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Editorial

Syndromes of Schizophrenia

Classic Literature

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In the 29 November 1993 issue of *Current Contents* (vol. 21, no. 48, pp. 8–9), papers by Andreasen (1982), Andreasen & Olsen (1982) and Crow (1980) were nominated as 'Citation Classics'. These papers had, respectively, been cited in more than 395, 480 and 585 publications. The three authors of this article were invited to comment upon the papers.

Peter Liddle

In their classic descriptions of the illness that came to be called schizophrenia, Kraepelin and Bleuler presented it as a persistent illness characterised by fragmentation of mental function. In particular, Bleuler regarded clinical features such as loosening of associations and blunted affect as fundamental, and more transient features such as hallucinations and delusions as accessory. However, in the subsequent quest for greater reliability of diagnosis, Schneider attributed special importance to certain hallucinations and delusions that are common in schizophrenia and rare in other disorders. The focus on hallucinations and delusions was reinforced by the success of dopamine-blocking drugs in alleviating these symptoms. The efficacy of dopamine-blocking drugs became the central buttress supporting the hypothesis that schizophrenia is a neurohumoral disorder involving excessive dopaminergic neurotransmission. Despite the success of dopamine-blocking drugs, many patients remained seriously disabled, their lives fragmented by persistent Bleulerian symptoms. A new concept of the illness was required.

On the basis of work by his team at Northwick Park Hospital in the 1970s, Crow (1980) advanced his two-syndrome model. He proposed that there are two major dimensions of psychopathology in schizophrenia: type I, comprising positive symptoms, such as delusions, hallucinations and formal thought disorder, that tend to be transient; and type II, comprising negative symptoms such as poverty of speech and blunted affect that tend to persist. He proposed that these two syndromes reflect two dimensions of pathophysiology: a neurohumoral disturbance generating the type I syndrome, and structural cerebral abnormality generating the type II syndrome.

Crow's concept of negative symptoms focused on poverty of speech and blunted affect, deficiencies in mental activity that can be assessed in a clinical interview. However, many patients suffering persistent disability in daily life exhibit neither poverty of speech nor blunted affect of marked degree. Should the negative syndrome be more broadly defined?

Andreasen (1982) provided a broader concept of the negative syndrome and also a comprehensive rating scale, the Scale for the Assessment of Negative Symptoms (SANS), which comprises five subscales: blunted affect; alogia; avolition; anhedonia; and attentional impairment. Many of the items, especially in the avolition and anhedonia subscales, are scores of reported performance in daily life. SANS embodies a broader concept of negative symptoms, but is it too broad? A variety of factors might impede performance in daily life.

A decade later, as we look back on these papers by Crow and by Andreasen, several questions must be answered. Do the symptoms of schizophrenia segregate into two distinct syndromes, and if so, how broad should the concept of negative symptoms be? Does the evidence support the proposal that negative symptoms arise from abnormal cerebral structure while positive symptoms reflect dopaminergic imbalance?

The segregation of schizophrenic symptoms

Many investigations have used factor analysis of symptom scores to identify groups of symptoms that commonly coexist in a patient. Virtually all such studies have identified more than two factors, although in most studies at least one positive syndrome factor and one negative syndrome factor emerged. In some of the studies, the scores entered into the factor analysis were subscale global scores for each of the five SANS subscales and for the subscales in Andreasen's Scale for the Assessment of Positive Symptoms. These studies, reviewed by Klimidis *et al* (1993), reveal at least three major groups of symptoms: core negative symptoms; delusions and hallucinations; and a third group whose cardinal item is formal thought disorder. This third group had been named the disorganisation syndrome by Liddle (1984).

The various studies examining SANS subscale scores differ in details of the composition of the three syndromes identified. One possible explanation for this inconsistency can be found by inspecting the composition of SANS subscales. In the 1982 version, all of the subscales contain a mixture of negative symptoms with features that probably belong to the disorganisation syndrome. For example, the blunted affect subscale includes inappropriate affect, the alogia subscale includes poverty of content of speech, while within the other three subscales many items refer to impaired living skills likely to be influenced by both negative features and by disorganisation.

