control. The indicators of prostaglandin metabolism are related to the HbA_{1c} concentrations—namely, to the different stages of diabetic control. It is reasonable to suppose that the uncontrolled diabetic state and the shift in the balance of two antagonistic prostaglandins towards pathogenic direction might have a role in diabetic microangiopathy. Our observations support the authors' opinion.

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2 Klein RK, Klein BEK, Moss SE, Davis MD, DeMets DL. Glycosylated haemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 1988;260:2864-71.

Treatment of hypertension in older adults

SIR,—The recent report on the principal results of the Medical Research Council's trial of treatment of hypertension in older adults¹ has led to a suggestion that hydrophilic and lipophilic β blockers differ in terms of their cardioprotective effects.² Such a suggestion deserves careful consideration in view of its widespread implications, if true.

Martin J Kendall invokes the literature on the long term use of β blockers in secondary prevention as evidence for the hypothesis.² This is indeed the most extensive and well documented source of controlled (and relevant) data. The original overview of the trials included over 20 000 patients treated long term³; the updated analysis added two more trials,⁴ and to these should now be added the APSI trial,⁵ making a total of over 24 000 patients.

The hydrophilicity of the β blockers in these studies can be quantified by their distribution coefficients between octanol and aqueous buffer.^{6,7} Dividing the range of values of the distribution coefficients into equal and logical intervals on a logarithmic scale separated the β blockers into four groups with similar degrees of hydrophilicity (see table) and had the added statistical advantage of dividing the clinical trials into four roughly equal sized groups in terms of total patient numbers. The apparent mortality benefit was calculated separately for each group of β blockers over the relevant subset of trials using standard methodology.³ The table shows the results.

No relation was immediately evident nor was it disclosed by more careful statistical testing either with a general test for heterogeneity³ ($\chi^2=0.64$,

$p=0.89$) or with a more specific test for trend in the odds ratio ($\chi^2=0.45$, $p=0.5$). For each separate category of β blockers there was a significant mortality benefit of a size consistent with the overall 22% reduction in mortality. More detailed analysis based on individual β blockers led to the same conclusion.

Great care needs to be taken when assessing relations between the properties of individual β blockers and their benefits. Even those thrown up by overviews themselves can be illusory. The original overview suggested that intrinsic sympathomimetic activity was an undesirable property based on mortality results³; subsequently analysis of non-fatal reinfarction and updating of the mortality data led one of the same authors to dismiss this finding.⁸

In terms of secondary prevention of mortality, hydrophilic and lipophilic β blockers seem to be equally cardioprotective.

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1 Medical Research Council Working Party. MRC trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;304:405-12. (15 February.)
2 Kendall MJ. Treatment of hypertension in older adults. *BMJ* 1992;304:639. (7 March.)
3 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Progress in Cardiovascular Diseases* 1985;27:335-71.
4 ISIS-1 Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986;iii:57-66.
5 Boissel J-P, Leizorovicz A, Picolet H, Peyrieux J-C. Secondary prevention after high-risk acute myocardial infarction with low-dose acebutolol. *Am J Cardiol* 1990;66:251-60.
6 Cruickshank JM, Prichard BNC. *Beta-blockers in clinical practice*. Edinburgh: Churchill Livingstone, 1987:177.
7 Bax NDS, Lennard MS, Al-Asady S, Deacon CS, Tucker GT, Woods HF. Inhibition of drug metabolism by β -adrenoceptor antagonists. *Drugs* 1983;25(suppl 2):121-6.
8 Peto R. Why do we need systematic overviews of randomised trials? *Statistics in Medicine* 1987;6:233-40.

Storing vaccines at the correct temperature

SIR,—Yogini Thakker and Sheila Woods found that vaccines stored in community clinics and in general practice were exposed to temperatures that might reduce their potency.¹ They concluded that adequate equipment and training for staff in maintaining the cold chain were essential for the success of an immunisation programme.

In Harrow I received a telephone call from a health visitor who was worried about the temperature of a particular general practitioner's refrigerator. Discussion with staff working in both general practice and community clinics showed that this was a fairly widespread problem.

