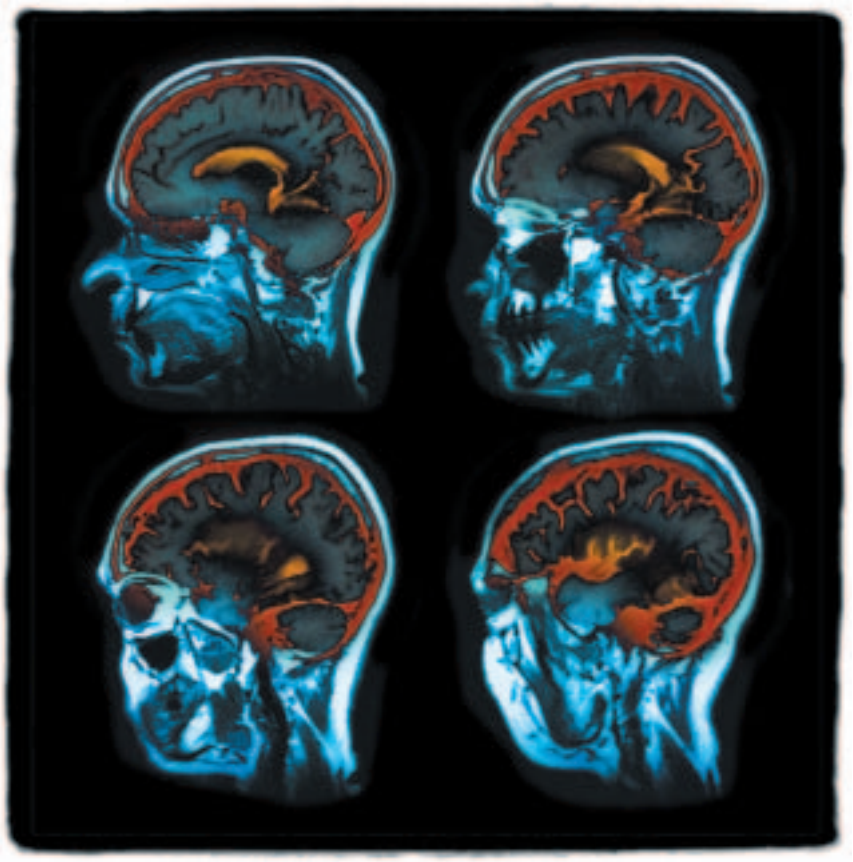
THE marker

Huntington's Disease Society of America



HDSA Research Update 2001

PROGRESS IN RESEARCH

HD KIDS

LIVING AT-RISK

CARE

a message *from*

In the 1960's, activist and entertainer Woody Guthrie was well known throughout the world, but the disease that ended his life was not. One of the greatest challenges that faced Marjorie Guthrie when she founded the organization that was to become the Huntington's Disease Society of America was the fact that HD was a "family" secret, misunderstood and often misdiagnosed. Educating healthcare professionals, elected officials and the general public about Huntington's Disease, and the challenges faced by those who live with it, has always been an integral part of HDSA's mission.

I am very pleased to report to you the success that HDSA has achieved this past year in increasing awareness on all levels through a new public awareness program. Many of you have seen the eye catching ads for HD and HDSA that have appeared in major national magazines, including *Business Week*, *Newsweek*, *Bon Appetit* and dozens of others, thanks to the generosity of an in-kind donation program with a major media placement firm. Public Service Announcements (PSAs) have aired in the top 25 radio markets in the US and represent a gift of more than $306,000 of free radio time. Millions of people who may never have heard of HD now have a greater understanding of the devastation it causes and our optimism that a cure is on the way.

In our Nation's Capital, HDSA advocacy efforts have been unflagging. As a result of our awareness building efforts, HDSA was invited by Connecticut Senator Christopher Dodd in March to testify before his Senate Biotechnology caucus. In May, HDSA was invited to partner with the National Institute of Neurological Disorders and Stroke (NINDS) in a pilot project that was reported in the last issue of *Toward a Cure*. In June, HDSA appeared at a Health Policy Briefing, hosted by the National Health Council, along with several other voluntary health agencies, to bring issues of concern to the HD community to congressional staffers. Our dedication to increasing awareness about this deadly disease, and sharing our message of hope through research with our elected officials, remains a priority as we move forward in this congressional session. Their understanding of the multiple issues that face HD families as they battle this progressively degenerative disease can lead to increased support for HD research and new legislation on issues of importance to our HD families and friends.

Through these advocacy efforts and the recent amazing advances in HDSA sponsored research, scientists worldwide now view HD as a "model" for other neurodegenerative and hereditary diseases. HD is now being linked to Parkinson's disease and ALS (Amyotrophic lateral sclerosis) to advance awareness in ads created specifically by those organizations.

Truly, the answers we find for Huntington's Disease may well serve as the key to effective therapies or even cures for all neuro-degenerative and/or hereditary disorders.

The HDSA Therapeutics Initiative will bring the research, conducted by our HDSA Coalition for the Cure investigators and Grant and Fellowship recipients, to clinical trials more rapidly. But to continue these intensive research efforts, HDSA must pledge even more to fund the needs of our investigators. To that end, HDSA launched phase two of *Generation 2000: Fulfilling the Promise* in an effort to raise $25 million for HD research over the next five years. The answers are close at hand. I ask that you consider making a generous donation to this research campaign today. Every dollar contributed will be matched by the *Research Matching Gifts Challenge Fund*. Won't you please join with me in helping to *make this the last generation with HD?*

Sincerely,

Don King, Ph.D.

The Marker is an official publication of the Huntington's Disease Society of America, Inc.
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The Marker, a periodical of the Huntington's Disease Society of America, Inc., is published twice annually. Its purpose is to provide information and opinion and to relay items of interest to individuals with Huntington's Disease and their families, health care professionals, and interested friends and supporters.

HDSA, Inc. is a national not-for-profit organization founded in 1986 to help individuals with Huntington's Disease and their families.

The Society is a member of the National Health Council, the National Foundation for Brain Research, the International Huntington Organization, the National Organization for Rare Disorders, the National Voluntary Health Agencies, the Alliance of Genetic Support Groups and the Independent Sector.

The Huntington's Disease Society of America meets all nine standards of the National Charities Information Bureau.

About the front cover:
Different views of brain imaging.

a message *from*

As we enter this season of giving, let us pause to reflect on all that we have been able to accomplish through the generosity and dedication of our HD families, friends and corporate supporters.

We began 2001 auspiciously with the announcement that phase one of *Generation 2000 - Making This the Last Generation with HD* had raised more than $2.7 million for HDSA research initiatives. This more than surpassed our original goal of $500,000 and even our dream of raising $2 million. Building on the incredible momentum of phase one, HDSA launched phase two - *Fulfilling the Promise* - in January 2001 with a goal to raise $25 million for HDSA research programs and initiatives over the next five years. Spurred on by the success of HDSA's original Matching Gift Fund, several HD families came forward to create a new matching fund for *Fulfilling the Promise* that would challenge our friends and families to increase their level of support in order to attain our $25 million goal. This *Research Matching Gifts Challenge Fund* currently stands at $2.5 million and all gifts made to *Generation 2000: Fulfilling the Promise* will be matched dollar for dollar.

As part of the annual leadership conference held in March, HDSA leaders met with their elected representatives in Washington, DC for a *"Day on the Hill."* Advocacy training was conducted by McDermott, Will and Emery with additional follow up training for "home office" visits and continued contact with their elected representatives.

In May, the National Institute of Neurological Disorders and Stroke (NINDS) invited HDSA and ALSA (Amyotrophic Lateral Sclerosis Association) to partner with them on a $1.2 million pilot project aimed at developing assays that would be tested against 1,000 FDA-approved compounds for possible therapies. This historic collaboration coincided strategically with HDSA's invitation for Coalition for the Cure researchers to advance projects through the new HDSA Therapeutics Initiative that will use high-throughput screens to assess potential therapeutic applications.

In July, at the 16th Annual HDSA Convention, the much anticipated *Journal of Hope* was presented to those in attendance with a direct mail follow up to those who contributed but were unable to attend the convention. More than 350 inspiring and oftentimes poignant messages accompanied the listing of the more than 2,400 individuals, families and corporate friends who made phase one of *Generation 2000* an astounding success.

On September 11th our nation faced its gravest threat to our freedom yet known. On that sunny Tuesday morning, forces that do not believe in the very freedom that we take for granted attacked us. Many innocent people were killed and a nation mourned the loss of those lives and a way of life that we will never know again. In the intervening months, each of us has picked up the pieces of our lives and, as our President asked, done our best to return to a normal routine. I, for one, plan to honor our fellow Americans lost

on that cataclysmic Tuesday by remembering them with gratitude, living each day with hope, and continuing my work until it is done - until a cure is found for Huntington's Disease.

Today, as we enter the season of thanksgiving and renewal, I invite you to join with me to give a gift of hope to your family, friends and associates that will last for years to come. The Christopher Radko Company has created a limited number of very special mementos that symbolize our hope for a future free of Huntington's Disease. Every dollar raised through the *Gift of Hope* campaign will go to HDSA's research programs and initiatives. Personal messages will accompany keepsakes that have been purchased for family members, friends and associates. Please take a few minutes to read about our partnership with the Christopher Radko Company on page 33 and please consider giving a *Gift of Hope* this year. We have come so far in the last five years. We cannot give up now. Together, we can *make this the last generation with HD*.

Sincerely,

Barbara Boyle

Barbara T. Boyle

table *of*

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Our special thanks

to

AstraZeneca

for the

Community Service Grant

that has made this publication possible

Fighting Back Against HD

by Christopher Ross, M.D. Ph.D.

This past year has seen great progress in the war against HD. Scientists in laboratories and clinics worldwide have collaborated to advance our basic knowledge of HD, and are now beginning to translate this understanding into the development of treatments. We hope that 2001 will be seen as the year in which we turned a corner and went from fighting a purely defensive battle to directly attacking HD.

The first goal in war is to "know your enemy." This year advances were made on two fronts. The first provided an increased appreciation that HD may kill neurons in the brain by interfering with the activity of key genes that are necessary for neuronal survival. Initial work was performed in the laboratories of HDSA Coalition for the Cure investigators, Drs. Jang-Ho Cha and Leslie M. Thompson, and of HDSA Coalition for the Cure Steering Committee member, Dr. Kurt Fishbeck. Our own laboratory at Johns Hopkins University followed up on some aspects of this preliminary work and uncovered evidence that a specific mechanism may interfere with key genes. We found that the expanded polyglutamine stretch in the huntingtin protein may interact directly with a short polyglutamine stretch in a key cellular molecule called CBP. The function of CBP in cells is to assist the gene activity of many other genes including some critical for neuronal survival. This work was published in the preeminent journal *Science* this past spring.

At the same time, another group of Coalition investigators lead by Dr. Elena Cattaneo, in collaboration with Dr. Michael Hayden, focused on a closely related aspect of regulating gene transcription. They found that the mutation in the huntingtin protein interferes with the production of an important cellular growth factor called brain derived neurotrophic factor or BDNF. This mechanism could involve the CBP effect described above. But another interesting possibility is that a function of normal huntingtin might be to increase the levels of BDNF activity. If so, then the mutation that causes HD could actually be interfering with the normal function of huntingtin to help protect neurons.

These studies suggest that one approach to treating HD may be to find drugs that enhance gene activity. Several members of the HDSA Coalition for the Cure, as well as other labs, are now exploring this approach. Dr. Leslie Thompson's group has striking evidence that one of these drugs can ameliorate the effects of the huntingtin mutation in a fruit fly model of HD. This work is currently in press in *Nature*.

The collaborative work of these investigators serves as a perfect example of the significant advances that can be achieved when scientists share ideas and approaches through a cooperative research program like the HDSA Coalition for the Cure.

A second front in our battle with HD examines how the mutation in huntingtin could kill nerve cells. Dr. Ron Kopito, a past member of the HDSA Steering Committee, has worked on the basic cellular responses to protein aggregation. This has proven to be an important area in HD, since we know that the polyglutamine protein accumulates inside nerve cells. These aggregates can disrupt the function of a key cellular protein complex called proteasome. Proteasomes are normally responsible for clearing misformed proteins from the cell and also for regulating the levels of certain proteins which are involved in cell survival. Proteasomes would normally clear proteins, including huntingtin, from the cell when their function was no longer needed. Dr. Kopito's laboratory has found that when huntingtin has the polyglutamine expansion mutation that causes HD, the huntingtin aggregates disrupt the function of the proteasome. He has used elegant cell biological techniques to make the cells with disrupted proteasome function actually glow so they could be identified in cell cultures.

An exciting aspect of this work is that this could be a general mechanism for other degenerative diseases besides HD.

Since both Parkinson's disease and Alzheimer's disease involve abnormal protein aggregation, it is possible that they also involve inhibition of the proteasome. If this is true then this will provide insights that will help scientists to apply an understanding of more common diseases like AD and PD to the study of HD. Dr. Kopito's work was also published in *Science* this past spring.

One of the reasons HD research has progressed so rapidly has been the availability of several different kinds of "models" of the HD disease process. These models involve using the abnormal HD gene to replicate some feature of HD in the laboratory so it can be studied. These models include biochemical models, cell models, invertebrate models (such as *Drosophila* models) and transgenic mouse models.

This year also marked the development of an important partnership between one of the National Institutes of Health (NIH) and HDSA (with other private foundations). This historic collaboration coincided with the initial funding of an HDSA "Therapeutics Initiative" that would use these disease models in the development of therapeutics. The partnership with NIH will greatly accelerate this process. The National Institute of Neurological Disorders and Stroke (NINDS) announced this pilot program, that would fund HD researchers using their models of the HD disease process, to test for drugs that might slow the effects of HD. Several projects were funded this year. Each will be testing a thousand different compounds that NINDS has identified as initial targets for study. This exciting example of the potential for collaboration between private foundations such as HDSA and the NIH should speed the development of candidate compounds that might be developed into effective drugs.