The confounding within subscales can be reduced by entering SANS item scores rather than subscale scores into the factor analysis. Adopting this strategy, Liddle (1987) found three syndromes:

(a) psychomotor poverty (poverty of speech, blunted affect and decreased movement), closely resembling Crow's narrowly defined negative syndrome
(b) reality distortion (various delusions and hallucinations)
(c) disorganisation (formal thought disorder, inappropriate affect and poverty of content of speech).

Other studies employing SANS items (e.g. Malla *et al*, 1993) or other rating scales such as the Manchester scale (Frith, 1992) have confirmed this pattern, although the status of poverty of content remains controversial (Peralta *et al*, 1992).

The studies that have found three syndromes have not included the entire gamut of schizophrenic symptoms. If affective items and features of over-arousal are included, two additional syndromes, depression and psychomotor excitation, can be identified (Liddle, unpublished data). In conclusion, factor analytic studies confirm the existence of two distinct syndromes corresponding approximately to the two syndromes originally proposed by Crow (1980), but the full picture is more complex. Most importantly, formal thought disorder appears to belong to a separate group of symptoms, the disorganisation syndrome.

The relationship between symptoms, cerebral structure and cerebral function

One of the cardinal studies by the Northwick Park group on which Crow based his type I/type II proposal showed that patients with negative symptoms had more cognitive impairment, and that cognitive impairment was associated with enlarged cerebral ventricles, but there was not a significant association between negative symptoms and ventricular enlargement (Johnstone *et al*, 1978*a*). Andreasen & Olsen (1982) reported that patients with predominantly negative symptoms have impaired cognitive function, and also enlarged cerebral ventricles, when compared with patients exhibiting predominantly positive symptoms. Subsequent studies have confirmed the association of negative symptoms with cognitive impairment, especially with impairment in frontal lobe tasks (Liddle & Morris, 1991), but the findings regarding negative symptoms and ventricular enlargement have been less consistent. In a review of computerised tomography studies, Lewis (1990) reported that only 5 of the 18 relevant studies found a significant relationship between negative symptoms and ventricular enlargement.

While the relationship between negative symptoms and abnormal cerebral structure has proven to be weaker than implied in Crow's hypothesis, the relationship between negative symptoms and disordered cerebral function has proven robust. Not only is there an association with poor performance in tests of frontal lobes, several studies have shown that negative symptoms are associated with decreased frontal cerebral blood flow or metabolism in the resting state (Liddle *et al*, 1992; Wolkin *et al*, 1992) and with impaired ability to activate frontal cortex during frontal tasks (Andreasen *et al*, 1992). These findings have been reported in medicated and in unmedicated subjects. Furthermore, it appears that the pattern of cerebral activity associated with negative symptoms is not a static loss of frontal function, but part of a dynamic imbalance between cortical and subcortical activity (Liddle *et al*, 1992).

With regard to positive symptoms, definitive evidence for a neurohumoral mechanism is still lacking. Changes in symptom severity are associated with a complex pattern of changes in the metabolites of monoamine neurotransmitters, but many of the observed associations apply to both positive and negative symptoms (Kahn *et al*, 1993). Furthermore, the partial success of atypical antipsychotics in alleviating all three of the major dimensions of schizophrenic symptoms (Meltzer, 1992) shows that negative symptoms are subject to pharmacological influence in some circumstances.

Conclusions

The seminal papers of Crow and Andreasen defining positive and negative dimensions of schizophrenia revitalised attempts to relate the symptoms of schizophrenia to disorders of cerebral anatomy and physiology. Subsequent studies have vindicated the

multi-dimensional approach to schizophrenia, but demonstrate that the illness cannot be confined to two dimensions. Nonetheless, the core negative features – impoverishment of speech, affect and motor activity – have emerged as a clearly defined dimension. There is substantial evidence that this dimension of psychomotor impoverishment reflects frontal underactivity within a pattern of dynamic imbalance between areas of association cortex and related subcortical nuclei.

