HUNTINGTON'S DISEASE

Huntington's disease (HD) is an inherited (autosomal dominant) degenerative disease of the central nervous system that is named for the three generations of general practitioners who studied its prevalence among families in East Hampton, Long Island, New York, in the mid- to late nineteenth century. Subsequent work in other parts of the world has traced its origin of many cases to southern England, where a common progenitor lived in the mid-seventeenth century. Although there have been no clearly documented cases of new mutations since HD was first reported by George Huntington in 1872, the presence in isolated geographic regions of Huntington patients and families whose ancestry is not clearly traceable to southern England indicates that new mutations occur at a low but regular frequency.

Clinical Features

The clinical signs of Huntington's disease are diverse, but the most common are choreiform involuntary movements and dementia. Clinical expression of HD is usually insidious, beginning in the third or fourth decade of life with an average duration before death of 17 to 20 years. Although the presumed single-gene defect of HD, recently localized to the short arm of chromosome 4 (see below), is completely expressed when present, wide-ranging clinical variability is the rule between and within affected families. In one survey of over 240 families, age of onset of symptoms among the affected members varied from the first to the eighth decade. Only a small minority were clinically affected in childhood, and most of these victims had paternal transmission of the gene. Rate of progression is more rapid in these early onset cases, and the clinical profile of a typical case is dominated by a rigidity that resembles parkinsonism. Conversely, disease that starts after age 50 is relatively more benign and is associated with paternal transmission. The hastening effect of paternal transmission on clinical expression is currently unexplained.

The most recognizable and familiar signs of HD are the choreiform involuntary movements of the arms, legs, and trunk of the body as well as the muscles of the face. These manifest as widespread, quick, nonperiodic random, usually jerky movements of low amplitude that are subtle at onset but later interfere with coordination and function. The patient initially conveys a general impression of restlessness, but as the movements become more pronounced, focal twitching of various body parts becomes obvious. The result is facial grimacing, slurred speech, clumsy hands, unsteady walking, and abnormal posturing. The patient may attempt to hide an embarrassing involuntary movement by incorporating it into a concurrent or improved purposeful action, such as combing the hair, clearing the throat, straightening a garment, and so forth. A mixture of choreiform movements, dystonic (twisted) postures, and ataxic or uncoordinated purposeful muscle activity is not uncommon in the middle phase of evolution of the clinical disease. The patient can no longer hide the movements: constans writhing and twisting are the rule. In the more advanced stage of the disease, movement is limited by increasing rigidity, and walking becomes all but impossible. Self-care is completed impossible. Behavioral and psychological deficits may precede the onset of involuntary movements by years and therefore escape diagnostic recognition. An affected person may be described as impulsive, erratic, difficult, unimhibited, depressed, or clearly psychotic before the onset of involuntary movements clarifies the clinical picture. It is uncommon for HD patients to be diagnosed initially as
schizophrenic with the diagnosis of HD becoming clear later with the expression of choreiform movements. Insightful patients are aware that something is seriously wrong, even when the total clinical picture is still vague. Huntington's patients tend to seek relief from depression and anxiety by drinking alcohol, sometimes heavily. Excessive drinking can aggravate any of the behavioral signs of the disease and can incorrectly suggest to observers and family members that alcoholism is the sole cause of the patient's altered behavior. A family history of HD raises suspicion that the altered behavior may be the first overt sign of the disease. However, the proper diagnosis may be delayed because many victims of HD and family members are unaware of the family's medical history, or may be misled by inadequate or erroneous information, e.g., the misinformation that only children are affected with HD as the disease progresses, cognitive dysfunction gives way to gross dementia. In the terminal stages, the patient is usually mute and withdrawn because of disorientation, apathy, depression, severe rigidity, and total lack of coordination of the muscles of speech articulation.

Pathogenesis
Pathogenesis of HD involves the loss of neurons in the corpus striatum, a region involved in the control of movement. The pathology in HD is most concentrated in the region of the corpus striatum (caudate and putamen) (see Chapter 11 where medium-sized GABAergic spiny neurons, whose axons project outside the striatum, selectively degenerate and are replaced by a proliferation of glial cells. Loss of striatal neurons is neither uniform, nor morphologically homogeneous. The dorsal striatum is the initial site of pathology, which spreads ventrally as the disease progresses. Even at the end, when the patient is severely disabled, the dorsal striatum shows the greatest pathological change. Neurons in other parts of the brain are also affected: cerebral cortex, thalamus, brainstem, and spinal cord, but much less so than in the striatum. Progressive loss of neurons causes generalized cerebral and focal caudate atrophy on computerized images of the brain computed tomography and magnetic resonance imaging. This finding can be useful when the diagnosis of HD is suspected but not certain based on family history or clinical presentation. The large striatal aspiny interneurons containing ACh, as well as the aspiny interneurons that contain somatostatin and neuropeptide Y, are largely spared in HD, whereas the medium-sized spiny neurons that contain GABA are lost. These spiny neurons also have peptide cotransmitters, either enkephalin (Enc; Fig. 8) or substance P (Sub P, Fig. 8). Enk-containing neurons projecting to the external globus pallidus and Sub P-containing neurons projecting to the pars reticulata of the substantia nigra degenerate early in the course of HD, whereas Sub P-containing neurons that project to the internal globus pallidus and the pars compacta of the substantia nigra are spared until late in the disease (Fig. 8). In contrast to PD, the nigrostriatal dopamine input to the striatum is generally unaffected.