Finally, there could be no treatment for HD without studies in human patients. The largest study of therapeutics in HD to date was completed this year. This multi-center collaborative study, sponsored by the Huntington Study Group, involved two agents, coenzyme Q_{10} and remacemide. The CARE-HD clinical trial involved 340 individuals with HD over thirty months. A report on CARE-HD may be found on page 16.

Based on what we have learned so far, we are very hopeful that the studies in HD models will give us additional candidate compounds that may be used for drugs, and that the next series of studies in HD patients will be designed using evidence provided by these genetic models. Thus, we believe 2001 will be marked as the year in which we began to truly fight back against HD, to attack the disease at its cellular source, and made significant strides toward finding a cure for HD.

About the author: Christopher Ross, M.D. Ph.D. is a Coalition for the Cure investigator at Johns Hopkins University School of Medicine. His work on polyglutamine pathogenesis was published in the journal Science *in March 2001. A synopsis of this work appears on page 8.*

WFN and IHA Convene in Copenhagen

The 19th International Meeting of the World Federation of Neurology (WFN) Research Group on Huntington's Disease and the 14th International Meeting of the International Huntington Association (IHA) were held in Copenhagen from August 25-28, with the latter group continuing their meeting until the 30th in Elsinore, Denmark. While most of the sessions were held separately, the two groups did collaborate for some sessions and social events, thereby enabling a cross-fertilization of ideas and identification of issues.

The WFN meeting, consisting primarily of doctors and other health professionals, highlighted basic and clinical research that has occurred since the 1999 meeting at The Hague, in the Netherlands. The IHA meeting, composed predominantly of lay delegates from various HD societies throughout the world, focused on genetic testing issues, family services, and caregiver concerns.

Dr. Oliver Quarrell, a representative from the WFN, reported to the IHA on the latest work being discussed by the professional community. The doctors and researchers are beginning to fill in new findings that create a coherent story, leading from:

genes fi proteins fi cell biology fi brain fi signs and symptoms fi therapies

As highlighted in recent HDSA publications, Dr. Quarrell noted that proteasomes and chaperone genes continue to be an active avenue of investigation in HD laboratories. He reported that scientists have made a new HD model by inserting a virus carrying the gene into one side of a rat brain, thus allowing researchers to compare changes that occur within the same animal.

IHA meeting highlights included sessions on understanding challenging behavior in HD, an exploration of the dental care needs of HD patients, as well as investigations and surveys into assessing stress and risks experienced by caregivers and long-term care facility staff. An overview was also given on neural transplantation work that has occurred in recent years.

HDSA staff had the opportunity to interact with both scientists as well as colleagues from other nations, who face common issues in Huntington's Disease. While not all issues (such as health insurance) are shared by each country, the participants were unified in their goals for improving care for HD patients now and eradicating HD for people living at-risk.

HDSA Coalition *for the Cure*

The Coalition for the Cure is an innovative program created to study Huntington's Disease with a goal of discovering treatments and therapies. These HDSA-funded scientists, representing 17 labs worldwide, investigate targeted research areas and then meet twice yearly to review the results as a group. New research is then focused on the most promising results. The Coalition targets four basic areas for research: Biochemistry, Cell Biology, Cell Models and Animal Models. In 2000, the HDSA National Board of Trustees voted to include a Therapeutics Initiative in the Coalition's plan of work in order to move promising research into clinical trials more quickly.

Once a year, members of the Huntington Study Group (HSG) meet with Coalition scientists to discuss the most effective ways to move potential therapies from the laboratory into clinical trials.

The HDSA Coalition for the Cure is made possible by the following Founding Leadership Gifts: The Anonymous Fund for a Cure, The Helen Becker Memorial Research Fund, The Woody and Marjorie Guthrie Research Fund as well as The Kent Westbrook Endowed Research Fund. In 1999, HDSA committed $2.1 million to the HDSA Coalition for the Cure. In 2001, total research funding will exceed $4 million.

The HDSA Coalition for the Cure consists of ongoing research projects. Below are updates to that current research.

Gillian P. Bates, Ph.D.

Kings College London, London, England

Slice Culture Assays to Assess Approaches Aimed at Modifying Polyglutamine Aggregation in HD and the Characterization of Transgenic Models Designed to Dissect the Molecular Basis of the Phenotype

To facilitate the testing of compounds, which are potentially therapeutic in HD, brain slice tissue cultures have been successfully made from R6/2 transgenic mice. It is now possible to culture this tissue for the entire duration of the disease process. This work was done by Donna Smith. Researchers then used this "organotypic" slice culture to discover the proper dosage for the compound, Congo Red, which has been shown to inhibit the formation of huntingtin aggregates by Dr. Erich Wanker in Berlin. In this case, it was determined that the highest concentration tested was not the optimal dosage.

Investigations are also being made into the comparative effect of huntingtin aggregates when they form outside and inside brain cell nuclei. This work was performed by Caroline Benn. The study is not yet complete, but from the analysis conducted to date, the onset of symptoms appears to correlate with the appearance of nuclear aggregations. The support of HDSA is crucial to the completion of the generation and analysis of the mouse line needed to bring this project to completion.

M. Flint Beal, M.D.

Weill Medical College of Cornell University, New York, NY

Bioenergetic Defects, Oxidative Damage and Therapeutic Strategies in Transgenic Mouse Models of Huntington's Disease

This research project investigates the various ways in which mutant huntingtin affects energy production and use in the brain. A unique type of magnetic resonance imaging (MRI) was used to measure phosphocreatine, a marker for energy production in the brain. In mouse models expressing the Huntington gene, the levels of this marker were abnormally elevated. In other studies, it was found that glucose utilization is also elevated in transgenic HD mice. The role of this increased energy use in the progression of the disease is still not fully understood.

In additional research into energy use and its role in HD, the functioning of mitochondria, taken from transgenic mice, was closely studied. This has led to further evidence of a direct effect of the HD mutation on mitochondrial function.

Nancy Bonini, Ph.D.

University of Pennsylvania, Philadelphia, PA

Drosophila Models of Polyglutamine Repeat Disease

New research using fruit flies has revealed that increasing levels of chaperone genes assist mutant huntingtin proteins in refolding into a non-toxic form, even if the mutant protein has been expressed for a long time. Surprisingly, the introduction of the chaperone genes appears to stop the expression of the mutant protein in neighboring cells. This has tremendous importance for the development of a treatment for HD in humans. The study is being extended to see if the refolded mutant proteins then function normally. This is being done by expressing the disease genes in eye cells from fruit flies, which makes them blind. The goal is to discover whether the function of the cells is restored when the disease is suppressed.

Additional research includes screening for novel types of genes that are not involved in disease progression, genetically crossing them and then looking for mutations that stop disease progression. It is hoped that these new genes will define additional pathways that will serve as drug targets in the treatment and cure of Huntington's Disease. The HDSA Coalition for the Cure has helped to speed progress toward treatment of Huntington's Disease by finding novel pathways and treatments.

David R. Borchelt, Ph.D.

Johns Hopkins University School of Medicine, Baltimore, MD

Gene Expression in Models of Huntington's Disease

Two lines of transgenic mouse models, each with a different CAG repeat disorder (HD and DRPLA), are being compared to learn more about them. Researchers hope to identify what is common to both and to distinguish genetic differences that may be specific to each disorder. Much has already been learned about the neuropathological changes that are common to both and which portions of the mutant genes appear to trigger these changes.

In other research, gene chips have been used to test the hypothesis that mutant huntingtin inappropriately binds to other proteins (factors) that serve to regulate the expression of genes, diminishing the ability of the factor to do its job. These costly gene chips allow the expression of thousands of genes at one time. This research has revealed that mutant huntingtin in the nucleus does not disrupt the expression of the majority of genetic information. The next step in this research is to analyze the mouse models in earlier stages of the disease and thus create a pattern of evolution of the gene changes that do occur through the course of the disease. The ultimate hope is to identify a set of genes that share common regulatory elements, pointing towards a dysfunction of a specific regulatory factor, which can then be targeted for treatment.

Elena Cattaneo, Ph.D.

University of Milano, Milan, Italy

Role of Huntingtin and its Contribution to HD Pathology

While the function of normal huntingtin in the brain is not yet fully understood, this research has identified one role, which is to regulate the production of BDNF, a protein essential for the survival of neurons in the brain. Since this activity is not supported by mutant huntingtin, neurons are vulnerable to damage. As the transcription of the BDNF gene is impaired, lower levels of this neuron-protecting protein result. Researchers are optimistic that understanding this process will lead to the development of therapies to boost the activity of normal huntingtin or to increase levels of BDNF in the brain.

This research has broad implications. HD is recognized as a "model" for other neurodegenerative diseases. Similar combinations of a mutant gene and the loss of essential proteins may play a role in Parkinson's, Lou Gehrig's (ALS) and Alzheimer's disease.

Jang-Ho Cha, M.D., Ph.D.

Massachusetts General Hospital, Boston, MA

Transcriptional Dysregulation in HD

While all cells in the body have the same genes, or DNA, cells express different sets of proteins. The proteins that a cell expresses determine in a large part what functions that cell can perform. With the goal of determining how mutant huntingtin interferes with the normal transcriptional program of susceptible neurons, three lines of research have been pursued.

The first approach is to use a microarray screen to analyze the pattern of mRNA expression in nerve cells, from both cell cultures and HD mouse models, that have been subjected to toxic "insults" that have been postulated to play a role in HD.

The second approach involves investigating how mutant huntingtin decreases specific gene expression. To do this, a

"reporter" molecule will be attached to a gene which is known to be decreased in HD brains and the activity of that gene will be tracked.

The third approach involves examining the interaction of mutant huntingtin with molecules that are known to be involved in "transcription" (the normal pattern of gene expression encoded in DNA), using neuronal cell lines provided by Dr. Leslie Thompson (UC Irvine) and Dr. Erik Schweitzer (UC Los Angeles) which can be induced to express either the normal or mutant form of huntingtin.

Stephen W. Davies, Ph.D.

University College London, London, England

An Ultrastructural and Molecular Characterization of Neuronal Cell Death in Huntington's Disease

Substantial progress has been made in understanding the changes that take place within the nucleus of neurons with the HD gene. The earliest aggregates of mutant huntingtin in these nuclei are found in the Cajal Body (CB), a subnuclear structure which appears to be associated with the genetic transcription process. To further investigation into CBs, new advanced skills and techniques are being pursued.

In related research, it has been shown that the ends of neuronal cells, known as dendrites, atrophy and degenerate in neurons with the HD gene. By collaborating with Dr. Rene Hen and graduate student Ai Yamamoto of Columbia University, and Dr. Peter J. Detloff of the University of Alabama, progress is being made in determining the extent to which the neuronal dysfunction and degeneration can be reversed.

Marian DiFiglia, Ph.D.

Massachusetts General Hospital, Boston, MA

Early Events in HD Pathogenesis

Cell death in HD may be caused by the diversion of critical cell energy to the process of excess protein removal by autophagosomes, which are organelles found within cells. This may explain the deficits of energy metabolism in the brain of HD patients. To test this hypothesis, the huntingtin protein was modified by removing a sequence of prolines, which are naturally occurring amino acids, located next to the polyglutamines. This manipulation dramatically reduced the number of autophagosomes. Discovering a means to reduce autophagosome formation produced by mutant huntingtin could be therapeutically beneficial. A high-throughput drug screen is being developed for drug testing based on these observations.

In other research, it was observed that both normal and mutant huntingtin undergo the same series of protein cleavages in the brain. Identifying the specific proteases that cause this huntingtin cleavage is significant, because specific protease inhibitors can block certain proteases. The use of protease inhibitors could be an effective way to reduce the accumulation and harmful effects of mutant huntingtin in neurons. HDSA continues to support this basic research into the causes of cell death in HD while also funding the use of this knowledge in the pursuit of therapies through drug screening assays.

Robert M. Friedlander, M.D.

Brigham and Women's Hospital, Boston, MA

Mechanisms and Modulations of Caspases in HD

Over the past year, significant advances have been made in understanding the pathways that are abnormally activated in HD, as well as therapeutics to slow the progression of the disease in transgenic mice. Evidence was produced last year that the activation of the caspase-1 enzyme triggers cells dysfunction and cell death. HD mice treated with a caspase inhibitor experienced a delay in the onset of symptoms and were stronger and survived longer. The first caspase inhibitor tested proved too toxic for human clinical trial.

However, another drug candidate has been identified as a caspase-1 inhibitor. Minocycline, a common antibiotic, which has had FDA approval for over 30 years, delays the progression of HD in HD mice and prolongs their survival. It has also been shown to penetrate the brain when given orally, which is an important prerequisite for a drug to be effective as an HD therapy. Currently, there are applications for governmental funding to carry out human trials of minocycline for HD.

In additional research, it has been shown that minocycline also acts as an inhibitor of caspase-3 and another protein called iNOS, which activates the production of damaging free radicals in the brain. This research on minocycline may lead to the first therapy to be effective in slowing the progression of HD.

J. Timothy Greenamyre, M.D., Ph.D.

Emory University, Atlanta, GA

Mechanisms of Mitochondrial Dysfunction in HD

The central objective of this research is to discover how mutant huntingtin kills the brain cells that die in HD. It has been shown that normal mitochondria can be induced to behave abnormally by exposing them to mutant huntingtin. In ways that are significantly different from normal mitochondria,

HD mitochondria lose their normal electrical potential and "spill" calcium and other chemicals inside the cells, causing neuronal damage and cell death. Details of how this occurs are currently being pursued, using mitochondria from the brain cells of transgenic mouse models developed by other Coalition scientists. The Coalition has provided the funds to design and purchase an instrument with which the researchers can - for the first time - simultaneously measure calcium, mitochondrial membrane potential and pH. Preliminary results support the contention that HD mitochondria behave abnormally.

