tends to occur, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset, a phenomenon referred to as anticipation. There is also evidence of somatic gene expansion that occurs over time.

The *huntingtin* gene encodes the highly conserved cytoplasmic protein huntingtin (HTT), which is widely distributed in neurons throughout the central nervous system (CNS). Mutated HTT RNA is toxic. Mutant HTT disrupts transcription, impairs immune and mitochondrial function, and is aberrantly modified post-translationally. Genome-wide association studies have nominated DNA repair pathways as modifiers of somatic instability and disease course in HD. Fragments of the mutant HTT can also be toxic, possibly by translocating into the nucleus and interfering with transcriptional regulation of proteins. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins. There is also interest in the possibility that protein accumulation and aggregation in HD, like Alzheimer's disease **(Chap. 431)** and PD **(Chap. 435)**, may be critical to the disease process and reflect a prion-like disorder **(Chap. 438; see also Chap. 424)**. Models of HD with striatal pathology can be induced in multiple transgenic animals that express the mutant gene and by excitotoxic agents such as kainic acid and 3-nitropropionic acid, which promote calcium entry into the cell and cytotoxicity.

TREATMENT

Huntington's Disease

Although the gene for HD was identified more than 25 years ago, there is still no disease-modifying therapy for this disorder, and symptomatic treatment is limited. Current treatment involves a multidisciplinary approach, with medical, neuropsychiatric, social, and genetic counseling for patients and their families. Dopamine-blocking agents may control the choreatic movements. Tetrabenazine (a presynaptic dopamine-depleting agent) has been approved for the treatment of chorea but can cause secondary parkinsonism. Deuterated tetrabenazine (Austedo) has also been