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## Four decades of neurodegenerative disease research: How far we have come!

Anne B. Young, MD, PhD\*

Neurology Service, ACC 720, Massachusetts General Hospital, Boston, MA 02111

### Introduction

My patients frequently ask “Why does research take so long?”, “Why is progress so slow?” and “Why don’t we have effective therapies for these devastating diseases?” At first thought, these questions seem correct. But with further contemplation, it is also remarkable how far we have come even in my professional lifetime.

### Clinical Neurology

Neurology, in 1969, was focused on diagnosis of the disease, primarily by physical examination. People going into neurology were always warned that it was a specialty in which one could diagnose, but not treat. Epilepsy, migraine and Parkinson’s disease had the most effective therapies.

At this time, diagnosis depended almost completely on the physical exam because examination of the brain during life was very primitive. Plain x-rays could show a skull fracture or a shift in the pineal gland (as a measure of a mass). Pneumoencephalograms were x-rays of air that was injected into the spinal fluid space. The air would flow into the ventricles when the person was turned upside down and back and the air distribution would should show masses or anomalies that impinged on the ventricular system. Myelograms depended on injecting dye into the spinal fluid space and looking for blockage or distortion of the spaces. Arteriograms revealed blood vessels after injecting dye, which delineated aneurysms, arteriovenous malformations, arteritis and masses. Electroencephalograms showed evidence of seizure or slowing neuron function from a mass or stroke (Adams and Young, 1970). Only the latter two tests are still done routinely today. CT, PET or MRI scans, which are the main scans used today, were not yet available.

Although examination of the living brain was difficult forty years ago, pathological studies of postmortem human brains had been performed for decades. These pathological descriptions, however, depended mostly on the standard histological techniques of the day (hematoxylin and eosin that stains proteins pink and nucleotides purple, respectively as well as silver stains that stain proteins and DNA black). Only a few neurochemical studies appeared in these years and there was no use of immunohistochemistry in that era of neuropathology. Even once immunohistochemistry of the central nervous system was introduced in the 1970s (Fuxe et al., 1970; LaVail and LaVail, 1974; McLaughlin et al., 1974; Saito et al., 1974), the human brain was for the most part ignored until the 1980s.

Work on neurodegenerative disease was not a major focus in neurology or neuroscience 40 years ago. When one searches PubMed for “Alzheimer” in 1969, only three articles are found.

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\*To whom correspondence may be sent: abyoung@partners.org, Phone: 617-726-2385, Fax: 617-726-2353.

The most studied neurodegenerative disease was Parkinson's disease followed by dementia, ALS and HD. In the last 40 years, neurodegenerative disease research has blossomed so that today there are journals entirely devoted to neurodegenerative diseases and articles on them are also prominent in all the major journals.

## General State of Neuroscience

Neuroanatomy was a prominent area of neuroscience in 1969 and neuroanatomists were doing beautiful work examining neurons, glia, myelin and synapse structure at the light and electron microscopic levels. Neuroanatomists, however, were not yet mapping neuronal connections with tracers. Instead, the main way neural pathways were traced was by making lesions and then doing silver stains to identify degenerating fibers and terminals (Fink and Heimer, 1967). Then, in the 1970's and 80's, methods to use horseradish peroxidase to trace pathways became popular (Ochs, 1972; Graybiel and Devor, 1974) and our understanding of neural circuitry advanced at a more rapid pace.

One discovery enabled an important advance in our ability to examine specific pathways. The natural neurotoxin, kainic acid or kainate, was found to kill neurons directly but not damage axons of passage when given systemically or micro-injected stereotactically into animal brain nuclei (Cooper, 1956; Olney et al., 1974; Coyle and Schwarcz, 1976). Tiny lesions could be made and then degenerating terminals from those cells identified by the Fink-Heimer technique (Fink and Heimer, 1967). Biochemical assays could be done in the projection areas to define neurotransmitters associated with these pathways (Penney and Young, 1981; Bromberg et al., 1987).

