should not be a matter for criticism. The aim of the new society is to provide an alternative to the existing bodies, not to replace them, and nor is it to disadvantage any other elements of the profession.

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"If We Can Keep a Severed Head Alive . . ."

In his review of my book (3 September, p 629) Professor T J Hamblin stated, "In [Fleming's] view a device to perfuse a human head might lead to horrific consequences, and so he has developed a fiendish plan to prevent one being developed." That is incorrect. As stated in the book, the technology for perfusing a severed head has important potential advantages, for research and for prolonging life in a conscious and communicative state with, probably, less pain than many dying people suffer today. The difficult question is whether the advantages outweigh the disadvantages and dangers. Therefore, instead of trying to stop this research, I proposed a system where any scientist or surgeon who wants to try the experiment in America, on either animals or humans, will need to consult three independent review panels that already exist at every university: animal care committees, which control experiments on animals; institutional review boards, which must approve experiments on human subjects; and institutional biosafety committees, which control genetic engineering experiments.

Some review panels are likely to approve such proposals, since perfusing intact heads will allow researchers to study the brain and sensory organs in ways that cannot be accomplished otherwise. This strategy will force the issues up to the surface for open debate, moderated and judged by impartial experts who have nothing to gain personally from the research.

The reviewer also suggested that only one experiment had been done to keep a severed head alive. In fact, many such experiments have been reported in scientific journals. In the experiments by White *et al* transplanted monkey heads remained fully conscious for 36 hours.¹ They died because of heparin overuse, a problem which can be overcome today using an extracorporeal heparin remover. Research is being done today on intact brains which continue to generate brain waves after the sensory organs and the skull have been cut away.

It is far more difficult to obtain a prophetic patent in America than Professor Hamblin suggests. Such patents usually must be limited to mechanical systems, since mechanical components are more predictable than chemical reactions or experimental drugs. Every component must be publicly available and the inventor must describe explicitly how to assemble and use them. If I hadn't been a patent attorney specialising in biochemistry and medical technology and if I hadn't spent hundreds of hours researching each component and consulting surgeons and biochemists I couldn't have obtained the patent.

Your reviewer asks: Would anyone want the operation? I have been contacted by half a dozen people who want to know how soon the operation will be available and how much it will cost. Some are dying; others are paralysed. Most said that if the mind remains clear and the head can still think, remember, see, read, hear, and talk and if the operation leads to numbness rather than pain below the neck then they would want it.

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1 White RJ, Wolin LR, Massopust LC, Taslitz N, Verdura J. Cephalic exchange transplantation in the monkey. *Surgery* 1971;70:135-9.

Drug Points

Phenytoin interaction with rifampicin

Dr F J ABAJO and others (Hospital del Insalud "La Paz," Madrid 28046, Spain) write: An 82 year old man being treated with rifampicin 600 mg daily and ethambutol 1200 mg daily for pulmonary tuberculosis was admitted with generalised seizures. He had a history of idiopathic focal seizures, which had been successfully treated with combined phenytoin and phenobarbitone. As he had been virtually free of seizures for more than 10 years, however, the treatment had been withdrawn nine months before admission. Phenytoin treatment was restarted as monotherapy, and a daily dose of 400 mg was required to obtain adequate control. Serum concentrations of phenytoin ranged from 17.3 mg/l to 18.2 mg/l (therapeutic range 10-20 mg/l) as measured by the enzyme multiplied immunoassay technique (coefficient of variation between days was <6%).

Two weeks before completing his treatment for tuberculosis, when he had been taking 400 mg phenytoin for eight weeks, the dose of phenytoin was reduced to 375 mg. The serum phenytoin concentration was 14.4 mg/l immediately before withdrawal of rifampicin and ethambutol. At the end of the first week after withdrawal the serum phenytoin concentration was 13 mg/l but it rose to 22 mg/l in the second week. The daily dose was then reduced to 350 mg, but the serum concentration continued to increase, reaching values above the therapeutic range (22.1 mg/l) in the ninth week after withdrawal, and the dose was further reduced to 325 mg. Subsequently stable serum concentrations of 13.6-15.3 mg/l were maintained. Samples of blood for drug assay were always taken 10-12 hours after last dose, and compliance was excellent.

This case shows an interaction between the treatment for tuberculosis and phenytoin that might have resulted in clinically important toxicity if the serum phenytoin concentration had not been closely monitored. Kay *et al* reported that phenytoin clearance increased to almost double in volunteers after two weeks of treatment with rifampicin.¹ We do not, however, know of such an interaction during clinical use.^{2,3} Because rifampicin induces human microsomal enzymes⁴ and phenytoin is metabolised by the microsomal system it seems reasonable that enzyme induction provoked by rifampicin is the mechanism operating in the interaction. In addition, the fact that the serum phenytoin concentration took a week to increase after withdrawal of rifampicin and continued to increase over eight weeks supports this hypothesis. A return to normal metabolic activity after withdrawal of drugs that induce enzymes may take several weeks.⁴ Ethambutol is not a known inducer of enzymes and probably played no part in the interaction.

