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.

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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 affected 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 epidemically 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.

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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 disease² 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.

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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

major oncology centre. If the management is directed by the major centre there should be an adequate check on standards and back up in the event of complications.

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Outcomes research in clinical practice

Descriptive studies are unhelpful

EDITOR,—In the issue that included an editorial discussing the importance of outcome research in clinical practice,¹ the paper by D J Houghton and colleagues concluded that "general practitioners should no longer request sinus radiography" without measuring any outcomes at all.²

This was a descriptive study in which local general practitioners' knowledge of indications for sinus radiography was assessed. The authors extrapolated the fact that half the population have minor changes on such radiographs and concluded that the indications given were worthless. The requests perceived as due to patient pressure were dismissed on the grounds that general practitioners should invoke the college guidelines. Studies have shown that using the guidelines reduces the number of referrals,³ but in an age of patient's rights it is difficult to dissuade a demanding patient completely.

A more appropriate method would have been to examine the actual requests received by a radiography department and measure the outcomes of these in terms of radiological findings, clinical outcomes, and patient satisfaction. Apart from principals answering a questionnaire, the general practice input is non-existent and consequently is unlikely to change clinical practice.⁴ As it is, the authors should remember that a descriptive study has the weakest methodological rigour and is certainly not the basis for such sweeping conclusions.

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Patients' views ignored

EDITOR,—Andrew Haines and Roger Jones give a welcome reminder of the importance of implementing findings of research into medical practice.¹ If it is true, as has been suggested,² that no more than 15% of all practice within the NHS has been properly evaluated, there is a long way to go before we can claim with any confidence that the health service is demonstrably cost effective.

However, there is a serious bias in the article. In all the examples given and strategies suggested it is implicit that the experts decide what is effective treatment and that health professionals are then suitably persuaded to change practice (sometimes by the indirect route of informing the public of research results). What is missing is the involve-

ment of patients and public in assessing the outcomes of care in the first place. The conference on outcomes research in clinical practice noted that the list of possible groups concerned with outcomes failed to mention patients at all.³ The bias against including patients' experience seems pervasive.

There is one area of developing practice where this bias is apparent and particularly topical: the use of counselling in general practice. A review last year stated that "many attempts to evaluate its effectiveness have shown little or no benefit,"⁴ and this is the tone of many such reviews in the medical press. Such a conclusion is seriously at odds with the positive experience of patients and doctors in practices where counselling is provided.

In fact there is good evidence of benefits from a systematic meta-analysis of all British studies of counselling in general practice that fit precise selection criteria.⁵ It is possible that the review articles are seriously biased in not taking into account subjective experience and in considering only benefits at longer term follow up at one or two years. The value of counselling, which may be rapidly apparent to patients and general practitioners, could be reduced for many patients with self limiting emotional problems. Neither general practitioners nor patients are likely to accept that weakening effects over time are a justification for declaring such treatments as ineffective.

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Use of benzodiazepines

EDITOR,—Neil Wright and colleagues report a 0.5% point prevalence in a single general practice for prescribing of benzodiazepine anxiolytics taken during the day.¹ Furthermore, they found that almost half the patients in their study wished to continue taking benzodiazepines.

However, the level of prescribing of benzodiazepines may reflect the policies of only the general practitioners concerned. We are currently carrying out a study of benzodiazepine prescribing in 16 Leicestershire practices, total population 117096, and have found wide variation in the prevalence of long term benzodiazepine users between practices. The range for users of anxiolytic benzodiazepines was 0.3% to 1.9%, and for users of hypnotic or anxiolytic drugs was 0.6% to 3.9% of the practice populations, indicating that the practice in the study reported by Wright and colleagues had a relatively low proportion of long term users.

Patients in our study were classed as chronic benzodiazepine users if they had taken the drug for longer than one month, to accord with the Committee on the Safety of Medicines' guidelines, which state that benzodiazepines should be prescribed for only two to four weeks.² Although this cut off point is earlier than that of Wright and colleagues, this cannot account for the difference in prevalence levels as 96% of the patients in our study had been taking the drug for more than a year.

Our study has identified a total of 2178 long term benzodiazepine users (hypnotic or anxiolytic). Even if only half of these want to stop taking their

medication, as indicated by Wright and colleagues, we have found just over 1000 patients from 16 practices who may benefit from being offered assistance with withdrawal. Therefore it would be unwise to imply that withdrawal programmes are not required.

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Health needs of elderly people

EDITOR,—In her editorial on priorities in geriatric research, Christine K Casel states that the world's elderly population is increasing dramatically and most visibly in "developed" countries.¹ This reflects our society's myopia with respect to the health of those in so called "developing" countries, where the majority of the world's elderly live.

The world population aged over 55 years increases by one million people per month. Eighty per cent of growth is in developing countries where, by the year 2020, the elderly population is likely to exceed one billion. Over the next 30 years the proportion of the world's elderly population living in developing countries is projected to increase from 58% to 72%.² Current public health policies in many Third World countries, supported by international agencies, focus on maternal health, contraception, and infant health. The result will be the aging of society in Africa, Asia, and South America, and chronic, non-communicable diseases in these populations will become a prime health concern.

Is this not evidence enough to support the urgent need for research into the health care needs of elderly people worldwide? We must be less parochial if we wish to address the genuine needs of the world's elderly population. The effects of demographic changes on patterns of health demand that we formulate plans to deal with the associated medical problems in rich and poor countries alike.

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Management of mild dyskaryosis

EDITOR,—Flannely and colleagues,¹ Soutter and Fletcher,² and Hammond³ all recommend immediate colposcopic referral for mild dyskaryosis. This policy would have significant implications for the colposcopy workload, and although immediate referral would reduce the volume of pre-colposcopic surveillance, colposcopy itself often leads to frequent follow up smears. Selective referral according to smoking habit is an increasing possibility and might have public health benefit. In any event, continuing education about cervical