Neurophysiology in 1969 was quite sophisticated and was a major focus of neuroscience at this time. Both intra- and extra-cellular recordings of central nervous system neurons were being done routinely (Brock et al., 1952; Eccles, 1952). Neurotransmission at the neuromuscular junction and at the input from the 1a afferent to the motoneuron showed a synaptic delay of about 0.5 msec that could not be decreased experimentally. This observation was thought to be evidence of chemical transmission (Mountcastle and Baldessarini, 1968).

At the time, neurochemistry was defining the levels of amino acids, lipids, small peptides and metabolic pathways in brain. Glutamate, glycine and most peptides were found to have neuroactive properties, but they were not known to be neurotransmitters (Cooper et al., 1970). Various neurotransmitter receptors were largely unknown, except physiologically, including the catecholamines, serotonin and acetylcholine receptors (Cooper et al., 1970).

## Neurotransmitters in Neurodegenerative Diseases

### Dopamine in Parkinson's Disease

In 1969, the Society for Neuroscience was founded. The most impressive discovery made in the previous decade about neurodegenerative disease was that loss of dopaminergic cells in the substantia nigra causes Parkinson's disease and that the symptoms could be treated with levo-3,4-dihydroxyphenylalanine (L-DOPA), a dopamine precursor. As a beginning medical student in 1969, I'll never forget the class in which a person with Parkinson's disease came up on the stage of the lecture hall. He was stooped over and could barely walk. His hands were glued to his side and shook. His voice was nearly unintelligible. He was given a dose of L-DOPA and asked to sit down. The professor gave his talk and at the end called the patient to come up on stage again. It was like the Lazarus effect! He jumped up, came quickly swinging his arms and walking with agility. His voice had returned and he related what a miracle this drug was for him.

This incredible medical advance was made possible by the work of several researchers in the 1950s. Carlsson had discovered that reserpine depleted dopamine in the brains of animal models. These animals developed the reserpine syndrome: slowness and rigidity similar to that seen in Parkinson's disease and importantly, L-DOPA reversed these symptoms (Carlsson et al., 1957; Carlsson, 1959). Shortly after, Hornykiewicz and Ehringer (Ehringer and Hornykiewicz, 1960) described a loss of dopamine in the brains of individuals who died with Parkinson's disease. Birkmayer and Hornykiewicz (Birkmayer and Hornykiewicz, 1961) then described the beneficial effects of a single intravenous dose of L-DOPA administered to patients with Parkinson's disease. The next decade of research resulted in mapping the dopamine pathways (Dahlstroem et al., 1964) and assessing their effects on movement and behavior via administration of reserpine or the toxin 6-hydroxydopamine (6OHDA) in animal models of Parkinson's disease (Ungerstedt, 1968). Investigators also measured dopamine content in the brains of people who died with Parkinson's disease, as well as other neurochemicals such as GABA, serotonin, norepinephrine and epinephrine (Bernheimer et al., 1961; Bernheimer and Hornykiewicz, 1965; McGeer et al., 1973; McGeer and McGeer, 1976; Penney and Young, 1982; Young et al., 1983; Kish et al., 1986; Kish et al., 1987). At the same time, L-DOPA was developed as a therapy for patients suffering from Parkinson's disease (Cotzias et al., 1968; Yahr et al., 1968). This discovery has changed the lives of millions of patients with Parkinson's disease and remains one of the most important advances for treating neurodegenerative disorders.

