EDITORIAL

The neuropathology of schizophrenia

The distinguished American neurologist, Plum (1972), once called schizophrenia ‘the graveyard of neuropathologists’. Certainly the topic of neuropathological change in schizophrenia has been nearly as silent as a tomb for almost three decades. Interest in the neuropathology of schizophrenia was still high in 1952 when leading neuropathologists of the world, meeting at the First International Congress of Neuropathology in Rome, devoted many hours to formal presentations and discussions of pathological material from schizophrenic patients who died in mental hospitals on both sides of the Atlantic. Although more than 250 published papers had already appeared concerning the pathology of schizophrenia or dementia praecox prior to this Congress, neither the previous work nor the new material presented led to a consensus of opinion as to the neuropathological characteristics of this common disorder. On the contrary, perusal of the Congress Proceedings suggests that a dichotomy of views emerged, with most of the central European investigators, maintaining, as they had in earlier reports, that rather specific changes occurred in basal ganglia (Hopf, 1952; Vanderhorst, 1952; Fungfeld, 1952), basal forebrain (Buttlar-Brentano, 1952), or cerebral cortex (Josephy, 1930; Buscaino, 1924; Fungfeld, 1952; Hyden, 1952). Their colleagues from England and America, on the other hand, generally reported non-specific alterations which they attributed to convulsive treatments, surgical, agonal or post-mortem changes (Meyer, 1952; Rowland & Mettler, 1949).

NEURONE PATHOLOGY IN SCHIZOPHRENIA

An exception was Bruetsch (1952) of Indianapolis, who maintained that a subgroup of approximately 9% of schizophrenics displayed minute acellular areas in the cortex secondary to rheumatic occlusive endarteritis. A similar observation was reported earlier by Winkelman & Book (1949) and was confirmed by the Vogts (1952). Earlier findings included grape-like metachromic globules in basal ganglia and white matter (Buscaino, 1924) and focal areas of demyelination (Ferraro, 1943). Josephy (1930) described lipoid accumulations in pyramidal neurones of layer II in pre-frontal cortex and hippocampus similar to those described by Spielmeyer (1931), as well as calcifications in globus pallidus and glial nodules in the basal ganglia, thalamus and brain stem.

Cecil and Oscar Vogt (1952), in a monumental series of studies commencing at the turn of the century, were the first to compare serial sections of whole brain specimens from schizophrenic patients and normal control subjects. Together with their collaborators they described numerous alterations in schizophrenic brains, including cell loss in cingulate and inferior temporal cortex, “dwarf” cells (Schwarzellen) in basal ganglia and dorsal medial thalamus, apparently preceded by peculiar vacuolization and lipoid inclusions in clusters of neurones. From the same institute, Hopf (1952) reported ‘dwarf cells’ in basal ganglia of nine of ten patients with catatonic schizophrenia; Buttlar-Brentano (1952) described similar changes, i.e. progressive vacuolization, balloon cells, shrinkage and disappearance of cytoplasm in neurones in the nucleus basalis of substantia innominata, bed nucleus of stria terminalis, and periventricular, supraoptic, tuber and mammillary nuclei. Similar neuronal alterations and glial proliferation had been previously reported in hypothalamus, especially tuber cinereum by Dide (1934) and Morgan & Gregory (1935).

Most neuropathologists of Great Britain and the United States remained sceptical, however, and in 1957 David, in an extensive review of the reported pathology of schizophrenia, dismissed...
Buttlar-Brentano’s observation of ‘dwarf’ cells in substantia innominata, commenting ‘It is difficult to envisage how an alteration of as unspecific a region as this could have the systemic effects presumably required to induce schizophrenic behaviour.’