The support of the Coalition has allowed this lab to add Claudia Test, M.D., Ph.D., who has developed a technique of "organotype slice culture" in which brain tissue can be kept alive for months at a time. Using this technique, it will be possible to examine how abnormal mitochondrial functions affect cellular inclusions and nerve cell death and also look for ways to protect against the formation of inclusions.

James F. Gusella, Ph.D.

Massachusetts General Hospital, Boston, MA

Multi-Level Approach for Discovering Novel HD Interventions

Investigations have been performed that pursue a multi-level approach to preventing or slowing the progression of HD. The first uses neuronal cells produced by two members of the Coalition, Drs. Marcy MacDonald and Elena Cattaneo, to replicate a mechanism found in roundworm models. This mechanism is one where a double-stranded RNA copy of a gene prevents expression of a normal double stranded DNA gene. It is possible that this mechanism might be used to prevent the expression of mutant huntingtin.

Another investigation is a pilot screening of 1,000 compounds already approved by the FDA to determine if any prevent or promote protein clumping in cells where mutant huntingtin has been expressed. Any compound(s) that affect clumping will be tested in neuronal cells and transgenic mouse models in collaboration with Dr. MacDonald.

A third approach focuses on slowing or preventing the progression of mutant huntingtin through the identification and study of genes and gene variations that appear to affect the age of onset in HD gene carriers. This study uses genetic samples from persons with HD where the age of onset is known precisely. To date, one gene, which forms part of the receptor for glutamate, has been shown to be responsible for significantly earlier than expected onset of HD. As these investigations yield new clues, they will be pursued full-force to determine whether they can lead to an effective therapy.

Michael R. Hayden, M.D., Ph.D.

University of British Columbia/Centre for Molecular Medicine and Therapeutics, Vancouver, BC, Canada

Assessment of *in vivo* Caspase Inhibition on the Pathogenesis of Huntington's Disease in YAC Transgenic Mice

Caspase enzymes cleave the Huntington gene into small fragments. It had been thought that only the break up of mutant huntingtin had an effect on the progression of the disease. Surprisingly, it is now known that normal huntingtin is neuro-protective and that when normal huntingtin undergoes cleavage, it can no longer protect cells. This indicates that cleavage of both normal and mutant huntingtin by caspases may play a role in cell death.

Caspase inhibition has promise as a potential therapeutic for HD, by preventing the cleavage of both normal and mutant huntingtin. YAC transgenic mouse models are being used to test cell permeable caspase inhibitors to see whether these drugs influence the course of the illness. Collaboration of Coalition members supported the development of this mouse model, which has been utilized by investigators worldwide.

Steven M. Hersch, M.D., Ph.D.

Massachusetts General Hospital, Boston, MA

Neuropathology of HD Transgenic Mice

It now appears that normal huntingtin may play a role in protecting brain cells from death. Research is being performed to determine if increasing the levels of normal huntingtin protein in the brain may counteract the negative effects of mutant huntingtin.

Completed investigations into the potential therapeutic use of creatine in HD, using transgenic mice, have generated a five-year grant from the NIH for a human trial of creatine, **CREST-HD**, which will begin enrolling in a few months. Investment in the Coalition for the Cure has led directly to the government increasing its own investment in HD research. Additional compounds targeted at preventing brain cell injury and death are now being tested in transgenic mice.

Marcy MacDonald, Ph.D.

Massachusetts General Hospital, Boston, MA

Early Molecular Events in Huntington's Disease

Understanding critical early changes in HD, in cells that are not yet gravely sickened,

may offer a route to an intervention that can thwart ongoing disease triggers in individuals that carry the HD mutation.

By comparing the brains of normal mouse models with transgenic Hdh knock-in mouse models at different ages, progressive changes have been delineated which strongly suggest that this trigger is an entire mutant protein and not a toxic fragment as previously thought. The earliest changes noted in very young Hdh^{Q111} mutant mouse models show an altered formation of full-length mutant huntingtin, long before the appearance of intranuclear inclusions and amyloids.

It appears that the origin and formation of a mutant fragment does not alter the death of striatal neurons carrying the HD defect. One hypothesis is that toxic fragments may play a role in the death of already sickened cells as the disease progresses.

Currently, gene products and agents are being assessed to determine whether any of these modify the process triggered by full-length mutant huntingtin in the Hdh knock-in mice and in cultured striatal cell lines. This research complements the work of other Coalition investigators. Through this continued collaborative effort, an effective therapeutic will be developed.

Richard Morimoto, Ph.D.

Northwestern University, Chicago, IL

Studies on Polyglutamine Expansions in *Caenorhabditis Elegans*

The nematode (worm), C. *elegans*, has proven to be a useful model in the study of HD. CAG expansions in the worm result in the appearance of aggregates in their body wall muscle cells. These repeats appear early in life and affect the development and lifespan of the worm. It appears that an expression of only 19 CAG repeats causes neuronal cells to exhibit hypersensitivity to polyglutamine-containing proteins and that 40 or more CAG repeats has a direct effect on lifespan. The extensive genetic analysis of this model has allowed research into the effect of CAG repeats on the functioning of specific subsets of cells - for example, those used in egg laying or for chemosensory purposes.

Use of C. *elegans* has led to the identification of cellular defense genes ("chaperone" genes) that prevent the aggregates from appearing. It is also used to screen potentially therapeutic small molecule drugs which are those that can potentially cross the brain cell membrane in humans.

Christopher A. Ross, M.D., Ph.D.

Johns Hopkins University School of Medicine, Baltimore, MD

Glutamine Repeat Interactions in HD Pathogenesis

Researchers believe that mutant huntingtin must interact with other proteins within the cell to cause toxicity. It now appears that mutant huntingtin "hijacks" an important cellular protein called CBP, leading to disruption of basic cellular functions. CBP is a key molecule in regulating the activity of genes necessary for neuron survival and normal functioning.

These experiments have shown that huntingtin and CBP interact only when the huntingtin protein has the HD mutation. This interaction has been found in cell models, mouse models and in HD post mortem brain tissue. In the cell models, the interaction with CBP is a major component in the cellular toxicity caused by mutant huntingtin. Results of these collaborative studies were published in the journal *Science* in March 2001. The data to date indicates that this is an important clue to understanding HD. The kinds of interactions found in this study can be used to screen possible therapeutics. High-risk, high yield experiments like these require the support of a source such as the HDSA Coalition for the Cure.

Erich Wanker, Ph.D.

Max-Planck Institute for Molecular Genetics, Berlin, Germany

Identification of Huntingtin-Cleaving Proteases and Characterization of Neuronal Inclusions in HD Transgenic Mice and Patients

The expression of toxic fragments of mutant huntingtin *in vitro* and *in vivo* have resulted in increased aggregate formation and toxicity. This has led to a working hypothesis that generation of these fragments of mutant huntingtin are an important step in Huntington pathology.

Using a high-throughput screening assay, pools of cloned human brain cells were used to screen for proteases that cause the mutant huntingtin to cleave into the fragments which may trigger protein clumping. Among the 1,056 pools, 50 tested positive for an increase of aggregation over a background level. Clones of these pools will be tested further in mammalian cells. The screening will also attempt to identify other factors that are biologically relevant in HD.

Huntington Study Group Research Study Update

Exciting new initiatives designed to obtain information regarding the symptoms and progression of Huntington's Disease (HD) continue to be developed by the Huntington Study Group (HSG). The HSG is funded in part by a yearly grant from the Huntington's Disease Society of America.

At-Risk Research Studies

In order to develop clinical trials aimed at postponing or preventing the onset of HD, the accuracy of measures used to detect the onset of the disease must be studied in "at-risk" individuals. The HSG has developed two observational (no drug is given) research studies: **PHAROS** (**P**rospective **H**untington **A**t **R**isk **O**bservational **S**tudy) and **PREDICT-HD** (Neurobiological **Predict**ors of **H**untington's **D**isease).

PHAROS

This study, launched in July 1999, is seeking men and women between the ages of 30 and 55 years old who are at-risk for HD. Research participants will be examined every nine months for a minimum of three years. Testing for the HD gene will be performed at the beginning of the study, but individual results will never be revealed to either the research participants or the investigators. The **PHAROS** study is currently enrolling participants who have no definite signs of HD and who have never been tested for the HD gene. Enrollment ends in November 2001. *If you are interested in participating in* ***PHAROS*** *please call the HSG today.*

PREDICT-HD

PREDICT-HD, which recently received funding from the National Institutes of Health (NIH), is a parallel study developed by the HSG to define the earliest neurobehavioral and radiographic markers of HD. This study will also recruit individuals between the ages of 30-55 years. Participants will be examined regularly for a minimum of three years, and will undergo brain imaging (MRI) as well as clinical evaluations. *Enrollment in* ***PREDICT-HD*** *will begin in January 2002 for participants who have no definite signs of HD but already know they carry the HD gene.*

Therapeutic Trials in Progress

MINO (**MINO**cycline Dosing and Safety in Huntington's Disease) is a multicenter double-blind, placebo-controlled study of Minocycline. Minocycline is a Federally approved antibiotic drug that may have anti-cell death and anti-oxidant properties. The study is designed to assess the safety and tolerability of Minocycline. This study will recruit 63 participants who are 18 years of age or older and who have early manifest HD. *Research participants are currently being recruited in the US and Canada for this trial.*

Completed Therapeutic Trials

The **RID-HD** (**Ri**luzole **D**osing and Safety in **H**untington's **D**isease) trial was designed to assess riluzole's short-term impact on the motor, cognitive, and behavioral symptoms of HD, and to study the safety and tolerability of riluzole. Preliminary results were presented by Dr. Frederick Marshall at the 19th Annual International Meeting of the World Federation of Neurology in Copenhagen, Denmark, in August 2001.

How do I get involved?

If you are interested in learning more about the HSG or any of these studies and a participating HSG site near you, please contact the HSG by calling our toll-free number 1-800-487-7671 or logging on to our web site at www.huntington-study-group.org for more information.

GRANTS & FELLOWSHIPS

HDSA GRANT AND FELLOWSHIP RECIPIENTS 2001-2002

The second arm of HDSA's research initiative is the Grant and Fellowship program, which provides essential funds to research projects in their early stages of development. This "seed money" allows HDSA grant recipients to advance their research from preliminary data to a mature project that will then be eligible for greater monetary support from larger national agencies such as the National Institutes of Health. The HDSA Grant program provides grants of up to $100,000, payable over two years if renewed. HDSA Fellowships were created to expand the pool of young investigators who are interested in studying Huntington's Disease. HDSA Fellowship awards can total up to $80,000, payable over two years upon renewal. Initiative Grants are one-time awards that allow a scientist to investigate or develop a project that has little data. An Initiative Grant may award up to $20,000. In 2001/02, HDSA will fund almost $1 million in Grant and Fellowship projects.

The HDSA Grant and Fellowship program is made possible by Founding Leadership Gifts from the Smith Family Research Fund in Memory of Gretchen Ferris Smith, the Dobis Family Fund, the Milek/Fecca/Baker Family Research Fund, the Pilskaln Family and Friends Research Fund and individual Family Fund sponsors.

New Grants for 2001-2002

Lisa M. Ellerby, Ph.D.
Buck Institute for Age Research,
Novato, CA

Cell-Death Proteases in Huntington's Disease

There is preliminary evidence that toxicity seen in cells in HD involves the abnormal interaction of the expanded form of huntingtin with caspase-2 and other protease enzymes involved in signaling the cell to die. A series of experiments have been designed to examine whether the interaction of huntingtin with cell death proteases is a critical step in disease progression. This work may lead to the design of molecules that specifically block this interaction of huntingtin with the caspase-2 complex and therefore delay disease progression.

Robert J. Ferrante, Ph.D.
Bedford VA Medical Center,
Bedford, MA

Transglutaminase Inhibition Using Cystamine Therapy in HD Mouse Models

The precise progression of events that leads to neuronal death and the clinical symptoms of HD is still unknown. Many researchers believe that it is the clumping, or aggregation, of huntingtin that causes the dysfunction and subsequent death of neurons in this disorder. It has been shown that an enzyme, transglutaminase, is increased in the brains of HD patients. This enzyme has also been shown to potentially cause huntingtin aggregation. The goal of these studies is to treat transgenic HD mice with the compound cystamine, with the intention of inhibiting trans-glutaminase activity. It is hoped that this treatment will prevent neuronal death, extend survival, improve the clinical symptoms of these mice, and identify the most effective dosing. If the treatment works in mice, this potential therapy may then proceed to clinical trials in humans.

New Grants for 2001-2002

David Sulzer, Ph.D. (and Anna Maria Cuervo, Ph.D.)

Columbia University (& Tufts University), New York, NY

Autophagy of Huntingtin Protein

Autophagy refers to the removal of cell material by enzymes of the same cell and is normally a protective mechanism. The extremely high rate of autophagy in HD may explain cell shrinkage and loss of body mass in HD patients. It may be that when too much autophagy occurs, neuronal death is initiated. Research has found that the HD mutation, combined with oxyradical stress in neurons caused by dopamine, is sufficient to induce severe autophagy and apoptotic cell death.

In other research, the first neuronal culture system that provides long term survival (over two months) of high quality HD striatal neurons has been developed. Cultures which survive through the progression of HD are invaluable to research.

Alan M. Tartakoff, Ph.D.

Case Western Reserve School of Medicine, Cleveland, OH

Rapid Screening Procedures to Identify Genes and Drugs which Reduce the Consequences of Polyglutamine Expression

Identification of genes and drugs, which can reduce the expression of polyglutamine repeats, requires screening of vast numbers of potential therapies. Using a strain of yeast that expresses stretches of polyglutamine repeats, this research project will observe changes in the process by which DNA directs protein production, and also identify and measure proteins that interact with this polyglutamine stretch. This information will then be used in the production of a "reporter" strain of yeast, which will be used to identify genes and drugs that decrease these interactions. These genes and drugs may then be tested in transgenic HD mice. Additional research will examine how cells cope with the presence of polyglutamine stretches by identifying yeast mutants which do not tolerate their presence.