In 1979, an experiment of nature took place that changed our thinking about Parkinson's disease. A drug addict attempted to make meperidine in his own home laboratory. After taking the preparation, the addict developed severe parkinsonism and a postmortem examination showed a loss of dopaminergic neurons in the substantia nigra (Davis et al., 1979). It was discovered that the preparation – by mistake - contained 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al., 1983). MPTP is a very potent dopamine neurotoxin. A metabolite, MPP+, is taken up selectively into dopamine cells (Javitch and Snyder, 1984; Langston et al., 1984) where it poisons complex I of the mitochondrial electron transport chain (Kindt et al., 1987; Mizuno et al., 1987). The use of MPTP – experimentally in mice, rats and primates to create models of Parkinson's disease – has advanced our understanding of the mechanisms and consequences of dopamine cell death. Several people who had injected subclinically toxic doses of MPTP were subsequently found to have decreased dopamine terminals on PET scans (Calne et al., 1985). Some of these individuals have since developed Parkinson's disease and illustrate how environmental exposures can predispose people to dopaminergic cell death (Vingerhoets et al., 1994).

### **GABA in Huntington's Disease**

During the 1970s, detailed reports of the selective neuronal vulnerability in various neurodegenerative diseases were common. Parkinson's and Huntington's diseases were thought to be subcortical diseases and Alzheimer's a cortical and hippocampal disease. After the success of discovering dopamine to be a critical factor in Parkinson's disease, detailed studies of the distribution of various neurotransmitters, including neurotransmitter precursors and neurotransmitter metabolites were made in postmortem human control and diseased brains. Many of these studies were dependent on freezing samples of postmortem brain so that biochemical studies could be done and brain banking became critical for studying neurodegenerative disorders (Bird and Vonsattel, 1993).

In Huntington's disease, GABAergic markers were found to be selectively decreased in the striatum (Bird et al., 1973; McGeer et al., 1973; Perry et al., 1973). This observation was accompanied by the prediction that GABA agonists might help HD the way L-DOPA helped PD. Unfortunately, the GABA agonists in HD did not result in the same Lazarus effect that

was seen with L-DOPA in PD. This is due, in part, to the fact that the GABAergic striatal efferents synapse with pallidal GABAergic neurons resulting in disinhibition of the thalamus, a target of the pallidum (Roberts, 1974; Penney and Young, 1981). GABAergic agonists will act on the GABA receptors in pallidum and thalamus, thereby negating the double inhibition.

### Acetylcholine in Alzheimer's Disease

Similar to Huntington's disease, neurotransmitter studies were of limited use for unraveling Alzheimer's disease. Acetylcholine levels, however, were found to be markedly decreased, first in the cerebral cortex and subsequently in the basal forebrain of individuals with Alzheimer's disease (AD) (Davies and Maloney, 1976; Whitehouse et al., 1981). Choline as a precursor and cholinesterase inhibitors were all predicted to be beneficial in patients with AD (Davies, 1979; Maire and Wurtman, 1984). Cholinesterase inhibitors are one class of drugs now used to treat AD, but they produce very modest improvements, at best (Comfort, 1978; Rabins and Lyketsos, 2006).

### Protein Aggregates in Neurodegenerative Diseases

During the 1960s and 1970s, Glenner was attempting to purify and characterize various amyloid proteins, including those found in brains of people who died with Alzheimer's or Down's syndrome. After decades of perseverance, in 1984, he was finally successful. He described the first purification of the beta-amyloid protein (Cleveland et al., 1977; Glenner and Wong, 1984). Around the same time, researchers were closing in on the other protein critical to unraveling Alzheimer's disease, tau, the phosphorylated form of which forms neurofibrillary tangles. Cleveland, Hwo and Kirschner first purified tau in 1977 (Cleveland et al., 1977). These two proteins, beta-amyloid (a major component of senile plaques) and tau (the protein making up neurofibrillary tangles) deservedly became the focus of attention in the Alzheimer research field. There were the 'BAPTists' (BAP = beta amyloid protein) and the 'tauists,' who each claimed that their protein was most likely to cause AD (Trojanowski, 2002). The BAPTists dominated, but meetings were heated and sometimes rancorous between the two groups. This is still a hot topic, especially as there are other neurodegenerative disorders in which the primary pathology is exemplified by changes in tau (for example, frontotemporal dementias) leading to the idea that many diseases should be classified as tauopathies (Bird et al., 1997; Spillantini and Goedert, 1998).

