

# Hereditary Disease Foundation

Huntington's Disease 2000 - Change, Advances, and Good News (CAG)<sub>n</sub>

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Prepared by Lisa J. Bain

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**Abstract:**

At the Hereditary Disease Foundation sponsored, August, 2000 Huntington's Disease research conference in Cambridge, Massachusetts, "Change, Advances, and Good News (CAG)<sub>n</sub>," progress was reported in numerous areas yet the unanswered questions continued to outnumber those for which there were clear answers. New or modified models for studying the basic biology of the disease and developing new therapies were described. Research aimed at clarifying the relative importance of proteolysis, aggregation, and chaperone proteins were explored, as were the resulting cellular changes, including alterations in gene expression and transcription, electrophysiology, and apoptosis. While no single mechanism emerged as one that would adequately explain this complex disease, increasing effort is being expended towards the goal of finding a treatment. Several new high-throughput screening methods for compounds were described. At least two agents are already in human clinical trials, and other possible therapeutic approaches are under study, including environmental enrichment, inhibition of aggregation, and various approaches that aim to either correct the genetic defect or eliminate or interfere with the mutant protein.

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At the Hereditary Disease Foundation sponsored, August 18-20, 2000 Huntington's Disease research conference – "Change, Advances, and Good News (CAG)<sub>n</sub>" Alexsey Kazantsev showed videotaped footage of polyglutamines forming aggregates in mammalian cells. Following a slow nucleation step, aggregation proceeded rapidly, with a single "seed" gathering all soluble polyglutamines

in the cell into a single aggregate within 40 minutes.

Would that the fragments of knowledge about HD come together so rapidly and cleanly. As demonstrated by the range of topics discussed at the meeting, HD researchers have yet to identify a single event that would clarify the pathogenic mechanisms of this devastating disease. Yet while the HD picture remains murky, significant progress was reported in understanding the biology of the disease; and emerging from the soup were several promising therapeutic strategies, including a few approaches already moving into clinical trials.

**New models**

Key to understanding the molecular biology of HD and devising potential therapeutic strategies has been the development of new animal and cellular models of the disease to complement and confirm the existing mouse models, especially the R6/1 and R6/2 mice created by Gillian Bates.

Peter Detloff described a "knock-in" mouse model, in which the short CAG repeat of the mouse HD gene homolog (Hdh) was replaced with expanded CAG repeats even larger than those associated with human HD. Detloff's mice with 150 repeats exhibit a late-onset severe phenotype, with behavioral and neuroanatomic abnormalities consistent with HD as well as the formation of ubiquitinated inclusions relatively specific to the striatum. Such inclusions have previously been found in the brains of HD patients.

Another approach to genetically modifying mice that simulate HD was described by Blair Leavitt, who developed a yeast artificial chromosome (YAC) transgenic mouse containing one to two

copies of the full-length human HD transgene with 72 CAG repeats. Leavitt said that because the YAC transgene includes all the endogenous regulatory proteins and the endogenous promoter from the human HD gene, the transgene is expressed in a developmentally appropriate manner and in different tissues with expression very similar to that of endogenous protein in humans. The YAC72 mice have now been followed for 24 months and appear to replicate the slowly progressive neurodegenerative phenotype of human HD. At 12 months of age, progressive degeneration of the medium spiny neurons in the striatum is observed, and by 18 months of age, intranuclear aggregates can be found. Yet at 24 months of age, these mice exhibit no increase in mortality, no increased level of weight loss, and no evidence of diabetes. They do, however, display a biphasic movement disorder, with hyperactivity between zero and twelve months, followed by a return to normal or hypoactivity.

These mice will be valuable for studying the early pathogenic processes; to find out what is happening to the full-length protein, what is causing neuronal dysfunction, and what precedes neuronal degeneration, said Leavitt. But the slow onset of pathology limits their practical use as screening reagents. In order to create a mouse with an earlier readout, Leavitt's group generated several lines of YAC72 mice with increased transgene copy numbers that express mutant htt at up to four times the endogenous level. High expressing lines exhibit abnormal motor behavior, decreased body weight and increased neurodegeneration. Striatal degeneration begins at four months of age in these mice, with massive degeneration by six months. These mice, said Leavitt, will make it

possible to screen reagents with potential therapeutic value.

“What we're really focusing on is a hard endpoint for these therapeutic trials,” said Leavitt. “We don't want to find symptomatic treatments, we want to find treatments that affect neurodegeneration of the medium spiny neurons.”

David Borchelt described yet another transgenic mouse model, one in which the transgene is under the control of the prion protein promoter. By comparing mice transgenic for HD and for dentatorubral and pallidoluysian atrophy (DRPLA), another neurodegenerative disease caused by polyglutamine expansion, Borchelt's group has demonstrated the influence of protein context on the phenotypic expression of polyglutamine toxicity. According to Borchelt, these two groups of mice exhibit similar pathology early on, but distinct behavioral phenotypes. Both models develop neuronal intranuclear inclusions; however, cytoplasmic aggregates of protein form only in the HD mouse.

