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EDITORIAL

How do the neuropathological changes of schizophrenia relate to pre-existing neurotransmitter and aetiological hypotheses?[1]

Up to the first half of the twentieth century there seemed little doubt about the presence of structural changes in the brains of schizophrenics the first report of such changes often being attributed to Alzheimer (1897). Certainly by the 1950s (Vogt & Vogt, 1952), a multitude of neuropathological abnormalities were detected and dilated ventricles had been noted as early as 1927 (Jacobi & Winkler, 1927). Many differing and conflicting cellular changes were seen and taken together seemed to provide no evidence for a discrete structural abnormality.

The ascendancy of a strong antipsychiatry movement (e.g. Laing, 1985) along with burgeoning research in epidemiological, social and neuropharmacological aspects, which took little heed of earlier biological research, led to a rapid decline in the popularity of neuropathological research.

Although not a novel finding the report by Johnstone *et al.* (1976) of dilated ventricles in elderly schizophrenics stimulated a resurgence of interest in the search for structural abnormalities in schizophrenia. Imaging studies will not be discussed here. In addition several reviews have now comprehensively detailed the neuropathological findings (e.g. Lantos, 1988; Meltzer, 1987). The aim of this short editorial will be to discuss how these structural changes relate to the dopamine hypothesis and other neurotransmitter theories of schizophrenia, what the changes may tell us about aetiology and what implications novel findings and progress in neurochemical pathology have for the development of novel therapeutic interventions in schizophrenia.

NEUROPATHOLOGICAL FINDINGS: THE BASIC FACTS

Interest has principally focused on the temporal and frontal lobes. In morphometric studies, the volumes of the hippocampus, parahippocampal gyrus and amygdala (Bogerts, 1984; Bogerts *et al.* 1985) are all reduced. Brown *et al.* (1986) have shown reductions in parahippocampal gyrus and lateral ventricles. Falkai & Bogerts (1986) while confirming reduced numbers of pyramidal cells in the hippocampus noted no change in glial numbers and Roberts *et al.* (1987) show no difference in glial fibrillary acidic protein (GFAP) as judged by quantitative immunochemistry. Two studies have shown abnormalities in pyramidal cell orientation with cellular disarray in the CA1/CA2 region (Scheibel & Kovelman, 1981; Kovelman & Scheibel, 1984). Another study (Jakob & Beckmann, 1986) shows abnormal spatial arrangement of cells in the nearby entorhinal cortex.

Frontal lobe neuropathology is less well defined. The 'hypofrontality' hypothesis is not new (Kraepelin, 1950); however, in modern times the evidence for hypofrontality is derived from studies of regional cerebral blood flow (e.g. Weinberger *et al.* 1986; Buchsbaum *et al.* 1984), magnetic resonance imaging (Andreason *et al.* 1986) and neuropsychological studies (Weinberger *et al.* 1988), although neuropathological support has been sparse. Neuronal loss has been reported by Colon (1972) but this may be age related and only minor ultrastructural anomalies could be found by Tatetsu (1964) and more recently by Schitz & Winkelman (1981). More recently Benes *et al.* (1986) have shown reduced neuronal density in various cortical regions including frontal.

UPDATE OF NEUROCHEMICAL PATHOLOGY

The dopamine hypothesis for schizophrenia has always been a subject for vigorous debate (e.g. Iversen, 1987; Kerwin, 1988). However, the dopamine hypothesis remains the most robust explanation of experimental findings and at the very least convincingly explains the antipsychotic

