attendance of those invited was poor. The result—a reduction of population mortality from breast cancer of 29% in women aged 55 plus—despite the poor attendance is actually most impressive for this seven year (relatively early) analysis of results. It is in line with those of the other randomised trials of screening in Scandinavia and New York.

R W BLAMEY

City Hospital,
Nottingham NG5 1PB

1 Weston S. Breast screening in Scandinavia. *Br Med J* 1990; **300**:352. (10 February.)

**We apologise for this editorial error.—ED, *BMJ*

HIV infection and tuberculosis

SIR,—In their editorial Mr John M Watson and Mr O Noel Gill discussed the increasing prevalence of tuberculosis in patients infected with human immunodeficiency virus type I (HIV-I).[1] They concluded that the increasing incidence of tuberculosis is not seen only within the United States[2] but is also emerging in Great Britain. In the United States tuberculosis is most prevalent in intravenous drug users infected with HIV,[3] and thus it will be even more important in European countries such as Spain, Italy, and Austria, where an unproportionately high percentage of patients with AIDS are drug users. For example, one third of patients with AIDS in Barcelona have tuberculosis.[4]

We would like to add our experience in the Austrian Tyrol of tuberculosis in people with HIV- I infection. In 1988 in Innsbruck 12 patients were diagnosed as having AIDS. Extrapulmonary tuberculosis was the indicator disease in four of them.[5] Diagnosis was proved by culture—for example, from urine, stool, or pleural samples. The concentration of urinary neopterin—a marker for activated macrophages[6]—was greatly increased in all of the patients. Interestingly, the four with tuberculosis had far higher urinary neopterin concentrations (range 1189-6671 μmol neopterin/mol creatinine) than the eight other patients (589-1663 μmol neopterin/mol creatinine; $p=0{\cdot}03$, Wilcoxon rank test), three of whom had *Pneumocystis carinii* pneumonia, two had cytomegalovirus retinitis, two had AIDS dementia complex, and one had candida oesophagitis. Concentrations of β_2-microglobulin and CD4+ T cell counts did not differ between the two groups of patients. During antituberculous treatment neopterin concentrations immediately started to decline.

The early diagnosis of tuberculosis in patients who are positive for HIV antibody is well known to pose problems. As extremely high neopterin concentrations were seen in our four patients with tuberculosis it is likely that neopterin testing could help as an early indicator of tuberculosis in such patients. Tuberculosis cannot easily be distinguished from other diseases that are associated with similar constitutional symptoms. Skin testing is not useful in people infected with HIV who received BCG vaccination in their childhood. Sputum culture can be too time consuming for an early decision. In addition, determination of neopterin concentration may prove helpful to monitor the response to and to optimise the duration and dose of tuberculostatic treatment.

ROBERT ZANGERLE
PETER FRITSCH
DIETMAR FUCHS
HELMUT WACHTER

Department of Dermatology and Venereology and Institute of Medical Chemistry and Biochemistry,
University of Innsbruck,
A-6020 Innsbruck, Austria

1 Watson JM, Gill ON. HIV infection and tuberculosis. *Br Med J* 1990;**300**:63-5. (13 January.)
2 Handwerger S, Mildvan D, Senie R, McKinley FW. Tuberculosis and the acquired immunodeficiency syndrome at a New York City Hospital: 1978-1985. *Chest* 1987;**91**:176-80.
3 Selwyn PA, Hartel D, Lewis VA, *et al*. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* 1989;**320**: 545-50.
4 Batalla J, Gatell JM, Cayla JA, Plasencia A, Jansa JM, Parellada N. Predictors of the survival of AIDS cases in Barcelona, Spain. *AIDS* 1989;**3**:361-6.
5 Fuchs D, Hausen A, Reibnegger G, Werner ER, Dierich MP, Wachter H. Neopterin as a marker for activated cell mediated immunity: application in HIV infection. *Immunology Today* 1988;**9**:150-5.
6 Zangerle R, Fritsch P, Fuchs D, Wachter H. Is neopterin helpful in distinguishing between different disease patterns in AIDS? *Pteridines* (in press).