William T. Carpenter

Crow's two-syndrome model and Andreasen's method for assessing positive and negative symptoms have proven heuristic and influential in the study of schizophrenia. These highlights in scientific progress were anticipated by conceptual developments and followed by significant modifications.

Kraepelin conceptually separated dissociative and avolitional psychopathologies, but unified them in a disease entity construct. Bleuler noted heterogeneity of symptoms, but argued that fundamental symptoms, such as dissociative thought and affect pathology, were found in all cases. This reinforced the single-disease approach to schizophrenia that has dominated research designs throughout this century.

In contrast, Strauss *et al* (1974) observed that pathological features within the domains of positive, negative and interpersonal symptoms were related across time, but that between-domain correlations were minimal. They proposed that three symptom complexes be studied independently rather than as variable expressions of the same disease process. Crow put this proposition into action, hypothesising that cell loss caused irreversible negative symptoms, low IQ, poor treatment response, and the chronic defect state. Positive psychotic symptoms and good neuroleptic response were associated with increased activity of dopamine receptors. This lessening of the heterogeneity of the clinical syndrome excited optimism that more specific and replicable findings, especially from brain imaging and neuropathology, would be forthcoming.

Andreasen provided a method to assess negative symptoms (the SANS) and, together with Olsen, established an approach to distinguishing positive from negative schizophrenia. These landmark developments have been followed by important modifications in concepts and methods.

First, the inverse positive/negative symptom relationship suggested by Crow and reported by Andreasen & Olsen has not been observed in subsequent studies. Rather, the earlier view of the semi-independence of these pathological domains has been substantiated, and the symptom complexes of interest have been redefined.

Fifteen studies (Buchanan & Carpenter, 1994) suggest that a three-compartment (sometimes four) solution accounts for the symptoms of schizophrenia better than a two-compartment model. However, a significant modification is required of the three-compartment model of Strauss *et al* (1974). Formal thought disorder (disorganised or dissociative thinking) appears to be independent of hallucinations and delusions, and negative symptoms. Positive psychotic symptoms are best defined by hallucinations and delusions. Attentional impairment, poverty of content of speech, and incongruity of affect have not fitted neatly with negative symptoms, and this domain is best defined by restricted affect, anhedonia, avolition, asociality, and alogia.

A third modification is the emphasis on distinguishing primary from secondary negative symptoms (Carpenter *et al*, 1985). That social withdrawal can be secondary to psychosis or socio-environmental deprivation has been documented (Wing & Brown, 1970); anhedonia is a manifestation of depression and demoralisation; and restricted affect expression may be neuroleptic akinesia. To study the avolitional syndrome of Kraepelin or the irreversible negative symptoms of Crow or the deficit syndromes (Carpenter *et al*, 1988), it is necessary to differentiate primary from secondary negative symptoms. This was implied by Crow, but the SANS explicitly avoids this distinction. A reliable and valid approach to the differential diagnosis of primary negative symptoms for categorical assignment is available (Kirkpatrick *et al*, 1989), but a method for rating change restricted to primary negative symptoms is not yet established.

A final consideration involves concepts of symptom heterogeneity in schizophrenia. If viewed as a single disease entity with diverse manifestations, the distinction between different symptom complexes is less important. Studies of aetiology or pathophysiology necessarily involve contrasts with non-schizophrenic comparison groups. However, in a syndrome model positing different aetiopathophysiologies for common features (e.g. psychosis), the presence or absence of negative symptoms may distinguish two different aetiologies of psychosis. An application of the Crow two-syndrome model is based on the hypothesis that the presence of irreversible negative symptoms distinguishes between a psychotic disease caused by dopamine dysregulation and a psychotic disease caused by alteration of brain structure. A third model, favoured by our group for heuristic reasons (Carpenter *et al*, 1993), proposes a different

aetiopathophysiology for each symptom complex. When the Crow hypothesis is applied in this context, the negative symptoms are based on structural brain changes, and the psychosis of both type I and II would share the dopamine pathophysiology. In the latter application, type I/II contrasts are informative about the psychopathology of negative symptoms. In the former application, type I/II contrasts are informative about two different psychoses. Selection between these three models, therefore, has profound implications for hypothesis-testing research. Unlike the first model, within-schizophrenia comparisons are facilitated by models two and three, an effective way to control for artefacts such as neuroleptic drugs which regularly confound schizophrenia/non-schizophrenia comparisons.