David suggested that only quantitative cell counts in schizophrenic and matched control material could confirm or deny the reports of focal neuronal degeneration. Negative results of such an undertaking had been previously reported for cerebral cortex by Dunlap (1929). Colon (1972) reached an opposite conclusion, finding a 70% reduction of neurones in cortical layers IV and V in selected areas of the frontal cortex of schizophrenic brains compared with controls. More recently, Dom et al. (1981) reported that cell counts on serial sections of basal ganglia and thalamus showed a 50% decrease in small neurones in pulvinar and large neurones in nucleus accumbens in brains of schizophrenics studied at the Vogt Institute. The difficulty of such studies are well known, and it is not surprising that psychiatrists turned with relief to the more easily quantified new technologies of gas–liquid chromatography, mass-spectrography and ‘grinding and binding’ for the measurement of biochemical constituents and receptor sites in schizophrenic and control brains.

The first International Congress of Neuropathology coincided with, but was too early to profit from, MacLean’s (1952) heuristic introduction of limbic system anatomy pathology and physiology to psychiatry or David might not have dismissed Buttlar-Brentano’s report of pathology in nucleus basalis so lightly. Assuming that the profound disturbances in higher nervous functions must involve cerebral cortex, a majority of studies of schizophrenic neuropathology has concerned cerebral cortex. Moreover, with few exceptions, the pathological material was generally stained only with conventional neuropathological techniques for myelin, Nissl substance and occasionally axis cylinders and lipoids.

**GLIAL CHANGES**

Employing the lithium carbonate stain for glia, Scharenberg (1952) reported a marked astrocytic proliferation in cases of fatal catatonia. Five years later, Nieto, also using the lithium carbonate method, reported a pathological increase of fibrillary gliosis in periventricular and periaqueductal regions of the diencephalon and mesencephalon in a majority of schizophrenic brains. In a subsequent publication Nieto & Escobar (1972), emphasized that the same sections of the brain displaying intense fibrillary gliosis with the lithium carbonate method were quite unremarkable in Nissl or myelin preparations. More recently, Fisman (1975) reported glial nodules in brain stem, especially the medial reticular area and trigeminal nucleus, in six of eight schizophrenic brains, noting a resemblance to viral, in particular herpes zoster, encephalitis. Both of these studies may be criticized as patients were generally of advanced age, the criteria for diagnosis were not specified, and material from ‘blind’ controls was not included.

Using stringent criteria for diagnosis of schizophrenia and restricting the specimens examined to patients under 54 years of age, we recently compared histological material from the brains of 28 patients meeting International Classification of Disease criteria for schizophrenia with similar material from age-matched non-schizophrenic control patients who died in the same hospital during the same period with a variety of neuropsychiatric disorders and with neuropathological material from age-matched patients deceased in a general hospital of medical or surgical causes (Stevens, 1982a, b). Nissl, myelin or hematoxylin-eosin stains of this material revealed striking pathology in a few of the schizophrenic patients. A marked dropout of large neurones in the globus pallidus was apparent in three cases, and there was bilateral infarction in the inner or outer segment of pallidum in two cases. All five of these patients had admission diagnoses of catatonic schizophrenia and followed a course typical of chronic schizophrenia. Heavy deposits of iron–calcium concretions in globus pallidus, infiltration of the basal forebrain with corpora amylacea and abundant ependymal granulations, all common during middle and advanced age in normal controls’ brains, were present in the brains of schizophrenic patients who died in their 20s and 30s.

The most prominent and ubiquitous pathology, however, appeared only with the Holzer stain for glial fibrils. With this method, 70% of schizophrenic patients demonstrated increased fibrillar...
gliosis affecting primarily the periventricular regions and the anterior and inferior horns of the lateral ventricle, third ventricle, periaqueductal gray or basal forebrain. The gliosis was similar in distribution to that reported by Nieto (1957) and Nieto & Escobar (1972). Although gliosis in mesencephalic tegmentum was also common, the discrete glial nodules described by Fisman (1975) were seldom seen. The location of gliosis varied greatly from case to case, being more pronounced in basal forebrain (substantia innominata, lateral hypothalamus, bed nucleus of stria terminalis) in certain cases, while in others periaqueductal, interpeduncular, dorsal medial thalamus or hypothalamic regions were principally affected. An attempt to correlate the subtype of schizophrenia with the pathological findings was entirely unsuccessful. This was not surprising, as a review of the clinical charts indicated that the patients diagnosed as catatonic schizophrenia on admission (as a majority were) generally proceeded during subsequent years of hospitalization to manifest flattened affect, isolation, delusions, ideas of reference, or pathological suspiciousness typical of paranoid schizophrenia. Subsequently, a majority progressed to states of abulic amotivational incoherent or hebephrenic behaviour or autistic preoccupation, with auditory hallucinations occasionally interrupted by episodes of severe agitation or assaultiveness. A correlation between location of the pathology and specific clinical phenomenology was sometimes suggestive – for example, sleep and feeding disturbances with hypothalamic gliosis, speech disturbance with pallidal pathology.