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mechanism of neuroleptics (Iversen, 1987; Crow, 1987). Notwithstanding this honourable position it is unlikely that it will yield radically different pharmacological treatments. It is therefore important to consider other neurotransmitter or metabolic processes (be they primary or secondary) which may be amenable to pharmacological manipulation. There is a vast and confusing literature on the post-mortem biochemistry of schizophrenia which is impossible to review here, but has been elsewhere (e.g. Reynolds, 1988; Deakin, 1988). However, worthy of special note are two recent findings. Of many neuropeptides studied in schizophrenia cholecystokinin is emerging as an interesting candidate. Dopamine neurones contain cholecystokinin (CCK) as their co-transmitter (Hökfelt *et al.* 1980). In experimental protocols CCK is neuroleptic-like, reducing dopamine turnover (Fuxe *et al.* 1980) and reversing behavioural responses to dopaminomimetic agents (Nemeroff *et al.* 1983). Post-mortem studies remain inconclusive (Kleinman *et al.* 1983), but Ferrier *et al.* (1983) have claimed a loss of CCK receptors in the temporal lobe of patients with negative symptoms. A recent literature survey of all patients having received CCK analogues has shown that its efficacy as a treatment remains unproven (Montgomery & Green, 1988). Glutamate is another interesting candidate for pharmacological manipulation. Direct abnormalities in glutamate systems in post-mortem schizophrenic brains have been found including increased prefrontal cortical binding of the 'kainate' receptor subtype (Nishikawa *et al.* 1983), frontal cortical loss of the N-methyl-D-aspartate subtype (Kornhuber *et al.* 1988), loss of hippocampal kainate receptors (Kerwin *et al.*) 1988 and increased amygdala aspartate uptake on the left (see Deakin, 1988).

The release of glutamate and dopamine are under each others' reciprocal control in a way which suggests the primary abnormality may be glutamatergic (Meldrum & Kerwin, 1988). Finally, phencyclidine and other psychotomimetics may be non-competitive antagonists at some recognition site on the N-methyl-d-aspartate (NMDA) receptor (see Meldrum & Kerwin, 1988 for review). Therapeutic agents acting at glutamate receptors are currently under development, none have yet been administered to schizophrenics.

RELATIONSHIP OF NEUROPATHOLOGICAL FINDING TO NEUROTRANSMITTER THEORIES

The notion of schizophrenia as a temporal lobe disorder is becoming extremely strong and is derived from EEG studies, symptomatology seen in temporal lobe epilepsy, outcome studies in temporal lobectomized patients, psychophysiological studies, neurochemical studies and now neuropathological data (for review see Andreason, 1986; Stevens, 1988). How does temporal lobe pathology relate to neurotransmitter hypotheses? Paradoxically, the dopamine hypothesis is the most difficult to reconcile with these findings. The hippocampus is traditionally considered to be devoid of dopamine (Swanson, 1982), although complete noradrenergic lesions do not completely deplete the hippocampus of catecholamine metabolites (Scatton, *et al.* 1980). Minute amounts of tracer leucine can be seen in the dentate gyrus after injection into ventral tegmental dopamine (DA) cells (Beckstead *et al.* 1979). A fluorescent tracer 'True Blue' labels a small number of ventral tegmental cells when injected into the hippocampus and these cells also stain positively for tyrosine hydroxylase (Ishikawa *et al.* 1982). However, microscopical techniques have not confirmed synaptic terminal plexi for these putative dopamine afferents (Björklund & Lindvall, 1984).

In the efferent systems a small but well defined excitatory output from the hippocampus converging onto the dopamine terminal site, nucleus accumbens, is well characterized (De France *et al.* 1980) and of particular interest is the observation that accumbens dopamine receptor sensitivity increases in animals with hippocampal kindled seizures (Csernansky *et al.* 1988). The neuropathological change in the amygdala is not so problematic. The amygdala is moderately innervated with DA fibres (Fuxe *et al.* 1974) and while the increase in DA concentrations in the left amygdala is an intriguing finding (Reynolds, 1983) further information is required on the laterality of the cellular changes before it is possible to explain the relationship.

The situation is different for glutamate as there is a substantial input of glutamate fibres from

cortical afferents, with both the dentate gyrus and pyramidal cells receiving fibres, the intrinsic Schaffer collaterals also utilizing glutamate as a transmitter (Otterson & Storm-Mathisen, 1984). The kainate and NMDA receptor subtypes are differentially localized on CA3, CA4 regions and dentate gyrus, CA1 regions respectively and represents one of the densest concentrations of these receptors in the central nervous system (Patch *et al.* 1986).

As for CCK, numerous terminals are found throughout the hippocampus and these are probably interneurones in their own right rather than within DA terminals (Vanderhaegen, 1984). Its action in the hippocampus is an excitatory one similar to that of glutamate (Dodd & Kelly, 1981). The most substantial regional loss of CCK from postmortem schizophrenic brain is from the hippocampus (Ferrier *et al.* 1983; Farmery *et al.* 1985).