Many studies have been reported in the positive/negative framework. Findings are often not definitive. This is, in part, because measures of a fluctuating clinical state are often correlated with trait brain measures, and because secondary negative symptoms confound interpretation of data. Nonetheless, the proposition that these three symptom domains differ in natural history and neural circuit involvement is supported (see, for example, the eloquent studies of Fenton & McGlashan (1994), and Liddle *et al* (1992)). Our work on the deficit syndrome (redefining type II with the sole criterion of trait, primary negative symptoms and applying it within model three) implicates limbic circuitry in psychosis and dorsolateral prefrontal cortical circuitry (DLPFC) in the deficit syndrome (Tamminga *et al*, 1992), findings compatible with Liddle *et al* (1992). Studies of Weinberger (1987) support the plausibility of a structural lesion in DLPFC underlying negative symptoms and secondary dopamine disinhibition in limbic circuitry causing positive symptoms. This Jacksonian single-disease model is viable. However, our studies suggest that these findings might apply only to type II or deficit schizophrenia (Buchanan *et al*, 1990; Tamminga *et al*, 1992).

Finally, the general proposition that only schizophrenia with negative symptoms manifests structural brain changes has not been supported. Early reports have been inconsistent as to whether structural changes are skewed toward negative symptoms, and Gur *et al* (1994) reported a clear negative study using general brain measures underlying the Crow hypothesis. Buchanan *et al* (1993) report that a small hippocampus (perhaps the most consistent schizophrenia brain finding) is more notable in non-deficit patients, and diminution of prefrontal white matter was restricted to the non-deficit group.

Much work remains to be done, but the creative conceptual and methodological contributions in these Citation Classics provided a springboard for progress.

Tim Crow

Invited to review the neurochemistry of schizophrenia, I summarised the background to the dopamine hypothesis and the work that my colleagues and I in the Clinical Research Centre Division of Psychiatry had been doing to test it. A trial of the stereo-isomers of flupenthixol (Johnstone *et al*, 1978*b*) had subjected the dopamine antagonism explanation of the antipsychotic effect to a relatively stringent test and it had survived. A post-mortem study (Owen *et al*, 1978) revealed no evidence of increased dopamine turnover but a modest excess of butyrophenone binding sites that was interpreted as compatible with an increase in numbers of D_2 receptors. One could take the view, therefore, that the symptoms of schizophrenia were due to a (potentially reversible) disturbance of neurohumoral transmission. But awkward for this conclusion were the facts that some symptoms (e.g. negative symptoms in our study) and some diseases are relatively resistant to D_2 receptor blockade. In addition, we had already shown (Crow & Mitchell, 1975; Crow & Stevens, 1978) that some patients have features, such as temporal disorientation, that suggest an 'organic-type' dementing process, and in the first computerised tomography study of schizophrenia (Johnstone *et al*, 1976) we found that a group of chronic patients (including some with 'age disorientation') had larger cerebral ventricles than age-matched controls.

Struggling to apply Occam's razor, I concluded that neither a simple neurohumoral hypothesis nor a view of schizophrenia as a low-grade organic condition (implying progressive loss of cortical function) was tenable. One had to accept there was an element of both – 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) often respond well to neuroleptic medication, negative symptoms (diminution or absence of normal function) are less responsive, but are more frequent concomitants of the intellectual loss that is present in some patients with persisting impairments (the 'type II syndrome'). In this way the hypothesis of 'two dimensions of pathology' (neurochemical and structural) was related to the clinical distinction between positive and negative symptoms that had been adopted by W. T. Carpenter, J. K. Wing and

and others – for an account of the historical background, see Crow (1985).

Does the evidence of the past 14 years support the pathophysiological predictions? That there are morphological changes in the brain is generally accepted, but the identity of the key element is obscure (see below for one interpretation). On the whole, such changes are more readily demonstrable in patients with the more severe outcomes (who are more likely to have negative symptoms) but the relationship is weak (perhaps *because* the key change has not been identified), and it certainly is not true that morphological change is confined to a subgroup of 'organic-type' illnesses. In some sense, psychosis is a disorder of brain structure.

