Psychiatric Symptoms in Transsexualism

SIR: Before we draw the obvious conclusion from the paper of Mate-Kole *et al* (*Journal*, April 1988, **152,** 550–553) that treatment of transsexualism by adopting the preferred gender role and later surgery reduces their psychological symptoms, we need to know the characteristics and numbers of those who drop out between the stages of treatment described in the paper. It is possible, but unlikely, that there are a few highly psychiatrically disturbed individuals who present for assessment but drop out before they are accepted for the waiting list or before surgery takes place. This would alter the means and standard deviations of the scores of the groups in the directions of improving the scores who continue in treatment. Such an effect would be ruled out with the prospective study mentioned by the authors, but in the meantime it would be nice to be reassured on this point.

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SIR: The study as indicated was retrospective, and at the time of examination there were no drop-outs in the two pre-operative groups. Table 1 of our paper elaborates on the psychiatric background of these patients.

It is not uncommon in our daily clinic practice for patients to drop out between treatment stages, bearing in mind that a sizeable proportion of patients who present in gender identity clinics display other gender identity disorders and psychiatric disturbance, and therefore do not fit the criteria for diagnosis of transsexualism (Mate-Kole & Freschi, 1988). Certainly, in our clinic less than 20% of the patients ever reach the operation stage (Mate-Kole *et al*, 1987), this being the reason that we suggested rigorous prospective studies be conducted.

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Risk Factors in Schizophrenia

SIR: We were interested to read Baron & Gruen's study (*Journal*, April 1988, **152,** 460–465) showing an increased risk for schizophrenia and 'spectrum' disorders among first-degree relatives of schizophrenic patients born in the winter or spring. We have recently studied the relationship between season of birth and a number of variables, including family history, in a sample of 126 patients who fulfilled the RDC for schizophrenia or schizoaffective disorder, schizophrenic type. Patients were judged to have a positive family history if a first-degree relative had suffered from schizophrenia, schizoaffective disorder, manic depressive psychosis (as defined in ICD-9), or unspecified psychosis.

A positive family history was found in 25 out of 67 (37%) patients born in the winter or spring (December–May), compared with 12 out of 59 (20%) born in the summer or autumn (June–November). This difference just failed to attain statistical significance at the 5% level ($Z=1.88$, $P=0.06$, Fisher's exact test, 2-tailed).

Drs Baron & Gruen actually failed to find differences between family history positive and negative cases. In their study a relationship between familial load and season of birth was only seen when morbid risk data were analysed. As they, and others, have pointed out, classifying patients into familial and non-familial cases has a number of limitations, all of which reduce the likelihood of demonstrating relationships between familial load and other variables. It seems likely that our modest success in demonstrating a relationship between family history and season of birth was due to the fact that our sample ($n=126$) was larger than Drs Baron & Gruen's ($n=88$).

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Therapy-Resistant Depression

SIR: Leonard (*Journal*, April 1988, **152,** 453–459) argues that lithium enhances presynaptic serotonergic transmission in animals and that its effect in man is related to its antidepressant effect by synergism with serotonergic postsynaptic enhancing drugs. Part of his argument is based on the assertion that lithium is "a poor antidepressant when used alone". I do not want to rehash arguments I have already made about the interpretation of the literature (Worrall, 1986) but I am surprised at the two references he quotes to support his assertion. Mendels

et al (1972) showed that lithium produced at least a 50% reduction in Hamilton Rating Scale for Depression scores in nine out of twelve patients, whereas their comparative tricyclic produced as good an improvement in only six out of twelve patients. Goodwin *et al* (1972) paper lithium antidepressant response in bipolar and unipolar patients and showed 80% of bipolar patients improved compared with 33% of unipolar patients. No comparative antidepressant was used. The most notable observation in the Nelson & Mazure (1986) paper he cites was that in tricyclic-neuroleptic combination failures, a lithium-neuroleptic combination was strikingly effective in bipolar patients (eight out of nine) but not in unipolar patients (three out of twelve). The rapidity of the combined response in the De Montigny work he quotes has not been confirmed in a later controlled study (Heninger *et al*, 1983) or a larger series (Price *et al*, 1986).

The most consistent finding from the literature is that lithium used alone has a highly predictable antidepressant response in bipolars but not unipolars. By definition, the lithium responders in the majority of the combined lithium-tricyclic studies are tricyclic non-responders. Professor Leonard's hypothesis fails to explain these discrepancies.

An alternative hypothesis that takes into account the animal work he cites and the clinical studies is that there are at least two distinct groups of depressed patients where serotonergic transmission is relevant to treatment. One group preferentially responds to postsynaptically enhancing drugs (tricyclics), the other to presynaptically enhancing drugs (MAOIs, lithium). Clinically the first group comprises most unipolar and some bipolar patients, and the second most bipolar and some unipolar patients. A prediction from this hypothesis is not that clinically significant synergism will never occur between a drug from the first and the second group, but that reliable potentiation will only occur between two drugs from the same group; more specifically, that in patients who do not respond to a tricyclic alone, a MAOI alone or lithium alone, a lithium-MAOI combination will be more reliable than a lithium-tricyclic combination. The observations of a lithium-tranylcypromine response in just such patients by Price *et al* (1985) is consistent with that prediction.

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SIR: Leonard's review (*Journal*, April 1988, **152**, 453–459) on the biochemical aspects of therapy-resistant depression merely re-emphasised the well-known hypothesis that there is a central serotonergic defect in severe endogenous depression. He could not point out any difference in central serotonergic function between therapy-responsive and therapy-resistant depression. It is also disappointing that his review did not mention the increasing number of studies on sodium-potassium-sensitive adenosine triphosphatase (Na^+/K^+-ATPase) activity in severe endogenous depression. We have recently reviewed these studies (Chiu & Rimon, 1988). Our conclusion was that only some depressed patients had decreased Na^+/K^+-ATPase activity and that this activity often did not increase with recovery of depression; i.e. it appeared to be a trait rather than a state marker. In our recent report on successful treatment of a therapy-resistant depression by adding only four days of lithium to clomipramine (Chiu & Rimon, 1987), we hypothesised that a possibly genetically-determined impairment of Na^+/K^+-ATPase activity might account for the non-response to tricyclic antidepressants. Lithium might correct this by inhibiting a recently-discovered central ouabain-like compound (Lichtstein *et al*, 1985).

Two further pieces of indirect evidence suggest that lithium in therapy-resistant depression probably acts by increasing Na^+/K^+-ATPase activity rather than by facilitating serotonergic neurotransmission. Firstly, unlike tricyclic antidepressants, lithium is a poor antidepressant by itself. Also, lithium or tricyclics alone do not work in therapy-resistant depression. Yet when the two are given simultaneously, therapy-resistant patients often have a dramatic response. Such a response is not typical of the addition of two similar but partial effects. Instead, it suggests the combination of two entirely different mechanisms, either of which alone is not effective. As tricyclic antidepressants are thought to act by increasing