

## Perspective

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# Huntington's Disease – A Brief Historical Perspective

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**Abstract.** Although the disease today known as Huntington's was described as early as the mid-19th century, knowledgeable physicians despaired of finding successful therapies and affected families largely kept it hidden. Starting in the late 1960s, the confluence of grass-roots advocacy by HD family members, advances in Parkinson's treatment, and the development of molecular genetics and neuroscience helped turn HD into a focus of growing biomedical research. While therapies lag behind laboratory discoveries, disease altering interventions are now moving closer to the clinic. *The Journal of Huntington's Disease* is a welcome new resource in this effort.

**Keywords:** Huntington's, history, HD, advocacy, lay association, Hereditary Disease Foundation, Huntington's Disease Society of America, Marjorie Guthrie, Milton Wexler

The launch of a journal entirely devoted to Huntington's disease marks both a sweet and a sobering moment in the history of this disorder. In the excitement of the abnormal gene identification in 1993, many of us in HD families imagined that a cure – or at least an effective treatment – was close at hand. That dream has not yet been realized. But if the history of Huntington's can provide clues for the future, it suggests that change does not always happen gradually. Change can also happen swiftly. And that, I believe, is a great source of hope.

A glance at the history of HD reveals the uneven tempo of change. Although clinical accounts of this malady date back to the mid-19th century, as late as the 1960s few doctors outside of neurology, psychiatry, and medical genetics knew anything about it. Those who did know despaired of finding effective treatments. Families with the illness tried hard to keep it hidden. Then all of a sudden in the late

1960s everything began to change. HD families largely prompted this transformation, along with a small international network of neurologists inspired by advances in Parkinson's research to form a Research Group on Huntington's Disease within the World Federation of Neurology. In the USA Alice Pratt's Wills Foundation, Marjorie Guthrie's Committee to Combat Huntington's Disease (CCHD) – precursor to today's Huntington's Disease Society of America (HDSA) – and Milton Wexler's research-oriented Hereditary Disease Foundation (HDF) all started up in the late 1960s. During the 1970s, lay HD associations also formed in countries such as the Netherlands, the UK, Canada, Germany, France, Australia, and Belgium, with many more to follow.

Meanwhile the recombinant DNA revolution of the 1970s revolutionized all of biology and genetics, making it possible to visualize and manipulate DNA. A newly organized field of neuroscience further enhanced the appeal of HD as a subject for biomedical research. Especially after the genetic marker discovery in 1983 and the start of presymptomatic genetic testing in 1986, Huntington's disease research intensified,

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with a growing international network of HD investigators, knowledgeable clinicians, brain banks, tissue repositories, institutional affiliates, and increasing funds for postdocs and grants.

Huntington's research reached a dramatic turning point in 1993, as the CAG expansion in the abnormal *HTT* gene explained the complex genetics of this disorder, revealed the genetic basis of anticipation and made possible an array of entirely new models and experimental approaches. To name just a few, in 1996 Gillian Bates and colleagues created the first mouse model of HD. The following year, Gillian Bates and colleagues identified intranuclear inclusions (NII) in the brains of HD mice, which they noted were consistent with findings in human brain biopsies from persons with HD, reported in 1974. Within a month Marian DiFiglia and Neal Aronin described similar aggregates of abnormal Htt in the brains of people who had died with HD. These discoveries suggested one of the fundamental processes of the disease across species. Since that time, with additional support from a new research organization, CHDI Inc., scientists around the world have created many more animal and cell models, explored post-translational modifications of the huntingtin protein, and enhanced clearance in the cell. They have

identified potential genetic modifiers and illuminated many aspects of neuronal dysfunction. They are also testing methods of gene silencing and other novel therapeutic strategies in a variety of animal models.

For families and individuals struggling daily with HD, effective therapies cannot come soon enough. But while major discoveries in the lab have not yet been matched by similar advances in treatment, the volume of research has increased tremendously in the past decade. Disease-altering interventions are now moving closer to the clinic. *The Journal of Huntington's Disease* provides a welcome new resource in our campaign to heal a formidable yet ineluctably fascinating disease.

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