Renewing Grants for 2001-2002

Sarah Augood, Ph.D.

Massachusetts General Hospital, Boston, MA

Molecular Analysis of Neuronal Vulnerability in Huntington's Disease Caudate Using Microarray Gene Profiling of Discrete Cell Populations

Within the HD brain, there appears to be a population of cells that are relatively resistant to cell death and that are morphologically and chemically different from cells that do degenerate. The newly developed technique of laser-capture microdissection (LCM) will be used to identify genes that may offer cellular resistance. These neurons will be laser dissected so that their molecular profile can be compared and contrasted to better understand the process that underlies neuro-degeneration. To date, techniques to optimize the quality of the RNA extracted, while using the least amount of tissue, have been perfected. Additional progress relates to the testing of donated post mortem brains from control and Huntington's Disease patients for the integrity of the RNA they contain.

Renewing Grants for 2001-2002

Susan E. Browne, Ph.D.

Weill Medical College at Cornell University, New York, NY

The Role of Energy Metabolism in Pathogenesis in Transgenic Mouse Models of HD and Another CAG Repeat Disorder

This research will determine whether brains affected by the HD mutation show the abnormal levels of energy production found in human HD patients, with a specific goal of pinpointing the cellular source of the abnormality. Results will be compared with similar studies of another "model" polyglutamine CAG repeat disorder (spinocerebellar ataxia 1) to determine whether these changes are common to all CAG repeat disorders.

To date, a significant increase in glucose metabolism has been found in the brains of HD mouse models. The increase is dependant on the number of glutamine repeats in the mutant huntingtin. Alterations in the activities of enzymes involved in energy production within the cells have also been found. The effects of certain potential therapeutic drugs will be tested for improvements in energy metabolism, lifespan, and behavior.

Christine Fennema-Notestine, Ph.D.

University of California San Diego, CA

Fronto-striatal Activation and Morphometry in Subjects At-Risk for Huntington's Disease: A Functional and Structural MR Imaging Study

Using two types of Magnetic Resonance Imaging (MRI), the structure and function of the brain in subjects at-risk for HD is measured while subjects perform complex tasks. A unique aspect of this program is that complete structural brain anatomy (from an sMRI) is available with the functional data (from an fMRI). The application of this combination of imaging provides promise for a direct, non-invasive method of measuring brain changes that begin early in HD. It can also be used to precisely assess the effects of pharmacological treatments. To date, data on seven subjects with a family history of HD have been collected, as well as data on four control subjects with no family history of HD. All imaging datasets are currently in the preprocessing stages of analysis. Recruitment for this study is continuing.

Jeffrey N. Keller, Ph.D.

University of Kentucky, Lexington, KY

Involvement and Characterization of Proteasome Inhibition in Huntington's Disease

Proteasomes are enzymes that are responsible for removing damaged proteins from brain cells. They appear to be inhibited in HD by the action of oxidative stressors such as reactive oxidative species (ROS). It has been thought for some time that ROS toxicity is a factor in HD but the target of ROS was not known. Using HD mouse models, pharmacological treatments that inhibit ROS production will be tested, to see whether they are effective against HD toxicity. These treatments have been approved and are currently in use for the treatment of Parkinson's disease. Optimal treatment conditions and the mechanisms for drug action will be investigated in order to lay the groundwork for future human clinical trials.

Renewing Grants for 2001-2002

Lynn A. Raymond, M.D., Ph.D.

University Of British Columbia, Vancouver, BC, Canada

Role of Subtype-specific NMDA Receptor-mediated Neuronal Death in Pathogenesis of Huntington's Disease.

This research has shown that certain neurons in the striatum of an HD mouse model are more likely to be vulnerable to cell death caused by the stimulation of certain glutamine receptors in the brain (NR1/NR2 NMDA receptors) than the same neurons with wild-type (normal) huntingtin. Moreover, the increased cell death is associated with the activation of caspase-3 and may involve impaired energy production by mitochondria. The fact that specific brain receptors are activated may indicate selective neuronal vulnerability to cell death and offer direction to the development of therapeutic strategies.

Akira Sawa, M.D., Ph.D.

Johns Hopkins University School of Medicine, Baltimore, MD

Role of p53 in Huntington's Disease Pathogenesis

In order to develop effective therapies for HD, an understanding of the signaling cascade that leads from abnormal huntingtin to cell death is critical. This research focuses on the events that follow the increased expression of a nuclear protein (p53). It appears that increased p53 interferes with normal gene transcription in mitochondria, leading to toxicity in cells as they divide and reproduce. A chemical inhibitor of p53 was found to increase the viability and lifespan of cells with mutant huntingtin. Further analysis at the molecular level in cellular and animal models will be very important to clarify the role p53 plays in the progression of HD and to yield a therapeutic target for future research.

Leslie M. Thompson, Ph.D.

University of California, Irvine, CA

Altered Gene Expression in a *Drosophila* Model of PolyQ Pathogenesis

Huntington's Disease and a number of other human neurodegenerative diseases are caused by the expression of an extended segment of polyglutamine within the corresponding disease protein. The mutation leads to changes in neurons that result in the characteristic symptoms and neuronal degeneration. Recent evidence from several labs has shown that changes in the expression patterns and levels of specific RNA's, directing the synthesis of specific proteins in neurons, may contribute to pathogenesis. The goal of these studies is to use the fruit fly, *Drosophila*, in which we can detect every gene that might be altered, combined with the power of whole genome technologies through the use of microarrays, or gene chips, containing over 13,500 *Drosophila* DNA sequences, to investigate changes in gene expression. It is hoped that these studies will lead to new approaches and targets for therapeutic intervention.

New Fellowships for 2001-2002

Saumitri Bhattacharyya, Ph.D.

University of Nebraska Medical Center, Omaha, NE

Modifier Genes for CAG Repeat Expansions

Significant changes in the length of a specific DNA triplet-repeat sequence (CAG) occurs in Huntington's Disease (HD). This study will focus on identifying the factors responsible for causing triplet-repeat expansions, using a strain of yeast (*S. cerevisiae*). The ease with which the genes of this simple organism can be manipulated allows researchers to assign physiological outcomes to the specific genes that are exposed. By identifying yeast genes that control triplet-repeat expansions, work can begin on identifying their human gene counterparts, or homologs, which will be key elements in explaining triplet-repeat instability in humans. This work may ultimately help explain differences in susceptibility to triplet-repeat expansions among different families.

Matthew T. Lorincz, M.D., Ph.D.

University of Michigan, Ann Arbor, MI

Use of Neuronally Differentiated Embryonic Stem Cells as Models of Huntington's Disease

Embryonic stem cells (ES) can be grown in culture, differentiated into neuronal cell lines, and subjected to genetic and environmental manipulation. Preliminary data indicates that neuronally differentiated ES cells from CAG repeat lines exhibit abnormal features. This research proposes to evaluate neuronally differentiated ES cells derived from two separate transgenic mouse lines as models for cellular pathology in HD. Cellular abnormalities typical of HD will be evaluated. This model may be particularly useful in determining the pathologic process(s) underlying neurodegeneration in HD and may serve as a screening tool for evaluating possible therapies in an easily manipulated *in vitro* system.

Kathy L. Newell, M.D.

Massachusetts General Hospital, Charlestown, MA

Evaluation of Neuronal Nuclear Inclusions in Postmortem Brains of Asymptomatic Subjects At-Risk for Huntington's Disease

Nerve cells in select areas of HD brains contain small deposits called neuronal nuclear inclusions (NNI) that are composed of abnormal huntingtin protein (also known as aggregates, or protein clumps). Normal brains do not contain NNI. As NNI in a mouse model of HD appear shortly before onset of symptoms, NNI might be present in carriers of the HD gene who died prior to onset of symptoms. Using autopsy brains from at-risk, symptomatic and control subjects, NNI have been detected in asymptomatic carriers of the HD gene, including otherwise apparently normal brains. The brains from the asymptomatic HD gene carriers will provide invaluable insight into early brain damage occurring in HD. Identifying the types of neurons susceptible to NNI formation in preclinical disease will contribute to the understanding of HD progression and the disease in its earliest stage.

Dinesh S. Rao, M.D.

University of Michigan, Ann Arbor, MI

The Role of Huntingtin Interacting Protein 1 (HIP1) in the Pathogenesis of Huntington's Disease

It is not known whether the abnormal huntingtin itself causes damage to cells or whether it causes other proteins to act abnormally. One such protein, Huntingtin interacting protein 1 (HIP1), shows a reduced interaction with mutated huntingtin protein. This reduced interaction may be responsible for the development of HD. In order to test this hypothesis, two novel mouse models are being developed to help understand the normal function of HIP1 protein in animals with an ultimate goal of developing strategies to treat Huntington's Disease.

Gabriella Stocca, Ph.D.

Vanderbilt University, Nashville, TN

Modulation of Synaptic Activity at Corticostriatal Synapses in a Transgenic Mouse Model of Huntington's Disease: A Presynaptic Study

Patients with Huntington's Disease (HD) often show disturbances in their motor skills. The appearance of these symptoms is correlated with the early loss of neurons in a brain region called the striatum. The brain cortex sends information to striatal neurons using a form of glutamate as a neurotransmitter. If too much glutamate is released, the neurons in the striatum begin to die. This research will investigate whether the neurons in the cortex of HD patients release too much glutamate onto neurons in the striatum or if the neurons in the striatum of a person with HD are abnormally sensitive to glutamate. This will assist in the design of drugs that can slow down or eliminate the toxic effect of the excessive glutamate release.

Renewing Fellowships for 2001-2002

Gloria J. Klapstein, Ph.D.

University of California, Los Angeles, CA

Cellular and Synaptic Changes Underlying Abnormalities in Neuronal Physiology in a Transgenic Mouse Model of Huntington's Disease

Analyzing brain slice cultures from both HD mice and normal mice which have been deprived of both glucose and oxygen for short periods of time, researchers have found that the neurons of the HD mice appear to have experienced many small energy depletion events prior to the onset of motor symptoms. Research is currently underway to understand why many of the electrical properties of striatal neurons are altered in mutant HD mice, and why their neural cells have fewer points of contact for cellular communication. These observations are apparent even in cells from young mutant mice, which have not yet developed symptoms. Both of these lines of research imply that therapies aimed at preventing or delaying progression of the disease may need to begin long before symptoms start to develop.

Renewing Fellowships for 2001-2002

Henry Speno, Ph.D.

Massachusetts General Hospital, Boston, MA

Characterization of Huntingtin Yeast Partners in Huntington's Disease Pathogenesis

HD may manifest itself because of an abnormal interaction of mutant huntingtin with a cellular binding protein. Thirteen of these proteins (HYPs) have been isolated and three of them have been studied as potential causative factors in HD. Nine of the remaining proteins are now being studied to determine their interaction with mutant and normal huntingtin. Antibodies will be used to detect a number of the HYP proteins in post-mortem brain tissue from control and HD patients. HYP interacting proteins may be important in the normal functioning of huntingtin. Further research is needed into the normal functions of huntingtin to help understand the mutant form that causes HD.

GLOSSARY

Aggregates/aggregation – Clumping of proteins in cells that interfere with cell functioning.

Caspases – Enzymes that trigger cell death (apoptosis).

Chaperones – Proteins found inside of cells which can diminish the toxicity of mutant genes and stop the degeneration caused by incorrectly folded genes.

Mitochondria – A small intracellular organelle which is responsible for energy production and cellular respiration.

Neuronal death – Death of nerve cells.

Phenotype – Visible characteristics of an expressed gene.

Polyglutamine CAG repeat disorder– An abnormally large number of a particular protein in the DNA string of a gene, causing protein clumping in cells.

Striatal neurons – Particular nerve cells in the brain.

Transgenic mouse model – Mice that have had genetic material inserted into their DNA, causing the expression of genetic disorders, which can then be studied in the lab.

Largest Clinical Trial to Date for HD Therapies

Four years ago, beginning in July 1997, **CARE-HD** (**C**o-Enzyme Q_{10} **A**nd **R**emacimide **E**valuation in **H**untington's **D**isease), the first multi-center clinical trial for Huntington's Disease, enrolled 347 individuals at 23 sites in North America to test two compounds in a double-blind study. The final **CARE-HD** participant completed their two and a half year course of drug treatment (with periodic evaluations) in January 2001. This was the largest clinical trial to date of potential therapies for HD. Conducted by the Huntington Study Group, the study was funded by the National Institute of Neurological Disorders and Stroke (NINDS), AstraZeneca Pharmaceuticals, and Vitaline Corp.

Results of the clinical trial appeared in the August 14, 2001 issue of *Neurology*, the scientific journal of the American Academy of Neurology. Results of the study may also be found at www.Huntington-Study-Group.org. While the results of the trial were not definitive, principal investigator Karl Kieburtz, M.D., professor of Neurology at the University of Rochester Medical Center, and co-investigator Walter Koroshetz, M.D. of Massachusetts General Hospital, believe that the size and length of this study point the way for future efforts in the search for a cure for HD.

CARE-HD

What the Latest HD Research Means to You

The AstraZeneca Research Forum

The fourth annual AstraZeneca Research Forum was held as part of the HDSA 2001 Annual Convention in San Diego, California. As an integral part of each convention, the Forum focuses on the most recent advances in both the basic and clinical aspects of HD research. Composed of leading researchers and medical experts, the AstraZeneca Forum provides the vital research information so essential to our HD families.

