neuropsychological dysfunction in this French study had cognitive impairments prior to hospital admission. Presumably, a large percentage of them developed neuropsychological dysfunction because of factors related to hospitalisation, such as depressive symptomatology, use of psychotropic medications (e.g. benzodiazepines), or sleep disturbance.

We assessed cognitive functioning with a shortened version of the MMSE (Breakhus *et al*, 1992) in 49 community-dwelling elderly people with fall-related fractures two months after a fall accident. Our sample consisted of 22 patients with ankle or wrist fractures and 27 with a broken hip. They had been admitted to a hospital, but were all discharged at time of testing. Mean (s.d.) age was 73.9 (8.5) years. In contrast with the results of Jabourian *et al* (1994), only 10 patients (20.4%) scored below the cut-off for cognitive impairments on the shortened version of the MMSE (normal value, >9). Sample differences may account for the discrepancy between the two studies (the patients in the French study were somewhat older). However, it might also be that several of the patients studied by Jabourian *et al* suffered from neuropsychological dysfunction due to factors related to hospitalisation.

From reading the letter by Jabourian *et al* (1994) one could (erroneously) get the impression that almost 90% of serious fall incidents are co-determined by cognitive dysfunction. King & Tinetti (1995) published a review of the literature on risk factors for fall injury and identified several risk factors for falls besides cognitive impairments. They made a distinction between intrinsic factors (e.g. medication use, certain chronic diseases, impairments in muscle strength, balance and gait) and extrinsic factors (e.g. poor lighting and slippery floor). According to King & Tinetti older persons are at increased risk for a serious fall when multiple intrinsic and extrinsic factors are present.

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Clozapine-induced hypersalivation

Sir: In a previous letter (Szabadi, 1996), I argued that the troublesome side-effect of increased salivation seen in patients taking clozapine was unlikely to be due to the blockade of alpha-2 adrenoceptors, as had been suggested by others (Corrigan *et al*, 1995). I concluded that "the way in which clozapine causes hypersalivation remains an enigma". Since then, a paper has come to my attention which may shed some light on the mechanism underlying clozapine-induced hypersalivation. Zorn *et al* (1994) have shown that clozapine, in a cellular preparation expressing all five subtypes (M_1–M_5) of muscarinic cholinoceptors, has a potent full agonistic effect at M_4 receptors, while having antagonistic properties at the other four subtypes. While M_3 is the predominant muscarinic receptor subtype in salivary glands (Leahy *et al*, 1997), there is evidence that M_4 receptors are also expressed in this tissue (Zorn *et al*, 1994). Therefore, it is possible that the net effect of clozapine on salivation reflects the relationship between M_3 receptor blockade, leading to a decrease in salivation, and M_4 receptor stimulation, leading to an increase in salivary output. In some patients taking clozapine, the effects of M_4 receptor stimulation may exceed those of M_3 receptor blockade, resulting in hypersalivation. Thus, clozapine-induced hypersalivation may reflect the subtype-selective agonistic effect of clozapine at M_4 muscarinic receptors (Zorn *et al*, 1994).

This mechanism may also underlie the clinical effectiveness of the antimuscarinic drug pirenzepine in relieving clozapine-induced hypersalivation (see Szabadi, 1996). Pirenzepine, apart from having the ability to block M_1 receptors, is also a potent antagonist of M_4 receptors (Caulfield, 1993).

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Clozapine, Chinese and blood

Sir: Despite the availability of clozapine and its efficacy in treatment-resistant schizophrenia, it has been difficult to persuade Chinese patients in our practice in Singapore to go on a trial of this drug. The reservation in many instances was often not due to the cost of the drug or the risk of agranulocytosis but the mandatory blood monitoring required. In a review on the experience of using clozapine in China, Potter *et al* (1989) reported that the doctors had to make "considerable effort to overcome many patients' concerns and superstitions about having blood drawn".

The traditional Chinese notion of blood differs very much from that in the West. Blood to the Chinese is an extremely precious commodity, as is summed up by the Chinese saying that "one hundred grains of rice make one drop of blood". This has led to a fear of losing even a small amount of blood – a fear that would seem disproportionate to a Western observer. Reassurance that such monitoring would not have any detrimental effect is usually met with disbelief and scepticism. In their belief in the need to make good the blood loss, many would ask for "tonics", which are a traditional Chinese treatment for anaemia. These tonics are usually in the form of extracts, wines, herbs, food containing high-quality proteins and, in a syncretism of traditional Chinese concepts with Western medicine, vitamin tablets (Koo, 1984). We find that the judicious prescription of vitamin tablets goes a long way in allaying this fear of losing too much of this precious fluid in many of our Chinese patients.