A different type of genetic animal model of HD was described by Nicole Deglon. She used lentiviral vectors to deliver the genes coding for the first 171 amino acids of htt with either 19 or 82 CAG repeats to the striata of rats. She reasoned that this approach would allow her to assess the pathogenic consequences of overexpression of htt fragments in the CNS. She observed pathologic features only when the expanded length htt was injected: accumulation of htt protein, ubiquitinated neuronal inclusions, and shrinkage of the striatum. The model not only helps define how polyglutamine length contributes to the pathology, but also is being used to test potential therapeutic agents.

Mice, of course, are not the only models that have proved useful for studying genetic diseases. Leslie Thompson, for example, is one of several researchers working with a *Drosophila* model, in which expanded polyglutamine expression induces cytotoxicity, neuronal degeneration, and early death regardless of the gene into which the polyglutamine tract is inserted. And Christian Neri has developed a transgenic *C. elegans* model to study the effects of expanded polyglutamine tracts in neurons. He reported polyglutamine length-dependent loss of touch sensitivity in the tails of young adult worms but no evidence of cell death, indicating cell dysfunction. Both the *Drosophila* and *C. elegans* models provide new avenues through which to explore the consequences of polyglutamine expansion, as well as new platforms for screening of potential therapeutic agents.

Whether more different animal models are needed, said Peter Detloff, is an unanswerable question. As new therapeutic strategies are developed, the key may be to find something effective in all the animals, and then translate it to humans. Multiple strains of mice also offer the opportunity to explore the influence of genetic background, gene expression, and protein context, among other aspects.

### Pathogenic mechanisms

The expanding number of animal and cell models to study HD has yet to yield a coherent picture of the mechanism of pathogenesis. Rather, what appears to be emerging is a complex pathway from expression of the mutant gene to disease, with multiple trouble spots.

#### *Proteolysis*

Previous work has suggested that cleavage of mutant htt by proteolytic enzymes may be aberrant, resulting in fragments that induce toxicity or cell death.

Vivian Hook examined the proteolytic fragments of htt in the cortex and striatum of human HD and normal brain tissue. Using domain-specific anti-htt antibodies, she identified different patterns of htt fragments in the striatum and cortex, indicating proteolysis at different “protease susceptible domains.” Further, she showed that the striatum is the only tissue in which there was a difference in htt fragments between HD and normal brains. She also demonstrated tissue-specific ubiquitination of certain fragments, with more prominent ubiquitination in the striatum versus the cortex. Her results suggest a possible mechanism that could help explain different pathologic features observed in those two areas of the brain.

Roy Dyer, however, presented different results. Also working in human brain tissue, Dyer’s results suggest that htt is not differentially proteolyzed in either a disease- or tissue-specific manner and exists mainly as full-length protein. He also found that htt is less soluble in HD brain than in control brain, suggesting that decreased solubility, rather than alterations in proteolysis, is an important feature of the disease; and that full-length htt, rather than small fragments, are responsible for the toxic effects.

In order to resolve the contradictory results presented by Hook and Dyer, Ethan Signer suggested the two researchers conduct side-by-side experiments.

Meanwhile, evidence from several laboratories implicates the caspase family of proteases in HD. In response to an apoptotic stressor, htt is cleaved *in vitro* by caspase-3 at two positions, and by caspase-6 at a third position. Cheryl Wellington presented evidence demonstrating a similar process *in vivo*, and proposed that the N-terminal htt fragments generated by caspase-induced cleavage contribute to apoptosis and

neurodegeneration. Wellington generated an antibody that recognizes the fragment that results from caspase-3 cleavage at amino acid 513, but does not recognize full-length htt. She used this antibody to test for htt cleavage by injecting kainic acid, which induces excitotoxic neurodegeneration. Following intraperitoneal injection of kainic acid, she demonstrated caspase-3 mediated cleavage of htt in hippocampal neurons undergoing neurodegeneration.

### **Aggregation**

One of the common features of polyglutamine expansion disorders is the presence of intracellular protein aggregates. While it remains unclear what role these aggregates play in the disease process, they have been the focus of much attention. Alexsey Kazantsev's videotape demonstrating the formation of a seed or nucleus as an intermediate of aggregation was but one of several bits of information helping to define the mechanism of aggregation. Kazantsev also showed that genetically-engineered protein suppressors of aggregation blocked polyglutamine aggregation in cells expressing high levels of extended polyglutamine tracts (104 repeats). Using these suppressor transgenes, Kazantsev plans to investigate the role of aggregates in the process of neuronal degeneration.

Tissue transglutaminase (tTG) has been previously implicated as playing an essential role in the formation of htt aggregates. However, research described by Mathieu Lesort suggested that tTG is not essential to the formation of aggregates *in situ*. He transfected cells with highly truncated htt protein expressing either 18 or 82 glutamine repeats. In those cells expressing htQ82, large insoluble htt aggregates were present, but these did not co-localize with tTG even when tTG levels were increased by retinoic acid treatment. Increasing the activity of

tTG did not appear to increase the size or number of aggregates or modify the protein.