With a theme *"From Models to Medicine,"* Christopher Ross, M.D., Ph.D. opened the Forum with an overview of what is currently known about the cause and the early steps in identifying the pathways of HD. Dr. Ross spoke enthusiastically about the recently completed Human Genome Project, which has created a draft of the entire genetic sequence of human DNA. He described how this has revealed similarities between the genetic sequences found in humans and those found in worms, flies and mice, which make them useful animal models in studying HD. Much of the work sponsored by HDSA utilizes these models to study ways to delay the onset of symptoms, slow the progression of the disease or even reverse brain cell damage. As Dr. Ross noted, "HDSA brings together scientists working on different aspects of the problem so they can work more effectively. It also brings scientists together with the families and patients they are working for, putting a face and a story on the disease so that

Shown left to right: Drs. Christopher Ross, Leslie Thompson, Henry Paulson and Robert Friedlander.

"HDSA brings scientists together with the families and patients they are working for, putting a face and a story on the disease so that they have a motivation and understanding to work harder."

-CHRISTOPHER ROSS, M.D., PH.D.

they have a motivation and understanding to work harder."

Leslie Thompson, Ph.D. spoke following Dr. Ross and described the progress being made in identifying the ways that cell proteins are affected by the presence of mutant huntingtin. Since mutant huntingtin inhibits the creation of specific proteins that are necessary to neuron functioning, discovering how it interferes with the creation of these cell proteins will help researchers to understand the very early events of the disease.

Dr. Thompson used the *Drosophila*, or fruit fly model, to investigate the effects of three specific compounds: minocycline, creatine and histone deacetylation, that appear to moderate or reverse the damage to neurons caused by mutant huntingtin. These compounds were first considered by fellow Coalition for the Cure investigator, Dr. Erich Wanker, at the Max-Planck Institute for Molecular Genetics in Berlin, Germany, using a microarray screening technique. This innovative technology takes mRNA genetic samples, from either normal or mutant huntingtin protein, and mixes it with specific chemical compounds, in order to screen them to compare the effects the compounds may have on either or both of the samples. While few compounds may yield a positive result, the large number of compounds that can be tested through microarray screening can greatly increase the probability that a researcher may be able to identify one or more compounds that could prove effective either in inhibiting or encouraging specific protein formation.

Henry Paulson, M.D. Ph.D. in his segment, *"Lessons from Flies and Fish,"* spoke of utilizing non-mammalian models, such as fruit flies and zebra fish, to investigate the basic cellular and intracellular phenomena of HD. Having the ability to easily and inexpensively insert genetic material into models means that many more genes can be tested to determine whether they affect the toxicity of HD, in what is known as the "candidate gene approach." The use of models has already uncovered protein surveillance pathways and chaperone genes that act as protein quality control agents within cells. "We hope that there are compounds which can manipulate this machinery in ways that will be therapeutic," Dr. Paulson stated.

" 'This isn't the end. This isn't the beginning of the end. This is the end of the beginning.' The CARE-HD clinical trial was the biggest clinical trial to date of a potential therapy for HD."

—KARL KIEBURTZ, M.D.
(*quoting from* WINSTON CHURCHILL)

Robert Friedlander, M.D. spoke on advances made in understanding caspases- a family of proteins that cause cell degeneration and death. These proteins appear in many neurodegenerative diseases, as well as in cases of stroke and brain injury. Compounds that inhibit the activation of

caspases have been shown to slow cell degeneration and death, but detecting a compound that inhibits caspase activation with acceptable toxicity has proven to be a major challenge. Dr. Friedlander and his group used HD mouse models to test minocycline, a drug used in human pharmacology for over 30 years, as a potentially therapeutic compound for inhibiting caspase activation. Because the exact mechanism of minocycline's positive effects is unknown, Dr. Friedlander hopes to move this compound into a Phase II safety trial.

Dr. Friedlander thanked the HDSA Keating Family Fund and HDSA for their financial support of his work.

In the final presentation of the Forum, which focused on the **CARE-HD** (**C**o-enzyme Q_{10} **A**nd **R**emacemide **E**valuation in **H**untington's **D**isease) clinical trial, Karl Kieburtz, M.D. introduced an analogy of the World War II "Battle of Britain" with a quote from Winston Churchill, "This isn't the end. This isn't the beginning of the end. This is the end of the beginning." The **CARE-HD** clinical trial (see page 16) was the biggest clinical trial to date of a potential therapy for Huntington's Disease.

Co-enzyme Q_{10} and remacemide were tested in a double-blind study of 347 participants that began four years ago. During the course of this clinical trial, each participant spent two and a half years actively engaged in taking the drugs involved with periodic evaluations. The compounds were given separately and in combination to determine whether either or both slowed the degeneration of total functional capacity that occurs during the progression of HD. While Co-enzyme Q_{10} reduced the rate of decline by approximately 13% and remacemide reduced the severity of chorea, neither compound showed improvements in a statistically significant way, which means that the results might have been caused by chance. Dr. Kieburtz was encouraged, though, that the clinical trial provided solid clues to follow for future investigation. He recommended that Co-enzyme Q_{10} be tested further to see if higher doses might provide greater benefits to symptomatic HD sufferers and also to see if the compound might delay onset of HD in presymptomatic individuals. Remacemide's ability to reduce chorea should also be pursued, he said. The collaborative efforts of HDSA, the Huntington Study Group, National Institute of Neurological Disorders and Stroke (NINDS), Huntington Society of Canada, Hereditary Disease Foundation, AstraZeneca and Vitaline were praised by Dr. Kieburtz and he also thanked AstraZeneca Pharmaceuticals for their regulatory and monetary support of the **CARE-HD** trial.

The AstraZeneca Research Forum is a unique opportunity for HD investigators to present their most recent research to scientists, healthcare professionals and interested members of the public. It also provides an opportunity for members of the audience to ask questions of leading HD researchers. HDSA wishes to thank AstraZeneca Pharmaceuticals for making the Forum possible.

The Co-enzyme Q_{10} used in the CARE-HD clinical trial may not be the same strength and composition as that found in health food stores. If you are interested in using Co-enzyme Q_{10}, please consult with your physician for the proper dosage and formulation.

HDSA *thanks*

The American Legion
Child Welfare Foundation

for their support of HDSA's Juvenile HD programs and sponsorship of the Juvenile HD section of ***The Marker***

HDSA *thanks*

The American Contract Bridge League
Charity Foundation

for their support of HDSA's Juvenile HD programs

HDSA *thanks*

OUR PARTNER

SunBridge Care & Rehabilitation

for their support

CAREGIVERS' LINK

HDSA *thanks*

The **Bess Spiva Timmons Foundation,** a Founding Benefactor, for its sponsorship of *Caregivers' Link*, which includes the following articles this month: *Advance Directives and End of Life Decision Making*, *Choosing Home Healthcare Assistance*, and *Communicating with Healthcare Professionals*

Advance Directives and End of Life Decision Making

Planning for the future takes on a special meaning for individuals and their families facing HD. Although it can be painful to talk about the progression of symptoms or the late stages of Huntington's Disease, it is important to do so. Addressing end-of-life issues while the individual is still in the earlier stages of the disease allows that person to have more say in their future care. By planning for the challenges ahead, those affected by HD, families and caregivers can ask questions, make plans that reflect their wishes and avoid crisis situations.

Advance directives are a way to prepare for a time when the person with HD becomes a patient and can no longer choose medical treatment for themselves, either because of physical or mental limitations. These written statements let family, physicians and hospitals know what level of medical treatment is desired by the patient and who will make medical decisions if the patient cannot.

It is very important to designate someone as a healthcare proxy for the patient. A healthcare proxy will have access to medical records and confidential information that may not be available even to family members. A proxy also has the legal right to stop treatment that the patient would not have wanted or that is not in the best interest of the patient.

Naming a healthcare proxy can cause its own problems. Members of the same family can have very different opinions about medical care. The person who has been named should know and agree to take on the responsibility. Only one person can be named as healthcare proxy, although an alternate can be named to cover emergencies. The healthcare proxy does not have to be a family member. Even the patient's doctor can serve as a healthcare proxy, but only if they relinquish care of the patient to another physician.

An advance directive may contain a "living will." The living will is a statement of what treatments the individual does or does not want. They might include end-of-life choices about feeding, hydration, use of antibiotics, hospitalization, resuscitation and autopsy. These deeply emotional decisions are ones that most people would want to make for themselves, although an individual may choose to allow their healthcare proxy some flexibility in making these decisions. Writing an advance directive makes their wishes a matter of record.

Once the advance directive has been written, it should be made part of the individual's

continued on page 36

Choosing Home Healthcare Assistance

Families facing HD are typically very self-reliant. Care is often provided at home during the progression of the disease and frequently by one family member. As symptoms worsen, the task of caregiving may become overwhelming. Obtaining professional home care assistance may improve the quality of life for both the caregiver and the patient. Caregivers cannot expect themselves to be cheerful and supportive all the time, while tending to the demanding physical and emotional needs of a person with HD. Respite is needed for the caregiver to "refuel" emotionally and physically.

After the decision is made to obtain assistance, the question becomes "What level of service is needed?" Caregiving assistance takes many forms. It may be as simple as employing a cleaning or laundry service. A housekeeper may be hired to cook meals a few days a week. Consistent relief from even a few tasks may help the caregiver get "out from under."

Due to the long-term nature of this disease, the support services a caregiver needs will change over time. Custodial tasks such as bathing, toileting, dressing and feeding may become difficult to manage because of the patient's size or behavior. A home health aide or certified nurse assistant can come into the home to provide personal care and assistance. These workers may be hired through an agency or directly by the caregiver.

…"a system of professional support, once it is in place, can give a caretaker precious time for their families, their work and themselves."

Home healthcare agencies recruit, train and supervise home health aides. Medicare may pay for services provided through a home healthcare agency, if a physician orders these services. To be eligible for services under Medicare, a patient must need skilled nursing assistance or physical, speech and/or occupational therapy. Home healthcare workers are a supplement to this care and are usually scheduled for three hours a day, several days a week. Talking to the patient's doctor or a social worker is the first step.

Questions to ask a home healthcare agency

- How are employees screened?
- Who supervises the workers?
- What type of training do the aides receive?
- Who will come when the worker is ill or on vacation?
- Are there limitations on tasks or times of service?
- Can the worker be replaced if the caregiver or patient dislikes the aide?

Once the aide has been hired, it is important that they be made aware, in words and in writing, of the patient's needs and routine. Accepting a new person into the household may initially be difficult for the HD patient, so it is critical that the aide understand the patient's likes, dislikes, personality and behavior patterns and that they follow the expected routine carefully. It is also imperative to assess the personality of the aide and the way they interact with the patient. The aide is being hired to support the caregiver and reduce the level of stress in the household. The caregiver will need to spend time with the aide until an acceptable relationship is established. If the aide cannot work well with the patient, or the caregiver, they should be replaced. Getting assistance with caregiving is a challenge. Paperwork and bureaucracy can be frustrating. At first, caregivers may feel that the effort causes more problems than it solves. But a system of professional support, once it is in place, can give a caretaker precious time for their families, their work and themselves.

We wish to acknowledge the Administration on Aging's website: www.aoa.gov, for support information used in the preparation of this article.

Communicating with Healthcare Professionals

People with HD require the assistance of a wide variety of healthcare professionals, from neurologists to social workers. Sadly, as the disease progresses, it reduces the patient's ability to speak and to reason, making it more difficult for them to get the care they need. The responsibility then falls on the caregiver to act as the patient's intermediary and advocate in medical settings. Learning to work effectively with healthcare providers, at all levels, will maximize the care that the patient receives.

HDSA Centers of Excellence for Family Services support caregivers with integrated healthcare services in many areas (see page 29), but caregivers in outlying regions may have to create a team spirit of their own. The goal is to foster communication between all the people involved.

Get Organized

Since the caregiver will be meeting with a number of healthcare professionals, at different offices and locations, creating a file with copies of all important records and reports and having it handy during appointments, may save return trips and reduce frustration. Each doctor should know who else is working with the patient. The caregiver must be firm in requesting that the healthcare professionals confer with one another to integrate the patient's care needs.

Learning more about HD makes the caregiver a better advocate. Often caregivers may have to alert a healthcare professional to aspects of care that are specific to HD. There have been many cases where a doctor is familiar with similar diseases, but has limited experience in dealing with HD.

Be Observant

Communication is a challenge for people with HD. They may get confused or distracted and forget to tell the doctor something important. An attentive caregiver knows more about the patient's physical and mental state than anyone else. A legal pad can be used to write down observations, questions or concerns as they arise between appointments. A busy waiting room is no place to try to remember details.

Be Prepared

Healthcare professionals are often very short of time, either because of managed care or heavy workloads. To get the most from a visit, the caregiver must be ready to share important observations and questions that have arisen since the last visit. If there are many questions or important decisions to be made, a consultation appointment should be scheduled, separate from the regular visit with the doctor, to allow adequate time to make an informed decision.

Avoid Rushing

In the hurried atmosphere of a busy office, there may be a tendency to "hurry up" and complete the appointment. Instructions from the doctor or therapist must be understood to be effective. Anything that is not clear should be questioned before the end of the appointment. Complicated directions should be written down and reviewed for accuracy. In cases where a decision is needed, ask the doctor if it must be made immediately or if there is time to think it over. Only a life-threatening situation needs immediate action.

Control Emotions

Caregivers are under tremendous pressure and this may affect their interactions with healthcare professionals. Many find it hard to keep their frustration and anger with HD from appearing as anger at the people who are trying to help in a difficult situation. It is possible to gently insist on a high level of care for a loved one without being abusive or aggressive. An effective long-term relationship between a caregiver and a healthcare professional has to be built on respect.

