contents and then swallowed as a glass of water is drunk.[4] If swallowing is impaired, nasogastric administration of the capsule's contents is indeed an alternative, albeit less accurate.

Rather than sublingual nifedipine being prescribed, it would be clearer and more accurate to prescribe nifedipine for oral administration, with additional instructions that the patient should bite the capsule before swallowing it while drinking a glass of water.

COLIN R MACFARLANE
Drug information pharmacist

Ashford Hospital,
Ashford,
Middlesex TW15 3AA

1 O'Connell JE, Gray CS. Treating hypertension after stroke. *BMJ* 1994;308:1523-4. (11 June.)
2 Hypertensive emergencies [editorial]. *Lancet* 1991;338:220-1.
3 Angeli P, Chiesa M, Caregaro L, Merkel C, Sacerdoti D, Rondana M, *et al.* Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies. *Arch Intern Med* 1991;151:678-82.
4 Saunders A. Chewing nifedipine. *Pharm J* 1992;248:176.

Reye's syndrome

EDITOR,—Maria Casteels-Van Daele and Ephrem Eggermont propose that Reye's syndrome is associated not with aspirin but with antiemetics given for the profuse vomiting which characterises this disorder and that antiemetic toxicity is often misclassified as Reye's syndrome.[1] As evidence they cite a paper describing two patients with classic extrapyramidal symptoms of antiemetic toxicity. Since these have been known for decades, it is unlikely that "better recognition" of these side effects could explain the decline of reported Reye's syndrome in the United States and the United Kingdom.

The authors criticise the North American case-control studies for recording only the drugs given before the onset of vomiting. They question whether this reflects the onset of Reye's syndrome itself. The onset is indeed hard to time precisely, but there is histological and ultrastructural evidence that Reye's syndrome is well established shortly after the onset of vomiting, before consciousness becomes impaired.[2]

Ironically, the early American case-control studies were accused of temporal precedence bias caused by analysing medications given both before and after the onset of vomiting.[3] In later studies, including one funded by the aspirin industry, a detailed definition of day of onset was used; it included both vomiting and neurological symptoms. Temporal precedence bias was avoided by analysing only onset exposures before onset.[4] No further criticisms of the timing of exposure to drugs have been published.

Casteels-Van Daele and Eggermont state that only drugs given before vomiting were registered in the second year of the Ohio study. Nevertheless data on phenothiazine ingestion throughout the illness were published. Although there was a significant excess among cases, only 19% had received an antiemetic compared with 100% exposed to aspirin. In the British study the corresponding figures were 14% and 59%. Thus if antiemetics do have a role in the pathogenesis of Reye's syndrome it must be substantially smaller than that of aspirin.

The authors further argue that the subjects in the case-control studies had a heterogeneity of conditions, including inherited metabolic disorders. Children with those inherited metabolic disorders that cause a Reye-like illness usually present in the first two years of life with an encephalopathy precipitated by a variety of viral infections. By contrast, Reye's syndrome in the United States in the 1970s and 80s occurred epidemically in association with influenza and endemically in association with chickenpox; patients had a median age of 8-9 years.

The problem of heterogeneity was addressed in the British study, which used a clinicopathological scoring system. Patients who scored highly satisfied all the criteria of the case definition *and* resembled clinically those recruited to the American studies. A significant correlation was found between increasing score and aspirin exposure, suggesting that there was indeed a "subset" effect.

Therefore, though Casteels-Van Daele and Eggermont correctly state that Reye's syndrome is a heterogeneous condition, there is evidence for the existence of a subset which is clinically and epidemiologically distinct and nearly always associated with exposure to aspirin. Not only have the numbers of reported cases in the United States and the British Isles declined since the aspirin warnings, but also the epidemiological and clinical pattern has changed. The median age has fallen dramatically; furthermore, the virologically confirmed cases associated with influenza and varicella have selectively declined in the British series since 1986.[5]

Better diagnosis of inherited metabolic disorders has probably also contributed to the fall in the number of cases of Reye's syndrome reported, although there is still a need for better recognition of those disorders that cause Reye-like illnesses. There is no evidence for an aetiological role for antiemetics.