Ronald Wetzel has developed *in vitro* assays of polyglutamine aggregation using chemically synthesized peptides to study the biophysical basis of aggregation. His group discovered a way to prepare soluble versions of polyglutamine peptides for aggregation studies. In a solution phase assay based on these peptides, they demonstrated that aggregation is polyglutamine-length dependent: with increasing polyglutamine length the lag time prior to aggregate formation shifted from days to hours. They also devised another assay in which polyglutamine aggregates are fixed to the wells of a microtiter plate, then incubated with soluble polyglutamine peptides to monitor their "recruitment" into the aggregate. Once a seed was present on the well, even peptides with shorter polyglutamine tracts were able to "join the party," said Wetzel, indicating that smaller polyglutamines can be recruited into the aggregate once the nucleus has formed. Interestingly, Wetzel has seen two different morphological forms of aggregates resulting from the same polyglutamine sequence: a small, filamentous form and a large ribbon-like form. In the microtiter plate assay, the small filamentous form was better than the large ribbon-like form in supporting the extension of aggregates.

Antonio Servadio presented data suggesting that aggregation is associated with conformational changes in the protein, which are induced by expanded polyglutamines. Using full-length ataxin-3 as a model molecule and increased temperature to accelerate the process, he showed that both normal and expanded ataxin-3 are prone to structural changes consisting of a decrease in alpha helical content along with a concomitant increase in beta sheet and aggregate formation. The

expanded protein is much more prone to these changes, he said. Indeed, at any temperature tested, aggregation and beta shift occur more rapidly for expanded than for normal protein. These results, said Servadio, “pave the way for development of drug screening methods for identification of chemicals capable of preventing beta transition and aggregation.”

The mechanism of aggregate and inclusion formation was discussed by several speakers. Michael Sherman presented evidence demonstrating that inclusion bodies form not simply from the tendency of polyglutamine-containing polypeptides to associate with each other, but from a regulated process that is enhanced by stressful treatments. Sherman’s results suggest that the protein kinase, MEKK1, stimulates recruitment of soluble polyglutamines to form aggregates and regulates nucleation of aggregates, a rate-limiting step in the formation of inclusion bodies. Crislyn D’Souza-Schorey studied a different component of this same signaling pathway, a protein called arfaptin 2. Her results indicate that this protein facilitates redistribution of htt to the microtubule organizing center and into the nucleus. Endogenous arfaptin 2 is associated with nuclear inclusions and appears to play a functional role in inclusion formation, said D’Souza-Schorey.

Paul Taylor’s work also indicates that inclusion formation is an active process. He demonstrated, in cell culture models of HD and Kennedy’s disease, that expression of mutant forms of the genes leads to formation of perinuclear inclusions that are dependent on polyglutamine length, level of expression, and overall protein length. He proposed that these inclusions are aggresomes, since they are associated with the microtubule organizing center; and that they represent a cellular response to excess

misfolded proteins. Aggresomes seem to recruit other proteins into them and become rich in proteasome subunits, heat shock proteins (Hsp), and ubiquitin. Yet the function of aggresomes, if any, remains unclear. They may play a protective role, protecting cells from an excess of protein, suggested Taylor. Another possibility that has been proposed is that they are a site of proteolytic degradation by proteasomes. Inhibition of microtubule function with nocodazole results in a significant reduction in the number of inclusions or in arrested development of aggresomes, said Taylor, yet does not appear to protect cells from the toxic effects of the protein. “Our observations suggest that reducing the number of aggresomes that occur has essentially no effect on the observed toxicity,” he said.

In fact, the question of whether aggregates cause neurodegeneration is still unanswered. Experimental models have yielded conflicting results, in some cases demonstrating aggregates without cell death while in other cases, cell death without aggregates. “There’s now a sort of dogma, widespread in the United States that aggregation is an epiphenomenon and not responsible for the disease,” said Max Perutz. “There are at least four lines of evidence, I think each of them conclusive in itself, which show that aggregation is not an epiphenomenon but the cause of the disease.”

The connection between aggregate formation and cell death was supported by the work of Erik Schweitzer. He engineered PC12 cells to express exon 1 of htt with either 25 or 103 glutamine repeats using an ecdysone-inducible promoter. Fusing green fluorescent protein to the transgene allowed observation of the expression and localization of the protein in living cells. Twelve hours after induction, diffuse

cytoplasmic fluorescence indicated the presence of soluble htt. By 24 hours post-induction, those cells expressing htt with 103 repeats form prominent cytoplasmic aggregates and the diffuse staining disappears while those cells expressing htt with only 25 repeats do not form aggregates. Without the inducer, the cells differentiate normally in response to nerve growth factor (NGF). After induction, NGF-differentiated cells expressing htt with 103 repeats form aggregates in the perinuclear cytoplasm and in the neurites.

The importance of aggregate formation in neurons was further investigated by Xiao-Jiang Li. He showed that in the brains of HD-repeat knock-in mice, mutant htt forms aggregates in the axonal terminals of striatal projection neurons. In cell culture, transfection with mutant htt resulted in neuritic aggregates and degeneration; and aggregates also bind to synaptic vesicles, inhibiting glutamate uptake. These observations might help explain the selective neuropathology of HD, said Li.