VENTRICULAR ENLARGEMENT IN SCHIZOPHRENIA

The introduction of computed tomography into psychiatric research (Johnstone et al. 1976) has led to a rediscovery of the ventricular dilatation so consistently reported in schizophrenic patients studied by pneumoencephalography more than half a century ago (Jacobi & Winkler, 1927). The new evidence of ventricular enlargement must now direct attention once again to the long disputed neuropathological studies of schizophrenia. If the ventricles are enlarged, something must have disappeared. Although Weinberger et al. (1979) observed no correlation between lateral ventricular size and length of illness, Tanaka et al. (1981) reported a positive correlation between the size of the third ventricle and the duration of schizophrenia. If confirmed in serial studies of individual patients, this observation indicates that a progressive destructive process occurs in this disease. These radiological findings alone are sufficient reason to return to the study of the neuropathology of schizophrenia.

SIGNIFICANCE OF MORPHOLOGICAL, ELECTROPHYSIOLOGICAL AND BIOCHEMICAL CHANGES FOR THE CONCEPT OF ‘FUNCTIONAL PSYCHOSIS’

As Yatsu, Professor of Neurology at the University of Oregon likes to say, ‘Gliosis is a tombstone’. So, of course, are lipoid degeneration, cell dropout, mineral deposits, ependymal granulations and, probably, corpora amylacea. These neuropathological gravestones spur the search for aetiology. Such studies should now include techniques which have developed since the pioneering, but long neglected, studies of Alzheimer (1897), Dide (1934), the Vogts (1952), and so many others. Evidence for biological antecedents of schizophrenia has grown appreciably in the past decade with the explosion of growth in neurobiomedical technologies. Increased dopamine binding sites (Lee et al. 1978; Owen et al. 1978), increased norepinephrine in schizophrenic basal forebrain (Farley et al. 1980; Kleinman et al. 1982), abnormal EEG spectra (Stevens, 1976; Stevens et al. 1979; Fenton et al. 1980), enlarged cerebral ventricles (Johnstone et al. 1976; Weinberger et al. 1979), atrophy of cerebellar vermis (Weinberger et al. 1980), and evidence of immunological incompetence (Liederman & Prilipko, 1976), autoimmunity (Semenov et al. 1961; Baron et al. 1977; Pandey et al. 1981) or viral residence in brain (Tyrell et al. 1979; Albrecht et al. 1980; Stevens, 1982a; Torrey et al. 1982) all challenge long cherished notions of psychogenesis.

Chemical and morphological abnormalities in schizophrenia also raise questions about the increasingly obsolete concept of ‘functional psychosis’ and research diagnostic criteria which
demand the exclusion of cases with evidence of organic brain disease from the schizophrenias.

Ferraro at the International Neuropathological Congress of 1952 enquired:

What should our attitude be in the presence of organic cerebral changes found in cases clinically diagnosed as functional psychosis? Must we adhere to the concept that a diagnosis of schizophrenia is incompatible with the presence of cerebral pathology? Must we every time that organic changes are found in the brain of a supposedly schizophrenic patient change our diagnosis into one of organic psychosis simulating dementia praecox? Must we talk in such cases of schizophrenia-like condition?

Clearly, a new definition is required, encompassing new findings disclosed by new technologies. This is even more likely to be the case as the revolutionary changes in neuropathology which have followed the introduction of immunohistochemistry are applied to the study of receptors, enzymes, peptides, viruses, and immunological reactions in schizophrenic brains.

