SECTION

VI

SCHIZOPHRENIA AND RELATED DISORDERS

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The schizophrenia section of the *Fifth Generation* reflects both a subtle shift in emphasis in schizophrenia research and a refinement of earlier trends. Molecular and systems neuroscience and genetics are the basic biological sciences of psychiatry, and their increasingly important role in research is reflected in the schizophrenia section. Schizophrenia research is inexorably on a path from clinical phenomenology to cellular and molecular pathogenesis. Although this complex disease will never be reducible to one gene or one signal-processing pathway, the molecular origins of risk and of manifest psychopathology are being elucidated. The main topics covered in the *Fourth Generation* volume, including treatment of acute psychosis, mechanisms of antipsychotic drug action, basic models of pathophysiology, application of brain imaging technologies, and efforts to characterize symptoms in terms of failures of specific neuronal systems, are represented here, but the presentations are more scientifically mature. Consistent with the completion of the reference sequence for the human genome and the increasing sophistication of approaches to complex genetic disorders such as schizophrenia, clinical and molecular genetics are now reviewed as a new chapter in this section. Because of the introduction of more effective and much better tolerated antipsychotic drugs, the economics of treating schizophrenia has changed, and this topic also is now covered as a new chapter. Finally, a new chapter is devoted to the issue of developing informative animal models of schizophrenia. The traditional view that a disorder of human perception, cognition, and comportment could not be modeled in the experimental animal has yielded in the face of heuristic models of neurochemical, physiological, and molecular aspects of schizophrenia. These models promise to open new pathways for drug discovery and to test specific hypotheses about etiology and pathophysiology.

Neuroimaging has been a popular tool for asking specific questions about brain anatomy and function that may help to unravel the pathophysiology of the illness. There is no doubt, after more than 2 decades of neuroimaging research in schizophrenia, that the schizophrenic brain is abnormal in a variety of experimental domains. The details of the abnormalities are still to be fully clarified, but the level of analysis has been meaningfully elevated. New technologies in brain imaging have allowed testing of much more sophisticated hypotheses. Magnetic resonance imaging has replaced positron emission tomography as the primary functional mapping tool, and new approaches to *in vivo* chemistry with nuclear medicine resonance spectroscopy and to anatomic tract tracing with diffusion tensor imaging have revealed abnormalities not approachable with earlier methods. Positron emission tomography has become primarily a neurochemical assay technique. Positron emission tomography imaging of dopamine systems has refined our understanding of the role of dopamine in the pathophysiology of a symptomatic episode and of the mechanism of an antipsychotic response.

Progress in schizophrenia research has followed discoveries in the basic neurosciences. This is illustrated in several chapters that address the development and plasticity of the prefrontal cortex and the importance of intrinsic prefrontal circuitry and prefrontocentric distributed networks to the pathophysiology of schizophrenia. The study of postmor-

tem tissues has been revived by the availability of cellular and molecular assay tools that permit surveys of gene and protein expression at an industrial scale. Numerous provocative molecular findings have emerged from these preliminary forays into the cell biology of the illness. Although the mystery of this devastating illness is still unsolved, the clues that have emerged in the past 5 years and the opportunities for discovery that now exist make it very likely that much more of schizophrenia will be understood at the cellular level in the next 5 years.

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