The observation that aggregates are generally ubiquitinated and contain components of the 26S proteasome and heat shock protein led Michael Kaytor to investigate the role of the ubiquitin-proteasome pathway in the neurodegenerative process of HD. One possibility, he said, is that “if a neuron is unable to properly degrade or keep up with the demand to degrade these aggregated proteins, you actually may get an imbalance between protein synthesis and degradation, which could be involved in neurodegeneration.” In order to study the mechanism of aggregate formation, Kaytor used a cell culture model with htt engineered to have a shortened half life. The protein was designed to alter the degradation rate through the ubiquitin-dependent N-end rule pathway. Aggregates containing the shorter

half-life htt with pathogenic polyglutamine tracts (128Q) were less toxic to cells than those containing htt with a longer half life, suggesting rapid clearance through the ubiquitin-proteasome pathway, slower aggregate formation and reduced cell toxicity.

### *Chaperone proteins*

The relationship between aggregates and cell death may involve abnormal interactions between the extended polyglutamines in htt with other proteins containing short polyglutamine tracts. David Rubinsztein, for example, presented work that suggested a deleterious role for aggregates in association with chaperone proteins. In mammalian cell models, he showed that fragments of the bacterial chaperone GroEL and the full-length yeast Hsp 104 reduce both aggregate formation and cell death.

One chaperone protein that has been frequently implicated in HD is CREB binding protein (CBP), a transcriptional coactivator that is found in inclusions both in human HD brain tissue and in mouse models of HD. CBP orchestrates nuclear responses to a variety of cell signaling cascades and mediates the neuronal response to survival factors. Alexander McCampbell, working in a cell culture model of another polyglutamine disease, spinal and bulbar muscular atrophy (SBMA, also known as Kennedy’s disease), showed that in cells expressing expanded polyglutamine, mRNA levels rise but soluble CBP is reduced. He also showed that overexpression of CBP rescues cells from polyglutamine-mediated toxicity, suggesting that sequestration of CBP in inclusions may be an important factor in the disease.

Christopher Ross also presented evidence indicating a role for CBP. In cell transfection experiments, he showed that

expanded htt redistributes CBP from its normal location in the nucleus into aggregates and that it blocks CBP-activated transcription. Atrophin-1 with expanded repeats has similar properties. Ross suggested that polyglutamine interference with CBP-regulated gene transcription may underlie the pathogenesis of polyglutamine disorders. Ross suggested a hypothetical model in which htt undergoes a conformational change that results in abnormal polyglutamine interactions, which could lead either to aggregates and inclusions or to interactions with other proteins that could mediate toxicity.

Marc Diamond presented evidence suggesting that glucocorticoids might regulate the conformational change of expanded polyglutamine proteins between a toxic and non-toxic form. Diamond's work was with the androgen receptor (AR), which contains expanded polyglutamine tracts in Kennedy's disease. He showed that activation of the glucocorticoid receptor (GR) prevents the formation of inclusions, but that if the N-terminus of GR is deleted, nuclear aggregates form in response to hormone in several different types of non-neuronal cells. These aggregates recruit the inducible stress protein Hsp72 and inversely modulate polyglutamine protein detergent-insolubility, induced stress responses, and cell death; suggesting that the toxicity of expanded polyglutamines is dependent on the conformation of the protein. The relationship between glucocorticoids and conformation of the protein may help explain why expanded polyglutamine proteins form nuclear aggregates in neuronal cells, but remain soluble or form cytoplasmic inclusions in non-neuronal cells, and may help identify drug targets to prevent conversion of polyglutamine proteins to the toxic form, said Diamond.

Other chaperone proteins that may modulate the formation of aggregates include the heat shock proteins. Paul Muchowski presented evidence indicating that Hsp70 and its co-chaperone Hsp40 suppressed the assembly of htt into amyloid-like detergent insoluble fibrils, resulting in the formation instead of amorphous detergent-soluble aggregates. Upregulation of Hsp40 and Hsp70 might, therefore, represent a possible therapeutic approach. He also showed in yeast that transient treatment of cells with microtubule-depolymerizing drugs blocked the formation of aggregates, but "unmasked" expanded polyglutamine toxicity under conditions in which htt exists in a detergent-soluble, non-aggregated state. He suggested that microtubules and chaperones are part of the cells' machinery that channels toxic forms of expanded polyglutamine proteins into non-toxic aggregates.

Andreas Wytenbach reported that HDJ-2, a human Hsp40 homologue, can either increase or decrease polyglutamine aggregation depending on the protein context and cell type.

Alfred Goldberg suggested that extended polyglutamines and chaperone proteins may target proteins for degradation in the proteasome, but that the proteasome can not handle these proteins. Chris Nichols showed data indicating that cells maintain steady-state levels of htt by matching the rate of synthesis with the rate of proteasome-mediated degradation. Cells treated with proteasome inhibitors are unable to degrade htt.

### **Cellular changes**

Whatever the role of aggregates and chaperone proteins, the result is cell dysfunction and death, although it is still unclear how much of the HD phenotype is the result of cell dysfunction and how much

to cell death. What has been noted, are changes in gene expression and transcription, electrophysiologic changes, neurotransmitter dysfunction, excitotoxicity, and apoptosis.

