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

serotonergic neurotransmission, it is likely that lithium acts by a different mechanism.

Secondly, many studies find that lithium can potentiate the antidepressant effect of tricyclics within three or four days (de Montigny *et al*, 1981, 1983; Chiu & Rimon, 1987). Compared with the slow onset of antidepressant action of tricyclics alone, the rapid potentiating action of lithium is not typical of changes in neurotransmission but is more consistent with changes in enzymatic reactions.

It should be emphasised that decreased Na^+/K^+-ATPase activity as a mechanism of therapy-resistant depression is only a tentative hypothesis that remains to be tested. Yet researches along that line are certainly worthwhile, especially if studies on neurotransmission do not yield further breakthroughs

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SIR: There were two purposes to my Annotation (*Journal*, April 1988, **152**, 453–459). The first was to emphasise the need to establish a definition of resistant depression that would be internationally recognised. The second was to speculate on the possible biochemical aetiology of resistant depression, with particular reference to changes in neurotransmitter function. As lithium has been advocated as a combination therapy with tricyclic antidepressants in the treatment of therapy resistance, I commented on the possible causes of such a beneficial interaction. It was not my intention to suggest that only the serotonergic system was involved, or that it was causally related to the condition or to the patients response to treatment. The involvement of serotonin has achieved prominence because its transport, receptor function, etc. can be measured in blood. Despite the assertion of Dr Chiu, there is reason to believe that the synergistic interaction between lithium and tricyclic antidepressants is associated with rapid receptor adaptation, as I indicated in my article. Undoubtedly such changes are associated with, or caused by, other changes in electrolyte flux as well as those in neurotransmitters whose activity in patients still awaits evaluation.

Regarding Dr Worrall's comments, the consensus concerning the efficacy of lithium in the treatment of endogenous depression is that the drug is not as effective as tricyclic antidepressants (e.g. Lader & Herrington, 1981). I agree with Dr Worrall that the reason for the greater efficacy of lithium in treating the depressive component of bipolar rather than unipolar patients is unclear and, in my opinion, will remain so until adequately controlled trials are undertaken in which neurotransmitter function, as well as clinical response, is assessed. Dr Worrall's proposal that there are two distinct groups of depressed patients that differ in the nature of their defect is appealing but, to my knowledge, remains to be proven.

While there may be differences of opinion over emphasis, I'm sure all readers will agree that only more research will provide the answers. If my Annotation has achieved nothing but this then it has achieved its purpose.

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Prescribing for the Long-Term Mentally Ill

SIR: Holloway (*Journal*, April 1988, **152**, 511–514) refers to the paper by Priern *et al* (1978) who point out that, for the purpose of assessing the appropriateness of drug prescribing, cross-sectional data is unsatisfactory and misleading and intimate knowledge of the patients' clinical details and treatment history are essential. Dr Holloway then proceeds to criticise the appropriateness of prescribing on the basis of cross-sectional assessment of mental state supplemented by history of illness and treatment from patients' recollections, with or without case notes. He emphasises that case notes were a "poor