The study of protein aggregates was advanced in the 1980s because immunohistochemistry of postmortem human brain was developing as an important tool in neuropathology. Prior to that, most brain was preserved in formalin or frozen. Once brain banks began preserving samples of key brain areas preserved in paraformaldehyde or other fixatives that allow the use of protein specific antibodies, our understanding of cellular changes in disease progressed rapidly.

One important discovery that immunohistochemistry enabled is that many neurodegenerative disorders are characterized by accumulations of misfolded and aggregated proteins. Sometimes these aggregates were not observed until the disease gene was identified and antibodies could be made against the disease-associated protein, but we now know them to be a universal feature of neurodegeneration (Trojanowski and Lee, 2001). In Alzheimer's disease, there are intra- and extra-neuronal aggregates. HD, PD and ALS are characterized by intra-neuronal aggregates. For many diseases, the native protein is unfolded – beta-amyloid, synuclein, tau and the androgen receptor – and when these proteins aggregate, they can wreak havoc (Klucken et al., 2004; Selkoe, 2008; Williams and Paulson, 2008; Spires-Jones et al., 2009a).

In recent years, much research has focused on how and why aggregation occurs and what could be done to prevent it. Chaperones play a critically important role in degrading misfolded proteins by refolding them or leading them to be cleared from the cell (Klucken et al., 2004).

The proteasome and autophagy are other vital cellular processes in clearing misfolded proteins (Goldberg, 2003, 2007; Levine and Kroemer, 2008). Mitochondrial dysfunction also plays a crucial role in clearance (since free radicals react with proteins and disrupt their tertiary structure) (Medicherla and Goldberg, 2008; Karch et al., 2009). Interestingly, the initial view that aggregates are detrimental has been challenged more recently. Now the current view is that misfolded protein monomers or oligomers might be the toxic species and that the larger aggregates might be neutral or protective (Selkoe, 2008; Williams and Paulson, 2008; Spires-Jones et al., 2009a). Numerous researchers are exploring how aggregation might be altered to prevent toxicity.

## The Imaging Revelation

When I was a neurology resident at University of California, San Francisco, we did not have a CT scanner until 1976. Then the hospital scanner was reserved for only the most serious cases. Soon after, the MRI scanner came along. The resolution of the MRI was astounding, even in the early years of its development. It was like taking a picture from an atlas. Positron emission tomography scanning to examine brain function came in at multiple institutions in the 1980s. Together with CTs and MRIs, brain imaging became very sophisticated.

Imaging was immediately applied to the study of living patients with neurodegenerative diseases (de Leon et al., 1983; van Oostrom et al., 2005; Foster et al., 2007; Brooks, 2008). We can now look at the earliest stages of disease, not wait until the endstages, witnessed at postmortem. The most frequently used ligand for PET imaging is [ $^{18}\text{F}$ ]-2-deoxy-glucose (FDG) which is used for imaging patients with epilepsy or dementia. FDG uptake is characteristically altered in all the neurodegenerative diseases. Abnormalities of FDG uptake in HD, PD and AD have been seen presymptomatically and are now being followed longitudinally to see how the changes relate to disease onset (van Oostrom et al., 2005; Eckert et al., 2007; Feigin et al., 2007). Sophisticated imaging with dopamine ligands is revealing presymptomatic alterations in PD as well as early changes in D2 dopamine receptors in HD (Bohnen et al., 2006; Bohnen and Frey, 2007; Stoessl, 2007). Although PET scanning can demonstrate even subtle changes, currently, it is prohibitively expensive to serve as a widely used biomarker.

## The Genetic Revolution

In April, 1953, James Watson and Francis Crick reported the discovery of the structure of DNA (Watson and Crick, 1953). Their letter to *Nature* sent shockwaves around the world. Not only was the structure of DNA solved - but the way in which genetic information informs the future was evident just by the way DNA replicates. This incredible discovery set the stage for the genetic revolution that included the discovery of many disease genes and culminated in the sequencing of the human genome.