Self Care

Caregivers must consider their own health, physical and mental. Arrangements should be made for frequent respite from caregiving and time set aside for activities that can reduce

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Preimplantation Testing: One Family's Story

This story is about an HD family in Florida who chose to use genetic testing as part of their in vitro *fertilization process. It is published for informational purposes only. The parent's names have been changed to protect the privacy of the family.*

In July, a beautiful, healthy baby boy was born free of HD in Central Florida. Because his father, Martin, carries the HD gene, normally this baby's chances of inheriting the disease would be 50/50. But, through preimplantation techniques for genetic testing, his parents knew that he would never have to live at-risk. "We were having trouble conceiving a child," Becky, his 33 year-old mother says. "We were already going to a fertility clinic when my husband's father was diagnosed with HD."

Martin's uncle had been diagnosed with HD in his 40's, but his father had shown no signs until his late 50's. "After my father's diagnosis, I also tested positive for the HD gene," he states. "We considered adopting a child, but then we read about preimplantation testing on the Internet." Their fertility doctor said that the test would only add a small additional step to the regular *in vitro* fertilization process. "We thought about it long and hard. After all, if my parents had done it, I would not have been born," says Martin.

Getting involved with the support group of the Central Florida Chapter of HDSA helped them through the difficult decision to proceed. "Our families were also very supportive," says Becky. "They knew about the Huntington's in Martin's family."

The doctor from their fertility clinic contacted Dr. Mark Hughes at Wayne State University Center for Molecular Medicine and Genetics in Detroit, Michigan. Dr. Hughes has had great success with preimplantation genetic diagnosis (PGD). "The testing is funded by donations, so there is only a minimal additional cost," Martin remembers. "We only paid for the staff member to fly down to Florida."

In preimplantation genetic diagnosis (PGD), patients undergo *in vitro* fertilization. Only those embryos that test negative for the disorder are implanted in the mother's womb. A report on PGD, coauthored by Dr. Hughes and physicians at the Weill Medical College of Cornell University, was printed as the lead article in the May 12 issue of the *Journal of the American Medical Association* (JAMA). Wayne State University is one of only four centers in the country routinely using PGD, which can currently also be used to test for certain genetic diseases, including cystic fibrosis, hemophilia, Down's syndrome, Duchenne muscular dystrophy, as well as Huntington's Disease.

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In Vitro Fertilization (IVF) and Preimplantation Testing

In vitro fertilization is a procedure where the union of egg and sperm occur in the laboratory and the resulting embryo is implanted into the uterus of the birth mother. Typically, ripe eggs are harvested after a course of fertility drugs, which encourage the body to produce more than one ripe egg. The eggs are placed in culture medium prior to fertilization. Not all fertilization attempts are successful and not all eggs then mature. If fertilization is successful, implantation is performed in three days. Between fertilization and implantation, genetic tests may be performed. Embryos that do not show the presence of the gene tested for are then selected for implantation. Once the embryo(s) are implanted, another course of hormones are given to increase the chance for a successful pregnancy. Since 1985, a little over 15% of implanted embryo procedures performed in IVF clinics resulted in clinical pregnancies. HDSA recognizes that choosing IVF and preimplantation testing is a complex personal decision and offers information about these techniques so readers may reach an informed decision.

Youth and Juvenile HUNTINGTON'S DISEASE

Seeking Diagnosis, Care and a Cure for Juvenile HD

HD families are just that - families. Within the family, there may be symptomatic, asymptomatic, at-risk and HD-free individuals. The Pillis Family has them all. How each member has been touched by juvenile HD shows clearly the breadth of the challenges this disease creates.

For five years, Pat Pillis knew something was wrong with her son Shane. While she was told that Attention Deficit Hyperactivity Disorder (ADHD) was causing his unpredictable behavior, she was sure he was misdiagnosed. "From the time he was 10, I knew he was sick, but I couldn't get anyone to listen." Pat suspected juvenile Huntington's Disease. Pat and Paul Pillis have four children. Three are sons whose birth mother was affected by Huntington's Disease. "I took the boys to visit their birth mother every three months," Pat recalled. "Once you see Huntington's, you know what it looks like. I saw it in Shane." When Shane was finally diagnosed, at age 15, it was actually a relief. "It was very frustrating," noted Shane's older brother Kevin. "When things started going crazy, my Mom would talk with me, trying to figure out what was bothering him. The diagnosis answered our questions." "Before we had the diagnosis, we spent thousands of dollars on therapists for Shane and they would say, 'I can't reach this kid'," added Pat. "After the diagnosis of juvenile HD, we started going to a family counselor and things got better." Shane's little sister Shannon, eight years his junior, found that the diagnosis changed everything. "Dad was convinced that Shane was a bad kid. Everyone was getting violent and mean. Once he was diagnosed, we knew that if he hit Mom, it wasn't because he hated us, it was because he was sick."

> *"For the first time in his life, Shane felt that he fit in."*

Shannon described what she experienced before the diagnosis. "When I was in elementary school, I acted like the big sister to him. When people would whisper, 'What's wrong with him,' I always wanted to protect him." At times, though, Shannon felt afraid of her brother. "When he got violent, I would hide in the corner of my Mom's walk-in closet. I knew he didn't mean what he did. One time he was kicking me and crying at the same time. He didn't want to do what he was doing." As she got older, Shannon was able to share her feelings with the school guidance counselor. "In sixth and seventh grade, I was close to this one guidance counselor. At that point, I was old enough to have feelings about it. Before that you're just a little kid."

> *"…'It was amazing what they could do for him there'…"*

Shane's school tried to accommodate his illness, as

required under the Americans with Disabilities Act (ADA), but they were unsuccessful. "Because Shane likes cars, they put him in an automotive mechanic program, but with his chorea, he couldn't do it," Pat observed. "That's when we began an extensive search for a residential school." The Pillis Family was fortunate to find the Crotched Mountain School in Greenfield, NH. Shane was the first student at the school with HD. "The school is set up for students with multiple disabilities, both mental and physical. For the first time in his life, Shane felt that he fit in." Shane has been at the school for three years and will remain there until he turns 21, next summer. "It was amazing what they could do for him there," said Kevin. "He thinks of it as college," added Shannon. "He can live on his own in a house, like a dorm. We couldn't give him much freedom."

Many things changed for the family when Shane moved to Crotched Mountain. "When Shane was still living with us, I always made time for Shannon by using after school respite. That way she could have her piano lessons and I could go to all her games. But it was hard. We were trying to live a halfway normal life, with people going in and out. Shane felt left out of that and also stressed at school," said Pat. "It's a lot more quiet in the house now," added Shannon. "I miss Shane, but I don't think we could handle him now. I know we couldn't."

"I am hopeful for a cure… a cure in time for both Kevin and Shane. I don't feel hopeless at all."

While Pat always had the feeling that Shane had HD, it was more of a shock when his brother, Kevin tested positive in June 1999. Kevin, now 24, shows only the earliest symptoms of HD. He currently works 4 days a week at a facility for troubled kids. Kevin places his hope for the future on a cure. Shannon agrees. "I definitely want a cure for my brother Kevin. A cure that could stop HD exactly where it is or reverse it." Shane and Kevin's older brother Fred, now 27, has shown no symptoms of HD and has not been tested.

Because Shane's HD is advanced, Pat's wish for the future involves care, as well as a cure. When Shane reaches 21, he will no longer be able to live at Crotched Mountain.

Raising four children across the spectrum of the HD experience has been challenging for the Pillis Family. They credit their faith with guiding them. Pat is also very involved with HDSA on the national level. "Since my first convention in Rochester, I have been very active. I have led the juvenile HD workshop at the National Convention and I contributed in a small way to HDSA's new *Juvenile HD Handbook*. I am hopeful for a cure," she concluded. "A cure in time for both Kevin and Shane. I don't feel hopeless at all."

FINDING TIME FOR FUN

In the midst of all the challenges that accompany a diagnosis of juvenile HD, it is easy to overlook one of the main things that life is about - having fun. Setting aside time for enjoyable activities can create memories that will sustain both the family and the child as the disease progresses.

Fun means different things to different people. A special trip or long distance visit can be enjoyable, but fun can also mean taking time from the daily schedule to swing on a tire swing or simply be together, without a task to complete.

For a child or young person with HD, activities must be matched with their abilities. In the middle stages of HD, children become less able to handle complicated schedules or multiple activities. New, fast-paced or confusing situations may cause behavior problems and not be fun at all. On the other hand, familiar activities may be particularly enjoyable: swimming at the "Y", going out for pizza or ice cream, or attending church or temple services may all fall into this category. The emphasis should be comfort and enjoyment rather than working too hard to finish a lot of tasks on a schedule.

Pets can provide fun and comfort. As long as the young person isn't aggressive, a dog or cat may be a friend and companion, one who will accept the child or teen just as they are. Caregivers can talk to their doctor or a veterinarian about the right kind of pet for the child's personality.

Pets can provide fun and comfort. As long as the young person isn't aggressive, a dog or cat may be a friend and companion, one who will accept the child or teen just as they are.

As HD progresses, maintaining friendships may be hard. Old friends will be learning new things, while the child with HD may be losing some skills. Joining a small, friendly group for short activities may be very rewarding.

Adolescents with HD face the greatest challenges. Many children with HD become lonely in their teenage years as HD robs them of their ability to initiate or maintain social relationships. Dating and driving may both be unavailable to a teen with HD. Social contact through school or church groups, well supervised, may keep the teen connected. For some young people, spiritual beliefs and activities provide remarkable comfort and reassurance when life becomes difficult and lonely.

There are some summer camps and weekend retreats for people with HD. These can be wonderful outlets for kids with HD. Information is available from local HDSA chapters or the national office at 1-800-345-HDSA.

Young people with HD face a limited life span. Make time for fun *now*, as opportunities for enjoyment will decrease as the disease progresses. A photo album or scrapbook of the good times will be a source of pleasurable memories in future years.

This article was adapted from The Juvenile HD Handbook, *written and edited by Martha Nance, M.D., with additional editing by Randi Jones, Ph.D., Suzanne Imbriglio, P.T. and Betsy Gettig, M.S., C.G.C. This handbook is available from HDSA. Contact the National Office at 800-345-HDSA or visit the web at www.hdsa.org.*

Chapters

HDSA's 34 volunteer-based chapters serve as the vital link between the Society and our HD families. HDSA chapters bring the mission of the Society to those in need at the local level by providing services, support and education in the field. Chapters also work to increase awareness about HD in their community and to raise the necessary funds in the battle against HD.

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HDSA Centers of Excellence are major medical facilities that have been recognized by the Huntington's Disease Society of America as being committed to the understanding and treatment of HD. Once designated, each Center is awarded a grant to serve as a regional hub that provides comprehensive medical support and services to HD families. Presently HDSA funds more than $1.1 million in annual grants for the Centers.

While each Center has unique programs and services, all Centers offer a core set of services which include: neurologists; speech, physical and occupational therapists; genetic counselors and genetic testing services; trained social workers; regional referrals and nutritional guidance. The HDSA Centers of Excellence also serve as ongoing information and training resources for area physicians and neurologists, as well as allied healthcare professionals. The Centers act as regional representatives of HDSA, building understanding and support for the HD community through outreach programs, community-based "Celebration of Hope" events and regional fundraising activities.

With the addition of six new Centers of Excellence, HDSA will have 17 Centers in operation. The growth in this program stems directly from HDSA's long-term commitment to the care and understanding of HD.

What is an HDSA Center of Excellence *for Family Services?*

New HDSA Centers of Excellence

HDSA Center of Excellence at the University of Alabama at Birmingham

The clinic at the Birmingham School of Medicine was opened in 1994 and now serves as the Center of Excellence for the entire state of Alabama and portions of Mississippi, Florida and Tennessee. The Center has outreach efforts and support groups for HD families and caregivers. It also coordinates visits to nursing homes to provide in-service training.

HDSA Center of Excellence at the University of California at San Diego

This Center provides core services through the HD/Genetically Handicapped Persons Program (GHPP) clinic, including support groups for patients, caregivers, and at-risk populations. The clinic also delivers a comprehensive training curriculum to skilled and non-skilled care facilities. A mini-residency program is planned for incorporation into the medical school training program.

HDSA Center of Excellence at Baylor College of Medicine

Located at the Texas Medical Center, the largest medical care complex in the world, this Center provides core services to the vast area of Texas and neighboring Louisiana, Oklahoma, New Mexico and Colorado, while serving referrals from the entire United States, Canada, Mexico, Central and South America, the Middle East and Europe.

HDSA Center of Excellence at the University of California Davis Medical Center

From its location in central Sacramento, this Center serves HD patients and their families from a large geographic area including Northern California (including San Francisco and the Silicon Valley), as well as referrals from Nevada and Southern Oregon.

HDSA Center of Excellence at the University of Washington Medical Center

The University of Washington has offered genetic counseling and testing to HD families since 1957. Now, as a Center of Excellence, it provides clinical services to HD families in Washington, Wyoming, Alaska, Montana and Idaho and supports medical genetics outreach clinics in Alaska and Washington.

HDSA Center of Excellence at Washington University School of Medicine

The Movement Disorders Center of the HDSA Center of Excellence at Washington University School of Medicine, located within the Barnes-Jewish Hospital complex in St. Louis, Missouri, incorporates a comprehensive program that includes clinical care for patients, therapeutic trials, basic research and training of clinicians and scientists. The Center serves Missouri and Southern Illinois.

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Contact information may change after publication. Please contact the National Office at 800-345-HDSA or visit the web at www.hdsa.org for updated information.

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MIDWEST *(continued)*

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HDSA *2001* Annual Convention

The 2001 Annual Convention was held in San Diego, CA from June 29 - July 1. More than 665 attended the Forums, workshops and networking sessions during the three-day conference.

Barbara Boyle, HDSA National Executive Director/CEO and Donald King, Ph.D., Chairman of the Board of Trustees welcomed HD families from across the United States and reported on the state of the Society during their opening remarks. John Madden, Ph.D., chair of the 2001 Convention Steering Committee, and W.D. "Sandy" Sanford, President of the host chapter, greeted convention attendees and introduced California State Senator Dede Alpert during the Opening Session.

