use the full doses at which the efficacy of dothiepin was established. There is also inadequate discussion of the reasons for the more frequent withdrawals from dothiepin during the prophylactic phase. Is it possible that patients themselves recognised that dothiepin was no more effective than placebo?

There are studies that provide clear-cut evidence of the prophylactic efficacy of antidepressants in reducing the risks of new episodes of depression (reviewed by Montgomery & Montgomery, 1992). This is not one of them.

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AUTHORS' REPLY: If Montgomery thinks we "have not entirely understood [the] arguments" for separation of continuation therapy from prophylaxis, he has not read our paper carefully enough. We do discuss these arguments in some detail (p. 180; paragraphs 2 & 3) and explain why we did not apply the distinction strictly to our elderly patients, as might have been appropriate for a younger group. To reiterate and amplify the point, we were dealing with a population which has been consistently shown by research to contain only about 20% of people, or less, who will not experience a further episode of major depression; whereas the remaining 80% or so are liable either to suffer from chronic affective symptoms or one or more rapid relapses. The key question, therefore, is whether – the patient's physical state permitting – treatment should ever be stopped.

Having made the presumption that our study should have been conducted according to the design he prescribes, Montgomery employs inappropriate statistical methods to analyse it as if we had conducted it that way. In spite of our explanation (p. 177; first paragraph, second column), he does not appear to have understood the error of using cross-sectional analysis (χ^2 tests) on longitudinal data. His statements about significance have no valid statistical foundation. In fact, his assertion that "analysis at the six-month point makes sense" makes no sense at all. Our Table 2 clearly shows how relapses occurred over a two-year period, and the higher incidence in the placebo group is evident. We had hoped to make it abundantly clear that P values obtained from χ^2 tests were mentioned only to underline how misleading they can be when incorrectly applied (as, alas, they so frequently are in studies of this kind). The analysis which is appropriate to longitudinal data, such as these, is to fit a survival curve. In this instance a proportional hazards model was fitted and the survival curves speak for themselves. Clearly, it would have been preferable to have a larger sample since the consequent increase in power would have made it possible to detect a smaller difference between the treatment groups but, in the event, the difference was found to be large enough for the sample size to be acceptable.

Montgomery accuses us of giving an eccentric definition of relapse of one point more than the recommended cut-off. Where does he get this idea from? There is no inconsistency between having a criterion MADRS response < 11 and a definition of relapse > 10 because, provided the individual scores are integers (which they are), the two sets are mutually exclusive and exhaustive. The mean MADRS score on relapse was 24.01.

There was no discussion of suicide or serious side-effects in the interests of brevity. There were no suicides during the trial. Nor were there serious side-effects, which were carefully monitored throughout in accordance with international standards. However, if it were to give Dr Montgomery some peace of mind, none of the psychiatrists taking part in this trial have an 'axe to grind' about tricyclics in general, or dothiepin in particular. The important point is the maintenance of effective pharmacological treatment, without which the great majority of this group of patients can expect their relatively short remaining life-span to be blighted by continuous or recurrent illness.

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Sex and schizophrenia: vive la différence

SIR: Lewis provides an interesting review of the literature investigating the sex differences in

schizophrenia (*Journal*, October 1992, **161**, 445–450). The findings suggest that men have an earlier age at onset of illness which is characterised by a more protracted course and poorer prognosis. He suggests that men with schizophrenia have a poorer premorbid adjustment. Also, men have a slightly higher risk of developing the disorder, although the family of schizophrenic men may have a lower morbid risk of developing the disorder. Together with evidence supporting greater structural abnormalities in male schizophrenic patients, Lewis proposes that non-genetic factors, such as neurodevelopmental factors, may be more important for the development of schizophrenia in men. Such a neurodevelopmental hypothesis, proposed by Weinberger (1987) and Murray & Lewis (1987) suggests greater vulnerability of the male foetus to factors important in the aetiology of schizophrenia. Lewis postulates various mechanisms which might explain the sex differences in this disorder and argues that men are more likely to develop this 'neurodevelopmental subtype' of schizophrenia. Lewis concludes that research criteria should be defined on the basis of neurodevelopmental subtyping.

The question must be asked as to whether we truly need to add more diagnostic criteria of this kind? The continued attempt to operationalise schizophrenia in this way has led to numerous criteria being developed (and discarded). These have tended to confuse rather than clarify the position. For example, the DSM – III criteria require that an organic factor be excluded, even though, as Mesulam (1990) points out, some patients with schizophrenia have detectable structural and physiological abnormalities. In Lewis's concept of 'neurodevelopmental schizophrenia', the operational criteria supporting such a typology would suggest an underlying organic factor at work. If this is the case, then patients with this kind of schizophrenia would necessarily be excluded from other diagnostic systems. However, although one or other aetiological factor may be important in causing schizophrenia, it may require a number of factors acting concurrently to precipitate an episode of illness in an individual. Thus an individual's susceptibility may be multifactorial, so that no single variable is important in itself. By using operational criteria, consistently to include or exclude various factors, we may be excluding the very factors we are interested in examining. Consequently, as we understand more about the underlying basis of the disease, it will become increasingly difficult to continue with any diagnostic criteria. Although operational definitions have previously been helpful because of our limited understanding of the psychoses, it may be time for a shift in perspective.

Mesulam (1990) suggests, "Schizophrenia, as currently defined, is quite probably an umbrella term for several different diseases". Perhaps another way to view schizophrenia is to consider this condition as having a number of possible aetiologies. Thus, we recognise that as well as genetic influences, other conditions such as epilepsy of temporal lobe origin, or other temporal lobe pathology, basal ganglia disorders such as Huntington's disease, psychostimulants such as amphetamines, as well as psychosocial factors, and so on, may all precipitate a schizophreniform psychosis or exacerbate existing psychosis. Now there is evidence suggesting that problems early in development have an important impact in the later development of schizophrenia and that male patients may be more prone to such neurological insult. For other patients, however, no clear aetiology can be identified. Is this situation so different to other pathological conditions in medicine, for which we identify a number of aetiologies and for which we consider a differential diagnosis? Although operational criteria have attempted to identify those who would have been considered idiopathic, this would now appear to be an ever diminishing group. We should now consider schizophrenia as the manifestation of a number of disorders; there is a differential diagnosis which must be considered whenever we assess a patient with such an illness. The use of operational criteria can be distracting and unhelpful in our care of such patients. The danger is that as we understand more about what causes schizophrenia, we gradually exclude patients from our diagnostic criteria on the basis of the identified factors. Alternatively, the particular aetiological factor is used to define the condition, as with 'neurodevelopmental schizophrenia'. Although this may be a reasonable way to tease out the causes of schizophrenia, it is not a way of defining the condition. We are gradually stripping the illness of its flesh, in the hope of identifying an elusive and ever diminishing core.

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