#### ***Gene expression and transcription.***

Ruth Luthi-Carter used gene expression profiling in R6/2 mice to compare the effects of mutant htt on gene expression in the striatum and cerebellum. Humans affected with HD show severe cell loss in the striatum and less severe cell loss in the cerebellum. She identified three groups of genes that were changed in comparison to wild-type mice: those that were changed only in the striatum, those that were changed only in the cerebellum, and those that were changed in both the striatum and the cerebellum. Changes unique to the striatum included decreases in retinoic acid receptor RXR $\alpha$ , calcineurin B, neuron-specific enolase, CAMK IV, GluR6, and plasma membrane calcium-ATPase; and an increase in the heterotrimeric G-protein subunit G $\beta$ 3.

Further analysis of the genes with decreased expression revealed evidence suggesting a role for retinoid signaling, according to Jim Olson. Noting that mice genetically deficient in certain retinoic acid receptor genes develop motor deficits similar to R6/2 mice, and that in striatal glial cells the production of endogenous retinoids is inversely related to neurodegeneration, he proceeded to explore whether reduction in retinoid signaling contributes to the aberrant gene expression profiles and whether this difference could be eliminated by the restoration of retinoid signaling. He fed animals all-trans retinoic acid (ATRA) or placebo and then studied their striatal gene expression profiles. Nine genes were decreased less frequently in the presence of ATRA and he observed a delay in the development of clasping; however, he saw no effect on weight loss, motor function, or

survival. He suggested that the experiment may have used too low a dose of ATRA, and will be repeated with a higher dose.

#### ***Electrophysiological changes, neurotransmitters, and excitotoxicity***

Michael Levine examined electrophysiologic changes that occur in two different HD mouse models, the R6/2 mouse with 150 CAG repeats and a model generated by Neil Aronin and Marian DiFiglia with 100 CAG repeats (TG/CAG100). He observed three common cellular changes: enhanced responsiveness to activation of NMDA receptors in the striatum associated with increased cellular Ca<sup>2+</sup> flux, decreased K<sup>+</sup> conductances, and a decrease in excitatory synaptic inputs to medium-sized striatal neurons. He also looked at the morphology of the neurons. In the R6/2 mice, he saw a reduction in the number of spines, where the cortex makes excitatory synapses. However, in the TG/CAG100 mice, he observed no change in spines but a change in dendritic morphology and alterations in the cortical pyramidal cells. He and his collaborators are now going backward in time and looking at these same parameters in presymptomatic mice, moving towards intervening in the presymptomatic mice to prevent the electrophysiologic changes.

Altered hippocampal LTP and learning in transgenic HD mice supports the idea that NMDA receptors (NMDAR) may play an important role in the disease process. Research from the laboratory of Jang-Ho Cha suggested that alterations in NMDAR subunit expression may underlie behavioral and electrophysiologic abnormalities. He investigated gene and protein expression of NMDARs in two transgenic mouse models: R6/2 and YAC72 mice. In the R6/2 mice, expression profiling of striatal mRNA revealed no difference in levels for NR1,

NR2a, or NR2b. However, whole brain mRNA expression profiling showed no difference for NR1, but decreases in expression of NR2a and NR2b. *In situ* hybridization revealed no difference in expression of NR1, but decreased expression of NR2 and NR2b in the hippocampus. YAC72 mice demonstrated no differences in NMDAR binding or expression.

Lynn Raymond used whole-cell patch clamp recording to look at NMDA receptor activity in acutely dissociated medium spiny neurons from YAC72 mice. She found that most of the NMDA-evoked current was carried by the NR1/NR2B subtype of NMDA receptors and that the NMDA-evoked peak current amplitudes were significantly larger in YAC72 mice compared to wild type littermates. She also exposed cultured striatal neurons to NMDA and glycine and found that cell death was dose dependent and higher in YAC72 and YAC46 cultures. Caspase-3 activity was also elevated in YAC72 culture extracts following NMDA treatment. She concluded that the increased vulnerability of MSNs expressing htt is triggered by activation of NMDA receptors, and hypothesized that NMDAR activation in these cells results in increased mitochondrial depolarization, caspase activation, and cell death.

The glutamate transporter GLT2 (EAAT2) is also down-regulated in R6/1 and R6/2 mice, according to research presented by Jean Charles Lievens. He also showed a decrease in glutamine synthetase RNA in R6/1 brains at nine months. These data indicate that excitotoxic insult is occurring in these mice and suggests the involvement of glia in the pathogenesis of HD. Lievens also noted that polyglutamine aggregates can be detected by eight weeks in glial cells of R6/2 mice, and that this appears to be responsible for astroglial dysfunction in HD. He suggested two

possible mechanisms: direct action of the mutation of astroglial gene expression or defects in neuronal factors that control astrocyte function.

Although excitotoxicity has been implicated in HD pathogenesis, R6/1 and R6/2 mice have been shown to develop a resistance to excitotoxicity. According to Patrik Brundin, this resistance is age and CAG repeat-length dependent. His data indicate that in R6/1 mice, injection of quinolinic acid at three weeks of age results in an increase in lesions, but that at eighteen weeks the mice are resistant to excitotoxic insult. The development of resistance corresponds to the appearance of symptoms. R6/2 mice, in contrast, become resistant to excitotoxic insult at six to twelve weeks; and HDex6 mice expressing 18 CAG repeats show no resistance. He concluded that resistance develops earlier in the R6/2 mice because of the long CAG repeats.

