LETTERS TO THE EDITOR

Medical restrictions to driving: the awareness of patients and doctors

EDITOR—Kelly *et al*'s study of knowledge of medical restrictions on driving reveals worrying deficits in doctors' knowledge.[1] This accords with results of previous studies[2] concerning knowledge of psychiatrists, but contrasts with a comparable study of knowledge[3] after dissemination of the Driving Vehicle Licence Authority's (DVLA) "at a glance guidelines".[4] For example, 93% of the sample of 89 psychiatrists were aware of DVLA regulations on late dementia, suggesting that ignorance can be countered by educational campaigns. However, even this study revealed inadequate knowledge of General Medical Council (GMC) guidelines on confidentiality, in which the trend was to underestimate the need for doctors to break confidentiality and to inform the medical adviser at the DVLA. For example, only 32% of respondents were aware that the DVLA should be informed when a patient continues to drive against medical advice. Information concerning the breaking of confidentiality is not explicit in the "at a glance guidelines", but is described with clarity by the GMC in *Duties of a doctor.*[5]

It seems likely that legal precedent will establish medical negligence when doctors fail to provide appropriate advice on driving regulations. The study of Morgan showed that junior trainees have least knowledge of guidelines,[3] and it would seem appropriate to make driving regulations a clearly defined topic for examination in Membership curricula. However, other doctors may require the threat of litigation to focus their minds.

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1 Kelly R, Warke T, Steele I. Medical restrictions to driving: the awareness of patients and doctors. *Postgrad Med J* 1999;**75**:537–9.
2 Thompson P, Nelson D. DVLA regulations concerning driving and psychiatric disorders. *Psychiatr Bull* 1996;**20**:323–5.
3 Morgan JF. DVLA and GMC guidelines on "fitness to drive" and psychiatric disorders: knowledge following an educational campaign. *Med Sci Law* 1998;**38**:28–33.
4 Medical Advisory Branch of the DVLA. *At a glance guide to the current medical standards of fitness to drive*. Swansea: DVLA, 1993.
5 General Medical Council. *Duties of a doctor (confidentiality)*. London: GMC, 1995: 11–12.

The authors respond:

The paper of J F Morgan[1] shows some improvement in psychiatrists' knowledge of driving restrictions after dissemination of the DVLA's "at a glance guidelines"[2] compared with the findings of Thompson and Nelson.[3] Even with these improvements the majority of respondents were incorrect for some of the clinical situations questioned (for example heroin, methadone, and cannabis use/dependence). Both studies used postal questionnaires and it may be that there was an increased awareness of where information could be obtained from, rather than an increase in working knowledge. Not knowing where to obtain the necessary information was apparent in our own study.[4] Our experience has been that attempts to increase the ability of doctors to consider fitness to drive has been difficult. We recently used an educational programme incorporating slide presentations and the display of relevant posters on the wards to try and increase awareness of driving restrictions. This produced only small improvements in the ability of doctors to record in the medical notes that they had considered a patient's driving status and had advised them appropriately.[5]

We would agree with Dr Morgan that making driving regulations a specific topic for examination in Membership curricula may increase doctors' awareness. However, undergraduate education should be the main priority. That way all doctors will learn to ask about driving as part of the routine social history and will hopefully, as a result, consider whether any of the patient's medical conditions impact on their fitness to drive.

1 Morgan JF. DVLA and GMC guidelines on "fitness to drive" and psychiatric disorders: knowledge following an educational campaign. *Med Sci Law* 1998;**38**:28–33.
2 Medical Advisory Branch of the DVLA. *At a glance guide to the current medical standards of fitness to drive*. Swansea: DVLA, 1993.
3 Thompson P, Nelson D. DVLA regulations concerning driving and psychiatric disorders. *Psychiatr Bull* 1996;**20**:323–5.
4 Kelly R, Warke T, Steele I. Medical restrictions to driving: the awareness of patients and doctors. *Postgrad Med J* 1999;**75**:537–9.
5 Kelly R, Warke T, Steele IC. Documentation of driving in case notes by medical staff. *Age Ageing* 1999;**28**(suppl 2):47.