**EVIDENCE FOR UNITY AS WELL AS DIVERSITY OF THE SCHIZOPHRENIC SYNDROME: THE DOPAMINE HYPOTHESIS**

If the increased neuroleptic binding found in the basal ganglia and forebrain of schizophrenic brains is not related to neuroleptic treatment, this finding is the most consistent contribution to the pathology of schizophrenia in the last decade (Lee et al. 1978; Owen et al. 1978). How can an increase in putative dopamine binding sites in the striatum be integrated with the gliosis, cell metamorphosis or loss and ventricular enlargement which, up to now, have been the principal neuropathological findings of schizophrenia?

There are a number of clues that schizophrenia is due to an encephalopathy resulting from activation of a latent infectious agent. The seasonal peak of births in early spring of future schizophrenics (Torrey & Torrey, 1979), the pockets of high incidence of schizophrenia in certain geographical areas (Torrey, 1980), and recent immunological findings in cerebrospinal fluid (Tyrell et al. 1979; Albrecht et al. 1980; Torrey et al. 1982) are consistent with repeated reactivation of a viral infection or immunological process in this disorder. Viruses and neurotransmitters bind to specific, apparently related, sites on neuronal membranes (Munzel & Koschel, 1981; Lentz et al. 1982). Viruses may alter binding of other substances to the cell membrane and, following entry of the cell, can direct the metabolic machinery without necessarily destroying the host cell (Glasgow, 1979). Reportedly abnormal T-cell response to mitogens (Liederman & Prilipko, 1976) and anti-brain antibodies in serum (Semenov et al. 1961; Heath & Krupp, 1967; Pandey et al. 1981) may also relate to the chronic residence of virus in brain.

The discovery of a viral aetiology for schizophrenia need not contradict the considerable evidence for hereditary factors in this disorder. Viral genome, incorporated in cell nucleus, can be transmitted with the genetic material of the host cell. If, as several studies suggest, cytomegalovirus, or varicella zoster virus, both members of the herpes family are associated with schizophrenia (Albrecht et al. 1980; Torrey et al. 1982; Stevens, 1982a), the reported amelioration of herpes zoster by treatment with L-dopa raises the possibility that virus and dopamine may compete for the same, or closely related, binding sites on neural membranes. The favourable effect of neuroleptics in schizophrenia could thus be only indirectly related to dopamine receptor blockade, but directly related to preventing viral binding and entry to the cell, to synaptosomes or to interference with replication of viral DNA within the cell (Hahn, 1979).

**NEEDED: A NEW SPECIALTY OF NEUROPSYCHIATRY OR PSYCHONEUROLOGY**

Neurologists have taken a long holiday from the study of psychiatry in general and from schizophrenia in particular. Equally remiss, an entire generation of psychiatrists has been trained with a curriculum often devoid of neuroanatomy, neuropathology and neurology, not to mention the explosion of new information and technology in neurochemistry, immunology, virology, and neuroradiology. In partial recognition of the growing similarity of both clinical problems and
technologies in neurological and psychiatric research, American neurologists have recently given birth to the new subspecialty of **behavioural neurology**, deliberately avoiding the uncomfortable possibility that this concept might be better called **psychiatry** or, at the very least, **neuropsychiatry**. **Pari passu**, psychiatrists, at least those not exclusively enamoured of the psychotherapies (increasingly the province of non-medical professionals), have rediscovered the importance and excitement of the study of the brain. Few psychiatric training programmes provide adequate preparation for such work. Psychiatry’s new horizons require retreading of practitioners as well as research physicians in the basic neurological sciences in order that the changes in these disciplines can be applied to the baffling clinical problems posed by the major psychoses. Clearly, neuropsychiatry (or psycho-neurology) like its enormously successful young parents, the neurosciences, is a specialty whose time has come, and for which appropriate training programmes are urgently needed by both psychiatrists and neurologists.

**REFERENCES**


Liederman, R. R. & Prilipko, L. L. (1976). The behavior of T lymphocytes in schizophrenia. In *Neurochemical and Immunologic...*


