Invited commentaries on: Obstetric complications and schizophrenia/affective psychoses†

DO OBSTETRIC COMPLICATIONS REALLY CAUSE PSYCHOSIS? WHY IT MATTERS

Kendell *et al*'s study (2000, this issue) is unusual in the psychiatric literature in that it addresses a hypothesis that the authors have previously espoused, generates new data which conflict with those of an earlier investigation, re-investigates the foundation of the previous conclusion and finds it wanting, and reaches a negative conclusion with respect to the original hypothesis. The findings are presented with exemplary clarity and honesty. The authors report that they are convinced that the results of their 1996 study were seriously misleading, and that the data they now present are accurate and dependable and fail to yield "any substantial evidence that the incidence of obstetric complications in people who subsequently develop schizophrenia is raised".

Previous literature

There were already grounds for suspecting this conclusion. In their meta-analysis Geddes & Lawrie (1995) noted significant heterogeneity of findings with respect to study design. The literature as a whole suggested an odds ratio of two for exposure to 'obstetric complications' on subsequent development of schizophrenia, but this depended upon the preponderance of studies that had used a retrospective case–control design. In the words of an early proponent (Lewis, 1989) of the birth complications hypothesis:

> "Paradoxically the main similarity between the studies is their collective weakness: the use of retrospective assessment of obstetric histories even if assessed blindly".

The possibility that the mother of a child who has developed psychosis will be biased with respect to the events of the pregnancy when asked to recall them, or even before this, is a real one. In addition, Geddes & Lawrie (1995) noted evidence (in a funnel plot) of a publication bias in favour of positive findings. The two cohort studies (Done *et al*, 1991; Buka *et al*, 1993) that avoided the recall bias gave an odds ratio of one, with the implication that obstetric complications and the development of schizophrenia are simply unrelated.

Meta-analysis is no defence against such biases. Geddes *et al* (1999) re-analysed the data from 12 studies, seven of which depended upon maternal recall, and five of which, including the original study of Kendell *et al* (1996), relied upon retrieval of obstetric records, but omitted the cohort studies. This time the pooled odds ratio was 1.4. The estimate reflects not only an aggregated bias (the 'Lewis effect') across maternal recall studies but, as Kendell *et al* (2000, this issue) now make clear, problems in the selection of the controls in retrospective comparisons of obstetric records.

The British Perinatal Mortality Survey recorded systematic data on the antenatal courses and births of 16 980 individuals born in the week 3–9 March 1958.

Those who had developed schizophrenia by either broad or narrow criteria by the age of 28 years were not more likely than the cohort as a whole to have experienced events predicting mortality in the perinatal period (Done *et al*, 1991). Nor were those 945 mothers who were recorded as suffering from influenza in the second trimester in the autumn of 1957 more likely to have children who later developed schizophrenia (Crow & Done, 1992; Crow, 1997*b*,*c*). A subsequent analysis of the many variables recorded in this cohort (Sacker *et al*, 1995) suggested that those indices that distinguished patients from controls related more to the characteristics of the mother (for example she more often had psychosocial problems, more often weighed less than 51 kg, and had fewer antenatal attendances) than to complications of the birth itself. Low birth weight (<2500 g) was more frequent in the patient group, as it was also in the recent cohort study of Jones *et al* (1998) who, as noted by Kendell *et al* (2000, this issue), concluded that the differences they found "appeared to be due largely to the characteristics of the child, not the delivery".

Core problem of aetiology

The cohort studies, consistent with the conclusions of Kendell *et al* (1996), thus give no support to the hypothesis that obstetric complications in general or any complication in particular is a cause of later schizophrenic illness. The importance of this conclusion is that it raises the question of whether there are any environmental contributions to the aetiology of schizophrenia. Only two – birth complications and prenatal exposure to influenza – have been seriously considered in the recent literature and both are now cast in considerable doubt.

This clears the air and brings the essential peculiarity of psychotic illness into focus – we are confronted with a phenomenon that is intrinsic, and therefore one might suppose 'genetic' in origin, and apparently universal in human populations (Jablensky *et al*, 1992) but that yet is associated with a substantial biological (fecundity) disadvantage. In what sense is this a disease? What sort of genes are these? Why are they not rapidly selected out of the population?

