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At Risk for Huntington's Disease

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## Yale's partnership against Huntington's disease: an alumnus reconnects and finds hope as scientists pursue 'Viagra for the brain' and other solutions

Kenneth P. Serbin  
*University of San Diego*

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# At Risk for Huntington's Disease

*HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.*

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## HD Links

[Huntington's Disease Society of America](#)

MONDAY, JUNE 04, 2012

## Yale's partnership against Huntington's disease: an alumnus reconnects and finds hope as scientists pursue 'Viagra for the brain' and other solutions

The revelation in 1995 that I was at risk for Huntington's disease, followed by my positive genetic test for HD in 1999, thrust me into a role as an activist, a journey to understand the biotechnological frontier, and a fight for my life.

However, for many years, and even after "coming out" in [a major speech to scientists](#) in February 2011, HD has remained my radioactive semi-secret because of the stigma surrounding the disease and my fear of genetic discrimination.

In those early years of confronting HD, I needed to open up to someone – and to seek help for the cause. Beyond some branches of my family and my local HD support group, I turned to the people I trusted most: fellow [Yale University](#) alumni, some close friends, others within a circle of trust. Many lent a sympathetic ear, offering donations, contacts, and advice.

Above all, they helped me feel less lonely inside the terrible "Huntington's closet."

[Dr. Martha Nance](#), a neurologist in Minneapolis dedicated to finding treatments for HD, became one of my closest HD confidantes. Brooklyn-based journalist [Norman Oder](#) suggested the idea for this blog. Editing nearly every article, Oder has become more than a friend: he is my Huntington's alter ego.



*Dr. Martha Nance and Gene Veritas in San Diego, 2007.*

Yale's seal, which includes the Latin phrase "[Lux et Veritas](#)" (light and truth), echoed in my choice of an HD pseudonym, "Gene Veritas," the "truth in my genes."

[International Huntington Association](#)  
[Huntington's Disease Drug Works](#)  
[Huntington's Disease Lighthouse](#)  
[Hereditary Disease Foundation](#)  
[Huntington's Disease Advocacy Center](#)  
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[Chris Furbee: Huntingtons Dance](#)  
[Angela F.: Surviving Huntington's?](#)  
[Heather's Huntington's Disease Page](#)

Now, in a way I would never have imagined, I have come to rely on Yale itself in my fight against HD.

At the CHDI Foundation's Seventh Annual HD Therapeutics Conference, held February 27-March 1 at the Parker Palm Springs in Palm Springs, CA (a hotel owned by fellow alum and real estate developer Adam Glick), I heard exciting news about how scientists in the Yale School of Medicine will help prepare the way for clinical trials of potential therapies.

(Backed by a group of anonymous donors, the non-profit [CHDI](#) once stood for "cure Huntington's disease initiative" but today simply represents the name of the foundation, which focuses exclusively on the search for HD treatments.)

In my unrelenting drive to translate HD science into understandable terms, I dubbed these compounds "Viagra for the brain," a phrase that refers not to the salacious aspects of the famous drug but to these compounds' biochemical similarity to Viagra.

I also decided to visit the scientists' labs to deepen my understanding of their crucial work, to offer my assistance, and to give myself a shot of much-needed hope.

Below, watch my short introductory video of the visit.



### Hope for for Huntington's Disease at Yale University: A Report from Gene Veritas

from [Gene Veritas](#)

04:17



#### An emotional return to New Haven

I had returned only twice to Yale – in 1983, a year after graduation, and, during a memorable [cross-country trip](#) with my wife and daughter in 2010 in my effort to enjoy life to the fullest before the inevitable symptoms of HD set in.

This time I arrived in New Haven on May 28 after a two-hour train ride from Manhattan.

That evening, walking through the Yale campus almost 30 years to the day after I graduated, I experienced a flood of memories – some painful, some hilarious, and many, many warm and wonderful.

