Renal failure after omeprazole

SIR,—An 86-year-old woman had a 10 year history of oesophagitis and had been treated intermittently with cimetidine or ranitidine. Because of progression in symptoms in 1989, omeprazole 40 mg daily was started. At that time the patient had normal serum creatinine concentration. 2 months later she was admitted with renal failure: maximum serum creatinine 858 μmol/L (normal < 120). A renal needle biopsy revealed interstitial inflammation, with plasma cells, lymphocytes, and eosinophils and patchy tubulitis but no effect on glomeruli, which is characteristic of acute interstitial nephritis.[1] 2 weeks before admission the patient had been treated with erythromycin for suspected pneumonia. Both drugs were withdrawn, and the patient regained normal renal function on treatment with diuretics. Erythromycin was suspected of being the drug causing the renal failure.

In 1992, during cimetidine treatment, the patient had a peptic stricture of the oesophagus and omeprazole was given with surveillance of renal function. Within a week the patient developed high temperature, a rash, eosinophilia, and diminishing renal function. The patient did not receive any other drugs, and omeprazole was withdrawn after 9 days. The renal failure progressed to anuria, and necessitated haemodialysis for a week. The renal function remained severely affected, and after 3 months serum creatinine had declined from 810 to 396 mmol/L.

Our patient had typical acute interstitial nephritis, with the triad of high temperature, rash, and eosinophilia.[1] The pathophysiology remains unclear, but cell-mediated immunity is probably important in most cases.[2] The allergic nature of our patient's disease is favoured by the fact that she had previously reacted with rashes to other drugs (amiloride with hydrochlorthiazide, phenylbutazone, and penicillin), and in 1972 she had had sarcoidosis (verified by mediastinal gland biopsy) that spontaneously subsided. Patients with sarcoidosis react with an enhanced T-lymphocyte-mediated immune response to various antigens.

This is the second case of acute interstitial nephritis due to omeprazole, and the diagnosis was confirmed by renal biopsy. The first case was a 74-year-old woman with oesophagitis who twice had increased serum creatinine and eosinophilia/eosinophiluria for weeks after treatment with omeprazole.[3]

The renal biopsy specimen was investigated by H. Starklint.

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Adverse events after triazolam substitution

SIR,—It is just over a year since the UK licensing authorities suspended the hypnotic triazolam.

To examine the effects of this regulatory decision on patients in general practice, whose insomnia had been successfully treated with triazolam, we retrospectively surveyed general practitioners who had to switch their sleep-disturbed patients suddenly to another hypnotic. 163 general practitioners reviewed 1193 patients' records (M/F 333/860, mean age 66·4) and completed a standardised questionnaire and individual case-record form that measured global clinical impression, daytime effects, tolerability, and preference for medication.

In response to an opinion-poll question, mean ratings on a visual analogue scale showed that the physicians questioned disagreed with the suspension of triazolam, felt that their prescribing flexibility had been compromised, and thought that the suspension of triazolam had not benefited their patients.

Temazepam was the substitute prescribed to 806 (67·6%) of the patients. Other substitute therapies were loprazolam (8·7%), nitrazepam (7·3%), lormetazepam (5·3%), chloral betaine (3·6%), and zopiclone (3·6%). Various antidepressants (0·5%), antipsychotics (0·2%), and anxiolytics (0·9%) were also used.

The number of adverse events reported for triazolam during the three months before the suspension was compared with that during the first three months of substitute therapy, as an index of the relative safety of triazolam. 284 (23·8%) patients reported side-effects while using triazolam compared with 378 (31·7%) with substitute therapy. The central nervous system (CNS) events reported with specific treatments (lormetazepam, 22%; nitrazepam, 21%; zopiclone, 19%; temazepam, 18%; chloral betaine, 18%; and loprazolam, 12%) were in excess of those reported with triazolam (9%). The most frequent reports with triazolam were insomnia and memory problems, both at 0·4%, whereas for the substitutes as a group, insomnia affected 7·0%, daytime drowsiness 1·3%, and anxiety 1·1%. For the most frequently prescribed substitute, temazepam, the most common CNS events related to treatment were insomnia 7·1%, daytime drowsiness 1·1%, and anxiety 1·2%.

