

MOVEMENT DISORDERS AND PROXYSMAL DISORDERS

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Diseases of the brain include human motor disorders and epilepsy, which are distinguished from primary behavioral disorders by the nature of their illness manifestations. These diseases have observable symptoms and, in several cases, cerebral pathology associated with genetic determinants. Especially the features of cerebral pathology and genetic association make it easier to model the critical disease elements in the animal and to move more directly to the neural underpinnings of pathology in human brain. Identified cerebral pathology provides an opportunity for targeting the involved central nervous system (CNS) regions and known brain networks for modeling and focused study. These kinds of CNS illnesses not only serve as models for behavioral disorders of a successful experimental approach, but also generate a valuable knowledge base for understanding human brain physiology in other human CNS illnesses. The known pathophysiology of Parkinson's disease (PD), not information on etiology, has allowed investigators in this field to focus on a relevant region of the brain to explain the neural substrate of Parkinsonian symptoms.

The chapter by Zigmond and Burke addresses the clinical features and critical pathophysiology of PD, and illustrates the value of critical genetic information in the understanding of PD, as well as clear descriptions of tissue pathology. The hypotheses of pathophysiologic mechanisms in PD, whether free-radical-mediated injury, programmed cell death, or effects of protein aggregation in tissue (or some combination of these processes) are identified. Moreover, the authors observe that this disease has been known for two centuries, and its critical pathology described for a half century, but it has only been in recent years that neurobiologic

understanding of PD is emerging; this presents a gauge for the difficulty of the work and insight involved in understanding the mechanisms of brain diseases.

The chapter by Wichmann and DeLong does a masterful job of presenting the molecular anatomy and physiology of the basal ganglia thalamocortical network as it relates to PD. It is this feature of network pathology, advanced for several decades by these investigators, that continues to inform not only motor disorder research but aspects of cognition and affective research as well. Moreover, identification of the importance of the structures in this network in these brain diseases has allowed many different investigators to contribute data to produce a rich anatomic and electrophysiologic database of broad relevance for neural mechanisms.

Gracies and Olanow's chapter complements the first two chapters, providing an exhaustive and up-to-date review of therapeutic approaches and their pharmacologic mechanisms. They weave together clinical experience and practical clinical findings with the known neuropharmacology of the illness. L-dopa, dopamine agonists, anticholinergics, and other drug treatments are critically reviewed in detail as are the newer surgical and transplantation therapies now widely discussed. The broad knowledge base available for understanding therapeutic approaches in PD is illustrated in the chapter. After encountering the significant advances made in PD, discoveries in other CNS diseases appear more modest.

Ross and Margolis articulate progress in the understanding of Huntington's disease (HD), the known autosomal-dominant disorder where the gene has been identified for nearly a decade. They describe the characteristic motor, cognitive, and psychiatric symptoms and the usual symptomatic treatments. The known genetic etiology of HD uniquely provides a range of diagnostic and research oppor-

tunities not available in other diseases, including the availability of a diagnostic test and a precise animal model. The genetic mechanism in HD has introduced the consideration of polyglutamine mechanisms in diseases of the brain and rational prophylactic therapies.

The chapter by Tamminga and Woerner presents the clinical course, risk factors, and pathophysiologic considerations for the iatrogenic hyperkinetic motor disorder tardive dyskinesia (TD). Since the etiology of this disorder is known, namely, chronic blockade of the dopamine receptor with antipsychotic drugs, it can be modeled in the experimental animal. This body of research has generated information relevant to TD pathophysiology and treatment, and has relied on the well-described experimental data characterizing basal ganglia structure, neurochemistry, and function.

Schwarcz, Scharfman, and Bertram complete this section with a chapter noting the contribution of extrahippocampal brain regions to the mechanisms of temporal lobe epilepsy. Although of considerable etiologic complexity, temporal lobe epilepsy demonstrates several common aspects of clinical presentation, molecular and cellular changes, and pathologic sequelae. These features are broadly developed in this chapter. The discussion of suspected cellular changes, synaptic reorganization, and neurogenesis in the manifestations of epilepsy makes the chapter an extremely timely contribution.

This section contains a diversity of cutting-edge presentations on human brain diseases that advance the boundaries of not only clinical phenomena but also neuroscience research.