I remembered the sacrifices my grandparents and parents had made to help me to attend one of the world's top institutions of learning. I recalled how, as the grandson of immigrant grandfathers and the son of working-class parents, I strived to reach the top academically and then

professionally.

As I peered into the darkened windows of the *Yale Daily News*, where I served as a reporter, I wondered whether my 12-year-old daughter, who writes well and recently sent letters to 35 U.S. Senators about my plight and the need to reverse their opposition to health care reform, might herself someday become a journalist. I imagined the two of us critiquing news articles together. She's finishing up sixth grade this month, and she says she wants to attend Yale. I imagined her striding confidently through the offices.

It seemed almost yesterday when I walked to classes and debated and laughed with friends in the dining halls of the university's grand gothic buildings. Once imposing, they no longer felt intimidating. Life is fast, I thought with a tinge of sadness.

*My* life was abruptly sidetracked by HD. My mother died in 2006, and my father, with a broken heart, followed her in 2009. I wondered: will HD prevent me from helping my daughter apply for college and begin her own path in life?

Yale has generated many of America's leaders, and it inspires leadership in various ways. I pondered how I had to rise, along with many others, to an unexpected leadership role in the fight against the disease. And I reminded myself that I must do my part to keep the flame of leadership burning, within myself, for as long as I can; within my family; and within the HD movement.

Back in my hotel room later that evening, I prepared for the next day's emotionally charged meetings at the School of Medicine. It was a place I didn't go to as an undergraduate, I thought, and represented a new phase in my HD activism, in my relationship with Yale, and in my life. These scientists could help save me.

### **Catching the disease early**

As part of a global effort to eradicate HD, the Yale scientists will play an important role in investigating some of the disorder's mysteries and in seeking effective treatments. The university's faculty in neuroscience, neuropharmacology, and other fields provide a supportive context for this work.

Two of the scientists, Hoby Hetherington, Ph.D., and Doug Rothman, Ph.D., are starting groundbreaking work on important facets of HD.

Dr. Hetherington will apply his knowledge of epilepsy, brain trauma, and brain scans to study an energy deficit in HD resulting from insufficient adenosine triphosphate, the basic fuel for our cells.

Using Yale's 7 Tesla MRI scanner, one of only a few dozen in the world with ultra-powerful magnets, Dr. Hetherington will scan humans using a method called MRSI (magnetic resonance spectroscopic imaging).

Dr. Hetherington hopes to determine whether the energy deficit in HD is a cause or an effect and, in the process, to produce a clearer picture of the disease as it actually occurs.

MRSI involves the MRI machine augmented with two pieces of additional equipment – a head detector and shim insert – permitting him to track the energy deficit by obtaining clear, high-resolution images of study participants' brains.

As Dr. Hetherington explained, the detector allows him to adjust the readouts of each scanned individual's brain by accounting for distortions in the magnetic field caused by the presence of the head. It also accounts

for the heat generated by the head. Using the detector, he can contour the magnetic field and also pick specific regions of the brain to excite.

Dr. Hetherington's lab designed and built the first generation of the detector and continues to develop and test new versions of the device. The detector is now in commercial development for more widespread use.

Dr. Hetherington will use the detector in his planned study of gene-positive, asymptomatic HD people like me.



*Dr. Hoby Hetherington places a special head detector in the 7 Tesla MRI scanner in his lab at Yale University (photo by Gene Veritas).*