I tackled the issue by producing a set of guidelines combined with a temperature chart to record daily maximum and minimum temperatures. The chart was designed to be kept on or near each refrigerator in which vaccines were stored. Each clinic or surgery would designate a member of staff to be responsible for the

refrigerator and for record keeping. The guidelines on the chart give clear advice on how to care for the vaccines and refrigerator and what to do if something goes wrong or if advice is needed.

I approached Brent and Harrow Family Health Services Authority through its drug and therapeutics committee, and the idea was received enthusiastically. The chart has now been produced as an A3 size plastic laminated poster that can be wiped clean. It has been distributed, with a special pen, to all general practice surgeries and clinics in the area covered by Brent and Harrow Family Health Services Authority. It has been well received and has given rise to several inquiries about storing vaccines. I hope that it will make community staff more aware of the need to store vaccines correctly and will help to ensure that all vaccines retain their full potency until they are used.

I thank the members of the drug and therapeutics committee of Brent and Harrow Family Health Services Authority for their help and enthusiasm in funding the production of, and distributing, this chart.

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1 Thakker Y, Woods S. Storage of vaccines in the community; weak link in the cold chain? *BMJ* 1992;304:756-8. (21 March.)

Myeloma and benign intracranial hypertension

SIR,—The report of H Wasan and colleagues on myeloma and benign intracranial hypertension provides insufficient data to justify their conclusions.¹ On the basis of the clinical history supplied, the diagnosis of benign intracranial hypertension in at least two of their cases is doubtful; few neurologists would accept dysphagia, dysarthria, psychomotor retardation, nystagmus, and unsteady gait as features compatible with this disease. No details of cerebrospinal fluid analysis are given, and there are no comments on computed tomographic appearances.

The authors have neglected to exclude the important possibility of dural sinus thrombosis, to which patients with myeloproliferative disorders are known to be susceptible. No mention is made in the report of investigations to elucidate such a diagnosis (contrast enhanced computed tomography, magnetic resonance imaging, or arteriography).

Finally, the authors' conclusion that all patients presenting with benign intracranial hypertension should be subjected to a myeloma screen, including bone marrow aspiration and trephine, is surprising. Most patients with benign intracranial hypertension are female; male patients with apparent benign intracranial hypertension should always be suspected of harbouring alternative pathology, particularly sinus thrombosis or diffuse meningeal tumour. Benign intracranial hypertension should therefore be a diagnosis of exclusion, especially in men, and bone marrow aspiration in typical female patients is not justified.

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AUTHOR'S REPLY,—We agree that dysphagia, dysarthria, and psychomotor retardation are atypical symptoms of benign intracranial hypertension. We do not attempt to attribute all symptoms to benign intracranial hypertension but have factually stated

Hydrophilicity of β blockers and its effect on long term mortality benefits after myocardial infarction

Distribution coefficient (K_p) in octanol/water at pH 7.4 (range)	β blockers	No of patients	Odds ratio	(95% confidence interval)
10.0-100.0	{ Propranolol Alprenolol }	6458	0.74	(0.63 to 0.88)
1.0-10.0	{ Timolol Oxprenolol }	6314	0.77	(0.64 to 0.92)
0.1-1.0	{ Pindolol Acebutolol Metoprolol }	6646	0.76	(0.63 to 0.91)
0.01-0.1	{ Practolol Atenolol Sotalol }	5137	0.82	(0.68 to 1.00)

the presenting features. All three patients were assessed and investigated by a neurologist, and no other diagnoses were obtained. Nystagmus, unsteady gait, and cranial palsies other than cranial nerve VI have, however, rarely been described in association.¹ The close temporal relation of the symptoms (including atypical symptoms and signs and lumbar puncture opening pressures) and successful treatment of the patients' myeloma strongly suggests an association but of course is not conclusive. Other mechanisms may be at play—the aetiology of mononeuritis multiplex in myeloma remains obscure.

Total protein content, sugar, and cytology of cerebrospinal fluid were all entirely within normal limits in all three cases. The computed tomography appearances were also normal (ventricles; no mass effect) apart from the empty sella as shown in our table.

