time, placing every bed and every tree. She accomplishes all she does with grace, hard work and compassion. From the rooms for children to the beautiful indoor plaza, everything has warmth and comfort. We are all enormously fortunate to enjoy such a remarkably talented, intelligent and committed First Couple of the State.

Governor Francisco Javier Arias is a man of his word and his principles. He keeps his promises. He is committed to aiding those in poverty and he accomplishes what he sets out to do. He understands that good health is as fundamental to the economic survival of the nation as oil.

How do I thank my friend and colleague, economist Mayor Saadi Bijani? The Governor and he have helped our Project each year by providing transportation and protection which has benefitted our research immeasurably. Saadi has been always accessible and responsive and we are immensely grateful that the largest concentration of families suffering from HD are under his careful watch.

I would particularly like to extend my profound appreciation to the following organizations and individuals:

1. **The U.S. Consulate** which, for the past 20 years, has assisted our collaborative Venezuelan and U.S. Team by facilitating the scientific

and humanitarian aspects of our research Project. Particularly when the consulate was still in Maracaibo and even now with one consulate in Caracas, we are continuously grateful for the help of the Consulate. I am delighted to make the acquaintance of The Honorable John Maisto, who has immediately grasped the special nature of our one large family—from Venezuela to the U.S. I also wish to thank my dear friend and brother Mr. Jorge Quintero, United States Consular Agent, Maracaibo, Venezuela, for his wonderful help and friendship over the last two decades. Thank you also to Cynthia Echeverria, Science and Technology Officer.



Children’s Room

2. **Public Works of the State**, for their dedication and professionalism in constructing a clinic of utility and elegance, especially Engineer Lenin Cardozo.
3. **FUNDASALUD:** When Dr. German Valero, Personal Secretary of the Governor and previous Secretary for Health, promised us that the Casa Hogar would be