The neurochemical component also remains obscure. There is little challenge to the dopamine hypothesis of the antipsychotic effect, but no positive support for a primary disturbance of dopaminergic transmission. Whether there is an increase in D_2 receptors is still debated, for example in relation to the findings from positron emission tomography (Farde *et al*, 1990; Wong, 1992), and it seems unlikely that a change in receptor numbers can contribute to pathogenesis. Conversely, there is no evidence that increased receptor numbers relate to the dyskinesias which are widely (but I think erroneously) attributed to neuroleptic medication (Crow *et al*, 1983). Some studies suggest that such abnormal movements, when persistent, are related to negative symptoms and intellectual impairments. They are, I believe, more a manifestation of the disease process than its treatment.

Several authors (Lorr *et al*, 1963; Liddle, 1987; Bilder *et al*, 1985) have suggested that thought disorder should be considered as a dimension that is relatively independent of both positive (delusions and hallucinations) and negative (flattening of affect and poverty of speech) symptoms. I agree that the evidence supports this, but in this case should one not also consider as possible dimensions elation and depression? I hold tenaciously to the view (notably without impact on the 1980 paper) that the Kraepelinian dichotomy between schizophrenic and affective psychoses is a brake to progress (Crow, 1994) and the categorical approach to psychiatric diagnosis unsustainable. But if there are dimensions (positive and negative symptoms, thought disorder, and affective change) of pathology, to what variations in normal function do these correspond? The question posed by Kretschmer's (1921) formulation now needs to be re-addressed.

The last paragraph of the 1980 paper looked forward to the discovery of a major environmental contribution (a virus) to aetiology. Four years later (Crow, 1984) I had convinced myself that no such discovery was to be made, a change of heart reinforced by the findings of the subsequent World Health Organization Ten Country Study on incidence (Jablensky *et al*, 1992). I now think that the origins of psychosis are intrinsic and to be sought in the genetic mechanisms associated with the evolution of language and the descent of *Homo sapiens* from a pongid ancestor (Crow, 1993*a*). At some point in this sequence a genetic change occurred that allowed cerebral functions to develop preferentially in one or the other hemisphere. From the potential for hemispheric specialisation, by means of a delay in maturation and an increase in brain size, evolved the capacity for a high degree of communication and social interaction, together with diversity in psychological style and a susceptibility to psychosis (Crow, 1991; 1993*a*). According to this view, the brain changes in schizophrenia can be seen to include 'an arrest of development' of cerebral asymmetry (Crow, 1990). A sex difference in the rate of hemispheric differentiation could account for the sexual dimorphism for cerebral asymmetry, be relevant to the sex difference in age of onset of psychosis, and provide a clue to the mechanism of these evolutionary developments (Crow, 1993*b*).

Conclusions

The two-syndrome concept attempted to correlate neurochemical and structural elements of the schizophrenic disease process with the positive and negative components of the symptoms. But the concept was pathophysiological rather than aetiological. As an approach to the fundamental problem, weaknesses of the hypothesis were that:

(a) it failed to specify the nature of the process (which remains obscure)
(b) it overlooked the continuity of schizophrenic and affective psychoses, and thereby (in at least one respect) oversimplified the dimensional problem
(c) it gratuitously invoked an environmental pathogen, and in this way defused the central question of aetiology.

An alternative approach (excluding extrinsic or environmental causation) is to consider the psychoses as boundaries of the variation which is intrinsic to *Homo sapiens*. Such variation may be presumed to relate to man's recent evolutionary history (including the evolution of the capacity for language) and to be subject to continuing selective pressures. In this context, the key question is what are the dimensions of variation of which the various pathological

syndromes (negative and nuclear symptoms, etc.) form the boundaries?

References

ANDREASEN, N. C. (1982) Negative symptoms in schizophrenia: definition and reliability. *Archives of General Psychiatry*, **39**, 784–788.