We agree that dural sinus thrombosis has to be excluded in patients presenting with benign intracranial hypertension. Our radiologists were specifically asked to exclude the possibility on the basis of contrast enhanced computed tomography scans. Magnetic resonance imaging and arteriography would be more sensitive methods but we did not feel they were justified as the presenting features were chronic in onset, the protein concentration in cerebrospinal fluid was not raised, and there were no red cells to suggest venous infarction. Most importantly, however, it would not have altered our management, anticoagulation being a contentious issue. Hypercoagulation symptoms are rare in myeloma, which is not a myeloproliferative disorder; indeed, a bleeding tendency is common through interference at many levels of platelet and clotting function.²

From published studies, we are not clear of the incidence of dural sinus thrombosis in benign intracranial hypertension. We suspect that most neurologists do not regularly exclude this condition in patients with suspected benign intracranial hypertension unless the clinical presentation is acute; mortality from dural sinus thrombosis is even higher in patients with malignant disease.

We maintain that myeloma should be included in the differential diagnosis of causes of benign intracranial hypertension. Most other associations are also rare,³ and the clinical course of two of our three patients obviated the need for further treatment of their benign intracranial hypertension.

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- 2 Penny R, Castaldi PA, Whited HM. Inflammation and haemostasis in paraproteinaemias. *Br J Haematol* 1971;20:35-44.
- 3 Digre KB, Corbett JJ. Pseudotumour cerebri in men. *Arch Neurol* 1988;45:866-77.

Missed neuroleptic malignant syndrome

SIR,—We agree with the statement by Deborah S Renwick and colleagues that greater awareness of neuroleptic malignant syndrome among physicians dealing with patients taking neuroleptic drugs may improve outcome and reduce mortality.¹

After we came to realise our own missed cases we devised a protocol to raise awareness of the syndrome and its treatment among medical and nursing staff. With the backing of local drug and therapeutic committees this protocol was circulated widely within our own and neighbouring hospitals, and it has been incorporated into ward nursing procedures and medical staff induction programmes. Vigilance for all features of the disorder is increased, and one of the cardinal changes in practice is simply to monitor the daily

temperature of patients who are receiving energetic treatment with neuroleptics. Any pyrexia in such a patient is attributed to neuroleptic malignant syndrome until proved otherwise. Accordingly, we have been able to make early diagnosis and intervention in recent cases of the syndrome. We strongly recommend the use of such a protocol and would be pleased to supply copies to those interested.

We are grateful to Dr P Clarke for assistance with preparation of the protocol.

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- 1 Renwick DS, Chandraker A, Bannister P. Missed neuroleptic malignant syndrome. *BMJ* 1992;304:831-2. (28 March.)

SIR,—In their lesson of the week on missed neuroleptic malignant syndrome Deborah S Renwick and colleagues recommend that "serum creatine kinase should be measured early in patients with any feverish illness who are taking neuroleptic drugs."¹ The implication seems to be that creatine kinase is of diagnostic importance in this condition.

It is true that Levenson uses creatine kinase as one of his three main diagnostic criteria,² but the creatine kinase level is simply a non-specific indicator of muscular catabolism and, as such, can be raised in many conditions that may be included in the differential diagnosis of the neuroleptic malignant syndrome. These include damage to skeletal muscle from any cause (for example, intramuscular injections), malignant hyperpyrexia, infectious diseases affecting muscle, coma, convulsions, and any cause of muscular rigidity.³ As an illustration of this, we recently reported catatonia with greatly increased creatine kinase levels in a patient who had not taken neuroleptic drugs at any time during the illness.⁴

The creatine kinase level should be used only as an indicator of (non-specific) muscle damage. It is by no means pathognomonic of the neuroleptic malignant syndrome.

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- 1 Renwick DS, Chandraker A, Bannister P. Missed neuroleptic malignant syndrome. *BMJ* 1992;304:831-2. (28 March.)
- 2 Levenson JL. Neuroleptic malignant syndrome. *Am J Psychiatry* 1985;142:1137-45.
- 3 Ford RD. *Diagnostic tests handbook*. Springhouse, Pennsylvania: Springhouse, 1987.
- 4 Craddock B, Craddock N, Milner G. CPK in NMS. *Br J Psychiatry* 1991;158:130.

