Correspondence

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Children, neurological soft signs and schizophrenia

In their recent article, Leask *et al* (2002) reconfirm the presence of neurological soft signs as a significant childhood finding among people who later develop schizophrenia in adulthood. In some earlier work using a similar, bias-proof follow-back design we had identified developmental problems (a pragmatic equivalent of soft signs), weaknesses in speech and language and difficulties in peer relationships as the strongest childhood precursors of adult schizophrenia, indeed easily more relevant than family history of psychosis or demographic characteristics.

As interest is developing in prodromes of psychosis and its early onset, we also have a far better-defined group of children who incorporate all the above parameters and factors. In our child psychiatric clinical practice, we are seeing increasing numbers of children with soft neurological signs and disturbed peer relationships who are diagnosed with Asperger syndrome. In effect, it would appear that even though neurological signs are not a central criterion, they are universally present and in exactly the areas Leask *et al* identified.

Could it be that these youngsters are indeed the most primary candidates for future schizophrenia? It would logically follow; and then our notions on continuities may need revising and, perhaps more relevantly, a target population may be identified where preventive input could be crucial. I would welcome comments from readers.

Ambelas, A. (1992) Preschizophrenics: adding to the evidence sharpening the focus. *British Journal of Psychiatry*, **160**, 401–404.

Leask, S. J., Done, D. J. & Crow, T. J. (2002) Adult psychosis, common childhood infections and neurological soft signs in a national birth cohort. *British Journal of Psychiatry*, **181**, 387–392.

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Authors' reply: Dr Ambelas raises the important relationship between the premorbid characteristics of individuals who later develop schizophrenic illnesses and the syndrome first described by Hans Asperger as 'autistic psychopathy' in childhood (Asperger, 1944). Asperger related his clinical picture to Bleuler's concept of autism in schizophrenia and wrote that, 'All but the last mentioned feature (dereistic thinking) can be found in the type of personality disorder to be described here'. But 'While the schizophrenic patient seems to show progressive loss of contact, the children we are discussing lack contact from the start'. Investigating this association, Tantam (1988) found that 18 (21%) of 86 people with Asperger syndrome later developed some form of psychosis.

The status of Asperger disorder/syndrome (DSM–IV (American Psychiatric Association, 1994) and ICD–10 (World Health Organization, 1992)) within the class of autistic spectrum or pervasive developmental disorders (DSM–IV) has been much debated. These disorders are characterised by delays or deficits in social relatedness, reciprocation, and understanding social interactions. The term pervasive developmental disorders was first introduced in DSM–III (American Psychiatric Association, 1980), with Asperger disorder only separated from other pervasive developmental disorders in DSM–IV. Pervasive developmental disorders not otherwise specified constituted the majority of cases in the DSM–IV field trials. Further subdivisions of pervasive developmental disorders are likely in revisions of DSM resulting from empirical evidence and consensus of opinion. Thus, Ambelas's target of a 'primary candidate' at this stage might be the broader class of pervasive developmental disorders, excluding autism, rather than Asperger syndrome *per se*.

Cohort studies such as the National Child Development Study (NCDS) cast some light on the issue. The epidemiology is arguably similar, with S+ schizophrenia having a lifetime prevalence of 8 per 10 000, and in the NCDS at age 7 the gender split was 20:13 (i.e. 1.5:1). While Ehlers & Gillberg (1993) using their own criteria estimated a minimum prevalence of 3.6 per 1000 children (7–16 years of age) and a male to female ratio of 4:1, using more liberal criteria their prevalence was 7 per 1000, with a gender split of 2.3:1.

Most authors agree with Tantam that the core of Asperger syndrome consists of disabilities in communication, socialisation and non-verbal expression, with conspicuous clumsiness and special interests. Cohort studies suggest that there are indeed deficits in at least some of these areas in children who go on to develop schizophrenia in adulthood. In the NCDS, we found these children more often rated as over-anxious and hostile in their relationships with adults and other children, and this was both more marked and present earlier in boys (Done *et al*, 1994). At ages 7, 11 and 16, their teachers noted the children were mispronouncing words more often than the rest of the cohort. At 11, there were increased rates of speech difficulties, and at 16 they were poor on English ability. There are therefore difficulties in communication, although it is not clear that these are comparable to the 'odd, pedantic, stereotypic speech' that is described in Asperger syndrome. Interestingly, at each age they were delayed in reading ability, although such deficits are not recorded as characteristic of Asperger syndrome. At age 11, girls but not boys among those who later developed schizophrenia were rated as withdrawn (i.e. distant, cut-off from people, avoiding communication), evidence perhaps of difficulties in non-verbal communication. However, at age 7 the girls in all respects manifested normal social behaviour, suggesting that girls who, in adulthood, develop schizophrenia might display a characteristic developmental trajectory (i.e. a decline in social relatedness and reciprocation between childhood and adolescence).

