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Neuroanatomical and Neuropathological Basis of Mental Illness

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1 Study of Brain Structure in Psychiatry

The role of neuropathology in the study of classical psychiatric diseases such as the schizophrenias, affective disorders, personality disorders, anxiety disorders, and obsessive-compulsive disorder was until recently highly controversial. Neuropathological findings have been largely impossible to demonstrate in psychiatric disease, except in the case of organic mental syndromes resulting from focal brain lesions or degenerative processes. A few structural abnormalities have been detected to date, but only with difficulty, with the aid of highly sophisticated techniques.

Neuropathological substrates for the schizophrenias and affective psychoses were long thought not to exist. Recent research, however, benefiting from statistical morphometric techniques and new histochemical techniques for postmortem analysis, as well as from in vivo techniques of structural and functional imaging, has revealed the presence of moderate abnormalities in certain brain areas in many patients. These macroscopic and histological abnormalities are not as extensive as those found in brain illnesses that are known to be organic; they are relatively inhomogeneous, both in type and in localization, and are found in only a subset of patients carrying the diagnosis of an “endogenous psychosis.” Sophisticated statistical methods are often needed to demonstrate a difference between a group of psychiatric patients and a normal control group. There is generally considerable overlap between the two groups, and the morphologic parameters of many patients lie within the normal range. No pathognomonic abnormalities of brain tissue have yet been found that might be used for a reliable differential diagnosis of schizophrenic and affective disorders, as these are defined in the current systems of disease classification. The pathological findings in this area are thus of an entirely different nature from those familiar to us from the realm of neurology and cerebral degenerative disease.

Many studies of brain structure in schizophrenic patients have been performed to date, but the affective disorders have been the subject of almost no neuropathological studies, and of relatively few structural imaging studies. There have been no neuropathological studies at all to date of the so-called neuroses or personality disorders, which is not surprising, as it is commonly assumed that these result from psychosocial factors or variations of normal personality traits (although genetic factors may also be important). It is quite conceivable that some structural features of the brain may represent “vulnerability factors” for the latter class of disorders; no postmortem studies have yet been performed to provide evidence for or against this hypothesis.

There are several reasons why discrete, homogeneous neuropathological substrates for the named psychiatric disorders are so difficult to find. The first reason is that the schizophrenias and affective psychoses, unlike the classical organic mental disorders, are not unitary diseases but, rather, conventional diagnostic constructs, whose neurobiological causes may be as diverse as their clinical manifestations. In psychiatry as in internal medicine, a given constellation of signs and symptoms may result from one of multiple biological substrates that exert their effects through a final common pathway (as is true of fever or hypertension, for example).

It is also possible that the brains of many of these patients are entirely normal in structure, and that their mental illnesses are caused by reversible neurochemical disturbances or by stress-induced changes in neurotransmitter or neurohormonal systems. Another reason is that the histopathological substrates of the typical psychiatric diseases may be too subtle to be detected by the traditional qualitative methods of neuropathological research or that they may lie in brain areas or cell types that have not yet been investigated. The functional importance of the limbic system, for example, was not fully recognized until the 1950s (McLean 1952), and it has only recently become a major object of investigation in the neuropathology and pathophysiology of mental disorders. The neurotransmitter systems of the brain were discovered in the 1960s (Dahlström and Fuxe 1964), and the cell types containing neuropeptides 10 years later (for a review, see Nieuwenhuis 1985). There has been no systematic histopathological study of these cell types to date, despite their major relevance to the theory and pharmacology of mental diseases.

One possible technical reason for the slowness of progress in this area was the lack, until recently, of adequate neuropathological techniques. It was only after the introduction of immunohistochemistry and in situ hybridization that neuronal subpopulations could be conveniently studied and observations regarding their function could be made (Table 1). These techniques were the first to add a functional dimension to the study of structural abnormalities, yielding important clues both to disease etiology (e.g. the expression of gene products) and to normal function (e.g. the characterization of inhibitory interneurons).

Another reason for the lagging interest in the neuropathology of mental illness is the conspicuous lack of success of neuropathological research on schizophrenia in the first half of the twentieth century. At that time, a dualistic attitude toward mind and