The brain in schizophrenia

To have forgotten that schizophrenia is a brain disease will go down as one of the great aberrations of twentieth century medicine. Kraepelin's concept of dementia praecox, invoking brain pathology as a substrate for the disease, was put forward in 1896 but quickly abandoned due to the inadequacy of research tools and the emergence of psychoanalysis and social psychiatry. Not until the advent of new imaging techniques in the 1970's, and consequent interest in the neuropathology, neurophysiology and neuropsychology of schizophrenia, have our views returned to the disease model. Our problem now is one of integrating in a coherent fashion the fragmentary, often contradictory, strands of evidence drawn from so many different directions. This editorial can only touch upon the most salient developments in recent years.

Structural brain abnormalities
Ventricular enlargement visualised by computerised tomography (CT) is no longer a controversial finding, although not specific to schizophrenia. Its exact prevalence is obscured by the large degree of normal variation in ventricular size, but we know that it does not progress in the majority of patients and that it is already present in the first episode of schizophrenic illness.

The confirmation of these diffuse indices of structural abnormality has been followed by the search for more specific pathology. Support for a reduction in volume of the hippocampus and parahippocampal gyrus, with significant reduction in the number of neurons in both structures, is growing. A preferential enlargement of the left temporal horn has also been demonstrated at necropsy.

These findings, taken in conjunction with the fact that gliosis is not observed in these limbic structures provide important clues about the nature and timing of the underlying neuropathological process. Attention is immediately directed to a possible developmental disturbance, since the gliotic response to pathological neuronal loss appears early in postnatal life. An excess of adverse antenatal and perinatal events in those later diagnosed as schizophrenics would support such an interpretation.

The pressure is now on to provide in vivo evidence of structural changes in the limbic system using magnetic resonance imaging. Some evidence has emerged that the temporal lobes are reduced in size, and a unique sample of monozygotic twins discordant for schizophrenia suggests that it is the hippocampus that is primarily affected.

Functional abnormalities
Using $^{133}$Xe Ingvar and Franzen demonstrated a decrease in blood flow in the prefrontal areas of schizophrenics compared with controls. This "hypofrontal" pattern has recently been replicated several times, not only using gamma emission techniques but also PET, and it is unlikely to be due to the effects of psychotropic drugs. Attempts to correlate specific clusters of clinical and neuropsychological deficits with patterns of altered metabolism using PET technology show considerable promise.

Further evidence of brain dysfunction in schizophrenia accrues from the presence of subtle neurological abnormalities (for example, difficulties in motor sequencing and coordination, sensory extinction and agaphasia) which may be present in as many as 60% of schizophrenics. Although such signs have been recorded in other psychiatric patients, even during childhood and adolescence, their prevalence in schizophrenia far exceeds that in other conditions and is not explicable purely as a medication effect.

Perhaps of greater interest is the dysfunction in eye tracking considered by some as a disease marker. Frequent saccadic intrusions during smooth eye pursuit and fixation occur in over two thirds of schizophrenics and in 45% of their first degree relatives. Both horizontal and vertical pursuit are affected, suggesting a dysfunction of the cortical modulatory inputs. These abnormalities, much less frequent in normals and in other psychoses are not caused by neuroleptics or by inattentiveness and appear unrelated to treatment response or chronicity. Based on twin studies Holzman et al. have advanced the hypothesis that schizophrenia and abnormal eye movements are two independent manifestations of the same latent trait.

Neurochemical abnormalities
Neurochemical studies at necropsy have experienced a simultaneous revival. The dopamine hypothesis still retains a prominent place, partly maintained by a replication of the finding that dopamine levels are selectively increased in the left amygdala. Interest is nevertheless shifting to other neurotransmitter systems. A predominantly left sided reduction of GABA uptake sites in the hippocampus has recently been described. Other indicators of predominantly left sided abnormalities are seen in the glutamate system, with reports of reduced aspartate uptake in the left amygdala and left hippocampus. Abnormalities in the glutamate system are so far the only neurochemical derangements found outside the limbic system, with increased kainate receptor binding in the frontal cortex. The links between these neurotransmitter abnormalities and the neuropathological changes remain to be unravelled.
Taken as a group, schizophrenics have significantly lower IQ's than their siblings or normal controls from the same social and educational background.31 This is already detectable at the time of the first episode32 and there is no definite evidence that deterioration takes place in the course of the illness. To decide whether this drop in IQ occurs just before florid symptoms develop or whether it is a longstanding abnormality is almost impossible for obvious methodological reasons. Meta-analysis of cases with available measures of premorbid IQ from school or army service33 suggests that IQ deficits may occur many years before the onset of psychotic symptoms, particularly in males. These longstanding abnormalities are perhaps one of the manifestations of developmental insults that occur well before the emergency of psychotic symptoms.

Other cognitive abnormalities encountered in schizophrenia have been reviewed,33 with attentional, memory and perceptual deficits described. Recent interest has focused on "frontal lobe tasks"34 which may be impaired in the absence of other cognitive deficits. Cognitive impairment is probably associated with negative symptoms, such as blunting of affect and psychomotor poverty, and with ventricular enlargement.35 It may also relate to abnormalities on event related potentials; such as increased latency and reduced amplitude of the P300 potential, and possibly higher amplitude of the somatosensory evoked potential.36 These abnormalities are unrelated to age, duration of the illness, or severity of psychotic symptoms.37

In this issue Murphy and Cutting38 put forward the view that the difficulty schizophrenics have in conveying specific emotions, absent in other psychoses, is an indication of right hemisphere dysfunction. However the issue of localised cognitive impairment will remain unresolved until more comprehensive neuropsychological studies are performed. A step in that direction is the use of tests with dissecutable cognitive components thought to involve discrete neural systems. Using such attentional tasks, obvious performance differences between schizophrenics and controls have come to light, but it may be premature to attribute them to unilateral hemisphere dysfunction.39

The neuropsychological and neurochemical evidence suggest that the left temporal lobe is preferentially damaged in schizophrenia. On the other hand the presence of neurological signs, diffuse cognitive deficits and a "hypofrontal" pattern of metabolism suggest a more pervasive disturbance of function for which there is no obvious neuropathological or neurochemical basis.

Conclusions
The occurrence of structural and functional brain changes in schizophrenia is now well established, but many research findings remain contradictory. To integrate them into a coherent whole and to link them with presumed aetiological factors such as genetic vulnerability, developmental disorders, viral agents, etc. is undoubtedly one of the greatest challenges facing psychiatry.

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