—— & OLSEN, S. (1982) Negative v. positive schizophrenia: definition and validation. *Archives of General Psychiatry*, **39**, 789–794.

——, REZAI, K., ALLIGER, R., *et al* (1992) Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Archives of General Psychiatry*, **49**, 943–958.

BILDER, R. M., MUKHERJEE, S., RIEDER, R. O., *et al* (1985) Symptomatic and neuropsychological components of defect states. *Schizophrenia Bulletin*, **11**, 409–417.

BUCHANAN, R. W., KIRKPATRICK, B., HEINRICHS, D. W., *et al* (1990) Clinical correlates of the deficit syndrome of schizophrenia. *American Journal of Psychiatry*, **147**, 290–294.

——, BREIER, A., KIRKPATRICK, B., *et al* (1993) Structural abnormalities in deficit vs. non-deficit schizophrenia. *American Journal of Psychiatry*, **150**, 59–65.

—— & CARPENTER, W. T. (1994) Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia. *Journal of Nervous and Mental Disease*, **182**, 193–204.

CARPENTER, W. T., HEINRICHS, D. W. & ALPHS, L. D. (1985) Treatment of negative symptoms. *Schizophrenia Bulletin*, **11**, 440–452.

——, —— & WAGMAN, A. M. I. (1988) Deficit and non-deficit forms of schizophrenia: the concept. *American Journal of Psychiatry*, **145**, 578–583.

——, BUCHANAN, R. W., KIRKPATRICK, B., *et al* (1993) Strong inference, theory falsification, and the neuroanatomy of schizophrenia. *Archives of General Psychiatry*, **50**, 825–831.

CROW, T. J. (1980) The molecular pathology of schizophrenia: more than one disease process? *British Medical Journal*, **280**, 66–68.

—— (1984) A re-evaluation of the viral hypothesis: is psychosis the result of retroviral integration at a site close to the cerebral dominance gene? *British Journal of Psychiatry*, **145**, 243–253.

—— (1985) The two-syndrome concept: origins and current status. *Schizophrenia Bulletin*, **11**, 471–486.

—— (1990) Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophrenia Bulletin*, **16**, 433–443.

—— (1991) Origins of psychosis and "The Descent of Man". *British Journal of Psychiatry*, **159** (suppl. 14), 76–82.

—— (1993*a*) Origins of psychosis and the evolution of human language and communication. In *New Generation of Antipsychotic Drugs: Novel Mechanisms of Action* (eds S. Langer, J. Mendlewicz & J. Racagni), pp. 39–61. Basel: Karger.

—— (1993*b*) Sexual selection, Machiavellian intelligence and the origins of psychosis. *Lancet*, **342**, 594–598.

—— (1994) The demise of the Kraepelinian binary system as a prelude to genetic advance. In *Genetic Approaches to Mental Disorders* (eds E. S. Gershon & R. Cloninger), pp. 163–192. Washington: American Psychiatric Press.

—— & MITCHELL, W. S. (1975) Subjective age in chronic schizophrenia: evidence for a sub-group of patients with defective learning capacity? *British Journal of Psychiatry*, **126**, 360–363.

—— & STEVENS, M. (1978) Age disorientation in chronic schizophrenia: the nature of the cognitive deficit. *British Journal of Psychiatry*, **133**, 137–144.

——, OWENS, D. G. C., JOHNSTONE, E. C., *et al* (1983) Does tardive dyskinesia exist? *Modern Problems of Pharmacopsychiatry*, **21**, 206–219.

FARDE, L., WIESEL, F. A., HALLDIN, C., *et al* (1990) D_2-dopamine receptor characteristics in neuroleptic-naive patients with schizophrenia: A PET study with [^{11}C] raclopride. *Archives of General Psychiatry*, **47**, 213–219.

FENTON, W. S. & MCGLASHAN, T. H. (1994) Antecedents, symptom progression, and long-term outcome of the deficit syndrome of schizophrenia. *American Journal of Psychiatry*, **151**, 351–356.

FRITH, C. D. (1992) *The Cognitive Neuropsychology of Schizophrenia*. Hove: Lawrence Erlbaum.