Åsa Peterson studied the effect of dopamine exposure in cultured striatal neurons from R6/2 mice. She showed that dopamine exposure resulted in enhanced cell death associated with nuclear inclusions, ubiquitinated cytoplasmic inclusions, cytosolic oxyradicals that colocalized with ubiquitinated aggregates, autophagocytosis, and altered lysosomal morphology. She concluded that expression of the mutation in combination with oxyradical stress results in neurodegeneration.

As mentioned earlier, Xiao-Jiang Li showed that htt aggregates bind to synaptic vesicles, inhibiting glutamate uptake. Jenny Morton looked at proteins that might interact with htt attached to synaptic vesicles and influence neurotransmitter release. In R6/2 mice, she found that complexin II, an inhibitory modulator of neurotransmission, was decreased in comparison to wild type. Later, complexin II appeared in neuronal

inclusions. These data suggest that a decrease in complexin II may be an early marker of neuronal dysfunction, and that it may compensate for and/or contribute to impairments in neurotransmission.

### ***Apoptosis***

The distinct pattern of cell loss seen in HD suggests that apoptosis may be an important pathogenic mechanism. Earlier work by Robert Friedlander had suggested that caspases, proteases that are part of the apoptotic cascade, might play a role in HD pathogenesis. Shi-Hua Li presented evidence indicating that intranuclear mutant htt induces the expression of caspase-1, which may then activate caspase-3 in trigger apoptosis. Elena Cattaneo suggested that wild type htt may act as an antiapoptotic protein by blocking the caspase cascade.

Abigail Hackham has been investigating the role of huntingtin interacting protein (HIP-1) on cell death in HD. HIP-1 is a pro-apoptotic mediator that induces caspase-3-dependent cell death. Hackham's data indicate that wild-type htt acts to sequester HIP-1, but in the presence of mutant htt, HIP-1 is released and can go on to induce apoptotic pathways. Bioinformatics analyses showed that HIP-1 has a domain with homology to the death effector domains (DED) present in caspase 8 and other proteins involved in apoptosis. These molecules pull together different pro-apoptotic mediators in order to initiate apoptosis.

### **Unresolved questions regarding mechanism**

There remain several unanswered questions regarding the mechanism of HD pathogenesis. Is symptomatology the result of cell death or cell dysfunction? What determines tissue specificity? Anton Reiner and Daniel Goldowitz have been interested

in studying why, in R6/2 mice, there is little cell death despite the formation of many inclusions; and why these animals die early. They have created chimeras of R6/2 and ROSA26 wildtype mice, reasoning that survival of R6/2 cells could be prolonged to allow study of the pathogenic process and the interaction of the mutant protein with wild type or R6/2 neurons. They have shown that chimeric mice live longer than pure R6/2 mice; yet even in these longer-lived animals, there is little evidence of neuronal death, said Reiner. Using GFAP (glial fibrillary acidic protein) staining to assess pathology, ubiquitin immunolabeling to detect R6/2 neurons, and X-gal histochemistry to detect ROSA26 cells, Reiner demonstrated that cortical pathology was associated with R6/2 cells but that this was not the case in the striatum. Striatal pathology, it appears, requires not the presence of R6/2 cells themselves, but the expression of the mutant protein in the part of the cortex that projects to the striatum.

For most of the chimeras, the percentage of R6/2 cells in the cortex and striatum directly correlated to the lifespan of the mouse. However, in a significant minority of these chimeric animals, there is a mismatch between the percentage of chimerism and survival. Goldowitz analyzed the percentage of R6/2 neurons along the neuraxis of these animals. His results indicate that the percentage of chimerism in the hypothalamus is more predictive of survival than the percentage in the cortex and striatum, suggesting that the hypothalamus may be an important cellular target in HD. He noted that several of the common symptoms of HD suggest hypothalamic involvement, including wasting, defects in metabolism and endocrine function, and autonomic defects.

Peggy Shelbourne presented evidence suggesting that the selective vulnerability of

medium spiny neurons may be the result of somatic instability of the CAG repeat mutation region of the HD gene. (Michael Hayden noted that he had previously demonstrated somatic instability of the HD gene in patient material.) Using small-pool PCR analyses of different tissues from HD mice, Shelbourne demonstrated tissue-specific differences in mutation length variation, with the largest CAG-repeat expansion and the most repeat instability in the striatum. She predicted that the increased polyglutamine load in the cells with the largest expansions may expedite downstream pathological processes. The mechanism of the repeat instability remains unclear. She speculated that it may not be replication based, but could be caused by multiple rounds of damage and repair initiated by increased oxidative stress in the striatum.

### Searching for answers

While the questions regarding mechanism continue to be debated, efforts are underway to translate what is known into possible therapies. Translational research not only brings the hope of a cure closer, it also yields new clues about the biology of the disease. Yet therapeutic strategies reflect the uncertainty among basic researchers about the mechanisms of pathogenesis. With all the new models available, a variety of readouts are possible for screening of reagents, yet it remains unclear which readouts will be most relevant to the human condition. *In vitro* and cell culture models may be useful to screen reagents for inhibitors of aggregation, cell toxicity, and cell death; yet animal models will undoubtedly be needed to determine whether those reagents mitigate symptomatology.

