and 0.657 (0.035) for their siblings. When analysis of covariance allowing for the effect of gender and BL (as a covariate) on HC was applied to the data, no significant difference in HC at birth was found between preschizophrenics and their siblings (F=0.43, d.f.=1,104, P=0.52), nor was there an interacting effect of gender and the case–sibling status on HC (F=0.00, d.f.=1,104, P=0.98). Next, we performed paired t-tests by selecting 11 male-male and 6 female-female sib-pairs. The mean (s.d.) HC in preschizophrenics and in their siblings respectively were 33.9 (1.5) and 33.4 (1.2) cm (t=1.40, d.f.=16, P=0.18). The HC–BL ratios (s.d.) were 0.660 (0.030) for preschizophrenics and 0.653 (0.034) for their siblings (t=0.78, d.f.=16, P=0.17). Again, no significant difference was detected. We also examined gestational age (weeks) at delivery, but no statistically significant difference was found between the two groups (the mean age was 39.2 in preschizophrenics and 39.7 weeks in siblings (t=0.98, d.f.=15, P=0.34).

Thus, we failed to confirm the findings reported by McNeil *et al*. This failure could be due to not all the comparison group having passed through the risk age of the disease. Also, the schizophrenic patients and their siblings will share genes which influence brain development – a comparison with siblings may have biased our study.

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H. KUNUGI
N. TAKEI

Institute of Psychiatry &
King's College Hospital
London SE5 8AF

S. NANKO
K. SAITO
H. KAZAMATSURI

Teikyo University School of Medicine
11–1, Kaga 2-Chome
Itabashi-Ku, Tokyo, 173

Lithium mutagenicity

SIR: Many fertile women receive prophylactic lithium carbonate treatment (Schou, 1990). It is not known whether the higher than expected frequency of congenital anomalies reported among the offspring of mothers receiving lithium therapy in the last two decades (Warkany, 1988) is related to a direct lithium toxicity, a mutagenic effect on germ cells, or both. To our knowledge this is the first case-controlled study blindly comparing patients taking lithium with normal controls with regard to the assessment of the frequency of chromosomal lesions.

Eight white Brazilian patients (mean (s.d.) age 37.50 (10.36) years) who had been receiving continuous lithium therapy (mean dose 768.75 (139.05) mg/day) for at least one year were selected from the Escola Paulista de Medicina's Affective Disorders out-patient clinic and compared with 10 psychiatrically healthy drug-free controls matched for sex and age who were concomitantly drawn from the otolaryngologic out-patient clinic of the same institution. A cytogenetic analysis was carried out using standard methods with blood lymphocytes cultured in a folic-acid free medium. A total of 100 mitoses per subject were analysed with the investigator blind to group assignment. Chromosomal lesions were observed by G-banding with trypsin stain for localisation of the lesions. The results showed a total of 102 and 96 lesions scored for cases and controls respectively. There was no difference between groups (P>0.10) concerning the number of lesions, and there was no evidence of a special distribution pattern of lesions throughout the chromosomal map in either group.

These findings suggest that lithium has no mutagenic activity at the level of resolution used (400 bands). Recent reports have suggested that the risk of thyroid and cardiovascular malformations, especially the rare Ebstein's anomaly, remains controversial (Zalzstein *et al*, 1990; Ferner & Smith, 1992; Jacobson *et al*, 1992). According to our results, a teratogenic effect of lithium would be more easily explained by a direct toxic effect of lithium carbonate rather than a mutagenic effect on germ cells.

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GUSTAVO TURECKI
MARÍLIA CARDOSO DE ARRUDA SMITH
JAIR DE JESUS MARI

Escola Paulista de Medicina
Rua Botucatu no. 740–3° andar
04023–900, São Paulo

High-dose antipsychotic medication

SIR: The problems of using high-dose antipsychotic medication are highlighted by Thompson (for the Royal College of Psychiatrists' Consensus Panel) (*BJP*, April 1994, **164,** 448–458, 1994) and Kane (*BJP*, April 1994, **164,** 431–432).

We have successfully reduced high-dose regimens in a number of patients with severe, chronic schizophrenia, in both in- and out-patient settings.

Case 1 is a 50-year-old married woman, an out-patient since her last admission 10 years ago, and maintained on daily doses of 600 mg chlorpromazine, 600 mg lithium, 60 mg diazepam (20 mg three times daily) and 20 mg procyclidine, together with 500 mg zuclopenthixol decanoate at 4-weekly intervals. In October 1993 we introduced treatment with risperidone, rising to a dose of 3 mg twice daily. At the same time, her other treatments were cautiously reduced, under the supervision of her community psychiatric nurse. Chlorpromazine was gradually withdrawn by reducing the dose by 50 mg each day over a period of two weeks, depot zuclopenthixol injections are similarly being reduced by 50 mg at each 4-weekly injection, diazepam was reduced to 5 mg three times a day, and both lithium and procyclidine were discontinued. Following the introduction of risperidone and the gradual reduction of her other medication, there has been a significant change in the patient's mental state. Not only has there been no return of active psychotic symptoms but she has changed from taking no part in family life to being able to manage home and kitchen duties and being active in conversations.

Three other out-patients with similar clinical and drug histories have gradually been switched to risperidone. All have succeeded in gradual transition without relapse and have experienced a return of interest, activity and social involvement. One example is case 2, a 34-year-old man maintained for a number of years on daily doses of 800 mg chlorpromazine, 40 mg zuclopenthixol, 10 mg diazepam and 20 mg procyclidine. He had a history of severe psychosis and violence, with little recent progress. He is now managed on 4 mg risperidone twice daily, having cooperated enthusiastically in the withdrawal of his other medication. His negative symptoms have ameliorated, he is more at ease with himself and appears to enjoy a better quality of life than before.

Patients may be weaned off high doses of neuroleptics and successfully maintained on risperidone. In such patients, gradual dose reduction of conventional neuroleptics is important in maintaining patients' confidence and to avoid rebound Parkinsonism which has been observed after more sudden withdrawal following very long-term treatment.

ERNEST H. BENNIE

Leverndale Hospital
Glasgow G53 7TU

Sinus bradycardia due to fluvoxamine overdose

SIR: We report a case of fluvoxamine cardiotoxicity that manifested as marked bradycardia, and required close medical monitoring.

Case report A 58-year-old woman with a bipolar affective disorder had been hospitalised due to a major depressive episode. Therapy with fluvoxamine was commenced at a daily dose of 250 mg. After a month of treatment, improvement was noted. A night prior to her scheduled discharge she attempted suicide by ingesting 5.5 g of fluvoxamine. On examination several hours later the patient was pale, severe sinus bradycardia was found (32 beats per minute), and she complained of severe fatigue. No medical intervention was necessary due to stable haemodynamic parameters. The patient returned to normal sinus rhythm within a couple of days.

Henry *et al* (1991) reported on sinus bradycardia in 15 of 310 cases with fluvoxamine overdose. Most patients had mild adverse effects, none of which required treatment. It is not clear what the direct cause of bradycardia was.

Szabadi (Burton, 1991) referred to this issue by mentioning that fluvoxamine blocks muscarinic responses. Although its antimuscarinic potency is a third of that of amitriptyline, it is usually prescribed at higher doses. In addition, high single doses of fluvoxamine seem to block β1 and β2 adrenoreceptors, as is shown by the reduction of exercise-induced tachycardia. Therefore, the muscarinic and β-blocking activities of fluvoxamine may account for the appearance of severe sinus bradycardia, and for some unexplained deaths following fluvoxamine overdose (Garnier *et al*, 1993).

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