

trials of β blockade after myocardial infarction the benefit conferred by β blockers was slightly better in those that used non-selective agents such as timolol and propranolol. A regionwide study in East Anglia is now directly comparing non-selective and β_1 selective blockade in secondary prevention. Meanwhile, an interesting testimony to the influences over prescribing habits is the fact that the most widely used β blocker in secondary prevention is atenolol, which has never itself been tested in a secondary prevention trial. Atenolol has survived questions about its disappointing efficacy in several other trials of outcome, perhaps related to its uniqueness as a water soluble β blocker. The first international trial of infarct survival studied short term use of atenolol in myocardial infarction, and it is again intriguing that the drug prevented cardiac rupture but not arrhythmias.

It is now becoming apparent that these large trials fail to shed light on interesting pharmacogenetic differences that may be more important to individual patients than small albeit significant differences between groups in trials. The β_2 adrenoceptor is one of several candidate genes for essential hypertension, in which both genetic polymorphism and a possible association with hypertension have been reported. The search for the genetic basis of hypertension and ischaemic heart disease might be helped by clinical identification of families in which paradoxical responses to non-selective β blockade are extreme. Until current trials tell us otherwise, therefore, doctors can be encouraged to use either type of β blocker and can expect to note individual differences in the short term changes in symptoms or blood pressure.

Above all, doctors should remember the injunction to first do no harm, and arguments about which β blocker to use pale into insignificance before the absolute indictment against any β blocker, even locally as eye drops, in patients with a history of asthma. Few clinicians may understand the niceties of

receptor selectivity. Fewer still understand that the high potency of a drug required to permit its local administration is synonymous with a high receptor affinity and very slow dissociation of drug from receptor. One drop of timolol down the lacrimal duct can kill.

MORRIS J BROWN
Professor of clinical pharmacology

Clinical Pharmacology Unit,
University of Cambridge,
Addenbrooke's Hospital
Cambridge CB2 2QQ

- 1 Cleophas TJM, Kawu FHW. More on paradoxical pressor effects of nonselective β -blockers. *Circulation* 1994;90:2157-9.
- 2 Drayer JIM, Keim HJ, Weber MA, Case DB, Laragh JH. Unexpected pressor response to propranolol in essential hypertension on interaction between renin, aldosterone, and sympathetic activity. *Am J Med* 1976;60:896-903.
- 3 Clutter WE, Bier DM, Shah SD, Cryer PE. Epinephrine increases plasma metabolic clearance rates and physiologic threshold for metabolic and haemodynamic actions in man. *J Clin Invest* 1980;66:94-101.
- 4 Ferro A, Kaumann AJ, Brown MJ. β_1 - and β_2 -adrenoceptor mediated relaxation in human internal mammary artery and saphenous vein: unchanged β - and α -adrenoceptor responsiveness after chronic β_1 -adrenoceptor blockade. *Br J Pharmacol* 1993;109:1053-8.
- 5 Armistead JG, Lightman SL, Brown MJ, Causon RC, Vaughan NJA. The effect of selective and non-selective β -adrenoceptor blockade, and of naloxone infusion, on the hormonal mechanisms of recovery from insulin-induced hypoglycaemia in man. *Br J Clin Pharmacol* 1983;16:719-21.
- 6 Karlsberg RP, Cryer PE, Roberts R. Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *Am Heart J* 1981;102:29-39.
- 7 Brown MJ, Allison DJ, Jenner DA, Lewis PJ, Dollyer CT. Increased sensitivity and accuracy of phaeochromocytoma diagnosis achieved by plasma adrenaline estimations and a pentolinium suppression test. *Lancet* 1981;ii:174-7.
- 8 Brodde OE. β_1 and β_2 -adrenoceptors in the human heart. Properties, function, and alterations in chronic heart failure. *Pharmacol Rev* 1991;43:203-42.
- 9 Hall JA, Petch MC, Brown MJ. Intracoronary injections of salbutamol demonstrate the presence of functional β_2 -adrenoceptors in the human heart. *Circ Res* 1989;65:546-53.
- 10 Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta-2 receptor stimulation by circulating epinephrine. *N Engl J Med* 1983;309:1414-9.
- 11 Struthers AD, Reid JL, Whitesmith R, Rodger JC. The effect of cardioselective and non-selective β -adrenoceptor blockade on the hypokalemic and cardiovascular responses to adrenomedullary hormones in man. *Clin Sci* 1983;65:143-7.
- 12 Hall JA, Kaumann AJ, Brown MJ. Selective β_1 -adrenoceptor blockade enhances positive inotropic responses to endogenous catecholamines mediated through β_2 -adrenoceptors in human atrial myocardium. *Circ Res* 1990;66:1610-23.
- 13 Hall JA, Petch MC, Brown MJ. In vivo demonstration of cardiac β_2 -adrenoceptor sensitisation by β_1 -antagonist treatment. *Circ Res* 1991;69:959-64.
- 14 Brown MJ. What do beta-blockers really do? A view from both sides of the receptor. *J R Coll Phys Lond* 1993;27:420-7.