SIR,—The lesson of the week on missed neuroleptic malignant syndrome presents an important, but incomplete, message.¹ The authors describe a patient with a feverish illness in whom the syndrome was diagnosed late, with a fatal outcome. When the diagnosis was made treatment with dantrolene was unsuccessful. But other treatments for the syndrome were apparently not tried. Some authors suggest that intravenous benzodiazepines, particularly lorazepam, may be helpful; others note that electroconvulsive therapy is useful. The idea that electroconvulsive therapy may help is not well known, the information being restricted to specialist journals as most cases of the neuroleptic malignant syndrome are reported in psychotic patients treated with neuroleptic drugs.²

A review of experience with various treatments in the neuroleptic malignant syndrome shows that the historic mortality associated with treatment with a specific drug (dantrolene or bromocriptine)

is 10% and that that associated with electroconvulsive therapy is similar. But the authors note that the deaths with electroconvulsive therapy were associated with the continued use of neuroleptic drugs during the course of treatment. In cases in which neuroleptic drugs were stopped the results were salutary. Electroconvulsive therapy, as presently administered under anaesthesia and with systemic monitoring, is remarkably safe. Colleagues and I have reported our successful experience with a severely ill, cachectic patient with a similar syndrome of fever, motor, and consciousness disorder.³

The pathophysiology of the neuroleptic malignant syndrome is considered to be a failure of dopaminergic transmission, hence the recommended use of bromocriptine. Electroconvulsive therapy increases brain dopaminergic activity, as reflected in numerous reports that it reduces symptoms of Parkinson's disease.^{4,5} Thus electroconvulsive therapy should be considered in cases of the neuroleptic malignant syndrome.

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- 2 Davis JM, Janicak PG, Sakkas P, Gilmore C, Wang Z. Electroconvulsive therapy in the treatment of the neuroleptic malignant syndrome. *Convulsive Therapy* 1991;7:111-20.
- 3 Fricchione GL, Kaufman LD, Gruber BL, Fink M. Electroconvulsive therapy and cyclophosphamide in combination for severe neuropsychiatric lupus with catatonia. *Am J Med* 1990;88:442-3.
- 4 Anderson K, Baldini J, Gottfries CG, Granerus AK, Modigh K, Svennerholm L, et al. A double-blind evaluation of electroconvulsive therapy in Parkinson's disease with "on-off" phenomena. *Acta Neurol Scand* 1987;76:191-9.
- 5 Fochtmann L. A mechanism for the efficacy of ECT in Parkinson's disease. *Convulsive Therapy* 1988;4:321-7.

AUTHORS' REPLY,—Max Fink refers to a patient with a syndrome similar to the neuroleptic malignant syndrome who was successfully treated with electroconvulsive therapy. The scientific literature contains other sporadic case reports of the use of electroconvulsive therapy in the neuroleptic malignant syndrome, but there have been no clinical trials to compare electroconvulsive therapy with the more conventional drug treatments for the syndrome (dantrolene and bromocriptine). Consequently the current role of electroconvulsive therapy in the syndrome is that of a second line agent, for use when conventional treatment has failed.

In the case we described the correct diagnosis of the neuroleptic malignant syndrome was obscured by the presence of a proved urinary tract infection, so that treatment with dantrolene was started only when the patient was already extremely unwell. The considerable risks of electroconvulsive therapy in patients critically ill with the syndrome include the induction of malignant hyperthermia by anaesthetic agents,¹ hyperkalaemia,² and potentially fatal cardiac arrhythmias.³ In this case we considered that these risks outweighed the possible potential benefits of the treatment.

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- 2 George AL, Wood CA. Succinylcholine induced hyperkalemia complicating the neuroleptic malignant syndrome. *Ann Intern Med* 1987;106:172.
- 3 Addonizio G, Suzman VL. ECT as alternative treatment for patients with symptoms of the neuroleptic malignant syndrome. *J Clin Psychiatry* 1986;47:42-3.