Surprisingly, Huntington's disease, a relatively rare disorder, played a crucial role in this revolution. In October, 1979, the Hereditary Disease Foundation held a workshop, organized by David Housman, a molecular biologist at MIT, which focused on how to use DNA markers to find the HD gene. Workshop participants proposed to map the entire human genome and then look for a marker that segregated with the HD gene - a process which could take over a 100 years to accomplish, given then current technology.

The Hereditary Disease Foundation, Milton and Nancy Wexler, together with the NINDS, decided to pursue this strategy to find the HD gene. In 1981, they organized the Venezuela Project - a group of interdisciplinary investigators who went to Venezuela to search for the HD gene. Venezuela was home to the largest known HD kindreds. The team conducted clinical examinations and collected blood for DNA extraction.



In 1983, much to everyone's shock and amazement – a DNA marker was discovered on the top of chromosome 4, tightly linked to the HD gene (Gusella et al., 1983)! The speed of this discovery astonished everyone! With the DNA marker in hand, the Hereditary Disease Foundation organized the “Gene Hunters,” also an international, collaborative group to identify the HD gene itself. It took fully a decade to isolate the HD gene (1993). Many of the technological innovations created by the group were used to advance the Human Genome Project and proved that the Human Genome Project could work.

The HD gene creates a protein called huntingtin and the disease mutation causes an expansion of CAG repeats in the gene, which is translated into an abnormal stretch of polyglutamines in the protein. Unraveling the cause of HD helped the discovery of other expanded repeats diseases – many of which also cause neurodegeneration – such as the spinocerebellar ataxias (SCAs) (Orr et al., 1993), Kennedy's disease or spinal bulbar muscular atrophy (SBMA) (La Spada et al., 1991), among others. The techniques developed, the DNA from an enormous multigenerational family and the genome maps used to isolate the HD gene led directly to the discovery of a gene for the amyloid precursor protein (Tanzi et al., 1987; Tanzi, 1989), which causes Alzheimer's disease and to finding the superoxide dismutase gene (SOD1), which causes an inherited form of ALS (Rosen, 1993).

Study of additional families yielded more disease causing genes, such as presenilin for AD (Sherrington et al., 1995) and, in the late 1990s, the alpha-synuclein protein, for Parkinson's disease was discovered (Polymeropoulos et al., 1997). Now we know that multiple genes are associated with AD, PD and ALS (Gasser, 2007; Bertram and Tanzi, 2008; Valdmanis and Rouleau, 2008). What were thought to be specific “diseases” are actually multiple disorders caused by multiple genes that produce similar phenotypes and pathologies. The discovery of genes causing these neurodegenerative disorders has sparked a huge effort to identify the function of the native and mutant proteins. As soon as gene mutations are isolated, the proteins encoded by these genes are identified and antibodies made against them. In situ hybridizations for mRNA and immunohistochemistry for the proteins are performed. Attention is riveted on elucidating these disease proteins themselves, their distribution and function in animal and human brain.

## Animal Models

Animal models of neurodegenerative disease have existed since the late 1950s when reserpine was used to deplete dopamine and cause a Parkinson's-like phenotype in animals (Carlsson et al., 1957). For the next three decades, animal models consisted primarily of using toxins such as 6-hydroxydopamine, kainate and quinolinate, to create lesions in specific brain regions to mimic various diseases (Ungerstedt, 1968; Schwarcz and Coyle, 1977; Schwarcz and Kohler, 1983). Strains of mice with spontaneous mutations were also studied. These animal models, despite their problems, played an important role in the elucidation of basic functional neuroanatomy and circuitry but could not help us address the underlying disease mechanisms.