Robert Hughes described a yeast system developed for rapid *in vivo* screening of

chemical diversity libraries. His approach was to construct a yeast strain with conditional lethality associated with expanded polyglutamine expression. This system assumes that the toxicity of expanded polyglutamine is related to inappropriate protein-protein interactions, and that reversal of these interactions may confer a therapeutic benefit. He chose the TUB1 gene, which encodes alpha tubulin. Expression of TUB1 fused to expanded HD exon 1 (75Q) confers lethality, whereas fusion to non-expanded HD exon 1 (23Q) does not. He put this into 96-well microtiter dishes for high-throughput screening of compounds. A collaborator will be screening a library of 10,000 pharmacologically active compounds and, after that, a library of 40,000 natural products extracts, while Hughes' lab will screen a commercially available library of pharmacologically active compounds. "What's nice about this screen is that the endpoint is life rather than death," said Hughes. "It's a very reduced system but it's *in vivo*, so potentially the hits will be bioavailable and non-toxic, at least to yeast."

Meanwhile, he has been developing another screening approach that looks at transcription changes in yeast as the primary readout of polyglutamine toxicity. "I think one of the interesting questions in the field is differential cellular susceptibility and that means we have to look at targets that are differentially expressed between cells, and transcription factors are certainly a classic example of things that differ quite a bit from cell to cell."

Other screening methods discussed included the *Drosophila* model described by Leslie Thompson, the *C. elegans* model discussed by Christian Neri, and the YAC transgenic mice described by Blair Leavitt (see "New Models" above). Potentially, hits in a high-throughput system such as that

described by Robert Hughes will then be tested in one of the animal models, prior to human trials.

### **Intervention strategies**

The research described by nearly all of the scientists at this conference is aimed ultimately at finding a treatment or cure for HD. Two approaches were described that have already been slated for human trials. Robert Friedlander plans to start a Phase II clinical trial of minocycline in the near future. This agent is a tetracycline derivative with proven safety, which inhibits caspase-1, caspase-3, and iNOS upregulation. Friedlander reported that in mice, minocycline delays disease progression and inhibits caspase-1, caspase-3, and iNOS activity. A phase I clinical trial of CNTF, a neuroprotective agent, is also currently being conducted in a collaboration between Nicole Deglon and Patrick Aebischer in Lausanne, Switzerland, and Marc Peschanski in Paris.

Other potentially promising therapeutic strategies being investigated include environmental enrichment, inhibition of aggregation or inclusion formation, inhibition of transglutaminase, treatment with retinoids, and various approaches that aim to either correct the genetic defect or eliminate or interfere with the mutant protein.

### ***Environmental enrichment***

Anthony Hannan discussed research examining the effect of environmental enrichment on neural activity in HD mice. Adding novel objects to the cages of these mice increased sensory stimulation and motor activity. The impaired performance of HD mice in behavioral tests was ameliorated by environmental enrichment. Possible mechanisms of this therapeutic effect, suggested Hannan, include modification of synaptic function and plasticity and activity-

dependent clearance of polyglutamine fragments. The research may suggest strategies for occupational therapy in HD patients, he added.

### ***Inhibition of aggregation***

Various approaches were described for inhibiting abnormal protein-protein interactions and aggregation. Leslie Thompson described research in *Drosophila* which builds on the work of Alexsey Kazantsev. A genetically engineered suppressor protein designed to block aggregation in cell culture was coexpressed with polyglutamine-containing peptides in *drosophila*. When the polyQ peptide is expressed alone, aggregates form in the nucleus or cytoplasm; yet when the peptide is co-expressed with suppressor, there was a reduction in polyQ expression and formation of aggregates. The suppressor was shown to increase viability and decrease neurodegeneration in the photoreceptors.

Ivelisse Sanchez used the dye, Congo Red, to inhibit polyglutamine aggregation in cells. In addition to inhibiting aggregation, the dye prevented polyglutamine-induced ATP depletion and inhibition of protein synthesis and blocked membrane permeability changes. According to Sanchez, Congo Red acts by promoting clearance rather than decreasing the synthesis of polyglutamine aggregates. After demonstrating the usefulness of the dye in cell culture, Sanchez took what she called a “big leap” to test the agent in R6/2 mice. Intracerebroventricular infusion of the dye produced more dramatic effects than intraperitoneal infusion did; resulting in better survival, more efficient rotarod performance, and decreased weight loss. Sanchez said she has now screened over 18,000 additional small molecules from combinatorial libraries in the search for compounds that have similar protective effects but an enhanced ability to cross the

blood brain barrier and lower toxicity. Several candidates have been identified and are currently being investigated further to determine their specific targets and efficacy in small animal models.