- 1 Kay L, Kampman JP, Svendsen TL, *et al*. Influence of rifampicin and isoniazid on the kinetics of phenytoin. *Br J Clin Pharmacol* 1985;20:323-6.
- 2 Baciewicz AM, Self TH, Bekemeyer WB. Update on rifampicin drug interactions. *Arch Intern Med* 1987;147:565-8.
- 3 Hansten PD. *Drug interactions*. 5th ed. Philadelphia: Lea and Febiger, 1985.
- 4 Pond SM. Pharmacokinetic drug interactions. In: Benet LZ, Massoud N, Gambertoglio JG, eds. *Pharmacokinetic basis for drug treatment*. New York: Raven Press, 1983:195-220.

Delirium induced by atenolol

Dr N ARBER and others (Beilinson Medical Centre, Peta Tiqva, Israel 49100) write: Psychiatric disturbances have rarely been associated with atenolol treatment.^{1,2} We report an acute episode of delirium in a patient taking atenolol that was completely reversed after the treatment was withdrawn.

An 85 year old woman who did not have a psychiatric history was admitted with rapid atrial fibrillation. She had had angina that was stable and chronic atrial fibrillation. She was treated with atenolol 50 mg twice a day, isosorbide mononitrate 20 mg three times a day, and diltiazem hydrochloride 30 mg four times a day. Physical examination disclosed an irregular heart rate (120 beats/minute) and a blood pressure of 135/80 mm Hg without signs of congestive heart failure. Her temperature was 36.4°C; her mental and haemological state were normal on examination. Atenolol was increased to 100 mg twice a day. Eight hours later

she became violent and confused; she had visual hallucinations and paranoid thoughts. Consultation by a psychiatrist suggested that the diagnosis was delirium induced by the drug. A metabolic cause could not be found for the change in her mental state, she was haemodynamically stable, and findings on electroencephalography and cranial computed tomography were normal. Atenolol was replaced by amiodarone, and within one day her mental state had returned to normal. She subsequently refused rechallenge with atenolol.

Delirium is usually associated with infections, drug intoxications, metabolic disturbances, cardiac decompensation, trauma to the head, or cerebral insufficiency, especially in the elderly.³ β Blockers, especially propranolol, cause the organic brain syndrome.⁴ Penetration of the central nervous system by atenolol is limited because of its hydrophilic nature, therefore its untoward effects on the system should be fewer compared with other β blockers. In this case the sequence of the development of the behavioural change after administration of a double dose of atenolol, the rapid improvement after its withdrawal, and the absence of any evidence of other possible causes strongly suggest that atenolol may have played a part in the development of the delirium.

We know of only two other cases of the organic brain syndrome induced by atenolol,^{1,2} and in both the clinical features were similar to those in our case. Our report suggests that atenolol at high doses, despite being hydrophilic, must be considered among the drugs that may cause the organic brain syndrome. The phenomenon may be more common in the elderly as delirium induced by drugs is much more prevalent in this age group.

- 1 Viadero JV, Wong SH, White WB. Acute psychotic behavior associated with atenolol. *Am J Psychiatry* 1983;140:10.
- 2 Kramer BA. Atenolol confusion and paranoia when administered with electroconvulsive therapy. *J Nerv Ment Dis* 1986;174:562-3.
- 3 Paykel ES, Fleming R, Watson JP. Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol* 1982;2:14-39.
- 4 Dukes MNG. *Meyler's side effect of drugs* 10th ed. Amsterdam: Elsevier, 1984:321.

Fatal triazolam poisoning

Drs J J O'Dowd (East Glamorgan General Hospital, Pontypridd, Mid Glamorgan), P P SPRAGG, and P A ROUTLEDGE (Llandough Hospital, Penarth, South Glamorgan) write: Dr J P Sunter and others (17 September, p 719) report three cases of death due to triazolam poisoning. We have recently seen a similar case in south Wales.

A 58 year old woman was being treated for depression and taking 0.25 mg triazolam at night. She had threatened to take an overdose of tablets many times, and on the day of her death she ran into a neighbour's house and stated that she had taken 70 tablets. She collapsed, became unconscious, and died shortly after reaching the accident and emergency department.

A postmortem examination showed mild atherosclerosis in the left anterior descending coronary artery with minimal changes in the right and left circumflex arteries. The rest of the postmortem examination showed normal results, and therefore no anatomical lesion accounting for death was found. Toxicological tests showed a blood triazolam concentration of 870 nmol/l, a blood alcohol concentration of 105 mg/100 ml, and a urinary alcohol concentration of 130 mg/100 ml. The peak plasma therapeutic concentration of triazolam is reported as 50 nmol/l.¹

This woman showed no gross or histological cause for her death, but she had taken an overdose of triazolam and had an alcohol concentration about one and a half times the legal driving limit. The balance of evidence therefore supports the conclusion that she died as a result of triazolam overdosage associated with alcohol consumption.

It is often stated that benzodiazepine poisoning is comparatively safe, but we would agree with Dr Sunter and others that patients who have taken an overdose of triazolam should be carefully monitored and that death can result from an overdose of this drug.

We thank Mr A Davies, the coroner for Mid Glamorgan southern district, for permission to report this case.

1 Eberts FS, Philipopoulos Y, Reineke LM, Vliek RW. Triazolam disposition. *Clin Pharmacol Ther* 1981;29:81-4.