stimulated the right carotid sinus by applying pressure with her hand or pillow when adopting her usual sleeping posture. Carotid sinus syndrome is an underdiagnosed cause of dizziness, falls, and syncope in the elderly. It is present in almost half the patients seen at syncope clinics.1 As in our patient, the right side is involved more frequently than the left.1,3 In addition to commonly described triggering factors such as head movements, local pressure, and local tumours, a number of unusual triggering factors have been noted such as prolonged standing, eating, micturition, defaecation, coughing, and exertion.1 Few conditions produce recumbent syncope. These include the supine hypotensive syndrome of late pregnancy as a result of inferior vena cava compression,1 syncope during dental surgical procedures attributed to reflex parasympathetic activity caused by trigeminal nerve stimulation,4 and, rarely, atrial myxomas. As this case illustrates, carotid sinus syndrome can present in unusual ways. It is a treatable cause of recumbent syncope in the elderly.

We thank Vladimir Hachinski and David Spence.

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**Fluoxetine and chronic fatigue syndrome**

Sir—The importance of Vercoulen and colleagues’ (March 30, p 858) investigation of the effect of fluoxetine treatment in chronic fatigue syndrome (CFS) cannot be underestimated, since between 0-5% and 1-5% of the population have this condition.1 Unfortunately, the data as presented suggest that this study does not generalise to most patients with CFS.

The first difficulty relates to the method of excluding psychiatric disorder other than depression in these patients. We are told that a structured psychiatric interview was given. Without details, it is unclear how people with somatisation disorder (SD) were excluded, which is important because, strictly speaking, such a diagnosis rules out that of CFS. Furthermore, the treatment response of SD is notoriously poor. Our second point relates to the length of illness in this sample. Individuals are included with illness durations up to 30 years, with the median being around 6 years. It is probable that this is a severely ill group of patients, since both community and tertiary care samples have average illness durations of around half this length. Finally, we are not told whether patients have previously tried or been unresponsive to other effective treatments such as cognitive-behavioural therapy.

One of the puzzling findings of the study is the absence of any placebo response in these patients. This result is in striking contrast with previous open studies of antidepressants (or other therapies) in CFS, in which rates are very high. There are grounds to suspect that the individuals entered into this study were a severe and unresponsive sample, with possibly a high frequency of undetected SD. Thus the results may not apply to those with the more commonly encountered forms of CFS. It is also possible to postulate that an important therapeutic response in CFS of such long duration requires more than 8 weeks of treatment, or some additional rehabilitative therapy. Preliminary results from a similar study comparing fluoxetine, placebo, and graded exercise showed that both active treatments were effective.

Additionally, we would not wish to discount the possible role of serotonergic abnormalities in CFS. Studies attempting accurately to assess serotonergic function in CFS patients must exclude comorbid psychiatric disorders such as depression, since these disorders can themselves affect serotonergic function.1 We tested non-depressed CFS patients with the prolactin response to d-fenfluramine as an index of functional 5-hydroxytryptamine (5HT) neurotransmission.1 There was evidence of serotonergic supersensitivity in CFS, and subsensitivity in a group of depressed patients, compared with healthy controls.1 Serotonergic supersensitivity in CFS was also shown by Bakheit et al who assessed 5HT2 receptor function.

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course of treatment under such circumstances may not be possible. Vercoulen and colleagues have tried to address this issue by analysing affective, cognitive, and somatic subset scores independently in both the fluoxetine and placebo condition. However, since they do not provide absolute subset scores it is not possible to deduce the degree to which somatic and cognitive factors obscure any changes in affect during the study. We were also surprised by the apparent lack of a placebo effect in this double-blind study. Since one would expect a 20–30% change in symptomatology attributable to such an effect.

Finally, we feel it necessary to point out that substantial evidence in published work points to a link between the 5HT system and the fatigue process. Exercise is accompanied by a supersensitive prolactin response to buspirone (a partial 5HT1a agonist). Our group has recently shown that endurance-trained athletes have a significantly reduced prolactin response to buspirone, compared with untrained controls, suggesting that the repeated activation of the 5HT system during endurance training may lead to a downregulation of 5HT1a receptors and improved exercise tolerance.

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fact that some studies reported an association between these types of attribution and chronic affective disorder in CFS, this is a plausible explanation for the above findings. We wondered if Vercoulen and co-workers are in a position to address this possible explanation for the low overall rate of placebo response.

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Author's reply

Sir—Clear and Wessely's main theme is that our patients were an unresponsive sample because of the long duration of their illness. In two prospective studies on the natural course in CFS patients with a similar length of illness we found that after 1-2 years improvement rate was 20% and after 4-5 years about 35% (Bazelmans E et al, unpublished). In addition, a similar group of patients, randomly selected from the same database, participated in cognitive-behavioural treatment and showed positive results. On the basis of these findings we conclude that these patients may well respond to treatment. They also argue that we might have included patients with SD. However, in a strict sense the diagnosis SD is not a reason for rejecting CFS according to British criteria or to the recent Centers for Disease Control and Prevention criteria. Moreover, SD is a descriptive diagnosis based on a number of rather arbitrarily chosen symptoms, and merely reflects patients with multiple physical symptoms for which no explanation can be offered. In a prospective study of our group number of complaints was no predictor for the course of complaints. Thus, it is unlikely that SD influenced results.

