where small effects can none the less reach statistical significance. We note that prior research has generally supported the validity of the EEA in regard to most psychiatric disorders (Kendler & Gardener, 1998), although bulimia is a possible exception (Hettema *et al*, 1995; Kendler & Gardener, 1998). Thus, we re-analysed our data to determine whether the EEA measures of childhood treatment and similitude materially altered our results. The approach is described more fully elsewhere (Hettema *et al*, 1995); briefly, when we fit statistical models to the trait of a history of lifetime vomiting that included additive genetic, specific common environmental (childhood treatment or similitude), residual common environmental, and individual-specific environmental effects, AE models again provided the best fit to the data. Moreover, heritability estimates from the full models were similar to those reported in our manuscript.

Hence, rather than considering the EEA as an 'all-or-nothing' rule as Curtis implies, our analyses indicate that even if the EEA were violated with respect to vomiting, its impact was evidently small and insufficient to alter either our results or our conclusions.

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Reserpine exhumed

Sir: The editorial on reserpine by Healy & Savage (1998) was provocative and interesting but appeared to be needlessly offensive in one minor respect. When questioning the ability of physicians to correctly diagnose depression, the authors note that the opinions of physician authors from Geelong and Otago need to be interpreted with caution. Why are the physicians from these two large regional towns in Australia and New Zealand singled out in this way when the physician authors of other similar reports are not? Are Healy and Savage implying that physicians in regional antipodean towns in the mid-1950s were in some way less competent than those in Britain and North America? If so, I doubt whether they can adduce any evidence that this was the case. I think the authors should withdraw these comments or inform us of the reason why these two towns were singled out for mention in their article.

Healy, D. & Savage, M. (1998) Reserpine exhumed. *British Journal of Psychiatry*, **172**, 376–378.

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Author's reply: The particular mention of authors from Geelong and Otago (Healy & Savage, 1998) stemmed from the fact that these were the authors of the two articles that immediately preceded the randomised trial of reserpine in depressive disorders conducted by Davies & Shepherd (1955). On two facing pages of this article you can see an article by Wallace from Geelong and the first page of the Shepherd trial. For anyone sensitive to defining moments in history this conjunction has considerable resonance. The authors of these pieces, therefore, were clearly the ones to focus on in order to bring out this aspect of the story. We took considerable care, however, to research the background of Dr Wallace, in particular, and to know a good deal about this career. In brief, he was a physician who appears to have been well esteemed by his colleagues but he was not one who appears to have had a particular interest in mainstream adult psychiatry at the time he wrote his report and did not develop one subsequently. In contrast, some of the other physicians referred to noted not only reserpine's capacity to cause distress but also its potential usefulness for the treatment of depression.

Healy, D. & Savage, M. (1998) Reserpine exhumed. *British Journal of Psychiatry*, **172**, 376–378.

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Clozapine-induced extrinsic allergic alveolitis

Sir: The following case highlights potentially life-threatening cardio-respiratory complications of clozapine. A 45-year-old male with schizophrenia, with a medical background of heavy smoking and asymptomatic right ventricular hypertrophy, had an uneventful commencement of clozapine. Fifteen days into treatment, on 200 mg twice daily, he presented with lethargy and pyrexia. Additional findings included: a leucocytosis with eosinophilia, elevated erythrocyte sedimentation rate (90) and irregular tachycardia/creatine kinase (124). Clinical examination was essentially unremarkable: clear chest, no increase in venous pressure, normal range blood pressure, no pericardial rub, no chest discomfort. However, malodorous smell and incontinence of urine were noted.

Despite a five-day course of antibiotics treatment for a presumed urinary tract infection, the pyrexia persisted, and additional symptoms appeared; non-productive cough and external dyspnoea.

The chest X-ray after commencement of clozapine revealed striking changes from the pre-clozapine X-ray, widespread abnormal markings in both lungs, which were reticular and linear were shown. There were also extensive septal lines in the periphery of the lung and a fairly dense perihilar haze. The appearances were suggestive of an acute inflammatory process. A computerised tomography scan showed small bilateral pleural effusions with widespread non-specific interstitial shadowing, having the appearance of a drug-induced reaction. Clinically, an elevated venous pressure and a gallop rhythm were noted. There was no demonstrated 'wheeze' or 'stridor'. Despite the advanced radiological and examination findings, the patient appeared surprisingly well. A diagnosis of extrinsic allergic alveolitis was made and the clozapine was discontinued.

Although echocardiography was unremarkable and neither bronchial nor cardiac biopsies were performed, the presumed explanation for the symptomatology was allergic alveolitis and myocarditis. The decision not to biopsy, but to treat on empirical grounds was based on clinical judgement. The response to treatment justified the conservative management.

Numerous organ systems have been involved in clozapine-induced allergy; myocarditis (Bandelow *et al*, 1995), colitis (Friedberg *et al*, 1995), pancreatitis (Chengappa *et al*, 1995), hepatitis (Thatcher *et al*, 1995) and cutaneous reactions (Stoppe *et al*, 1992) have been reported. Those reactions are invariably associated with eosinophilia.

To date, only one case of clozapine-induced allergic asthma has been reported (Stoppe *et al*, 1992). This case suggests that a separate entity be recognised: that of clozapine-induced allergic alveolitis. In this case the patient's symptoms showed rapid progression.

