Two syndromes—type I characterised by delusions, hallucinations, and thought disorder (positive), and type II by affective flattening and poverty of speech (negative symptoms)—in schizophrenia were advanced as possible correlates of two underlying "dimensions" of pathology, a neurochemical (reversible, and possibly dopaminergic) and a structural component (less reversible, associated with intellectual impairment). Type I, it was suggested, predicted neuroleptic responsiveness; type II, poor long-term outcome. [The SSCP and the SSCP indicate that this paper has been cited in more than 585 publications.]

Two Syndromes in Schizophrenia and Their Underlying Pathology

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Invited to review the neurochemistry of schizophrenia, I summarised the background to the dopamine hypothesis and work my colleagues in the Clinical Research Centre Division of Psychiatry (particularly F. Owen and E.C. Johnstone) and I had done to test it (in postmortem brain tissue and a trial of the isomers of flupenthixol) and asked how far such a neurohumoral theory could take us in understanding the disease process. The hypothesis survived, but there were two problems—some patients and some symptoms do not improve on medication, and some patients have gross cognitive impairments (e.g., temporal disorientation) that are unexpected if one thinks of the disease as a simple transmitter disturbance or as a "functional" (i.e., nonorganic) psychosis. Also we had shown, in the first computerised tomography study of schizophrenia, that the cerebral ventricles of some chronic patients are larger than those of age-matched controls.

Struggling to apply Ockham's razor, I conceded that neither a simple neurohumoral hypothesis nor a view of schizophrenia as a low-grade organic condition (implying brain damage) was tenable—one had to accept there was an element of both, i.e., a reversible and an irreversible component. But once this was accepted a relatively simple view of the relationship of these putative processes to clinical features was possible—positive symptoms (abnormal by their presence) respond well to medication, negative symptoms (diminution or absence of normal function) are less responsive to dopamine antagonist medication (as we had shown in the flupenthixol isomers trial) but are more frequent concomitants of the intellectual loss that is present in some patients with persisting impairments. The paper may have been well cited because the two-syndrome concept has some predictive validity in clinical practice, and the suggestion of separate underlying dimensions of pathology provides a target for research on mechanisms.

After 13 years how does the concept hold up? The dopamine hypothesis is hardly challenged as an explanation of the antipsychotic efficacy of neuroleptics, and most agree that positive symptoms respond better than negative. But an underlying disturbance of dopaminergic transmission remains elusive. (Positron emission tomography scan studies provide at best equivocal support for a change in receptors.) Structural changes are present and may be more marked in patients (more likely to have an earlier onset) with negative symptoms. Some (e.g., P.F. Liddle) now suggest that thought disorder is separable from both positive and negative symptom groupings. The evidence supports this, but what we lack is a concept of why these different components (two, three, or more) relate to each other. What is the underlying disturbance and what is its cause? I no longer believe that an exogenous agent (e.g., a virus) contributes. The problem, I now think, is a part of the evolutionary enigma of the origins of human diversity. The clue, I suggest, lies in the form of the structural changes—these are asymmetrically distributed to the two hemispheres.

6. ~~~~~~~~~~~~~~. Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophrenia Bull. 16:433-43. 1990. Received August 31, 1993