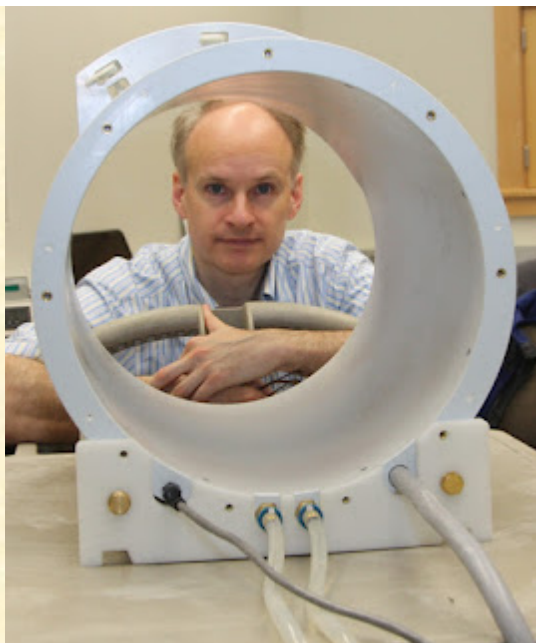


*Dr. Hetherington explains the innards of the head detector (photo by Gene Veritas).*

To compensate in yet another way for distortions in the scanner's magnetic field, Dr. Hetherington employs the shim insert, which he also helped to design. Like a common shim used to straighten objects in woodworking or masonry, the shim insert levels out the scanner's magnetic field. He uses the shim to do the opposite of what the head of the scanned individual does to the field. This makes the field uniform and thus easier to read.

A standard scanner shim typically can do eight adjustments, Dr. Hetherington explained. Yale's can do about 30.

This shim will play an important part in Dr. Hetherington's HD scans, in which he will examine areas of the brain (such as the basal ganglia) where distortions are created by the presence of the sinuses and the ear canals.



*Dr. Hetherington and the shim insert (photo by Gene Veritas)*



*Dr. Hetherington explains an actual anatomical image of the brain obtained from the 7 Tesla scanner (photo by Gene Veritas).*

“It’s catching the pathology before it’s become lethal or progressed,” Dr. Hetherington said of his lab’s technology during my visit while showing me images from an epilepsy study. “That’s the idea of trying to have an early marker of what’s going on. If the cells have died already, the structure gets small. You can see that on standard anatomical imaging, but that’s kind of too late.”

### **Boosting creatine**

Looking ahead 50 to 100 years, Dr. Hetherington speculated that patients with brain-based disorders such as HD and epilepsy may take a common drug to correct the problems they cause in bioenergetics.

Dr. Hetherington explained that the HD study will seek to measure phosphocreatine levels in the brain. Brain cells produce phosphocreatine, which is essential in bioenergetics, from creatine, which is also created by the body and can be taken in the form of a supplement.

Beginning with my participation in the [Huntington’s Disease Drug Works](#) (HDDW) program, I have taken creatine for nearly a decade in an effort to stave off symptoms. Creatine is currently under study in an HD clinical trial. ([Click here](#) to read more about HDDW founder Dr. LaVonne Goodman’s latest assessment of creatine and other supplements.)

“If you can boost the whole pool (of creatine), you’ll have more phosphocreatine around,” Dr. Hetherington said of the theory behind creatine supplementation.

### **Paralleling mice and humans**

Supported by CHDI, Dr. Doug Rothman, Ph.D. a pioneer in the use of magnetic resonance spectroscopy (MRS) and the Director of Magnetic Resonance at Yale, will employ MRS to examine another kind of energy deficits in the mitochondria, the powerhouses of the cell, in transgenic mice.

HD patients often need a higher-than-average caloric intake.

Rothman’s work could provide important clues as to how Huntington’s kills brain cells – and what treatments might stop it. He hopes to extend the experiment to humans, beginning with a 4 Tesla scanner and perhaps later using the 7 Tesla scanner and its accessories.

“It’s really important to keep an eye on what are the relevant aspects of a mouse model,” Dr. Rothman commented, noting that transgenic animals can manifest symptoms differently than humans, and that the mitochondria are more evolved in humans than in mice. “The only way to do that is to really explore, hopefully in parallel, what’s happening with human subjects.”



*Dr. Rothman at work in his office (photo by Gene Veritas)*

### **Alleviating symptoms, strengthening the brain**

Also with support from CHDI, two other Yale research groups will assess compounds that, if successful, would improve memory and cognition, arrest some of the psychiatric symptoms, and act as neurotrophins, so-called “fertilizers” for the brain. At least one of these neurotrophins (BDNF, brain-derived neurotrophic factor) is severely deficient in HD.