The importance of animal disease models has changed drastically in the last decade and a half because the identification of disease genes has allowed the creation of new models. Transgenic animals expressing the human mutant genes have been created, as have models in which the animals endogenous disease-associated gene has been mutated. The insights generated by studying these animals have revolutionized our understanding of these complex human diseases. In the past decade, molecular twists have been used to create transgenic models in which the transgene can be turned on and off and even selectively expressed in only certain neurons. Knock-in and knock-out models of genetic defects have also been made. In this genetic era, there are cell, yeast, fly (*Drosophila*) and worm (*C. elegans*) models of neurodegenerative

diseases. Most recently, in order to study more sophisticated transgenic models of HD, sheep, pig and primate models have been made.

These animal models have proved to be powerful tools for studying the biology underlying the disease process. Normal and abnormal protein function can be studied *in vivo* to identify protein interactors and elucidate the involved molecular pathways. Genetic screens in invertebrate models of neurodegenerative disease (including yeast) enable the identification of suppressors or enhancers that can modify the disease phenotype. Environmental conditions can be altered to study the intersection of genetics and the environment. For instance, HD is an autosomal dominant disease characterized by almost complete penetrance. The age of onset is inversely correlated with the CAG repeat size in HD and yet 44% of the remaining variability is accounted for by other modifying genes and environmental effects (Wexler et al., 2004). Animal models will allow the interaction of each predisposing factor to be studied. Finally, and perhaps most importantly, all of these processes can be studied throughout disease development – from the preclinical stage to advanced disease.

As new technologies have been developed over the decades, their application to animal models has led to important discoveries. For example, laser capture microdissection of transgenic animal models and even postmortem human brain gives us the capacity to analyze individual neurons quickly and efficiently (Bernard et al., 2009). We can capture levels of mRNA and protein in each neuron plucked from the neuropil. For the first time, this has enabled us to determine directly how different disease proteins act in specific cell types and may help us finally understand selective neuronal vulnerability. Imaging advances have been particularly important for the study of disease models. The use of lasers in microscopes has changed the resolution of immunohistochemistry and the development of fluorescent tags (Tsien, 2009) allows proteins to be tracked in living animals. Recently, multiphoton imaging has revealed senile plaques caught at the moment of creation. The skull of a transgenic Alzheimer's mouse is burred to a thin translucent covering so the brain underneath can be imaged and intravenous thioflavin is used to label the plaques. One can image the same plaque everyday – for weeks! One can also see the appearance of each new plaque. Brad Hyman used this approach to show that plaques can form in a day and then remain stable over many weeks (Meyer-Luehmann et al., 2008). Amazingly, antibodies to beta-amyloid reduced both plaque size and number (Spires-Jones et al., 2009b). This latter finding supports the use of vaccines or passive immunotherapy for AD and illustrates how these new techniques in animal models can fundamentally change our understanding of the disease process and its permanence.

## Pre-Clinical Testing

Transgenic models of neurodegenerative diseases have played critical roles in testing the clinical benefits of experimental therapies, purported to be effective for these diseases. Pre-clinical trials in animal models can be done in weeks or months rather than the years or decades required for human studies. “Protective” or “preventative” therapies can be directed at the primary protein defect, the proteins encoded by modifying genes and the secondary effects on cellular health and energy production. The goals of these “protective” trials are to delay onset and slow progression of the disease. Demonstration of pre-clinical efficacy can lead to new clinical trials in humans.

## Therapeutics

### Functional Neurosurgery Approaches – lesions, stimulation and transplants

In the 1990's, treatment of Parkinson's disease went full circle. In the 1950s, prior to L-DOPA, stereotaxic surgery was used to put lesions in the pallidum and the thalamus to treat Parkinson's disease (Cooper, 1956; Hullay, 1971). Destructive lesions were made with alcohol, freezing

or radiofrequency pulses. Surgery was reintroduced two decades later because the advances in imaging and electrophysiology allowed for more accurate localization of the lesion (Bakay et al., 1992; Laitinen et al., 1992). Curiously, these lesions ameliorate both symptoms of Parkinson's disease as well as L-DOPA-induced dyskinesias. This latter observation flies in the face of a popular theory of basal ganglia structure and function (Penney and Young, 1986; Albin et al., 1989; Alexander et al., 1990; DeLong, 1990). Why these lesions are effective in attenuating dyskinesias is still a mystery (Albin et al., 1995). More recently, the use of battery-implanted deep brain stimulation of the subthalamic nucleus is a popular therapy for patients with Parkinson's disease. It is especially effective for treating those with 'on/off' symptoms and dyskinesia (Limousin et al., 1995a; Limousin et al., 1995b).