The second annual Family Services and Care Forum, sponsored by Athena Diagnostics, featured speakers that provided insight and information from their experiences as a caregiver, spouse, youth, or individual living at-risk in an HD family. The Forum was introduced by Vince Bertolino and James Scaffidi of Athena Diagnostics, moderated by Jane Paulsen, Ph.D. and facilitated by Mark Jacobson, Ph.D.

Members of the HDSA Family Services and Care Forum, sponsored by Athena Diagnostics

On Saturday morning, Christopher Ross, M.D., Ph.D., chair of the HDSA Medical & Scientific Advisory Committee, introduced the fourth annual AstraZeneca Research Forum which featured research updates by HDSA- sponsored researchers, Leslie Thompson, Ph.D., Robert Friedlander, M.D. and Chris Ross, M.D., Ph.D. Additional HD research projects were presented by Henry Paulson, M.D., Ph.D., Anne-Catherine Bachoud-Levi, M.D., Ph.D. and Karl Kieburtz, M.D., M.P.H. The highlights of the AstraZeneca Forum may be found on page 17.

Workshops and networking sessions for those with HD were presented by allied

Barbara Boyle and Marie Nemec

healthcare professionals from across the United States and included topics ranging from "Taking Care of the Caregiver" to "Overview to Medications for HD" to "Clinical Drug Trials for HD." A reception on Friday evening featured the presentation of an award to Marie Nemec for her 2001 Bike for the Cure fundraising event in support of *Generation 2000*. To date, Marie has raised more than $36,000 for HD research in her three cross country bike rides.

Members of the National Youth Alliance

HDSA Youth Alliance

HDSA hosted a luncheon for the National Youth Alliance (NYA) on Friday afternoon. Members were brought together to network and discuss how they could best bring the message of hope to the general public while raising funds to help advance research. A silent auction, sponsored by the NYA during the Saturday evening Awards Dinner and Gala, raised more than $1,300 for HDSA's *Generation 2000* campaign. This amount was doubled by HDSA's *Research Matching Gifts Challenge Fund* for a total of $2,600. Congratulations to the National Youth Alliance and a sincere thank you for your efforts to help *make this the last generation with HD*.

Generation 2000 Awards Dinner

On Saturday evening, convention attendees were invited to attend the *Generation 2000* Awards dinner. During the evening festivities, Barbara Boyle with Mikal Kitchens and Roger Vaughan, Co-Chairs of *Generation 2000*, presented a final report on phase one of the campaign that raised more than $2.7 million for HD research. That night, they officially kicked off phase two of *Generation 2000: Fulfilling the Promise*, a campaign to raise $25 million for HD research over the next five years. A new video premiered that featured Joan Rademacher and her two daughters, Annie and Mary, in their long-term care residence at Tewksbury Hospital, Drs. Jang-Ho Cha, Robert Friedlander, James Gusella, Nancy Bonini and Richard Morimoto. Also lending their voices to this powerful video are Valerie, Chris and Wendy Smith, Pam and Corey Stewart, Karen Milek, Nancy and Barry Goldring, Sherry Haberman, Don King and Nora Guthrie. HDSA also wishes to thank the Woody Guthrie Foundation & Archives, JFK/Hartwyck and Tewksbury Hospital.

During the countdown to the 2001 BMW Sweepstakes, excitement grew. The grand prize, a 2001 BMW Z3 Roadster or $25,000 cash, was presented to an anonymous donor from Texas. The second place prize of $5,000 was won by Kathryn Holland of Wyoming. The third place prize of $2,500 was presented to Thomas Barr of Illinois. Two fourth place prizes of $500 each were awarded to an anonymous donor from Georgia and Don King of Connecticut. Thomas Barr and Don King immediately donated their prize money to *Generation 2000*. A special thanks to BMW North America for their continued support of this successful fund raising campaign.

Following the BMW Sweepstakes, Jim Calhoun, Chair of the National Field Committee (NFC), came to the podium to present the HDSA Chapter Awards, which recognize specific achievements within HDSA chapters. A list of award winners can be found in the special Awards box on the following page.

HDSA National Awards were presented to outstanding individuals for their service and dedication to both HD and HDSA. This year, National Awards were presented for research, fund raising, service, giving a voice to HD, *Generation 2000*, Youth Alliance, Person of the Year

and Commitment to Finding a Cure for HD. A complete list of award winners will be found below.

As the Society wrapped up yet another successful convention in San Diego, those in attendance were eagerly planning for next year in Columbus, Ohio. Please be sure to join HDSA and our host, the Central Ohio Chapter, from May 31 - June 2, 2002. For more information, please contact the Huntington's Disease Society of America at 800-345-HDSA or visit the national web site at www.hdsa.org. Information for 2002 will be available in March 2002.

2001 AWARDS

CHAPTER AWARDS

Excellence in Special Events - Fundraising— Georgia Chapter

Excellence in Special Events - "First" Event for a Chapter—Texas Chapter

Texas Chapter receives award from Don King.

Excellence in Special Events - "First" Event for a Support Group
Syracuse Support Group

Excellence in Fundraising - Non-Event—San Diego Chapter

Excellence in Volunteer & Board Development—Western Pennsylvania Chapter

Excellence in Innovation—
Illinois Chapter

Chapter/Affiliate of the Year
Massachusetts Chapter

Special thanks to our exhibitors for their support:

Athena Diagnostics
California Caregivers Resource Centers
Broda Seating
HDSA Central Ohio Chapter
HD Bracelets
HD Quilt
Huntington Study Group
Indiana University School of Medicine
Ross Products, makers of *Ensure*
HDSA San Diego Chapter
Senior Lifestyles, Inc.
SunBridge Care & Rehabilitation for Lowell

NATIONAL AWARDS

Awards of Appreciation were presented to outgoing National Board of Trustee members **Mark Morris** and **Stuart Montgomery** for their service and dedication.

An **Award of Appreciation** was also presented to **The Bess Spiva Timmons Foundation** for their commitment and support to Family Care and Services.

The **HDSA Marjorie Guthrie Award for Outstanding Service** to the HD Community was presented to **Mark Morris**.

The HDSA Research Award, given in honor of Milton Wexler, was presented to **Steven Hersch, M.D., Ph.D.**

The HDSA Outstanding Commitment to Finding a Cure for HD Award was given to **Bruce & Janet Bergman**.

The HDSA Outstanding Fund Raising Award was presented to **Dennis & Sandra Voydetich** (below).

The HDSA Service Award, given in honor of Ruby and Joseph Horansky, was given to **Jane Paulsen, Ph.D.**

The HDSA Giving a Voice to HD Award was presented to **Stuart Montgomery**.

The HDSA Person of the Year Award was presented to **Philip Hardt**.

An **Award of Appreciation** was also given to the **San Diego Chapter** for their partnership in the sixteenth annual HDSA Convention.

The HDSA Youth Alliance Award was given to **Lisa Roberson**.

The HDSA Giving a Voice to HD Award-Youth Division was presented to **Emily Viau**.

Emily Viau with her family, BJ, Bryan and Debbie

The HDSA *Generation 2000* Award was presented to the **Pilskaln Family & Friends**.

Hal and Isabelle Pilskaln with the Massachusetts Chapter

HDSA Juvenile HD Award, given in honor of Kelly Miller, was awarded to **Cindy, Candi and Wayne Walters**.

HDSA *Advocacy*

The HDSA Government Relations and National Advocacy Initiative actively seeks to influence legislation that will have an impact on HD families by educating and forging relationships with elected officials, community leaders and the general public. HDSA promotes one on one meetings with elected officials to increase their understanding of HD and to increase awareness about those issues of concern to the HD community.

Advocate Bulletins

To broaden the base of this effort, HDSA established a nationwide network of advocates who help educate public policy makers through emails, faxes and letters. One way to reach elected officials is through CapWeb, an Internet-based advocacy tool, that provides legislative alerts and background information on proposed legislation that is of interest to the HD community, as well as sample letters that can be personalized by any advocate who does not wish to create a letter of their own. Advocates may either email the sponsoring representatives directly from CapWeb, or print out their letter for faxing or mailing. A link to CapWeb is available directly from the HDSA website: www.hdsa.org. HDSA email bulletins support HDSA's advocacy efforts by alerting supporters to pending legislation that requires their support and intervention.

Advocate Efforts

In 2001, HDSA advocates sent letters and emails to elected representatives on proposed legislation including: the Medical Research Investment Act, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and both the House and Senate bills regarding genetic discrimination and testing. Advocates, including the HDSA National Board of Trustees, also contacted President Bush on the issue of embryonic stem cell use in research.

HDSA Initiatives

In March 2001, HDSA scheduled a "*Day on the Hill*," where HDSA leaders met with their elected officials to create awareness about Huntington's Disease. In April, HDSA submitted a written statement to the House Appropriations Subcommittee on Labor, Health and Human Services and Education to increase federal funding to the National Institutes of Health in 2002. In June, HDSA joined representatives from several voluntary health agencies at a Health Policy Briefing hosted by the National Health Council, where they addressed congressional staffers on the issues and concerns of their members. HDSA was also invited to testify at the Senate Biotechnology Caucus, sponsored by Connecticut Senator Christopher Dodd. These appearances and statements help members of Congress to recognize the important role HDSA plays in generating support for major issues at the federal level. From our partnership with the National Institute of Neurological Disorders and Stroke to the increasing visibility of our advocacy efforts on Capitol Hill, HDSA has established a strong advocate base that can influence legislation. To become an HDSA advocate, please visit the national web site at ww.hdsa.org (click on Advocacy) or call (800) 345-HDSA today.

Become an HDSA Advocate!

Your voice can make a difference in Congress! With the assistance of AstraZeneca Pharmaceuticals, HDSA has established a nationwide network of advocates who will help educate public policy makers about issues of importance to the HD community, such as NIH funding for HD research, health insurance coverage issues, and genetic privacy and discrimination. This year's goal: an HDSA Advocate in every congressional district in the country!

If you would like to know more about becoming an HDSA Advocate, please complete and return the form below or contact hdsainfo@hdsa.org.

Your Name

Mailing Address

City State Zip

Evening Phone Email

Be sure to include your e-mail so that we can alert you to important bills in Congress. HDSA, 158 W. 29th Street, 7th Floor, New York, New York 10001-5300

"Thanks to HDSA, the word 'hope' is in our vocabulary"

Hope. A simple four letter word that means so much to a family facing the devastation of a degenerative disorder like Huntington's Disease. Hello, I'm Meredith Patterson and I am at-risk for Huntington's Disease. Living with the prospect that you may have a hereditary brain disorder that will slowly rob you of your ability to walk and talk, and letting those outside your immediate family know, is never easy. But with the loving support of my family and friends, I am here to tell you that there is progress being made and I want to share with you this holiday message of hope.

In 1967, when legendary folk singer Woody Guthrie succumbed to complications from HD, little was known about this deadly disorder. But Marjorie Guthrie became the catalyst of change when she drew together a handful of HD families across the US. Through perseverance and strength of will, Marjorie and her volunteers forged what is today the Huntington's Disease Society of America and gave HD families their first ray of hope.

In 1993, long before the Human Genome Project, a team of HD researchers cracked the genetic code and identified the gene responsible for a deadly disease. Each succeeding year has brought new discoveries and a quickening to the pace of HD research.

In just the past four years, HDSA has dedicated more than $10 million to HD research. But as strong as our financial support has been, it is still not enough. To achieve our goal - to find an effective therapy and a cure - HDSA must increase its commitment to research and we need your help.

In recognition of the amazing progress and momentum that HDSA has brought to HD research, the Christopher Radko Company has designed and donated a limited number of very special keepsakes that commemorate our commitment to finding a cure for HD.

The delightful frosty snowman symbolizes our hope for a future free of HD. His mittened hands, joined at the waist, represent the two arms of HDSA's research program that work in tandem to bring the most promising research forward at an accelerated pace. The snowflake on each mitten embodies the two pronged commitment of HDSA to the care and cure of Huntington's Disease while the snowflake on each shoulder represents the symbiotic relationship our HDSA sponsored researchers have with our HD families.
It was only through their sacrifice, faith and hope that the gene was located in 1993 and it will only be through the support of our HD families and friends that an effective treatment and a cure will be found.

The HDSA *Gift of Hope* is a wonderful way to remember a special someone while making a difference in HDSA sponsored research. A *Gift of Hope* can be yours with just a $25 donation (includes shipping and handling). A thoughtful card is included so you may give a gift of hope to friends and family this holiday season. Additional keepsakes are available with a further donation of $20 for each memento. Proceeds from the *Gift of Hope* program will enable the Society to increase our commitment to HD research.

Meredith Patterson, star of Broadway's hit musical 42nd Street, *invites you to give a* Gift of Hope *this season.*

Won't you consider giving a gift that will give for years to come? Together, we can *make this the last generation with HD.*

Please complete the order form found on page 34 and return it to HDSA no later than December 15th to ensure holiday delivery. If you wish, you may place your order by visiting our national web site at www.hdsa.org. Click on "Ways to Give" and then *HDSA Market*. The HDSA web site is a secure server. The *Gift of Hope* is a perfect gift for those near and dear to you. Please don't miss your opportunity to own one of these limited edition keepsakes and to give a gift of hope for a future free of HD.

How You Can Make a Difference in HD

You are vital to our continued commitment to fund research that will lead to effective therapies while the search continues for a cure to this devastating disease. Your gifts offer hope to our HD families while providing services and support as they navigate through the various stages of HD. Your gifts also enable the Society to increase public awareness while educating health care professionals. Your financial commitment is most urgently needed as we work to make this the last generation with HD.

There are many ways to give to HDSA's research, family service and education programs. Every dollar contributed is used to advance the care and cure of Huntington's Disease.