GUR, R. E., MOZLEY, P. D., SHTASEL, D. L., *et al* (1994) Clinical subtypes of schizophrenia: differences in brain and CSF volume. *American Journal of Psychiatry*, **151**, 343–350.

JABLENSKY, A., SARTORIUS, N., ERNBERG, G., *et al* (1992) Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten country study. *Psychological Medicine* (suppl. 20), 1–97.

JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., *et al* (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, *ii*, 924–926.

——, ——, ——, *et al* (1978*a*) The dementia of dementia praecox. *Acta Psychiatrica Scandinavica*, **57**, 305–324.

——, ——, ——, *et al* (1978*b*) Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet*, *ii*, 848–851.

KAHN, R. S., DAVIDSON, M., KNOTT, P., *et al* (1993) Effect of neuroleptic medication on cerebrospinal fluid monoamine metabolite concentrations in schizophrenia. *Archives of General Psychiatry*, **50**, 599–605.

KIRKPATRICK, B., BUCHANAN, R. W., MCKENNEY, P. D., *et al* (1989) The schedule for the deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Research*, **30**, 119–123.

KLIMIDIS, S., STUART, G. W., MINAS, I. H., *et al* (1993) Positive and negative symptoms in the psychoses: a re-analysis of published SAPS and SANS global ratings. *Schizophrenia Research*, **9**, 11–18.

KRETSCHMER, E. (1921) *Korperbau und Charakter*. Heidelberg: Springer-Verlag.

LEWIS, S. W. (1990) Computerised tomography in schizophrenia 15 years on. *British Journal of Psychiatry*, **157** (suppl. 9), 16–24.

LIDDLE, P. F. (1984) *Chronic Schizophrenic Symptoms, Cognitive Function and Neurological Impairment*. Thesis, University of Oxford.

—— (1987) The symptoms of chronic schizophrenia: a re-examination of the positive–negative dichotomy. *British Journal of Psychiatry*, **151**, 145–151.

—— & MORRIS, D. L. (1991) Schizophrenic syndromes and frontal lobe performance. *British Journal of Psychiatry*, **158**, 340–345.

——, FRISTON, K. J., FRITH, C. D., *et al* (1992) Patterns of cerebral blood flow in schizophrenia. *British Journal of Psychiatry*, **160**, 179–186.

LORR, M., KLETT, J. C. & MCNAIR, D. M. (1963) *Syndromes of Psychosis*. Oxford: Pergamon.

MALLA, A. K., NORMAN, R. M. G., WILLIAMSON, P., *et al* (1993) The three syndrome concept of schizophrenia. *Schizophrenia Research*, **10**, 143–150.

MELTZER, H. Y. (1992) Dimensions of outcome with clozapine. *British Journal of Psychiatry*, **160** (suppl. 17), 46–53.

OWEN, F., CROSS, A. J., CROW, T. J., *et al* (1978) Increased dopamine receptor sensitivity in schizophrenia. *Lancet*, *ii*, 223–225.

PERALTA, V., DELEON, J. L. & CUESTA, M. J. (1992) Are there more than two syndromes in schizophrenia? A critique of the positive–negative dichotomy. *British Journal of Psychiatry*, **161**, 335–343.

STRAUSS, J. J., CARPENTER, W. T. & BARTKO, J. J. (1974) Towards an understanding of the symptom picture considered characteristic of schizophrenia: its description, precursors and outcome. *Schizophrenia Bulletin*, **1**, 61–69.

TAMMINGA, C. A., THAKER, G. K., BUCHANAN, R., *et al* (1992) Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Archives of General Psychiatry*, **49**, 522–530.

WEINBERGER, D. R. (1987) Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, **44**, 660–667.

WING, J. & BROWN, G. (1970) *Institutionalism and Schizophrenia*. Cambridge: Cambridge University Press.

WOLKIN, A., SANFILIPO, M., WOLF, A. P., *et al* (1992) Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry*, **49**, 959–965.

WONG, D. F. (1992) PET studies of neuroreceptors in schizophrenia. *Neuropsychopharmacology*, **7**, 69–72.

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