These lesion/stimulation treatments however will never offer more than symptomatic alleviation. This has led to recent attempts at transplant therapeutics that have potential to replace the lost neurons. Currently, the transplants being tried include fetal transplants and cellular transplants expressing growth factors and enzymes. Embryonic stem cells as well as induced pluripotent stem cells are also being developed with enthusiasm to create therapies for neurodegenerative diseases (Abeliovich and Doege, 2009). Early studies show promise for transplants, although in a recent study in Parkinson's disease, transplants survived but the transplants also developed PD pathology (Kordower et al., 2008) demonstrating that more research into these techniques needs to be done.

## Drug Design

Target based drug design has been possible over the last 4 decades. Each era has had its own frontiers, targets and successes. In the 1970s, the latest hypotheses in targeted therapy rested on the notion that effective therapy would consist of neurotransmitter replacement by giving precursors, releasing agents, uptake inhibitors, enzyme inhibitors, direct receptor agonists and second messenger modulators.

In the last two decades, focus has shifted to the problem of protein aggregation. The synthesis, processing and metabolism of the various proteins found to accumulate in the neurodegenerative disorders have been addressed. More recently, regulation of transcription and mRNA for particular proteins is also being targeted to control levels of abnormal proteins. RNA interference is an extremely promising avenue for therapeutics. Recently, antisense strategies – introduced by virus or by cells – are being vigorously pursued.

Excitingly, we now believe that these therapies might be able to do more than simply prevent disease progression and delay onset because an important piece of research has changed our way of thinking about neurodegenerative disorders. The neurodegenerative process can be turned off and, more impressively, reversed if caught in the early stages (Yamamoto et al., 2000). Furthermore, new data, obtained by multiphoton microscopy and other techniques, have shown that turnover of many culprit proteins is rapid – rather than slow (Meyer-Luehmann et al., 2008; Spires-Jones et al., 2009b). Aggregates can form quickly and dissolve. Conditional models of Huntington's disease revealed striking reversibility in caudate size, GFAP staining, aggregates, D1 dopamine receptor levels and, most importantly, behavior (Yamamoto et al., 2000). Once not under attack by the mutant protein, cells are able to discard the detritus of aging and rejuvenate themselves!

## The Next Forty Years

In the next 40 years, our goal is to have therapies that delay the onset and even reverse the symptoms of neurodegenerative diseases. Therapies will be personalized on the basis of genetic and biochemical studies. Biomarkers such as imaging and blood proteomics and/or metabolomics will be used as screening tools and predictors of subsequent disease. Effective



cures will normalize the biomarkers. In 40 years, I predict that we will have silver bullets for neurodegenerative diseases.

In experimental models, clever genetic techniques and drugs have been used to correct the effects of mutations. For instance, in spinal muscular atrophy, oligonucleotide or drugs are being successfully used to jump a splicing defect in the SMA2 gene (Mattis et al., 2009; Williams et al., 2009). This gene could be used to make a normal protein that would take the place of mutations in the SMA1 gene. The challenge with all such therapies is the delivery of antisense, oligonucleotides or other genetic tools to the whole brain.

Neurodegenerative diseases, collectively, are the leading cause of disability in the elderly. And science moves in baby steps – with an occasional leap to accommodate a paradigm shift. But I predict that research in these neurodegenerative disorders will accelerate over the coming years as tools and insights gain momentum. We are poised now to look deeper into cellular and genetic processes to understand fundamental insights and bring them creatively to the fore for novel therapeutics.

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