Huntington’s disease is a severe autosomal-dominant neurodegenerative disorder that involves chorea, cognitive decline, and psychological problems such as depression, delusions, and impulsive behavior. Nowhere are the manifestations more striking than around Lake Maracaibo in northwestern Venezuela, where the disease is almost epidemic. The Huntington’s disease kindreds in Venezuela encompass more than 18,000 persons spanning 10 generations. DNA samples from nearly 4000 patients and family members in this area were used to map the Huntington’s gene to chromosome 4 in 1983 and to identify the disease gene in 1993. Subsequent studies in this population have discovered modifiers of age at onset. A new prospective treatment specifically targeting the messenger RNA (mRNA) encoding the mutant protein has been tested in patients with Huntington’s disease, as now reported in the *Journal* by Tabrizi et al.

Huntington’s disease is caused by a trinucleotide repeat expansion that results in an expanded polyglutamine tract in the disease protein, huntingtin. The mutant protein is toxic and prone to aggregation in cell culture, animal models, and human brains. Remarkably, disease manifestations are reversed when the mutant gene is turned off or suppressed in transgenic mice, which suggests that this approach could be effective in humans. Oligonucleotides targeting mutant huntingtin mRNA for degradation did not result in adverse effects when delivered intrathecally in nonhuman primates, and they reduced huntingtin levels throughout the brain. Although complete loss of normal huntingtin results in embryonic lethality in mice, partial reduction in levels later in life has an acceptable safety profile. This allows a non–allele-specific approach, in which the treatment would be suitable for all patients. Importantly, the levels of huntingtin protein can be assessed in the spinal fluid and correlate well with levels in the brain, thus providing a measure of the biologic effect of the treatment.

The trial reported by Tabrizi et al. involved 46 patients who were randomly assigned to receive placebo or one of five doses of the oligonucleotide HTTRx and followed at nine centers in the United Kingdom, Germany, and Canada. The patients received four injections into the spinal fluid at 4-week intervals, with a 4-month follow-up. The trial agent was not associated with dose-limiting adverse events; the most common adverse effects were related to the lumbar punctures. There was a dose-dependent increase in the concentration of HTTRx and a decrease in levels of mutant huntingtin protein in the spinal fluid. Remarkably, the reduction in the levels of mutant huntingtin was in a range that is expected to have therapeutic benefit on the basis of studies in animals. This is a pathbreaking trial that strongly supports further development of HTTRx as a treatment for Huntington’s disease. A confirmatory phase 3 trial is now under way (ClinicalTrials.gov number, NCT03761849), with a plan to follow 660 patients worldwide for up to 2 years. Now, 26 years after the discovery of the etiologic gene, a path to modifying Huntington’s disease seems clear, with implications for other neurodegenerative diseases that have a known genetic cause. The next step is to determine whether HTTRx has a clinical effect in a larger number of patients followed over a longer period of time. The current trial was of insufficient size and duration to show a significant difference in clinical measures between patients given the ac-

Oligonucleotide Treatment for Huntington’s Disease

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tive agent and those who received placebo. How-
ever, an analysis after the trial showed a correla-
tion of such measures with levels of the mutant
protein in the spinal fluid, indicating that reduc-
ing the protein level could be beneficial.

The phase 3 trial that has just begun is ap-
propriately designed to determine whether this
intervention has a clinically meaningful effect.
The ultimate challenge will be to bring safe,
effective, and affordable treatment not only to
patients in North America and Europe but also
to patients with Huntington’s disease through-
out the world. For those in Venezuela who do-
ated the samples that made this promising
approach possible, the treatment should be free.

Disclosure forms provided by the authors are available with
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