Perhaps the most interesting parallel is the one to which Ambelas draws attention, between the increase in neurological soft signs that we have observed and the clumsiness and stereotypy of movement that is described in Asperger syndrome – a clue to the neurological basis or bases of the two clinical pictures. At age 7, the children who, in adulthood, developed schizophrenia were more likely to be rated as having difficulties in coordination, and at

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age 16 were more likely to be described as clumsy. Delays in learning to stand, walk or speak are linearly related to later risk of schizophrenia (Isohanni *et al*, 2001) as also was delay in potty-training, a finding that corresponds to an increased incidence of failures of continence observed in the NCDS cohort.

Each of these findings suggests some commonality between features of pervasive developmental disorders (including Asperger syndrome) and those that precede schizophrenia, notwithstanding obvious differences in methods of data collection. There remains the question of time course to which Asperger drew attention – the features of Asperger syndrome are present early, whereas those of schizophrenia show an element of progression. This difference is exemplified by a progressive decrease in language scores preceding the onset of schizophrenia (Fuller *et al*, 2002).

The key question is why does this constellation of features come together? One finding from the NCDS sample points to the neurological substrate. At age 7, children who, in adulthood, develop schizophrenia were more likely to be rated as ambidextrous for handwriting by their mothers and were less lateralised on a square ticking task at age 11. There is evidence that lateralisation is a major determinant of the acquisition of words as well as of other aspects of cognitive ability (Crow *et al*, 1998). We propose that development of hemispheric dominance for the components of language is relevant to the similarities of the conditions described by the term Asperger syndrome and those that precede the onset of schizophrenic psychoses, as well as to differences in their time course. Thus, language – the core characteristic of the species – with its context in social interaction and its matrix in the lateralisation to the two hemispheres, is the function that varies between individuals and accounts for the similarities between the early developmental anomalies that were identified by Asperger and those that can now be seen as precursors to psychotic illness.

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Genetics of early-onset depression

We were very interested to read the recent, thought-provoking editorial by Andrews *et al* (2002) on the prevention of depression in young people. However, we are concerned that they have understated the important role of genetics in early-onset depression. Contrary to their assertion that the children of parents with depression are likely to be at heightened risk for psychological rather than genetic reasons, available evidence suggests that childhood-onset depression represents a strongly genetic subtype of affective disorder (Neuman *et al*, 1997; Sullivan *et al*, 2000). Up to 50% of prepubertal children with depression eventually develop bipolar disorder (Geller *et al*, 2001) and recurrent, early-onset depression (defined as two or more episodes before age 25) is recognised as a malignant form of affective disorder characterised by high genetic loading, frequent recurrence and poor long-term outcome (Zubenko *et al*, 2001). Furthermore, one recent study suggests that the inheritance of depression in these families is compatible with a single major locus (Maher *et al*, 2002).

Preliminary findings from our own study of early-onset depression in a university population support the view that early age at onset defines a subgroup at very high genetic risk. Using the Family Interview for Genetics Studies (FIGS; National Institute of Mental Health, 1999), 76% of the subjects seen so far (36 out of 47) report at least one first-degree relative with affective disorder, with 87% (41 out of 47) reporting either a first- or second-degree relative affected. The mean age at onset in this group is 15.6 years (s.d.=2.6).

Population-based interventions are unlikely to reduce the prevalence of depression in young people as long as we have an incomplete understanding of how genetic and non-genetic risk factors interact to bring about the depressive phenotype. Interventions such as the cognitive therapy programme described by Clarke and colleagues (Clarke *et al*, 2001) might be cost-effective strategies if they can be targeted to high-risk groups. Unfortunately, we are not yet in a position to reliably identify those individuals at high risk.

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