Magnesium sulphate: the drug of choice in eclampsia

Definitive trial signals triumph for researchers in the developing world

Until this year, the pharmacological treatment of eclampsia has been determined largely by geography, habit, and prejudice. Magnesium sulphate has been the drug of choice in the United States; in Britain, diazepam and, more recently, phenytoin have been favoured.¹ None of these choices was influenced by strong scientific evidence.

A network of researchers has recently reported the first large randomised trial comparing these three drugs in eclampsia.² The collaborative eclampsia trial is the most important obstetric trial of the 20th century, and it has set new standards for vision and ambition in clinical trials in perinatal medicine. It included no fewer than 1680 eclamptic women recruited by local clinicians in west and southern Africa, South America, and India; and the trial was coordinated mainly by the National Perinatal Epidemiology Unit in Oxford. Data were obtained from more than 99.5% of the women recruited.

The trial has produced compelling support for the use of magnesium sulphate. Women were 52% and 67% less likely to suffer recurrent fits after treatment with magnesium sulphate than with, respectively, diazepam or phenytoin. They were 26% and 50% less likely to die after magnesium sulphate than with, respectively, diazepam or phenytoin (although these changes in death rates were not significant). No clear evidence emerged that treating mothers with magnesium sulphate was

either advantageous or disadvantageous to the fetuses, at least in the short term.

Traditional British arguments against the use of magnesium sulphate centre on its perceived toxicity and the difficulties in measuring magnesium concentrations during treatment. The issue of toxicity has been dispelled, at least in comparison with that of diazepam and phenytoin, and magnesium concentrations were not measured routinely (many centres would have found this impossible even if it were possible to determine the therapeutic range).

Complementary information on the value of magnesium sulphate now comes from the United States.³ In a trial of anticonvulsant prophylaxis in 2138 women with hypertension during labour 10 of 1089 treated with phenytoin went on to have eclamptic fits while none of the 1049 women treated with magnesium sulphate did.

If the case for using magnesium sulphate in eclampsia is now clear then the place of anticonvulsant prophylaxis in pre-eclampsia is less certain. If an anticonvulsant is to be given to pre-eclamptic women then magnesium sulphate is now the agent of choice. An estimated 5% of pregnant women in the United States, however, receive anticonvulsant treatment,³ which surely represents gross overtreatment; only 0.5% of treated hypertensive women in the Texas trial actually had convulsions.

Many clinicians now believe that the key initial step in stopping progression from pre-eclampsia to eclampsia is effective treatment of the hypertension. A strong case exists for a placebo controlled trial of magnesium sulphate in pre-eclamptic women. As well as addressing maternal outcomes, such a trial could clarify suggestions that exposure to magnesium sulphate in utero decreases the risk of cerebral palsy in very low birthweight babies.⁴

Broader issues also arise from the collaborative eclampsia trial. Firstly, for those interested in how research influences clinical practice this will be an interesting example to monitor because rarely does a trial produce such unambiguous findings and there are many countries, including Britain, where magnesium sulphate is little used at present. Secondly, clinical trials of treatments for other uncommon but important diseases may be best undertaken in the developing world. The collaborative eclampsia trial was such a success because of the large number of eclamptic women whom doctors in the developing world were able to recruit from their tertiary

referral centres.⁵ To those who might question whether the findings can be generalised one can point out the similar death rates in the magnesium sulphate arms of the trial and in eclamptic women in Britain in 1992.⁶ The network responsible for the trial is well placed to answer other important questions about obstetric care, including the optimal treatment of pre-eclampsia.