A clue to the answer lies in the nature of the brain changes. The three best established – an increase in ventricular size, a modest reduction in cortical mass and diminution or reversal of the asymmetrical torque across the antero-posterior axis (Bilder *et al*, 1994; DeLisi *et al*, 1997) – do not identify sub-populations, and must clearly be related. They cannot be attributed to birth injury or other environmental insult. They are present early in illness course, are 'developmental' in origin and reflect the nature of the genetic variation. Whereas it is often argued, particularly in the light of the apparent failure of the genetic linkage approach (DeLisi & Crow, 1999), that psychosis is the outcome of many genes of small effect, the morphology of the brain, as yet ill understood, suggests otherwise.

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The brain changes and their independence of environmental influence, along with universal incidence and persistence against a biological disadvantage (the 'central paradox'), indicate a homogeneity to the phenomena of psychosis that is close to the core characteristics of the species. The genetic variation therefore may differ from that associated with other 'disease-related' genes, for example, cystic fibrosis and Huntington's disease. One can ask is variation (apparently relevant to survival) that persists across populations independent of the environment the same as that which results from random mutation and inheritance within families according to Mendelian rules? This provokes the parallel question of whether variation within a species is of the same nature as that which separates species, a question that relates to the nature of species transitions.

Perhaps only when we are free from the concept of 'schizophrenia' as a categorical disease entity with multiple environmental causes yet to be discovered can we appreciate the true significance of psychosis as a component of the variation that identifies the species (Crow, 1998*a*). Such an insight helps us to understand the nature of the symptoms. The answer that I have given to the question first raised by Huxley *et al* (1964) of what the genetic advantage that balances the disadvantage associated with schizophrenia is is language. The capacity for language defines the species (Bickerton, 1995), it arose some time between 100 000 and 150 000 years ago, and was the result of a relatively discrete genetic change that occurred in a population in east Africa (Stringer & McKie, 1996). This event, perhaps because it introduced a differentiation of function of the hemispheres, allowed language to evolve.

Schizophrenia, according to this view, is the price that *Homo sapiens* pays for language (Crow, 1997*a*). It follows that schizophrenic symptoms can be understood as disorders of language, and more fundamentally as the key to the cerebral organisation of language. Nuclear symptoms can be understood as anomalies of the transition from thought to speech, and as an indication that a mechanism of 'indexicality' that distinguishes between what is self- and other-generated is a necessary component of the bihemispheric organisation of language (Crow, 1998*b*). Delusions can be understood as disorders of the transition from speech to meaning, that is as semantic deviations. The fact that nuclear symptoms and other types of delusion are so frequently associated, and that both these classes of psychotic phenomena are sometimes associated with 'thought disorder', indicates that the neural bases of syntax and semantics are not independent.

The reason why the disadvantageous 'genotypes' associated with psychotic symptoms are not selected out must be that the variation is inherent in the genetic mechanism, the characteristics of which reflect an origin in the transition (through a 'speciation event') from a precursor hominid to modern *Homo sapiens* (Crow, 1998*c*,*d*). It has been suggested that epigenetic modification (e.g. methylation) is particularly associated with species transitions (Vrana *et al*, 1998). Therefore, an alternative to the view that the inherited variation is polygenic and Mendelian is that it is speciation-related and 'epigenetic'. A recent twin study can be interpreted as consistent with this concept (Crow, 1999).

Why it matters

Why I think a resolution of the question of obstetric complications is important is that so long as it is believed that there are significant environmental causes of schizophrenic illness the central problem posed by the phenomena of psychosis is obscured. The singularity of the intrinsic variation and its wider significance for an understanding of language and the nature of speciation events is unappreciated. If as Kendell *et al* conclude "the evidence that schizophrenia is associated with a raised incidence of obstetric complications is weaker than has been assumed", some undergrowth that stands in the way of an understanding of the nature of the problem has been cleared away. As Darwin remarked: "False facts are highly injurious to the progress of science for they often endure long; but false views . . . do little harm, as everyone takes a salutary pleasure in proving their falseness, and when this is done, one path toward error is closed and the road to truth is often at the same time opened" (Darwin, 1871).

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NATURE OF OBSTETRIC COMPLICATIONS IN SCHIZOPHRENIA

While Kendell *et al* (2000, this issue) are to be commended for reporting what appears to be an artefact that renders their previous study unreliable, their present analyses raise new challenges. These largely (but not entirely) negative findings have to be interpreted in the context of: (a) the three recent birth-cohort studies cited by Kendell *et al*, each of which reports risk for schizophrenia to be associated significantly with one or more obstetric complication(s); and (b) a recent meta-analysis of 12 previous case–control studies which indicates in schizophrenia an odds ratio of 1.38 (95% CI 1.05–1.84, $P=0.02$) for exposure to at least one 'definite' complication (Geddes *et al*, 1999).