Pyrexia, although frequently a benign side-effect of clozapine, in fact, indicates the need for thorough investigation and clinical vigilance. The possibility of potentially lethal cardio-respiratory complications should be considered early, especially where there is eosinophilia, and a chest X-ray, electrocardiogram, erythrocyte sedimentation rate and echocardiograph may be regarded as necessary investigations for pyrexia.

The diligent reporting of such cases may assist in the identification of predictors of such potentially lethal allergic compilations, for example age, history of smoking, length of clozapine treatment and previous cardiorespiratory disease.

In terms of progress, the pyrexia abated two days after the cessation of clozapine. A chest X-ray performed five days after discontinuation of the clozapine showed complete resolution of the interstitial shadowing. The erythrocyte sedimentation rate dropped to 42. The patient showed dramatic clinical improvement.

Bandelow, B., Degner, D., Kreusch, U., *et al* (1995) Myocarditis under therapy with clozapine. *Schizophrenia Research*, **17**, 293–294.

Chengappa, K. N. R., Pelucia, M., Baker, R. W., *et al* (1995) Recurrent pancreatitis on clozapine re-challenge. *Journal of Psychopharmacology*, **9**, 381–382.

Friedberg, J. W., Frankenburg, F. R., Burk, J., *et al* (1993) Clozapine – caused eosinophilic colitis. *Annals of Clinical Psychiatry*, **7**, 97–98.

Stoppe, G., Muller, P., Fuchs, T., *et al* (1992) Life-threatening allergic reactions to clozapine. *British Journal of Psychiatry*, **16**, 259–261.

Thatcher, G. W., Cates, M. & Blair, B. (1995) Clozapine induced toxic hepatitis. *American Journal of Psychiatry*, **152**, 296–297.

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Prolonged bradycardia complicates antidepressive treatment with venlafaxine and ECT

Sir: We describe the case of a patient given venlafaxine and electroconvulsive therapy (ECT), where cardiovascular complications led to interruption of the ECT.

A 42-year-old man with a severe depressive disorder and suicidal ideation failed to improve despite venlafaxine (300 g/day) combined with flurazepam (15 g/day) over 44 days. Thoracic X-radiography, electroencephalogram (EEG), computed tomography, laboratory testing and serial electrocardiogram (ECG) recordings were all normal during venlafaxine treatment and before ECT. On the 45th day venlafaxine was reduced to 150 g/day (flurazepam unchanged). On the 46th day, 0.75 g atropine, 100 g propofol, 0.5 g norcurone and 50 g succinylcholine were given immediately before ECT (ThymatronDG, bilateral brief pulse, 100.8 mC). A generalised cramp was induced lasting 40 seconds. A rapid reduction in heart rate was followed by an asystole. After another atropine dose (0.5 g), a bradyarrhythmia (22–40 bpm) developed (for about 90 seconds) which spontaneously led to a bradycardial sinus rhythm. During three hours a normal sinus rhythm returned. Depressive symptoms completely receded with hypomania lasting about 16 hours; afterwards the depressive profile returned to its full extent. The cardiovascular events observed prompted further tests (echocardiography, 24-hour recording of ECG and blood pressure, stress-ECG) which produced normal results. Therapy administered during this phase (lithium, moclobemide, lorazepam) was unsuccessful. Six weeks later a second ECT course (seven rightside unilateral, one bilateral; 100.8–201.6 mC) did not produce cardiovascular complications. All psychopharmaceuticals except lorazepam had been discontinued 14 days before and the same pre-medication as given for the first ECT session. Starting with the third ECT, depressive symptoms gradually resolved.

Temporary arrhythmias and repolarisation abnormalities can occur in cardiologically-healthy subjects and may be physiological side-effects of ECT (Abrams, 1992). However, in our patient such effects were observed only after the combined use of ECT and venlafaxine and not at all after eight ECTs without antidepressants. ECT may enhance central serotonergic responsivity (Shapira *et al*, 1992). Venlafaxine inhibits both serotonin and noradrenaline uptake. We hypothesise that our patient experienced long-lasting bradycardia because increased serotonin in the central nervous system directly affected brainstem cardiovascular regulation (Shvaloff & Laguzzi, 1986). Alternatively, unknown interactions between venlafaxine and the anaesthetics used may have caused the adverse effect. Nevertheless, clinicians should note that prolonged bradycardia can complicate the combined use of venlafaxine and ECT.

Abrams, R. (1992) *Electroconvulsive Therapy* (2nd edn). New York: Oxford University Press.

Shapira, B., Lerer, B., Kindler, S., *et al* (1992) Enhanced serotonergic responsivity following electroconvulsive therapy in patients with major depression. *British Journal of Psychiatry*, **160**, 223–229.

Shvaloff, A. & Laguzzi, R. (1986) Serotonin receptors in the rat nucleus solitarii and cardiovascular regulation. *European Journal of Pharmacology*, **132**, 283–288.

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Doxazosin for reboxetine-induced urinary hesitancy

Sir: Reboxetine is a selective potent noradrenaline uptake inhibitor with clinically documented antidepressant properties. The drug is usually well tolerated; however, especially in elderly male patients, urinary hesitancy and/or retention can be a troublesome side-effect (Berzewski *et al*, 1997). Recently, we have found that this side-effect can be mitigated by the co-administration of doxazosin, an α_1-adrenoceptor antagonist indicated for the treatment of urinary retention associated with prostatism (Dollery, 1991).