Contributions to any of HDSA's giving programs may be made through the national web site at www.hdsa.org. To make a gift on-line, simply click on "Ways to Give" and then select the program to which you wish to contribute. To make a donation to HDSA's "Gift of Hope" please click on "Ways to Give" and then "HDSA Market."

HDSA Gift of Hope

In recognition of HDSA's commitment to HD families across the US, the Christopher Radko Company has created and donated a limited number of HDSA snowmen that represent a gift of hope this holiday season. With a donation of just $25 you can send a *Gift of Hope* with your personalized message to a beloved family member or friend. Additional mementos and opportunities to include a personal message of hope and cheer may be yours with a donation of $20 for each extra snowman. A complete description of the HDSA *Gift of Hope* may be found on page 33 and a convenient order form will be found on this page.

Generation 2000: Fulfilling the Promise

In January 2001, HDSA launched phase two of *Generation 2000: Fulfilling the Promise* in an effort to raise $25 million for HD research over the next five years. Our scientists tell us that we are close to developing effective therapies and ultimately a cure for this deadly disease. But to accomplish our goal, we need your help.

Through the generosity of a few HD families, HDSA has created a matching gift fund for phase two of *Generation 2000*. Every gift made, whether through a Family Fund, individual donation, tribute or memorial will be matched dollar for dollar by the *Research Matching Gifts Challenge Fund*. Please consider making your donation today. Together we CAN *make this the last generation with HD*.

HDSA Family Funds

The HDSA Family Fund program was created to provide family members and friends with the opportunity to contribute more than one might be able to individually. A Family Fund may be created in honor of your family or in memory of a loved one. With an annual gift, a Family Fund may sponsor or co-sponsor an HDSA Coalition for the Cure investigator or a grant or fellowship recipient or it may partially fund a research project. Family Funds may also be designated to support any of HDSA's family service or educational programs such as *The Marker* magazine or the *Family Guide Series* which provides free information to members of the HD family and healthcare professionals. To create your Family Fund, please contact the National Office.

Cash and Pledges

Charitable cash contributions and pledges provide significant tax benefits while supporting HDSA's three-pronged mission statement - to fund HD research, provide services and support for our HD families and educate the public and healthcare professionals about HD.

Pledges may be made over a period of three years or longer and may be payable quarterly, semi-annually or annually.

Tribute & Memorial Gifts

Gifts made as a tribute to or in memory of a loved one help HDSA to provide the support and commitment needed to advance the care and cure of HD. A personal acknowledgement is sent to the individual or family in whose honor the gift has been made and a separate receipt is sent to the donor for tax purposes.

Stock, Securities or Real Estate

Gifts of stock, securities or real estate provide tax benefits while avoiding all capital gain taxes. Gifts allow the donor to claim the current market value (not the purchase price).

Heritage Club

Individual planned giving - You can remember HDSA in your estate plans by joining the Heritage Club. Use your will, trust or estate assets to make a contribution to HDSA while receiving

valuable tax benefits.

Below are types of planned giving that you may consider:

* Bequests - remember HDSA in your will
* Gifts of Personal Residence or Farms with a Retained Life Estate
* Life Income Gifts - Charitable Gift Annuity, Pooled Income Fund or Charitable Remainder Trust
* Gifts of Insurance

For more information about HDSA's Heritage Club please contact the National Office.

Corporate Matching Gift Fund

You may double or even quadruple your gift to HDSA by enlisting in your company's matching gift program. To double your gift, simply include your employer's matching gift form with your individual contribution. To quadruple your gift, be sure to specify that both your gift and your employer's matching gift are to be included in the *Generation 2000 Research Matching Gifts Challenge Fund.*

United Way and Combined Federal Campaign

If you give through the United Way or Combined Federal Campaign, please be sure to identify the Huntington's Disease Society of America (HDSA) by using the number **0526** on your pledge card.

All Family Funds, cash gifts, pledges, tributes, memorials or bequests established or renewed in 2001 will be matched through the

Generation 2000: Fulfilling the Promise

Matching Gift Fund

HDSA Market

HDSA is pleased to introduce the new HDSA Market an on-line shopping experience that offers visitors quality service and superior gift ideas while providing financial support to HDSA's many programs. Each gift or service promoted below has pledged a minimum of 5% and up to 100% of its sale to HDSA. The percentage of giving is listed beside each item.

We invite you to use the HDSA Market for all of your gift needs now and throughout the year. Use it for your family, friends and business acquaintances. The Market will be updated regularly in order to augment or replace seasonal offerings. Give a gift that continues to help all year. To visit the HDSA Market, please go to the national web site at www.hdsa.org, click on "Ways to Give" and then "HDSA Market/Shopping."

The *Gift of Hope* Snowman (100% of proceeds goes to HDSA)

Through the generosity of the Christopher Radko Company, HDSA is able to offer this limited edition Gift of Hope Snowman with a donation of $25. Additional *Gifts of Hope* are available with further donations of $20 each. These delightful Snowmen arrive in attractive gift boxes with gift cards provided for your convenience. Consider a *Gift of Hope* for each member of your family, your friends and co-workers. Supplies are limited so act today. See page 33 for more information about this program and page 34 if you wish to place your order by mail.

HDSA Holiday Card Collection (40% of your order goes to HDSA)

The 2001 HDSA Holiday Card brochure can be found on page 26 of this magazine or on the national web site. These cheerful holiday cards bring greetings and best wishes to friends and family during a joyous season. Holiday cards can be ordered through December 3rd for Chanukah delivery and through December 15th for Christmas.

Please help to support HDSA through holiday cards. Place your order today.

FTD.com (15% of your purchases goes to HDSA programs)

Everyone loves to receive fresh flowers. Whether it's a birthday, anniversary, wedding or just to make someone feel good, flowers are an easy and thoughtful way to let someone know you care. FTD is one of the most widely respected floral delivery services worldwide. Through a special program with HDSA, FTD.com donates 15% of every order received through the HDSA web site or through a special code given on telephone orders. FTD offers a wide assortment of floral arrangements and general gifts. Please visit them today through the HDSA web site or call 800-SEND-FTD and be sure to mention department **3015** when ordering to ensure that your order is credited to HDSA.

GiftCertificates.com (5% of your gift certificate purchase goes to HDSA)

Gift certificates are a popular way to give a gift to someone from a favorite merchant without worrying about size or whether the recipient will like your selection. GiftCertificates.com provides original gift certificates to hundreds of stores, restaurants and services nationwide. When you order through the GiftCertificates.com link found on the national web site, HDSA will receive 5% of the designated amount of your gift certificate. You can order gift certificates to local restaurants, national mail order merchants and even nationally recognized mall stores including Bombay, J. Crew, Shaper Image, Blockbuster®, and Orvis.

Please support HDSA's research, education and family services program throughout the year by using the vendors and services that directly benefit HDSA. Together, we can make this the last generation with HD.

RESEARCH ALLIANCE AWARDS

HDSA Chapter Research Alliance Awards are presented each year to those HDSA chapters that make restricted gifts to research beyond their normal level of support. As of June 30, 2001, more than $317,500 in gifts and pledges has been made by the following chapters with South Florida contributing more than $80,000 through their signature event the Triathlon:

South Florida
Georgia
Indiana
Michigan
Central Ohio
Northern California
Northeast Ohio
Washington Metro
Massachusetts
Connecticut
Maryland
Upstate New York
Kentucky
Illinois
New Jersey
Oklahoma
St. Louis
Rocky Mountain
Arizona
Western Pennsylvania
Northwest Texas

ADVANCE DIRECTIVES continued from page 20

medical record. Copies should be given to the person's doctors, healthcare proxy and healthcare facility. If possible, it should be produced during any admission to a healthcare facility. An advance directive is only useful if its existence is known.

The decision to write an advance directive does not have to be made alone. An individual or family may choose to ask their family doctor, social worker, chaplain or minister to help them with the process. The goal is to create a document that gives direction to the family and healthcare providers and peace of mind to the person with HD.

Additional information on Advance Directives is available from your local department of health, the AARP (American Association of Retired Persons) at (800) 424-3410, or The Partnership for Caring at (800) 989-9455.

PREIMPLANTATION TESTING continued from page 23

Even after the testing, there were tense moments. "The chances for success with *in vitro* fertilization used to be 20%. They are up to 50% at the clinic we went to," says Becky. "But we were lucky. It worked the first time." Martin and Becky's baby was born on Dr. Hughes' birthday. This was the thirtieth baby born without HD, using this technique.

Would they recommend this process to other couples? "I would do it again," says Becky. "Even with the difficult things: the money, six weeks of hormone shots that made my mood go up and down, it was worth it when you consider what you end up with." Martin agrees. "It is a wonderful opportunity to take this disease out of your family."

Martin and Becky requested that their real names not be used because of concerns that this information might affect their ability to get insurance. HDSA invites you to be an advocate and work to protect the medical privacy rights of all people with HD (see page 32).

HEALTHCARE PROFESSIONALS continued from page 22

stress and keep the caregiver connected to the community. Given the level of stress involved in their task, caregivers must watch for the warning signs of depression: changes in sleep patterns, loss of interest in normal activities, feelings of hopelessness or overwhelming sadness. Support groups for caregivers are run by HDSA Chapters in many states. Information on HDSA Chapters can be found on page 27 while support group information may be found on the national web site at ww.hdsa.org (click on "Getting Help").

The editor wishes to thank the National Family Caregivers Association for information used in this article. Their website is www.nfacares.org.

HDSA *thanks*

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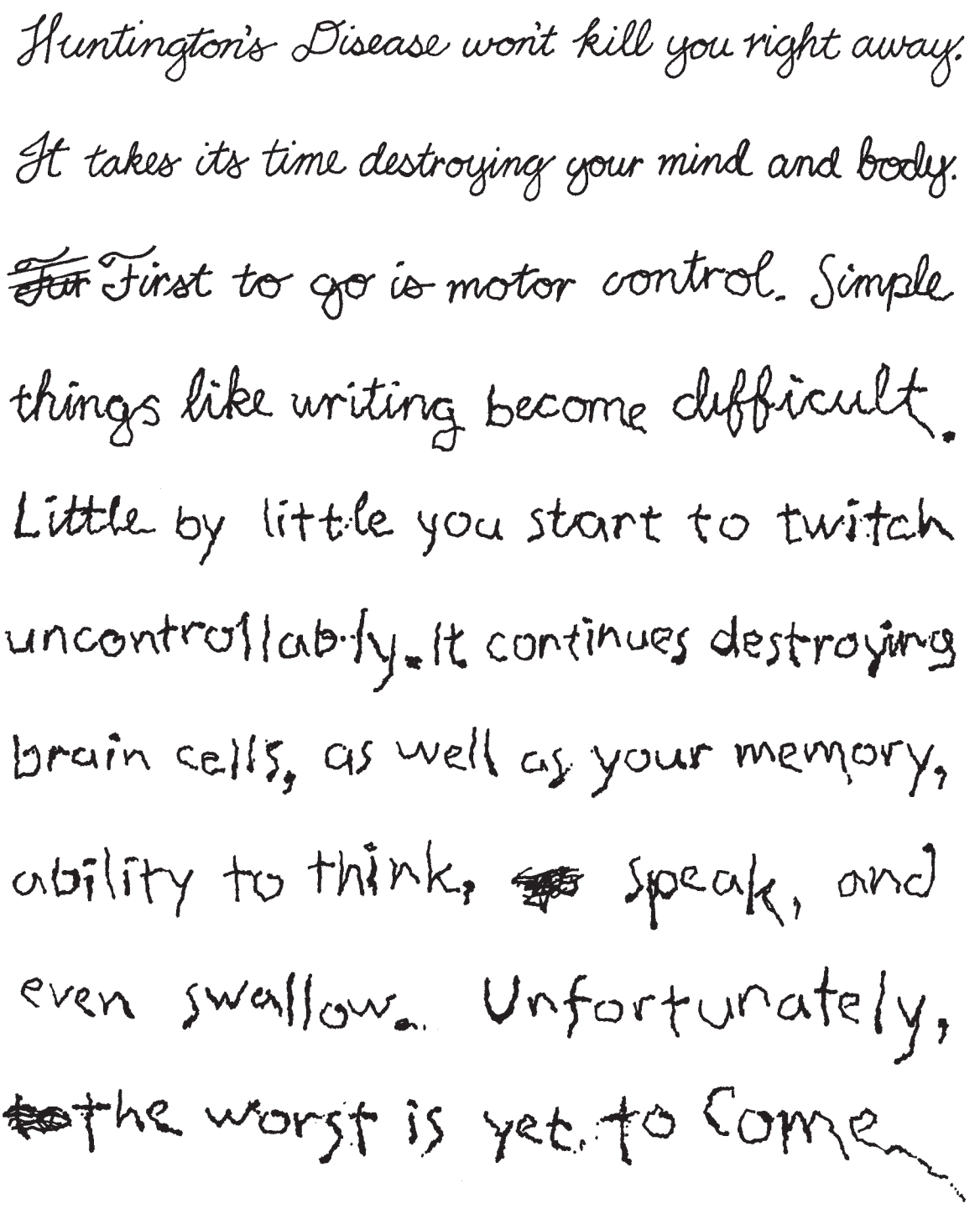
ATHENA DIAGNOSTICS

for their support



There is currently no cure for the hereditary brain disorder known as Huntington's Disease. But we're closer than ever to finding one. Your contribution could help stop the suffering of thousands. Please make your gift today and help HD research to continue.

You can double your gift today by indicating that you want it to be matched by *HDSA's Research Matching Gifts Challenge Fund* for *Generation 2000: Fulfilling the Promise.* Together, we CAN *make this the last generation with HD!* Visit our website at www.hdsa.org or call **1-800-345-HDSA.**

Huntington's Disease Society of America
158 West 29th Street, 7th Floor, New York, New York 10001-5300

Generation 2000: Fulfilling the Promise

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