SUSAN M HALL
Consultant epidemiologist

Children's Hospital,
Sheffield S10 2TH

1 Casteels-Van Daele M, Eggermont E. Reye's syndrome. *BMJ* 1994;308:919-20. (2 April.)
2 Lichtenstein PK, Heubi JE, Daugherty CC, Farrell MK, Sokol RJ, Rothbaum RJ *et al.* Grade I Reye's syndrome: a frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. *N Engl J Med* 1983;309:133-9.
3 Soller RW, Stander H. Association between salicylates and Reye's syndrome. *JAMA* 1983;249:883-4.
4 Forsyth BW, Horwitz RA, Acampora D, Shapiro ED, Viscoli CM, Feinstein AR, *et al.* New epidemiologic evidence confirming that bias does not explain the aspirin/Reye's syndrome association. *JAMA* 1989;261:2517-24.
5 Newton L, Hall SM. Reye's syndrome in the British Isles: report for 1990/91 and the first decade of surveillance. *Communicable Disease Report* 1993;3:R11-6.

Atherosclerotic disease and cognitive decline

EDITOR,—Monique M B Breteler and colleagues describe an association between the clinical manifestations of atherosclerotic disease and cognitive decline in elderly people. They conclude that atherosclerotic disease may account for considerable cognitive impairment and suggest it is time to study whether population wide atherosclerotic risk factor intervention can prevent such cognitive decline.[1]

The assumption made is that the potentially modifiable atherosclerotic process is the major determinant of the observed cognitive impairment. This may be so for "multi-infarct" dementia, but in many patients cognitive impairment will be due to Alzheimer's disease. As with atherosclerosis, this condition probably evolves from a complex interaction of genetic and environmental factors but is unlikely to respond to conventional risk factor modification. However, one common pathogenic mechanism may link these apparently distinct entities.

The e4 allele of apolipoprotein E has been independently linked with both atherosclerosis and Alzheimer's disease. Carriage of the e4 allele is associated with increased risk of coronary heart disease[2] and peripheral atherosclerosis,[3] clinical features used in the study as surrogate markers of the extent of cerebrovascular disease. The influence of apolipoprotein E4 is likely to be mediated through effects on plasma lipids as this isoform contributes to higher plasma low density lipoprotein concentrations than the wild-type E3, although apolipoprotein E may also regulate smooth muscle proliferation and differentiation.

Apolipoprotein E is also involved in brain lipid metabolism, and regeneration after injury to the peripheral and central nervous system. The e4 allele frequency in patients with Alzheimer's disease is reported as 0·40-0·50 compared with around 0·12 in control populations. In addition, apolipoprotein E accumulates in the amyloid plaques and neurofibrillary tangles found in this condition, with apolipoprotein E4 showing particular avidity.[4,5]

Thus the apolipoprotein E gene and its protein product may mediate two major mechanisms contributing to cognitive decline in the elderly. While the vascular component potentially related to apolipoprotein E4 may be influenced by targeting conventional risk factors for vascular disease as proposed by the authors, this strategy is unlikely to yield major preservation in cognitive function since the non-atherogenic expression of apolipoprotein E4 in this condition is currently not modifiable. However, intervention at the genetic and molecular level is worth further investigation as this may exclude both mechanisms and confer a dual benefit in apolipoprotein E related cognitive attrition.

M N PAYNE
Cardiology research fellow
A F JONES
Consultant chemical pathologist
R G MURRAY
Consultant cardiologist
J M BEATTIE
Consultant cardiologist

Birmingham Heartlands Hospital,
Birmingham B9 5SS

1 Breteler MMB, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people; the Rotterdam study. *BMJ* 1994;308:1604-8. (18 June.)
2 Cumming AM, Robertson F. Polymorphism at the apo E locus in relation to risk of coronary disease. *Clin Genet* 1984;25:310-3.
3 Hixson JE, P-Day Research Group. Apolipoprotein E polymorphisms affect atherosclerosis in young males. *Arteriosclerosis Thromb* 1991;11:1237-44.
4 Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH. Association of apolipoprotein E alle e4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467-72.
5 Poirer J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthiers S. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet* 1993;342:697-9.

Autografts of peripheral blood stem cells

EDITOR,—Autografts of peripheral blood stem cells offer additional advantages to those outlined by Tessa L Holyoake and Ian M Franklin.[1] At the moment, peripheral blood stem cells need to be harvested in a large oncology centre with the proper equipment and skill. However, the mobilisation before the harvesting, the intensive chemotherapy followed by reinfusion, and the supportive care may be provided locally in a district general hospital. Most such hospitals have consultant haematologists and nurses with considerable skill in looking after patients with severe pancytopenia for short periods; this experience comes from their management of patients with acute leukaemia.

The patient may need to visit the main oncology centre only as a day case or for an overnight stay. This type of shared care between a major centre and the local hospital offers several advantages. Patients should have most of their treatment locally, and this should be attractive to both patients and their relatives. Most purchasing authorities prefer treatment to be given locally. The cost of inpatient care in a district general hospital should be considerably less than that in a