As noted above, I dubbed these substances, developed by Viagra producer Pfizer, “Viagra for the brain” because the substances belong to the same class of drug as Viagra, an inhibitor of an enzyme known as a phosphodiesterase (PDE).

Although targeting different PDE families than the PDE-5 targeted by

Viagra, the biochemistry is very similar. Essentially, the new compounds are cousins of Viagra, aiming to inhibit other PDEs.

The Yale scientists will test these compounds in collaboration with CHDI's "drug hunters" and Pfizer. One coordinator of the three-way partnership is Ladislav Mrzljak, M.D., Ph.D., CHDI's director of neuropharmacology and a former postdoctoral fellow in Yale's Department of Neurobiology.

Scientists hope that inhibition of PDEs will compensate for some of the changes occurring in HD.

With new research showing that some PDE inhibitors reverse symptoms in mice, CHDI and Pfizer recently began collaborating with the ultimate goal of taking them into clinical trials.

"There are currently no PDE inhibitors marketed for central nervous system diseases," Christopher Schmidt, Ph.D., a senior director at Pfizer, explained. "This is new territory."

Mihaly Hajos, Pharm.D., Ph.D., a former Pfizer scientist and neurophysiologist with a background studying schizophrenia and Alzheimer's disease, aims to detect whether the same inefficient use of the brain's information processing (a so-called "auditory gating deficit") that occurs in humans with HD also occurs in mice and rats genetically engineered to have the disease. If so, Hajos will then test PDE inhibitors as a remedy.

The experiment also could validate the electrical signals as a good biomarker, or measure, of the inhibitors' impact on people.



*Dr. Mihaly Hajos (center) with assistants Elizabeth Arnold and Dr. David Nagy (photo by Gene Veritas)*

### **Studying nonhuman primates**

Another project involves the husband-wife team of Graham Williams, D.Phil., and Stacy Castner, Ph.D., neuroscientists in the Department of Psychiatry who are specialists on schizophrenia and substances known as "cognitive enhancers." The duo will test the effects of PDE inhibitors on cognition in normal, healthy nonhuman primates. These subjects contrast sharply with the transgenic, diseased mice, rats, flies, and even sheep and pigs used in other Huntington's research.

"We can't be dependent on the genetic model," Dr. Williams explained, emphasizing the need to view the disease and the effect of potential drugs from various perspectives.

If the inhibitors work, Drs. Williams and Castner will submit the animals to harmless brain scans using FDG-PET to localize areas of the brain affected. These measurements could help predict the impact of the



inhibitors in humans.

Successful studies in the nonhuman primates could help to accelerate the process of getting the inhibitors into human trials and ultimately approved as drugs, a process that could take five to ten years.

The PDE inhibitor projects seek ways to intervene early in the disease, before disabling symptoms occur. The potential therapies could help prolong my life and the lives of tens of thousands of gene-positive and symptomatic individuals.

### **A key workshop: from animals to humans**

On May 31 and June 1, I observed yet another aspect of Drs. Williams and Castner's research by participating with them in a CHDI meeting in Manhattan titled "Translatability of Cognitive Readouts Workshop." With some two dozen participants and organized by Dr. Allan Tobin, one of CHDI's two chief scientific advisors, the workshop aimed to help CHDI move from testing of potential treatments in animals to human clinical trials.

Dr. Mrzljak also took part, as did Dr. Ethan Signer, CHDI's other chief scientific advisor, Dr. David Howland, director of in vivo biology, and Dr. Beth Borowsky, director of translational medicine. Robi Blumenstein, the president of CHDI's sister management firm, kicked off the meeting.

CHDI will release the conclusions of the workshop in the near future. Watch my short interview about the meeting with Dr. Tobin in the video below.