At a general level, discrepancies between a meta-analysis and a subsequent large, controlled trial are a well-recognised phenomenon in medical research that attract considerable attention; the most parsimonious conclusion in such circumstances is that a discrepant controlled trial does not negate the meta-analytic findings but, rather, suggests heterogeneity between studies that prompts identification and incorporation of covariates which reduce such heterogeneity (DerSimonian & Levine, 1999). The same principle may be just as applicable to the conundrum of obstetric complications in schizophrenia, but what approach should be taken?

As noted elsewhere (Waddington *et al*, 1999*a*,*b*), schizophrenia researchers have concerned themselves overwhelmingly with which and how obstetric complications might impart damage to the nascent nervous system, in the manner of stochastic (random/probabilistic) events; conversely, obstetricians adopt a different perspective and vocabulary, concerning themselves equally with what is to them a fundamental issue of why vicissitudes of pregnancy and delivery occur, on the basis that they arise for a reason rather than stochastically. It is enigmatic why many schizophrenia researchers remain preoccupied with the concept of obstetric complications only as a source of direct cerebral insult to a previously normal foetus, when obstetricians themselves readily conceptualise such complications as arising in considerable part due to events acting earlier in pregnancy. Some of their epidemiological findings are of considerable relevance both to schizophrenia and to how the findings of Kendell *et al* might be accommodated.

Among the general population, complications of late pregnancy and delivery, the period implicated perhaps most consistently (although by no means exclusively) in relation to schizophrenia, are associated with events in early foetal life. For example, breech-birth and cord prolapse are each more common among babies having congenital anomalies, as are bleeding in early pregnancy, pre-eclampsia and premature delivery. Given the origin of congenital anomalies in dysmorphogenesis over embryonic and early foetal life, these findings relate such 'late' and other obstetric complications to, and at least in part 'root' them in, otherwise unspecified events which have already compromised the foetus over the first or early second trimester (see Waddington *et al*, 1999*a*,*b*).

On this basis, as patients with schizophrenia appear to show a characteristic topography of subtle, craniofacial and other dysmorphology (minor physical anomalies/dysmorphic features), arising most likely between weeks 9/10 and 14/15 of gestation, any excess of later obstetric complications therein could reflect an already compromised foetus (Waddington *et al*, 1999*a*,*b*); this would be in accordance with Kendell *et al* quoting that obstetric complications in schizophrenia "appeared to be due largely to characteristics of the child, not the delivery". There are few data on the relationship between physical anomalies and obstetric complications in schizophrenia, and these are not consistent (O'Callaghan *et al*, 1991; McNeil & Cantor-Graae, 1999). However, in focusing on the prior integrity of the conceptus, one might explain differences between studies in terms of developmentally determined severity/chronicity of patient illness in the face of as inherently high threshold/low sensitivity a measure as obstetric complications; it may be relevant that patients in the study of Kendell *et al* were aged between 18 and 26 years, and diagnosed using ICD–8/9 (World Health Organization, 1974, 1978), in whom severity/chronicity of illness would have been less clear, while the majority of patients in the meta-analysis of Geddes *et al* (1999) were of established chronicity and had been diagnosed according to DSM–III/III–R criteria (American Psychiatric Association, 1980, 1987). Furthermore, it is well recognised, even on meta-analysis (Geddes *et al*, 1999), that it is difficult to resolve any particular complication(s) as bearing a specific pathological relationship to schizophrenia; this might also be consistent with earlier events leading to diversity of sequelae along the complex time-line of human pregnancy. Such a line of reasoning might explain an apparently small population-attributable fraction for obstetric complications in schizophrenia (Geddes *et al*, 1999), and would predict further inconsistent findings among diverse patient populations; the 'true' picture is likely to become clear only on the continuing application of appropriate meta-analytic techniques, and by further study of what may be antecedent factors.

It should be emphasised that such a perspective in no way diminishes the adverse impact of 'late' complications on the nascent brain on an individual patient basis; rather, it focuses attention on earlier, primary events that contribute to the emergence thereof, and on their further adverse impact on an already compromised nervous system. The data of Kendell *et al* should be seen as an important stimulus for revising our perspectives on the nature of obstetric complications in schizophrenia.

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