Fish odour syndrome

EDITOR—We read with interest the excellent review article on fish odour syndrome (trimethylaminuria) by Rehman.[1] However the author does not address the clinical relevance of trimethylaminuria (TMA-uria) well beyond the intermittent unpleasant body odour. TMA-uria is caused by the deficiency of the flavin-containing monooxygenase isoform 3 (FMO3).[2 3] The *FMO3* gene has been described, and disease causing mutations have been reported.[2 3] In addition to TMA this enzyme is required for detoxification of many substances including endogenous amines, tyramine, nicotine, and drugs (for example, tricyclic antidepressants, ranitidine).[4] Zschocke *et al* have followed up patients with mild TMA-uria, and have examined the *FMO3* gene in them.[5] The molecular analyses revealed compound heterozygosity for mis-sense mutations on one chromosome and a variant allele with two amino acid polymorphisms (E158K, E308G) on the other chromosome. E158K (allele frequency 48% and 43% in German (n=230) and Turkish (n=68) control chromosomes, respectively) has been reported to reduce enzyme activity in an in vitro assay, whereas E308G, which is apparently always linked to E158K, has been reported without functional data. The variant allele (E158K, E308G) is very common in the white population, with reported frequencies of 20% and 6% in German and Turkish controls respectively.[5] Studies have shown that the variant allele is associated with markedly reduced FMO3 enzyme activity in vivo. Individuals homozygous for the wildtype sequence or compound heterozygous for wildtype/E158K showed normal TMAO (trimethylamine N-oxide)/total ratios in the same range as under physiological conditions (>94%). Individuals with mild TMA-uria showed very low TMAO/total ratios of about 30%. Homozygosity for (E158K, E308G), as found in 4% of controls, resulted in decreased TMA oxidation capacity (<50%), also indicative of mild TMA-uria.[5]

Thus FMO3 deficiency is not merely a rare recessive disorder but rather a spectrum of phenotypes of transient or mild malodour depending on environmental exposures. In view of its other physiological functions mild FMO3 deficiency may lead to an abnormal metabolism of drugs, hypertension, or increased cardiovascular risk. Two adults with mild TMA-uria (one homozygous for (E158K, E308G), one compound heterozygous for a severe mutation and the variant allele (E158K, E308G) presented with hypertension.[5] Population studies are required to analyse the spectrum of molecular variation at the *FMO3* locus, and to evaluate the clinical relevance of mild, normally unrecognised FMO3 deficiency.

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1 Rehman HU. Fish odour syndrome. *Postgrad Med J* 1999;**75**:451–2.
2 Dolphin CT, Janmohamed A, Smith RL, *et al*. Mis-sense mutation in flavin-containing monooxygenase 3 gene, FMO3, underlies fish-odour syndrome. *Nat Genet* 1997;**17**:491–4.
3 Treacy EP, Akerman BR, Chow LML, *et al*. Mutations of the flavin-containing monooxygenase gene (FMO3) cause trimethylaminuria, a defect in detoxication. *Hum Mol Genet* 1998;7: 839–45.
4 Cashman J. Structural and catalytic properties of the mammalian flavin-containing monooxygenase. *Chem Res Toxicol* 1995;**8**:166–81.
5 Zschocke J, Kohlmueller D, Quak E, *et al*. Mild trimethylaminuria caused by common variants in FMO3 gene. *Lancet* 1999;**354**:834–5.

The author responds:

I agree with Kashyap and Kashyap that TMA is required for detoxification of many substances including the ones mentioned by them in addition to TMA, amphetamine, metamphetamine,[1] clozapine,[2] chlorpromazine, and methimazole. The FMO gene family has been localised to chromosome 1q and various mutations have been described to cause the metabolic defect. Individuals with these *FMO3* gene mutations may have defective metabolic activity for many clinically used drugs. The human flavin-containing mono-oxygenase (FMO) gene family comprises at least five distinct members (*FMO1* to *FMO5*) that code for enzymes responsible for the oxidation of a wide variety of soft nucleophilic substrates, including drugs and environmental pollutants.

Apart from the two adults with mild TMA-uria and hypertension described by Zschocke *et al*,[3] I am not aware of any other related literature either to this particular