(a) Hospital or community tenure is probably more a function of policy than an index of illness severity except in extreme cases.

(b) This is true but it is a general problem with this patient group. Other successful psychosocial interventions, such as family management, also suffer from the difficulty of high attrition rates (see Leff *et al*, *Journal*, January 1989, **154,** 58–66; Tarrier, *Journal*, October 1991, **159,** 475–480), and it is a persistent difficulty with pharmacological and other forms of care. It is quite plausible that the group who remained in treatment were less intractable. However, the important point that Mirza *et al* appear to ignore is that these patients show significant improvements over and above those they were benefiting from medication alone. We were surprised by the magnitude of improvement made by some patients in response to the psychological intervention. This was especially so given the short duration of the intervention – ten sessions over five weeks – and we noted the potential of a longer intervention to produce a greater and more robust improvement.

(c) For obvious reasons extensive information about non-compliers is not easy to obtain, but we are attempting to address the questions of predictors of treatment response and attrition in a current study.

(d) Although fluctuations do occur in psychotic symptoms, there are a number of indications that random fluctuation was not responsible for sustained improvement of the magnitude reported in some of our patients: no such changes were observed in patients in the waiting-period group; patients were recruited into the study because their symptoms had not shown further improvement over the six months before inclusion, that is their symptoms were stable over a significant period of time before the intervention; improvement was generally maintained from post-treatment to follow-up, suggesting a treatment effect rather than random fluctuation; and improvement in symptoms was found to be associated with improved coping (Tarrier *et al*, 1993), again suggesting a treatment effect.

(e) While it is true that extensive data on the medication history of the patients were not collected, we are unconvinced that these data would have added more to our confidence that these patients were experiencing psychotic symptoms despite receiving the optimum pharmacological treatment available.

(f) The patients continued to receive medication over the period of the study and this point is stated in the text.

We have now embarked on a five-year study, funded by The Wellcome Trust, to examine an extended psychological intervention over three months. The intervention includes coping-training, problem-solving, and relapse-prevention strategies, and will be compared with supportive counselling. We intend to recruit patients who experience residual symptoms in the community and patients admitted to hospital for an acute episode. We are especially interested in investigating predictors of response to treatment and drop out.

TARRIER, N., SHARPE, L., BECKETT, R., *et al* (1993) A trial of two cognitive behavioural methods of treating drug-resistant psychotic symptoms in schizophrenia. II: treatment-specific changes in coping and problem-solving skills. *Social Psychiatry and Psychiatric Epidemiology*, **28,** 5–10.

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Lithium neurotoxicity at normal therapeutic levels

SIR: I read with interest the case reports on lithium neurotoxicity at normal therapeutic levels by Bell *et al* (*Journal*, May 1993, **162,** 689–692).

The authors have described the difficulties related to lithium therapy where (as it is recommended in clinical textbooks) we deal with patients and not laboratory results. As the authors have wisely shown, when we treat individual patients we should always be aware of the possibility of idiosyncratic reactions or 'lithium supersensitivity', as in those described cases of neurotoxicity.

There is, however, one issue I would like to point out: in their discussion the authors state that

> "As mentioned above, a high starting dose is a common factor in previously reported cases. Brain concentrations of lithium have been shown to rise higher than serum levels in both animals and man, reaching their peak 22–26 hours after lithium treatment, and a non-uniform uptake of lithium has been observed in the brain .... It is conceivable that with rapid dosage the 12-hour lithium level bears little relation to the lithium levels in the brain, which continue to rise for the next 12–14 hours, producing neurotoxicity. Intra-erythrocyte levels correlate better with cerebral levels ... ".

Lithium is known to be a highly hydrophilic agent, does not bind to plasma proteins, and crosses the blood–brain barrier with difficulty. The rate of absorption into the brain is apparently proportional to serum lithium concentrations. Brain lithium levels were shown to be even lower than serum concentrations (Gyulai *et al*, 1991; Kato *et al*, 1992).

Different results were found however, when comparing lithium levels in mouse brain and in plasma (Herteaux *et al*, 1991). Lithium had a half-life ($T_{1/2}$) of between 12 and 24 hours (up to 40 hours in some cases).

Plasma lithium peaks in one to two hours (taking more for the 'slow release' preparations). The assumption that brain lithium levels will continue to rise higher than the serum lithium concentration is not conceivable.