All your correspondents refer to the absence of a placebo response in the fluoxetine-treated patients. In the placebo-treated patients a normal placebo effect is seen in depression severity, but in fluoxetine patients a placebo effect is absent. This finding may suggest that fluoxetine in fact has a detrimental effect. This effect could well be due to the fact that fluoxetine is a serotonin reuptake inhibitor; two studies have shown that in CFS there may be serotonergic hypersensitivity, and from that perspective fluoxetine would do harm. Lynch and Seth's hypothesis as an explanation for the absence of a placebo effect seems unlikely because fluoxetine has been presented to the patient as a drug with a general effect on somatic processes, being effective in depression and possibly in fatigue. Thus, the drug was related to an effect on physical processes, and we do not suggest that the cause of complaints would be psychological.

With respect to Sharma and colleagues' points, first, we do not favour exercise testing as a means of measuring fatigue. Results of such tests are difficult to interpret because they are susceptible to confounding factors, such as physical deconditioning. Accelerometers, as we used them, yield highly reliable data and have been reported to be valid instruments measuring human physical activity; close
correlations were found with energy expenditure. In addition, the accelerometer provides measurements of physical activity during natural conditions and for long periods, and such data are clinically more important than laboratory-induced activities. We feel that the value of treatment of CFS especially should relate to clinical characteristics such as subjective feeling of fatigue and activity in daily life. Second, the use of a severity measure of depression in psychopharmacological research is not unusual. The use of the BDI on the other hand is not that common, but this method has excellent psychometric properties and can measure change. It is true that cognitive and somatic symptoms are components of the BDI score, but this is also true for the diagnosis major depression. Thus, deleting these symptom groups in both the BDI and the diagnosis would destroy the concept of depression.

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1 Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G. Prognosis in chronic fatigue syndrome (CFS): a prospective study on the natural course.
J Neurol Neurosurg Psychiatry 1996; 60: 480-94.

**Epidemiological perspectives on alcohol and the law**

Sir—In their April 13 commentary Alvarez and Del Rio1 raise the contradictions of modern medicine when they attempt to address social problems: why is it that, as epidemiologists, we should excel at sophisticated evaluation when the effects of cholesterol-lowering drug therapy, oral contraceptives or calcium inhibitors need assessing, but we are satisfied with the weakest of evidence when denouncing the assumed effects of alcohol on driving ability?

I have just returned from an 800 km trip on French motorways. I travelled at a constant 130 km/h, the maximum permitted limit. Throughout this trip, I overtook not more than ten cars. In practice, this means that more than 99% of cars travelling in the same direction as I was were blatantly exceeding the speed limit. And what about other dangerous behaviour, such as using the mobile phone (at 180 km/h), or not respecting safe distances between vehicles (or both at once)? When the law can be so regularly and flagrantly broken, I must admit to some difficulty in believing that respect for public order necessitates systematic checks of matters as private as consumption of alcohol. The paradox of road safety today is that the state seems to want to set limits for individuals (eg, checking their drinking habits), while giving up any idea of applying the law convincingly (eg, cracking down on such obvious illegal behaviour as exceeding the speed limit). Besides ethical issues raised by drink-driving tests, there is the difficulty of epidemiological justification: what proof exists of their efficacy? And who is capable of evaluating the importance of blood alcohol levels, in relation to all risk factors involved in driving accidents?

Hearing personally been in both situations, I honestly believe I am less dangerous on the road with a 0-5 g/L blood alcohol level, than when I have been working all night. In France, where drinking at meals is an important part of social life, it is hard for people to accept that one may be punished for drinking three glasses of wine, when everyone knows it is possible to go from Paris to Marseille at 200 km/h with little risk of being fined. The result is a complete breakdown of social consensus about driving behaviour, whose logical consequence is that state of anarchy illustrated by my recent experience: the population is less and less aware of the hierarchy of risks.

Now a signal function of epidemiology is to address distortions in perceived risks—we are not working in the public interest at all if we do to take on board what politicians are saying about drink-driving, without looking at it critically. Resistance to the effects of alcohol is, as everyone knows, highly idiosyncratic. Courage in epidemiology today, therefore, consists in stating that doing away with preventive checks is perfectly compatible with the requirements of public health, provided that blood alcohol tests are applied systematically after any highway offence, however minor. The impact of such a change on the way people think would be considerable. Whereas at present the detection of a proscribed level of blood alcohol does not go down well because everybody knows that it does not prove a state of danger, to check *a posteriori* would place the burden of proof on the driver, since every single time there was alcohol in the blood an offence would be linked with it. Such a situation, in which a high degree of alcohol consumption became synonymous with offences committed, would undoubtedly contribute to rebuilding the social consensus that is so badly lacking in the struggle against dangerous driving.

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**Benign adipic aciduria**

Sir—A 5-year-old girl from the former German Democratic Republic suspected of having Kearns-Sayres Syndrome was admitted to our department for diagnostic examination. On routine examination of organic acids in urine she was found to be excreting massive amounts of adipic acid but surprisingly without substantial amounts of suberic, sebacic, or ethylmalonic acids. Adipic acid excretion accompanied by these other metabolites is often a sign of several metabolic diseases. This perplexing finding was repeated in successive urine samples and seemed to have no relation to time of day or meals. Discussion with the mother, the child herself, nurses, and physicians gave no explanation for this metabolic pattern. During her stay the child developed a metabolic crisis requiring infusion of fluids and electrolytes. Under these conditions the adipic acid excretion disappeared. This was even more perplexing but did suggest that the adipic acid had something to do with her oral intake. In agreement with the treating physician the patient had been kept on her previous medication. Recourse was finally taken to direct examination of the patient’s medications which revealed that she was taking K and Mg in the form of the adipate salt (Kalium-Magnesium Apogepha). In the Federal Republic of Germany K and Mg were not previously available as the