## **Moving from Animals to Humans in Huntington's Disease Research: An Interview with Dr. Allan Tobin**

from **Gene Veritas**

08:12 |



The workshop was quite intense and intimate, to say the least. Sitting at a table with one another for eight hours on two consecutive days, and sharing dinner and drinks in lower Manhattan the evening of May 31, we formed new friendships and professional relationships. Dr. Tobin purposely plans the workshops in this way to extract the maximum of candor and new ideas.

I was invited to the meeting as an "observer." I thought I would quietly sit in the back and take notes.

However, to my surprise, Dr. Tobin seated me at one of the heads of the workshop table. Just before the event began at 9 a.m. on May 31, he asked if I would mind sharing my story with the scientists, and to be "interviewed" by Dr. Julie Stout, an American HD researcher based in Australia.

A number of the invitees, such as Drs. Williams and Castner, had devoted their careers to non-HD conditions and questions, so for many in the room I was a first contact with a person from an HD-affected family.

What I expected to be a few minutes of introduction to the disease turned into a 90-minute discussion about the many social ramifications of the disease. In an effort to contribute to the questions of translatability and cognition, I described such symptoms as my mother's depression, her loss of the ability to work, her inability to interact with her granddaughter and other family members, and the ways in which our family and her physicians attempted to deal with her symptoms. I also spoke about the fear surrounding genetic testing.

Dr. Stout commented that telling my story helped the scientists understand what it's like to live with HD. Scientists, she observed, need the collaboration of those confronting HD in the quest for solutions.

At the end of the workshop, I thanked Dr. Tobin, CHDI, and the scientists for allowing me to share my story – which, I pointed out, was just one of thousands of such stories one could hear from the HD community.



*CHDI translatability workshop participants, with Gene Veritas standing in back of room (photo by Jerry Turner, CHDI)*

### **Yale and the big picture**

Together with CHDI and Pfizer, Yale scientists will furnish pieces of a very large and complex Huntington's puzzle currently under study by researchers throughout the world in academic labs, pharmaceutical companies, and medical clinics. CHDI, as well as governments and other organizations, supports many of those projects in producing what most scientists project as an "HD cocktail" of therapies for managing the disease and allowing those affected to lead normal and productive lives. (Scientists don't speak of "curing" HD, because of its immense complexity and the fact that the defective gene cannot be removed from the body.)

The path, however, isn't simple. At Yale, Drs. Hetherington and Rothman voiced concern about the potential lack of volunteers for their research involving brain scans. Indeed, stigma and other factors threaten to leave scientists with too few research participants in which to adequately test drugs for safety and efficacy. Tragically, the drive to halt Huntington's could stall. I pledged to help spread the word of the scanning studies in the Huntington's community.

In the quest for treatments, scientists and patients depend on each other. Likewise, the many disease communities share a mutual goal. By helping to solve Huntington's, Yale's scientists will also assist those fighting Alzheimer's, Parkinson's, and many other conditions that afflict millions – as well as the estimated tens of millions of victims of thousands of other

genetic and orphan conditions, the focus of Yale's new [Center for the Study of Mendelian Disorders](#).

Yale, its alumni, and its scientists have lent an enormous hand in my family's fight. I have already gained strength and support from a network of Yale ties. Someday I may take a Huntington's drug tested in a Yale lab.

The place that ignited my intellectual passion and launched me into life once again holds one of the keys to my future. This is the American university at its best – engaging in cutting-edge drug discovery, aiding a community long beleaguered by stigma and hopelessness, and affirming life.

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Posted by [Gene Veritas](#) at [11:37 AM](#)



Labels: [activism](#) , [Alzheimer's](#) , [brain](#) , [CHDI](#) , [clinical trial](#) , [closet](#) , [coming out](#) , [discrimination](#) , [drug](#) , [gene-positive](#) , [Huntington's](#) , [leadership](#) , [PDE inhibitor](#) , [Pfizer](#) , [scientist](#) , [stigma](#) , [treatments](#) , [Yale](#)

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