These results must be viewed within the context of the limitations of a retrospective survey of patients with some tolerance of triazolam. Furthermore, we did not control for different regimens. However, the number of general practitioners surveyed would effectively reduce any systematic bias and, in the light of the media-driven commentary on triazolam, the reporting of CNS events with triazolam would be expected to be over-reported. Also, if any substitute therapy was perceived to be as effective and as safe as triazolam, this finding could easily have been reflected in our survey.

If the rationale for the suspension of triazolam was to ensure the safety of patients using hypnotics, the UK regulators' decision was faulty. None of the substitute therapies had a profile of CNS side-effects superior to that of triazolam. Indeed, most substitutes were associated in physicians' reports with noticeably more CNS side-effects—especially those likely to interfere with the daily wellbeing and safety of patients.

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Pathophysiology of obesity

SIR,—Dr Bradley (Oct 3, p 848) reiterates the once-popular notion that human obesity is caused by excessive consumption of sugar-containing and therefore palatable foods. His argument is based on the faulty premise that obesity was uncommon in traditional societies whose "bland and monotonous" diets provided an average of 50% of their energy from fat. On the contrary, most pre-industrial diets provided a very small portion of energy from fat. Subsistence-level farming chiefly involves tubers and starchy roots.[1] Field agriculture has allowed the cultivation of grasses such as maize, oats, barley, and sorghum, including such major food grains as rice and wheat.[1] Geographic location also plays a part. Thus manioc is still the basic foodstuff of African countries, maize is the staple food of Central and South America, whereas the Asian diet is based on rice. Most so-called traditional diets are very high in complex carbohydrates, but very low in fats and oils. Until recently, the Japanese diet provided less than 10% of daily energy from fat.[2] The few contrary examples of the cattle-rearing Masai of East Africa or the hunting and fishing Arctic Eskimos have long been known to anthropologists and nutritionists. Although these groups incorporate meat and fish into their diets, and so run counter to the norm, their fat intake is surprisingly low compared with that of many western societies.

Although animal fats were the most sought-after item in pre-industrial diets, their consumption was rare, and was often associated with feasts and ritual sharing.[3] It was economic prosperity that brought about increased meat consumption and the selective breeding of animals for the maximum fat content. The French sociologist Claude Fischler[4] notes that historians have long indexed the prosperity of an era, or the membership in a given social class, in terms of per caput meat consumption. Prosperity is

associated with increased consumption of animal fats and a decline in the consumption of grain products.

Bradley mistakenly equates palatability exclusively with the sweet taste of sugar. In reality, fats have a more decisive role in determining the palatability of the diet.[5,6] Fats endow foods with various flavours, aromas, and textures, and some of the most palatable foods in the human diet are those that are rich in fat. Taste-preference studies have shown that obese women gave highest preference ratings to stimuli that were low in sugar but were rich in fat.[7] Preferences for dietary sources of fat may in fact be a shared feature of human obesity syndromes. Whereas obese men typically listed meat dishes among their favourite foods, women were more likely to express preferences for sweet, fat-rich desserts.[8] Prosperity is, admittedly, also associated with increased sugar consumption, because sucrose and fructose replace dietary starches and grains.[5] However, although the typical American diet provides about 11% of energy from added sugars, 38% of the energy comes from fat, and, according to present medical consensus, fat is the most important dietary factor in the aetiology of obesity.