JAMES P NEILSON

Professor of obstetrics and gynaecology

University of Liverpool,
Liverpool Women's Hospital,
Liverpool L69 3BX

- 1 Hutton JD, James DK, Stirrat GM, Douglas KA, Redman CWG. Management of severe pre-eclampsia and eclampsia by UK consultants. *Br J Obstet Gynaecol* 1992;99:554-6.
- 2 Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. *Lancet* 1995;345:1455-63.
- 3 Lucas MJ, Leveno KI, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995;333:201-5.
- 4 Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995;95:263-9.
- 5 Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obstet Gynaecol* 1992;99:547-53.
- 6 Douglas KA, Redman CWG. Eclampsia in the United Kingdom. *BMJ* 1994;309:1395-400.

Short termism in the NHS

The national malady needs urgent treatment

In *The State We're In* Will Hutton catalogues the corrosive effects on British industry and services of putting short term gain before long term development.¹ Drawing on evidence from more successful economies, he argues persuasively for cheaper, more stable financing for businesses and strong long term collaboration between companies and their stakeholders (such as subcontractors, financiers, and staff). Although such work is informing the debate on the future of corporate governance in British industry, does it also have lessons for the health service?

Observers of the NHS will recognise many of the problems that Hutton identified in British industry, which is unsurprising as health care systems usually reflect wider social values. These include short termism and crisis intervention, a failure to develop sustained collaborative relationships between participants in the market, and a lack of involvement in decision making by key stakeholders. Examples of these problems in the NHS include the increasing number of managers on fixed term contracts lasting one or two years²; ministerial intervention to prevent the closure of University College Hospital when local purchasers tried to buy cheaper services elsewhere³; the near closure of a district ophthalmology department when a group of general practitioner fundholders tried to move their contracts⁴; and the demise of the old health authority structure, which offered some representation to non-managerial stakeholders in local services.

Although examples exist within the NHS of successful, intersectoral development of strategies for the medium term future, fragmentation is more common. Four years of reorganisation, mergers of purchasing organisations, and general practitioner fundholding are jeopardising the opportunities for collaboration.

Furthermore, the NHS's complex annual contracting cycle is expensive. Le Grand and Bartlett have noted that "the development of quasi-markets invariably results in an increase in the transaction costs of delivering welfare services,"⁵ and this is supported by American evidence.⁶ Surprisingly little formal evaluation has been conducted of these transaction costs, although the Audit Commission's

forthcoming report on general practice fundholding will provide some much needed information.

Two further similarities exist between the NHS and Hutton's analysis of contemporary British business. Firstly, the reformed NHS explicitly rejected the use of widely representative health authority boards involving key stakeholders. Secondly, since the Griffiths report hailed the end of consensus management,⁷ the NHS has rejected any form of the collaborative corporatism that contributes to industrial success elsewhere. It is worth considering both these points in more detail.

The NHS reforms introduced an Anglo-American model of industrial corporate governance, in which purchasers and trust boards are limited to executive officers and selected non-executive directors. Such boards fail to represent the interests of key stakeholders and arguably perpetuate the "them and us" mentality that has dominated Britain's postwar industrial decline and militates so strongly against collaboration. In contrast, in the much more successful economies in continental Europe and the Far East there is strong involvement by key stakeholders, such as banks, major shareholders, and workers who are often represented at board level. Stakeholders have a far stronger commitment to the long term success of organisations in which they have vested interests.

But it is not enough to say that key interests should be represented. Health authorities before the reforms showed how easily lay representatives could be left unsupported, and rendered effectively powerless as clinical and managerial priorities dominated agendas. To be effective, the inclusion of lay members on health authority and trust boards of the 1990s would have to be accompanied by a major cultural change in which their contributions were valued and their presence was not mere tokenism.

The style of consensus management seen in the NHS before 1984 had obvious shortcomings, dominated as it was by clinical professional interests and often with weak managerial input. Although the general management hierarchies that followed drove through efficiency programmes and helped to implement the increasing tide of central directives, they often failed to tackle the tense relationships between clinicians and