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Citalopram-induced decreased libido

Sir: Sexual dysfunction is a frequent but under-recognised side-effect of treatment with antidepressant drugs. It causes distress, impairs quality of life and reduces compliance with treatment. We report a case of citalopram-induced decreased libido which improved on discontinuation of the medication.

A 35-year-old man was referred with major depression of moderate severity. Despite his depression his sexual function was unimpaired. He was commenced on citalopram 20 mg daily and his affective symptoms improved by the third week of treatment. However, 10 days after commencing citalopram he had a complete loss of interest in sex. He subsequently discontinued his medication at the end of the fourth week, after which his libido returned within seven days. He refused to resume citalopram or any other antidepressant medication for fear of further loss of libido. Because of the complete loss of libido, the effects on other aspects of sexual function could not be assessed, nor did we have an opportunity for re-challenge.

Narango *et al* (1987) have reported decreased libido in subjects with alcohol problems treated with citalopram, and Nyth & Gottfries (1990) reported decreased libido induced by citalopram in elderly subjects. Citalopram is the most selective of the serotonin reuptake inhibitors. The decreased libido observed in this patient might be explained by the fact that sexual motivation and performance are inversely related to synaptic serotonin concentration (Ahlenius *et al*, 1989). The need to enquire about sexual function before initiation of antidepressant drugs and at subsequent follow-up cannot be over-emphasised.

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Clozapine treatment, eosinophilia and agranulocytosis

Sir: Amital *et al* (1997) report that initial eosinophilia in a 37-year-old man beginning clozapine treatment was followed eight weeks later by agranulocytosis and suggest a possible association.

The incidence they quote of clozapine-induced eosinophilia of 0.2–1.0% is based on spontaneous adverse event reporting and is almost certainly an underestimate. Amital *et al* refer to a paper by Banov *et al* (1993) in which an overall incidence of 14.4% is reported in a group of 118 patients. Gerlach *et al* (1989) have reported a survey of 354 patients starting clozapine treatment and undergoing full blood count with differential every week for the first 18 weeks of treatment. This group represents 30% of the total clozapine-treated population in Denmark between 1985 and 1987. Forty-one per cent of patients receiving clozapine as monotherapy had eosinophilia at some point. This is in close agreement with a rate of eosinophilia of 46% reported in 65 patients during up to eight weeks' clozapine treatment in a clinical trial by Claghorn *et al* (1987) in the USA. Hummer *et al* (1994) found an even higher incidence of 62% in a group of 68 Austrian patients. It is, however, surprising that, in a survey of the first 602 French patients to receive clozapine, an incidence of only 4.3% was found (Pere *et al*, 1992), despite weekly full blood count monitoring during the first 18 weeks.

The incidence of eosinophilia in clozapine-treated patients is, however, probably considerably higher than that of agranulocytosis. Thus, even if an association could be proven, the great majority of patients in whom a transient eosinophilia has been noted will not go on to develop an agranulocytosis; and so eosinophilia is of virtually no clinical utility in predicting clozapine-induced agranulocytosis.

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Pere, J. J., Chaumet-Riffaud, R. D., Bourdeix, I, *et al* (1992) La clozapine (Leponex) en France. *L'Encéphale*, **18**, 427–432

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Clozapine monotherapy and ketoacidosis

Sir: I wish to report an unusual side-effect of clozapine.

A 50-year old man with a 15-year history of DSM–IV schizophrenia was admitted to hospital with a view to a change in his medication regime. The patient had been treated with a range of neuroleptic medication with little effect on his delusions and increasingly hostile behaviour. Ten days before admission the patient received flupenthixol decanoate 80 mg in depot form. He was also taking chlorpromazine 150 mg every six hours, and procyclidine 5 mg every 12 hours. On admission routine blood chemistry was normal.

He was commenced on a reducing programme of his oral medication which was stopped three days after admission. Clozapine was commenced on the fourth day of admission at a dose of 25 mg daily. The dose was gradually increased over seven days to 100 mg in the morning and 200 mg in the evening.

The patient began to complain of lethargy and thirst on the tenth day after admission and shortly after developed chest pain and dyspnoea. Laboratory investigations revealed a serum blood glucose level of 23.5 mmol/L. Blood gasses revealed a pH of 7.091 and a P_{CO_2} of 8.5 mmHg. A hyperkalaemia (consistent with a diagnosis of a ketoacidosis) of 4.9 was potentially life-threatening.

Clozapine treatment was immediately suspended following confirmation with the Clozapine Patient Monitoring Service (CPMS) that at least one previous case of hyperglycaemia and ketoacidosis had been reported in the literature (Kostakoglu *et al*,

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