I was pleased to read Dr Crowley's in-depth understanding of the complexity and value of the altered state of consciousness. Thankfully, there are clinicians such as Dr Crowley with the confidence not to dismiss the non-ordinary state of consciousness as mere 'acute confusion', but to believe that psychedelics, and non-drug non-ordinary states of consciousness, can inform and enlighten us with new approaches to understanding the mechanisms (and associated pathologies) of the brain. Since the earliest human societies we have sought knowledge and healing from these states – perhaps now this technique can be utilised in a scientific and evidence-based approach to relieve the burden of anxiety disorders for today's patients.

I am most grateful to Dr Sandison for his kind and supportive words – and thank him for the correction regarding the date of the American Psychiatric Association conference in 1955. I share his astonishment at the medical profession's inability or unwillingness to embrace the therapeutic potential of psychedelic substances. This shortcoming is augmented by the fact that the hiatus in research over the past 40 years appears to have been for socio-political rather than scientific reasons – and it is those pioneering psychiatrists like Dr Sandison who are right to feel disheartened.

I am enthusiastic, however, at the current re-emergence of interest in this field. There are increasing numbers of randomised controlled trials of psychedelics (largely from the USA) and these may yield results that guide future therapeutic applications (http://www.maps.org; http://www.heffter.org). There is also increasing interest in using psychedelics in consciousness research in the UK (http://www.beckleyfoundation.org).

I do hope that my article, and a forthcoming meeting to be held at the College (contact me at drbensessa@hotmail.com for further details), can help raise awareness of this subject. I also agree with Dr Sandison in his plea for continued support from the College to bring this subject to the attention of doctors in the UK.

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Kraepelinian dichotomy

Craddock & Owen (2005) attribute the proposed demise of the Kraepelinian dichotomy to advances in genetic epidemiology, and rightly emphasise the need to integrate data across multiple domains in large numbers of people. However, it may also be important to use a population-based approach. This involves extra effort but avoids being misled by convenience samples which may not be representative of the population. This is illustrated by Fig. 1 in the editorial of Craddock & Owen which suggests that prototypical schizophrenia and prototypical bipolar disorder are relatively rare in clinical populations. Work in population-based samples suggests that there is an early, insidious-onset psychosis with a poor outcome affecting predominantly men – a 'neurodevelopmental' form of schizophrenia which is very close to dementia praecox (Castle *et al*, 1998). This prototypical form of schizophrenia together with protoypical bipolar disorder accounts for 50% of people with psychosis in a treated prevalence sample, demonstrating the utility of Kraepelin's division. In our experience affective and non-affective psychoses can be accounted for by these prototypical forms and a further two latent classes which appear to be valid (Murray *et al*, 2005). Whether such empirically derived classes might provide better phenotypes for genetic studies is as yet undetermined.

Until biological markers are identified there is perhaps only one way to improve our classification. Large-scale, empirical, population-based studies of psychiatric symptoms, demography, course, treatment response and outcomes are suggested to reclassify these disorders from first principles and provide an atheoretical framework which may capture underlying pathophysiological substrates. Such studies should, as described by Craddock & Owen, integrate both dimensional and categorical approaches but also require a developmental perspective across the life span. The debate about the Kraepelinian dichotomy illustrates the lack of evidence-based diagnostic classification in psychiatry as a discipline. It would be fitting if psychiatric genetics, which has been severely impeded by the lack of a robust nosology, focused the collective will of practitioners to establish the evidence base required for a psychiatric classification which at last reflects nature.

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Authors' reply: We are in full agreement with Dr Murray regarding the utility of large-scale, population-based studies. These are highly desirable and will, we hope, be facilitated by the recent establishment of the Mental Health Research Network (http://www.mhrn.info) under the auspices of the UK Clinical Research Collaboration (http://www.ukcrc.org). We also agree that longitudinal variables such as course, outcome and treatment response might be key to classification, as Kraepelin supposed. However, although we have not undertaken relevant population studies ourselves, we are not convinced that Kraepelinian dichotomous categories are any more useful in population-based samples than in clinical samples. We find the studies of Van Os and colleagues (e.g. Krabbendam *et al*, 2004) persuasive that dimensional measures are useful in describing psychosis-related morbidity in the general population and, contrary to the proposition of Dr Murray, we would expect dimensions to be *more* useful than categories in populations unselected for severe illness.

Finally, we would like to restate and further emphasise our optimism about the likely rate of progress in identifying biological markers that can validate psychiatric diagnoses. Markers (in the form of genetic polymorphisms) have already been identified that challenge current nosology. For example, using the Bipolar Affective Disorder Dimension Scale (which rates affective and psychotic dimensions; Craddock *et al*, 2004) in a study of over 600 cases each of schizophrenia and bipolar disorder, we have demonstrated that a risk variant within the *Neuregulin 1* gene, which has been associated with risk of schizophrenia in several samples (reviewed in Craddock *et al*, 2005), may confer

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