Left brain, retrotransposons, and schizophrenia

In 1915 E E Southard, Bullard professor of neuropathology at Harvard, wrote on schizophrenia: “The disease must be conceded to be in some sense structural, since at least 90% of all cases examined [50 cases, data of 1910 and 1914] give evidence of general or focal atrophy when examined post-mortem ... the atrophies and aphasies when focal show a tendency to occur in the left cerebral hemisphere. The coarse atrophy is usually of moderate degree, and often does not appreciably alter the brain weight, at least outside the limits of expected variation. More remarkable is the high proportion of cases of internal hydrocephalus (at least nine cases) ... Aside from left-sidedness of lesions and internal hydrocephalus, very striking is the preference of these changes to occupy the association centers of Fleschig.”

With remarkable prescience this 70 year old contribution reflects contemporary foci of research. Recent work based on computed tomography (CT) and earlier findings from air encephalograms—all in apparent ignorance of Southard’s work—provide strong evidence of some internal hydrocephalus, particularly in the more chronic forms of schizophrenia. Enlargement of the ventricles, most prominent in the temporal horn, has been confirmed in a recent necropsy study and may reflect atrophic changes in limbic structures. The weight of the brain was reduced by 5-6% in patients with schizophrenia by comparison with those with affective disorders.

Most striking is Southard’s insistence that the disease has a predilection for the left hemisphere. Laterality was introduced into discussions of psychosis in 1969 by Flor-Henry’s report that when psychosis develops in association with an epileptic focus in the left hemisphere it is schizophrenia like, while when the focus is in the right hemisphere the changes are primarily affective. These observations were widely seen to be relevant to temporal lobe epilepsy and its associated psychiatric changes rather than to the pathophysiology of the functional psychoses. Yet recent research has re-emphasised that schizophrenia itself may be a disease of the left, or dominant, hemisphere. The evidence comes from four sources.

Firstly, differences in laterality have been reported in some CT scan studies. For example, Largen et al found reductions in scan “density” on the left side in patients but no difference between the sides in controls. This observation has been replicated in a study of monozygotic twins discordant for schizophrenia (M A Reveley and A M Reveley, paper to Fourth World Congress of Biological Psychiatry, 1985). It seems less likely that reduced CT scan density reflects a change in actual brain density than that it indicates that cerebrospinal fluid spaces (not identifiable on the image) are increased in the left hemisphere—in other words that there is a reduction in tissue mass. An early air encephalogram study reported that nine of 27 chronic psychotic patients had ventricular enlargement restricted to the left side.

Secondly, two recent studies using computer controlled topographic electroencephalographic mapping (the BEAM (brain electrical activity mapping) technique) reported differences in laterality. Morihisa et al found increased fast beta activity in the left posterior quadrant in institutionalised patients with chronic schizophrenia and taking no drugs; this...
was accompanied by increased amplitudes of visual evoked potentials, a combination compatible with an irritable or epileptogenic focus. Morstyn et al recorded the P300 waveform (which may be generated in the hippocampus) of an auditory evoked potential and found that the greatest difference between the schizophrenic and control groups was in the left middle and posterior temporal regions. 6

Thirdly, in a neurochemical analysis of brain tissue taken at necropsy Reynolds found that the dopamine content of the amygdala was increased in patients with schizophrenia by comparison with controls on the left but not on the right side of the brain. 7

Finally, a necropsy study found that when patients with schizophrenia were compared with others with affective disorder the width of the parahippocampal gyrus was reduced, the difference between the groups being greater on the left side. 8

These diverse sources provide increasing evidence of a disturbance in the left hemisphere, perhaps particularly in temporal structures. It is as though a chronic and relapsing encephalitis has its focus in the left temporal lobe.

What could account for such selectivity? Since Broca's verification of the observations of Dax 9 it has been accepted that in most people speech is localised in the left hemisphere. More recently an anatomical basis for this specialisation has been uncovered. Asymmetries in the brain are well established and include particularly the planum temporale on the superior aspect of the temporal lobe. 10 This region, closely related to auditory association cortex, is bigger on the left side in most people, 11 particularly those who are right handed. 12 It also appears close to regions implicated by recent studies as the site of the disturbance in psychosis. The crucial question is whether the brain asymmetries and their determinants merely reflect the left hemisphere vulnerability to an exogenous pathogen or whether there is some more intimate connection between the disease and cerebral asymmetry. Might schizophrenia be a disease of cerebral dominance itself?

A genetic contribution to aetiology is established, 13-16 but firm evidence for an environmental factor is lacking. The age of onset is determined by genetic—or at least prenatal—factors. 17 In this sense the disease appears almost to be the expression of a developmental programme rather than a reaction to an exogenous event. One possibility is that it is due to a pathogen 18 (for example, a retrovirus or other type of transposable genetic element—that is, a "retrotransposon") 19 that is integrated in the human genome, which in episodes of illness is expressed as viral particles. If this element were integrated close to the genes (presumably growth factors) which determine cerebral asymmetry this might account for the predilection for the left hemisphere.

The effect of season of birth—the tendency for patients with schizophrenia to have been born in the winter—remains an unexplained observation. This effect seems to relate particularly to patients without a family history. 20,21 Though birth injury has been invoked as a possible explanation, temperature dependent genetic rearrangements occurring much earlier (for example, at fertilisation or even at gamete formation) might be relevant. Thus transposition of an element to sit within the genetic complex (the "cerebral dominance gene," or right side shift factor of Annett) 22 determining laterality and cerebral dominance might have the same outcome as inheritance of the pathogenic sequence in situ from a predisposed parent.

Another puzzle is the persistent high prevalence of schizophrenia which is apparently relatively constant in the popula-

5 Brown R, Colter N, Cornellis JAN, et al. Postmortem evidence of structural brain changes in schizophrenia. Differences in brain weight, temporal horn area, and parahippocampal gyrus shape compared with affective disorder. Arch Gen Psychiatry 1986;43:36-42.
10 Morstyn R, Duffy FH, McCrawey RW. Altered P300 topography in schizophrenia. Arch Gen Psychiatry 1981;38:729-34.
11 Reynolds GP. Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. Nature 1983;305:527-9.