Biochemistry and Molecular Pharmacology
The molecular pathology of HD is being clarified by focusing on the selective vulnerability of neurons of the corpus striatum. As with PD, the particular mechanism that leads to the premature death of certain neurons in the brain is unknown. The clear heritability of HD, however, reflects an ultimate genetic reason for the neuronal degeneration. One leading hypothesis holds that the medium-sized spiny neurons in HD are pathologically sensitive to the excitatory amino acid glutamate (as in AD; see above) that normally functions as a neurotransmitter in the corticostriatal pathway (Figs. 1 and 8). This hypothesis is supported by the following evidence: (1) cultured fibroblasts from patients with HD show a heightened sensitivity to ex-
FIG. 8. Diagrammatic representation of the dopaminergic and glutamatergic synapses in Huntington's disease (HD). Some circuits of the basal ganglia are depicted. The axons projecting from the putamen to the globus pallidus external (GPe), globus pallidus internal (GPI), and substantia nigra pars reticulata all utilize GABA as well as different cotransmitters. These include: (1) the pathway to the GPe containing GABA and enkephalin (GABA/Enk); (2) the pathway to the substantia nigra pars reticulata utilizing GABA and substance P (GABA/Sp P), and (3) the pathway to the GPI utilizing GABA and Sp P. As depicted in the inset, the dopamine nigrostriatal pathway is left intact in this disease, but the corticostriatal pathway may release more glutamate than in normal brain. Enhanced release may lead to the selective degeneration of certain types of neurons in the striatum. The selective loss of GABA/Enk pathway to the GPI and the GABA/Sp P pathway to the substantia nigra pars reticulata results in an imbalance in the output of the basal ganglia to the thalamus and of the thalamocortical pathways. The remaining striatal neurons continue to be sensitive to the effects of dopamine and contribute to the imbalance in the activity of the pathways. This may contribute to the motor symptoms (chorea) of this disease. The inset depicts the relative loss of certain neurons in HD and of thalamic receptors normally expressed by the striosome neurons (dopamine D1 receptors and NMDA receptors).
neuropathology, and disturbance in chemical neurotransmission. But these disorders are also tied together by their similarity: each is characterized by cognitive and motor impairments, each has prominent subcortical pathology and secondary distinct pathway degeneration: each is associated with a variety of depleted neurotransmitters, but with considerable overlap among them; even has a pathogenesis related to varying proportions in abnormal genes and the aging process.

PD is characterized by severe loss of dopamine-producing pigmented neurons in the midbrain substantia nigra and moderate loss of hypothalamic and serotonergic-containing neurons in the pons and locus coeruleus, raphe. Parkinsonian patients have the classic signs of rest tremor, rigidity, bradykinesia, cognitive dysfunction, and postural instability, usually starting after age 55. Treatments developed for this disorder (levodopa or direct dopamine agonists) were derived from animal models. Postural changes in receptor expression may contribute to the success of dopaminergic agents to reverse the symptoms of PD.

AD, the most age-related of the three disorders, affects neurons of basal nuclei in the mesencephalon and of the hippocampus in the temporal lobe. ACh is the principal depleted neurotransmitter, but the monoamines and glutamate are also affected. The histopathological signature is the neurofibrillary degeneration (SPs and NFTs) of neurons throughout the brain, but mainly in the hip- pocampus. Alzheimer patients are primarily

FIG. 9: Photomicrographs of the expression of dopamine receptors and dopamine terminals in the striatum of a normal (A, B, C), Huntington's disease (D, E, F), and schizophrenic G, H, lesion. Tissue sections have been labeled with radioligands that label D1 receptors (A, D, G), D2 receptors (B, E, H), or dopamine terminals (C, F, I) and exposed to film. The resulting images provide a baseline anatomic map of the distribution of these components in the dopamine system with higher numbers of sites showing up as gray matter. In Huntington's disease there is prominent cell loss from the dorsal caudate nucleus (CA1) and dorsal putamen (PUT), resulting in a 'shrunken' appearance. The cell loss is selective so that neurons expressing D1 receptors (compare C with A) are lost to a further extent than those expressing D2 receptors (compare D with A). Dopamine input (compare F with G) is relatively normal. The schizophrenic case is shown for comparison. From Joyce NM, London N, Bihl E, Winokur A. Organization of dopamine D1 and D2 receptors in human striatum. Receptor autoradiographic studies in Huntington's disease and schizophrenia. Synapse 1998; 2:540-557.