Correspondence

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Asphyxia at birth and schizophrenia

In our recent paper we reported that signs of asphyxia at birth were associated with the subsequent development of schizophrenia (Dalman et al., 2001). Crow (2001), in his invited commentary, suggested that the birth records were assessed by midwives who were not ‘blind’ as to case–control status. As stated in the paper, we took care to eliminate this possibility and think it highly unlikely that the midwives became unblinded. We should add that, following the Vancouver agreement (International Committee of Medical Journal Editors, 1997), the midwives were not listed as authors as they only contributed to data gathering. We understand that Professor Crow has also adopted this policy in relation to the National Child Development Study interviews (Done et al., 1991).

Why were our findings so clear-cut in relation to asphyxia? There are at least two possible reasons. First, we took care to adjust for confounders and also adjusted for the association between different pregnancy and delivery complications in order to examine for an association independent of other complications. Second, by using paediatricians to examine birth records we may have been measuring birth asphyxia more accurately than with the Apgar index, which is only poorly related to asphyxia (Sykes et al., 1982). Most of the other large studies carried out recently have relied upon routinely available data on pregnancy and birth complications. This might have introduced a random measurement error and could have obscured important associations.

Finally, the paper by Thomas et al. (2001) does not contradict that of Dalman et al. (2001). Thomas et al. (2001) were concerned only with the possibility that pregnancy and delivery complications were more strongly associated with schizophrenia in certain subgroups. The results indicated that there were no statistically significant interactions so the association between asphyxia and schizophrenia was apparent in the whole sample.


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Atypical antipsychotics, cortical D2 receptors and sensitivity to endogenous dopamine

Xiberras et al. (2001) report that atypical antipsychotics show a preferential cortical v. striatal dopamine D2 occupancy. This finding is not without controversy as Olsson & Farde (2001) failed to find such evidence and have suggested that an apparent cortical–striatal difference may be a methodological artefact. None the less, if the finding of Xiberras et al can be confirmed it prompts the question of why some drugs show a higher occupancy in one brain region compared with another.

Receptor occupancy by a drug is a function of its regional concentration and functional affinity for the receptor in that region. There are no data to suggest that the atypical antipsychotics show a higher regional concentration in the cortex; therefore, the difference is likely to arise because of higher functional affinity in the cortical regions. Functional affinity is determined by the receptor protein as well as local competition from endogenous neurotransmitters – dopamine in this case. The protein structure of the D2 receptors throughout the brain is similar and so is their in vitro affinity in the absence of competition (Seeman & Ulpian, 1983). This leaves one plausible explanation – that different concentrations of endogenous dopamine in cortical v. striatal regions may account for the difference in occupancies observed.

It has been suggested that a lower affinity and a faster off-rate (k off) may make atypical antipsychotics more susceptible to competition by the high levels of endogenous dopamine in the striatum compared with the low levels of endogenous dopamine in the cortex (Seeman et al., 1997; Kapur & Seeman, 2001). It is interesting that of the antipsychotics reported, the one with the lowest affinity, fastest dissociation from the D2 receptor and hence highest susceptibility to competition (clozapine) shows the greatest cortical–striatal difference, whereas the one with the highest affinity, slowest dissociation and least susceptibility (haloperidol) shows the least cortical–striatal difference. Furthermore, it seems that 5-HT2 blockade, or a multi-receptor profile, is not necessary to achieve this cortical–striatal difference since amisulpride, a relatively specific D2/3 agonist, also shows this effect. Thus, a lower affinity and a faster k off of the atypical antipsychotics at the D2 receptor makes them more responsive to endogenous dopamine concentrations and may account for the cortical–striatal difference noted by Xiberras et al.

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Diagnosis of vascular dementia

I read Dr Stewart’s article on vascular dementia (Stewart, 2002) with great interest. As a recently appointed consultant in old age psychiatry (having been trained in the ‘old’ way about diagnosing vascular dementia, i.e. sudden onset, stepwise deterioration, history of vascular risk factors, etc.), I started noticing a very different presentation of vascular dementia, especially in those with evidence of extensive periventricular disease on computed tomography. These cases commonly present with a range of frontal executive function deficits, with functional psychiatric symptoms of anxiety and depression and sometimes with progressive aphasia, and do not necessarily have the classical history of vascular dementia as described in textbooks.

The importance of the clinical findings is that as clinicians and educational supervisors we need to use more screening tests for frontal executive functions in routine assessments of dementia. In addition to the Mini-Mental State Examination (Folstein et al., 1975), verbal fluency and similarities (FAS; Thomas & O’Brien, 2002) tests are quick ways of testing frontal functions and should be encouraged among all members of a multi-disciplinary team. This has also been recognised in the new Cambridge Examination for Mental Disorder of the Elderly, Revised (CAMDEX–R; Roth et al., 1999).

Findings of periventricular ischaemia are controversial as far as their relevance to dementia diagnosis is concerned but patients who present with marked frontal functioning deficit and evidence of periventricular ischaemia on computed tomography should receive a diagnosis of vascular dementia. It is now known that ischaemia in periventricular areas interferes with the cortico-striato-thalamo-cortical loops which, in turn, affect functioning of frontal lobes.