GYULAI, L., WICKLUND, S., GREENSTEIN, R., *et al* (1991) Measurement of tissue lithium concentration by lithium magnetic resonance spectroscopy in patients with bipolar disorder. *Biological Psychiatry*, **29**, 1161–1170.

HERTEAUX, C., RIPOLL, C., OUZNADJI, S., *et al* (1991) Lithium transport in the mouse brain. *Brain Research*, **547**, 122–128.

KATO, T., TAKASHI, S. & INUBUSHI, T. (1992) Brain lithium concentration by 7Li- and 1H-magnetic resonance spectroscopy in bipolar disorder. *Psychiatry Research*, **45**, 53–63.

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AUTHORS' REPLY: We cannot agree with the assertion that it is "not conceivable" for brain levels of lithium to rise higher than those of serum. Several animal studies have shown that brain lithium levels can exceed serum levels: Plenge (1978) showed brain lithium levels above serum levels eight hours after an intraperitoneal injection of lithium chloride in chronically treated rats; and Schou (1958) showed that, following intravenous administration, the brain lithium level rises slowly, reaching a maximum in 22-26 hours (i.e. when serum levels are falling). The brain lithium level remains higher than the serum lithium level, decreasing in a parallel fashion.

In one of the references cited by Dr Moscovich (Herteaux *et al*, 1991; see above) it was shown, using stable isotopes of lithium, that, while the equilibration of lithium between serum and brain was almost instantaneous, lithium levels in grey matter were three to six times higher than in plasma under steady-state conditions. Moreover, it is clear that the uptake of lithium into the brain is not uniform. Herteaux *et al* (1991) showed high lithium levels in thalamus, neocortex and hippocampus (six times greater than plasma levels), with lower levels in striatum and cerebellum (three times greater than plasma levels), and reviewed several other studies which supported this observation. This phenomenon, which has also been seen in human studies, may well be relevant to the development of lithium neurotoxicity.

Kluge *et al* (1978) showed much higher levels of lithium in the brain than found in the serum in two cases who died of lithium intoxication – the highest concentrations were in the neocortex and brain stem. Kinetic experiments suggest that lithium in the brain may be in a 'deep compartment' with which equilibration is slow. This means that central effects may develop even in the presence of falling or low serum levels, and this observation may explain why the clinical signs of lithium toxicity may persist several days after successful haemodialysis which has lead to minimal concentrations of lithium in the serum. Amdisen *et al* (1974) showed high levels of lithium in certain areas of the brain (notably in the neocortical white and grey matter) in a case of lithium toxicity who died 20 days after serum lithium had been re-stabilised at 0.4 mmol/l.

We take issue with the respondent's assertion that we 'assumed' that lithium levels in the brain continue to rise higher than serum levels in all cases, all the time. We are arguing that, under certain circumstances, lithium levels in the brain can be higher than in the serum, that key nuclei can be particularly affected, and that the central effects of lithium may persist for some time after serum levels are lowered. Inter-individual variation in serum and red blood cell ratios are probably under genetic control and it may be that those rare individuals who manifest neurotoxic symptoms at therapeutic lithium serum levels are particularly prone to have higher lithium levels in the brain (perhaps site-specific) due to a state and/or trait tendency to accumulate intracellular lithium. Indeed, a number of separate studies have shown that it is possible to predict lithium toxicity by closely monitoring the red blood cell:serum lithium ratio. There is an increase in this ratio just before a neurotoxic episode (Tyrer & Shopsin, 1980).

We agree that the evidence regarding lithium distribution is complex and at times conflicting. It would be interesting to study lithium handling in those individuals who have manifested neurotoxicity at therapeutic lithium levels to see if this is abnormal.

AMDISEN, A., GOTTFRIES, G. C., JACOBSEN, L., *et al* (1974) Grave lithium intoxication with fatal outcome. *Acta Psychiatrica Scandinavica*, Suppl. 4, 25–33.

KLUGE, H., WALDMANN, K. D. & GREGER, J. (1978) Zur lithiumvertcilung im organismus nacht intoxikation. *Psychiatric Clinics*, **11**, 96–99.

PLENGE, P. (1978) Lithium effects on rat brain glucose metabolism in long term lithium-treated rats. In *Lithium in Medical Practice* (eds F. M. Johnson & S. Johnson), pp. 145–152. Lancaster: MTP Press.

SCHOU, M. (1958) Lithium studies. Distribution between serum and tissues. *Acta Pharmacology and Toxicology*, **15**, 115–124.