A different strategy for inhibiting abnormal protein-protein interactions was described by James Huston and Anne Messer. They designed single-chain Fv intracellular antibodies, called “intrabodies,” specific for the amino-terminal region of htt. In cells co-transfected with a Q72 analogue of htt and a plasmid encoding the anti-htt sFv intrabody, they demonstrated marked reduction in aggregation. According to Huston, the HD-specific intrabody intervenes in the aggregation process but leaves the C-terminal portion of the wild type protein free to carry out its normal functions. In addition, it does not bind to other cellular proteins. In order to be useful as a therapeutic strategy the intrabody would have to get into every cell, necessitating a vector delivery system.

Other anti-aggregation approaches that may be useful therapeutically were discussed by Michael Kaytor and Paul Muchowski. These have been described earlier in this report.

#### ***Treatment with transglutaminase and retinoids***

Although the work of Mathieu Lesort described earlier indicated that tissue transglutaminase (tTG) is not essential to the formation of aggregates, Marcela Karpuj has been studying the therapeutic possibilities of cystamine, which is a competitor and inhibitor of TG. Her data indicate that daily intraperitoneal injections of cystamine in R6/2 mice extended survival, reduced chorea, and ameliorated weight loss, yet had no effect on the size or number of neuronal inclusions. Taken together, these pieces of evidence may suggest a different role for TG

in the pathogenesis of HD.

The role of retinoid signalling in HD and the possibility of using retinoids as a treatment strategy was discussed by James Olson (described earlier in this report). More research on the efficacy and toxicity of retinoids will be needed.

#### ***Interfering with mutant htt***

An immunization approach may also have the potential to interfere with mutant protein and thus mitigate disease. Anne Messer described very recent research in which she immunized R6/2 mice with the plasmids containing the n-terminal portion of htt (17 amino acids) and polyglutamine. Plasmids with 104Q gave a 50% immunological response rate to the immunization. In responding mice, Messer reported a modest enhancement of survival but no long-term survival and definite neurological symptoms. The problem, she said, was that the resulting antibodies did not appear to get into the brain. Immunization also raises the possibility of induction of an autoimmune response. Further research to optimize the system and study the immunologic response in more detail may, however, yield new clues about immunologic treatments.

Paul Ko Ferrigno described another search for peptides that interact with, and potentially interfere with, the activity of mutant htt. Peptide aptamers are short peptides that interact with the target protein with a high degree of specificity through being constrained in three dimensions by a scaffold protein. Peptides that bind to mutant htt represent potential models for rational drug dosing. Ko Ferrigno screened three million members of a random aptamer library to find peptides that bind to the N-terminus of mutant htt. Seven peptides that show varying affinities for mutant or wild type htt have been cloned and sequenced,

revealing specific dipeptide motifs that may have importance in the interaction. In a separate study, Ko Ferrigno has also identified yeast mutants that die when mutant htt is expressed. Consistent with work in other model systems, these mutants also implicate a role for htt in transcription, specifically suggesting that the TATA binding protein may be a target for htt-mediated toxicity. Regardless of their biological significance, these strains may be useful for high-throughput screens for drugs that can reverse the toxicity of mutant htt.

### ***Interfering with the HD gene***

Two therapeutic approaches were described that would target the gene itself. Ruben Boado described work aimed at developing an antisense therapeutic strategy. Previously, he has shown that the human HD gene is susceptible to antisense-mediated downregulation both *in vitro* and in tissue culture. He has now also shown that brain mRNA transcripts in the brain can be targeted and imaged with antisense agents delivered intravenously. The antisense agent he used is comprised of an iodinated peptide nucleic acid (PNA) with a 16-mer antisense domain conjugated to a targeting antibody. His data suggest that antisense PNA-drug delivery systems maybe a useful approach for HD.

Eric Kmiec described an approach designed to interrupt long triplet repeats. Using chimeric oligonucleotides consisting of complimentary RNA/DNA residues folded into a double hairpin configuration, he targeted CAG repeats and introduced a single point mutation that changed a CAG codon to a CTG stop codon. In lymphoblastoid cells, the chimera achieved a correction frequency of 3-5%, a frequency which Kmiec described as “relatively low, but a step forward.” He noted that this was

achieved with only a single administration of the chimera. Disrupting the sequence for long triplet repeats may reduce the severity or onset of HD and other polyglutamine diseases. Animal trials of this strategy will be needed to determine whether disruption of the gene with this approach results in phenotypic responses.

### ***Suppressing polyglutamine toxicity***

In *Drosophila*, expression of 63Q or 127Q results in loss of the structural integrity of the eye. Parsa Kazemi-Esfarjani found a mutant that rescues the gene. The gene turned out to be a homologue of human myeloid leukemia factor 1 (MLF1), which appears to suppress polyglutamine toxicity in the eye and central nervous system but has no effect on inclusion formation. Further study will be needed to determine if this gene has therapeutic value; however, Kazemi-Esfarjani noted that the research highlights the potential of the *Drosophila* model system for discovering possibly therapeutic genes without prior knowledge of their function.

### **Conclusion**

The three-day meeting left little doubt that HD research is alive, vibrant, and diverse; and that there are many more mysteries to be explored. As is typical of these symposia, scientists freely shared their data, exposing their research to discussion, criticism, and suggestions. With the ever-increasing number of scientists involved in HD research, progress has been rapid, yet there still remains the imperative to move faster on the road to a cure.