As the neuropathological basis for hypofrontality is unsubstantiated the relationship to neurotransmitter systems in schizophrenia remains speculative. However, frontal cortical lesions can provoke subcortical DA receptor supersensitivity in rats (Pycock *et al.* 1980) and Weinberger (1987) has formulated a theoretical dopamine deafferentation hypothesis partly on the basis of this.

CCK receptors are certainly present in frontal cortex and apart from the hippocampus the only other reported loss of CCK sites in schizophrenia is from frontal cortex (Farmery *et al.* 1985).

RELATIONSHIP OF NEUROPATHOLOGICAL CHANGES TO AETIOLOGICAL THEORIES FOR SCHIZOPHRENIA

It is impossible to accommodate neuropathological findings into all the competing aetiological hypotheses, such as genetic contribution, viral hypotheses and obstetric complications as it would assume that these were all correct and given equal weight in any unifying hypothesis and would also assume that the disease was a homogeneous entity. Nevertheless, strands of information about aetiological events may be gleaned from some of the observations.

Studies on gliosis in schizophrenia have claimed that this represents an embryogenetic neurodevelopmental abnormality. Increased fibrillary gliosis in schizophrenia was originally claimed by Stevens (1982). But quantitative immunocytochemistry showed this not to be the case (Roberts *et al.* 1987) and more recent qualitative studies of cell numbers support this (Falkai & Bogerts, 1986). These findings suggest to some (see Roberts *et al.* 1987) that the neuronal degeneration occurs in early embryogenesis when the immature nervous system is incapable of gliosis. This is an elegant hypothesis – but dòes it take into account that a substantial proportion of the hippocampus is formed post-natally in primates (Rakic & Nowakowsi, 1981)? In addition GFAP staining cells (therefore mature astrocytes capable of proliferation) can be detected at the earliest stages of hippocampal development in primates (Eckenhoff & Rakic, 1984). It is also possible to explain these data by proposing an abnormality of glial proliferation.

The exquisite sensitivity of the hippocampus to ischaemia is well known (e.g. Balslev-Jorgenson & Diemer, 1982) as is the fact that hippocampal ischaemic infarcts produce schizophreniform psychoses (Mednick, 1970).

The observation of an excess of obstetric complications in schizophrenics (Lewis & Murray, 1987) is therefore of some interest. Indeed very transient hypoxia comparable to perinatal hypoxia produces selective loss of pyramidal cell neurones (Johansen *et al.* 1983). It is of particular interest in terms of glutamate hypotheses for schizophrenia that these ischaemic mechanisms are mediated via glutamate receptors and excitatory amino antagonists are protective (Meldrum, 1981). Also of interest to the obstetric complication hypothesis is the observation of Weinberger & Cohen (1982) that dopaminergic neurones are preferentially susceptible to transient ischaemia providing an explanation whereby dopamine receptor supersensitivity may ensue after perinatal hypoxia.

Another possibility is that the degenerative changes in schizophrenic temporal lobe structures may be excitotoxic. Glutamate is an endogenous excitotoxin and may be responsible for the neuronal destruction seen in Huntington's chorea (Schwarz *et al.* 1984). Such a mechanism may be a plausible possibility for cell loss in schizophrenia as the most degenerate regions in schizophrenia

have the highest density of glutamate receptors (Monaghan *et al.* 1983) and the observation of a loss of glutamate receptors from schizophrenic hippocampus (Kerwin *et al* 1988) has already been noted.

As for other aetiological factors such as the genetic contribution, season of birth or the viral hypothesis, there are as yet no clues linking these to the neuropathological changes.

CONCLUSIONS: THE FUTURE

The recent state of neuropathological evidence suggests that in part there is some structural substrate to the schizophrenic process and further studies are required fully to reconcile neuropathology with various neurotransmitter hypotheses. The neuropathological data more importantly give some clues as to possible aetiological processes in schizophrenia. An enormous mass of neurochemical work including recent studies on glutamate and peptides holds out some hope for new antipsychotic agents acting via manipulation of these sites. However, advances in molecular biological techniques mean that future studies of non-transmitter systems such as neurotrophic factors and second messenger systems may offer the best hope for radical therapeutic advances and more energy should be devoted to the study of these in schizophrenia.

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