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Genetic susceptibility to multiple sclerosis linked to myelin basic protein gene

SIR,—Dr Tienari and colleagues' report (Oct 24, p 987) implicates the myelin basic protein (MBP) gene or an associated gene in multiple sclerosis in high risk Finnish families. However, although their criteria for multiple sclerosis are clear, those for optic neuritis are not defined. Were these criteria clinical or based on laboratory tests, or both? In the three pedigrees shown there were 82 individuals of whom 53 had optic neuritis or multiple sclerosis. Yet there were 20 forebears in these pedigrees without any demyelinating disease. Surely this is remarkable for a genetic condition? It may be that in some, particularly pedigree 2 in which five generations were shown and would cover at least 100 years, the diagnosis was not made because the neurological conditions were not recognised—or were they truly absent? The ratio of optic neuritis to multiple sclerosis was about 3/2. Genetic studies of this kind should be done in parallel in more than one country to compare the patterns in different areas.

Although MBP sensitisation in rats and guineapigs induces experimental allergic encephalitis, this is not associated with demyelination, which is an essential pathological feature of multiple sclerosis. In the guineapig, environmental features such as pretreatment with a bacterial cell-wall component and non-encephalitogenic proteins[1-3] can predispose to demyelination. This finding suggests that demyelination is of multifactorial origin and that environmental factors may include bacteria, viruses, or components of microbial origin. In shiverer mice, in which the MBP gene is known to be defective, the illness is present from birth and affects all individuals, unlike multiple sclerosis. Apart from MBP, the possible role of other myelin proteins[4] and their genes and associated genes also require investigation for alleleic variations. Two factors that may contribute to demyelination are loss of tolerance to a myelin protein and damage to a surveillance system

that prevents demyelination. The latter factor may be of genetic origin and families prone to multiple sclerosis may be more vulnerable than normal, according to this theory.[5]

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Authors' reply

SIR,—Dr Colover's comment about the high frequency of optic neuritis in multiple sclerosis families was based on a mistake, which had escaped our notice. Unfortunately, the symbol for optic neuritis in fig 2 was wrongly assigned in the legend of the figure. The correct symbol for males with optic neuritis should be a half-filled square instead of an open square, which indicated unaffected males. The number of subjects with this condition in the pedigrees shown in fig 2 is therefore only 1, instead of 53. The diagnostic criteria for optic neuritis were both clinical and laboratory investigations: the patients had had one attack of monosymptomatic disease without any abnormal laboratory findings.

Colover questions the cause of demyelination in multiple sclerosis, which remains unknown and is probably multifactorial and therefore open to speculation. We regarded the following points as relevant to our report. First, MBP is a target autoantigen in experimental allergic encephalomyelitis of rodents and the analogy with multiple sclerosis is unclear. Second, molecular mimicry between MBP and viral proteins has been shown to be pathologically important in an animal disease model. Third, two mutations of MBP gene have been characterised in mice with shiverer phenotype (a demyelinating disease); it is relevant to address the known mutations of the MBP gene, although the disease caused by these mutations is distinct from multiple sclerosis. Finally, by finding linkage to MBP gene we can locate a genomic variation conferring susceptibility to multiple sclerosis close to MBP gene. However, linkage does not implicate MBP gene as the defective gene, although it is a candidate gene: therefore our conclusion remains that a polymorphism in the MBP gene or in close vicinity has a role in the aetiopathogenesis of multiple sclerosis.

The role of other myelin genes is highly speculative since dozens of other candidate genes could be implicated (eg, genes coding for components of the immune system). Among myelin genes the proteolipid protein gene is an unlikely candidate since it is located on the X chromosome and no evidence for X-chromosomal inheritance exists in multiple sclerosis. However, there are very few experimental data for these other myelin genes.

Many theories of demyelination mechanisms accord with MBP linkage, and the "damage to a surveillance system that prevents demyelination" suggested by Colover is appealing. Accordingly, demyelination in multiple sclerosis may well be secondary to reduced remyelination capacity. In view of our finding and with MBP as a candidate gene, this hypothesis could be explained by several genetically determined factors: low levels of MBP expression in multiple sclerosis patients; differences in MBP isoforms (ie, reduced amount of those isoforms, which are produced during active remyelination); and aminoacid variation in MBP leading to a functionally defective protein. However, we feel that the speculations regarding these mechanisms are, at this stage, premature.

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