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Prolonged QT interval with rivastigmine

Rivastigmine is an acetylcholinesterase inhibitor licensed in the UK since 1998 for the treatment of mild to moderate Alzheimer’s disease. Prolonged QT interval in association with this drug has not been previously described in the literature.

A 78-year-old man with dementia was commenced on rivastigmine for worsening of his cognitive decline and behavioural difficulties. He was receiving the following long-term medication: diltiazem, citalopram, furosemide, aspirin and ranitidine. His urea and electrolytes showed a low normal potassium of 3.4 mmol/l (normal 3.5–5 mmol/l). A pre-treatment electrocardiogram (ECG) showed evidence of an old inferior myocardial infarct, a QT interval of 382 ms and a QTc interval of 397 ms.

Seven days after commencement of rivastigmine a repeat ECG showed a QT interval of 476 ms and a QTc interval of 477 ms. Rivastigmine was the only recent additional medication and was therefore discontinued. No other changes were made. One week later the ECG showed a normal QT interval of 402 ms and a QTc interval of 399 ms. (An abnormal QTc interval is defined as >456 ms.) A repeat ECG 2 months later on his long-standing medication showed normal QT and QTc intervals.

Prolonged cardiac repolarisation (QT interval) is important as it may lead to potentially life-threatening ventricular arrhythmias (e.g. torsades de pointes; Thomas, 1994). Risk factors for prolonged QT intervals include: congenital long QT interval syndrome, clinically significant bradycardia or heart disease, electrolyte imbalance (hypokalaemia, hypomagnesaemia), impaired hepatic or renal function and concomitant treatment with drugs with potential pharmacokinetic/pharmacodynamic interactions (De Ponti et al., 2000).

To date, rivastigmine has been associated in very rare cases with atrioventricular block (see Exelon product data sheet; Novartis Pharmaceuticals UK Ltd, 2001). A literature search failed to identify any reports of QT interval prolongation associated with rivastigmine.

Confounding factors, such as comedication, electrolyte abnormalities and underlying disease, are more likely to occur in older people, who are the most likely age group to be receiving these drugs. Case reports such as this are an important method of reporting potential side-effects, particularly in the context of a newly introduced therapy.


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From mental hospitals to community care

The statistics on mental hospital closures given by Professor Leff (2001) will surprise not only lay people. I had no idea that hardly any mental hospital beds remain.
As someone whose career in psychiatry began in a 2300-bed hospital in 1957, I find it difficult to believe that this has actually happened.

I have no reason to doubt the sincerity of those people, medical and lay, who have enthusiastically advocated community care over the years. I am sure that they did not envisage that all the patients in the mental hospitals would eventually be discharged. Nor could they be blamed for failing to realise that the politicians, who hold the purse strings, would see community care not as an advance in treatment, but rather as a glorious excuse to save money.

One can see how the process developed: it must soon have appeared that discharging only some of the patients would not be enough, since, if community care failed, there would be demands for readmission. The only logical course was, therefore, to discharge all the patients, get rid of all the staff, demolish the hospitals and, as an additional bonus, sell off the land to property developers.

Unfortunately for the politicians, Griffiths reported that good community care would be very expensive, not cheap as they had hoped. They were faced with a new dilemma – what was the point in saving a lot of money by demolishing the hospitals if it all had to be redeployed for community care? The solution was obvious – restrict the amount of funding for community care!

It seems that, from now on, we will have the worst of all possible worlds – virtually no mental hospitals and poorly funded community care.


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Confusion
I read Dr Fleminger’s (2002) article with interest and in particular his description of hypoactive delirious states, which he ascribed to Lipowski in 1990. They were, in fact, first described by me (Philpott, 1989) as attenuated or negative confusional symptoms in my chapter on ‘Recurrent acute confusional states’ in The Clinical Neurology of Old Age. I emphasised that these are common, particularly when acute confusion occurs in the setting of patients with established dementia. Perhaps the fact that this is included in a textbook of neurology rather than psychiatry accounts for it being overlooked.


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One hundred years ago

Extract from ‘Crime in general paralysis’, by W. C. Sullivan, MD, Deputy Medical Officer, HM Prison Pentonville

H. F. – stole a piece of bacon from a stall outside a shop in a large thoroughfare; he simply picked the bacon up, hid it under his coat, and walked away; the shopman stopped him, he replaced the bacon on the stall, and waited till the police came and arrested him.

Prisoner is 55, painter by trade, married, has three children. Marked lingual and facial tremor, blurred speech, exalted patellar reflexes. No special ocular symptoms. No signs of alcoholism. Very demented, e.g. blunders over the names and order of the months, cannot calculate his earnings over more than two weeks, etc. Facile, self-satisfied in mood; no obvious delusions; has had several congestive seizures.

Asked why, being an honest man, he committed a theft, says he was in drink and did not know what he was doing. Says later that he is hard-working and devoted to his family, that he has not taken liquor for years; becomes emotional on the subject of his children. Asked now why he stole the bacon, says it was to take it home to his children who had nothing to eat.

Questioned about his work, says he is an excellent workman, gets good wages, has saved money, has £15 in the bank; beamingly optimistic. Asked now why he stole the bacon, says he did it for a joke. Reminded of his other explanations, says he does not know why he stole it, “it must have been for a joke.”

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