Assessment of care of children with sickle cell disease

SIR,—Dr R Milne assessed the quality of care of children with sickle cell disease discovered on neonatal screening.[1] In addition we wish to emphasise that carers should be alerted to observe affected children for signs that need prompt action—for example, increasing spleen size—and that such children have open access to a paediatric ward.

We have already commented on the experience in Reading,[2] where several factors have further improved the service, prompted by the realisation in October 1988 that a child with sickle cell anaemia had been born to a couple who were not aware of the implications of their risk state (A Burke, unpublished work). Of the 6000 children born in Reading a year, only 600 are born to parents from ethnic minorities, so we cannot yet justify screening all neonates.

The haematology laboratory recognised that it could diagnose and record carriers of haemoglobin disorders and issue cards with information. Couples at risk could be identified (as already undertaken for those at risk of rhesus disease); counselling and education would then take place and neonatal screening automatically follow, although existing routes whereby carriers are identified would continue to be encouraged. The medical laboratory scientific officers took a valuable initiative in collating the required computer data and organising a local haemoglobinopathy card, as a quality product, to encourage community participation.[3] The local support group, Reading OSCAR (Organisation for Sickle Cell Anaemia Research), and the laboratory joined in seeing that people could attend haemoglobinopathy counselling courses like that run at the Central Middlesex Hospital.[4] To date, two scientific officers, a hospital social worker, and three health professionals from the support group have acquired skills to help inform hospital and community members.

Most importantly the district medical officer and the district health authority supported our plea to make education the priority. They have funded a haemoglobinopathy counsellor, who links closely with the laboratory and obstetric department to distribute cards and information. She is responsible for seeing that a neonate identified as having a sickling disorder attends the joint haematology and paediatric clinic and that the family gets the support it needs. She offers continuing education for parents, while ensuring that the general practitioner and others concerned—for example, school teachers—are appropriately informed.

We believe that participation in the service and education will result in optimal management. We are watching closely the effect and acceptability of this programme in the community and hope to report more fully in the future.

C BARTON
M MICHAEL
J RICHMOND

Haematology Laboratory,
Royal Berkshire Hospital,
Reading, Berkshire RG1 5AN

1 Milne RIG. Assessment of care of children with sickle cell disease: implications for neonatal screening programmes. *Br Med J* 1990;**300**:371-4. (10 February.)
2 Barton C, Watson A. Neonatal screening for haemoglobinopathies. *Br Med J* 1988;**297**:200.
3 Richmond J. Haemoglobin card scheme. *Gazette of the Institute of Medical Laboratory Sciences* 1989 September:518-9.
4 Anionwu E. Running a sickle cell centre: community counselling. In: Cruickshank JK, Beavers DG, eds. *Ethnic factors in health and disease*. Bristol: Wright, 1989.

Haemolytic disease of the newborn

SIR,—We welcome Dr L A Derrick Tovey's informative article on haemolytic disease of the newborn, which reflects his long interest in the topic.[1] We have to assume, however, that he is expressing personal views when he says that it is recommended that prophylactic anti-D immunoglobulin should be given at 28 and 34 weeks' gestation and again when he says that it is recommended that antenatal prophylaxis is given at least in the first pregnancy. There is, in fact, no recommendation relating to the use of anti-D immunoglobulin for prenatal prophylaxis in the United Kingdom, either from the Department of Health, the Scottish Home and Health Department, or the Royal College of Obstetricians and Gynaecologists.

Dr Tovey's data from Yorkshire strongly suggest a beneficial effect from giving 500 IU at 28 and 34 weeks. There is also abundant circumstantial evidence from other sources that two doses of 250 IU may be similarly effective, and to test this hypothesis a multicentre trial has been designed and initiated and it is hoped that the results of this will facilitate the making of a formal recommendation so that the best use of limited supplies of anti-D immunoglobulin, which is prepared from human volunteers, is made. The trial is expected to provide conclusive evidence as to the value of prenatal prophylaxis within the next 18 months.

C R WHITFIELD

Queen Mother's Maternity Hospital,
Glasgow G3 8SH

D LEE

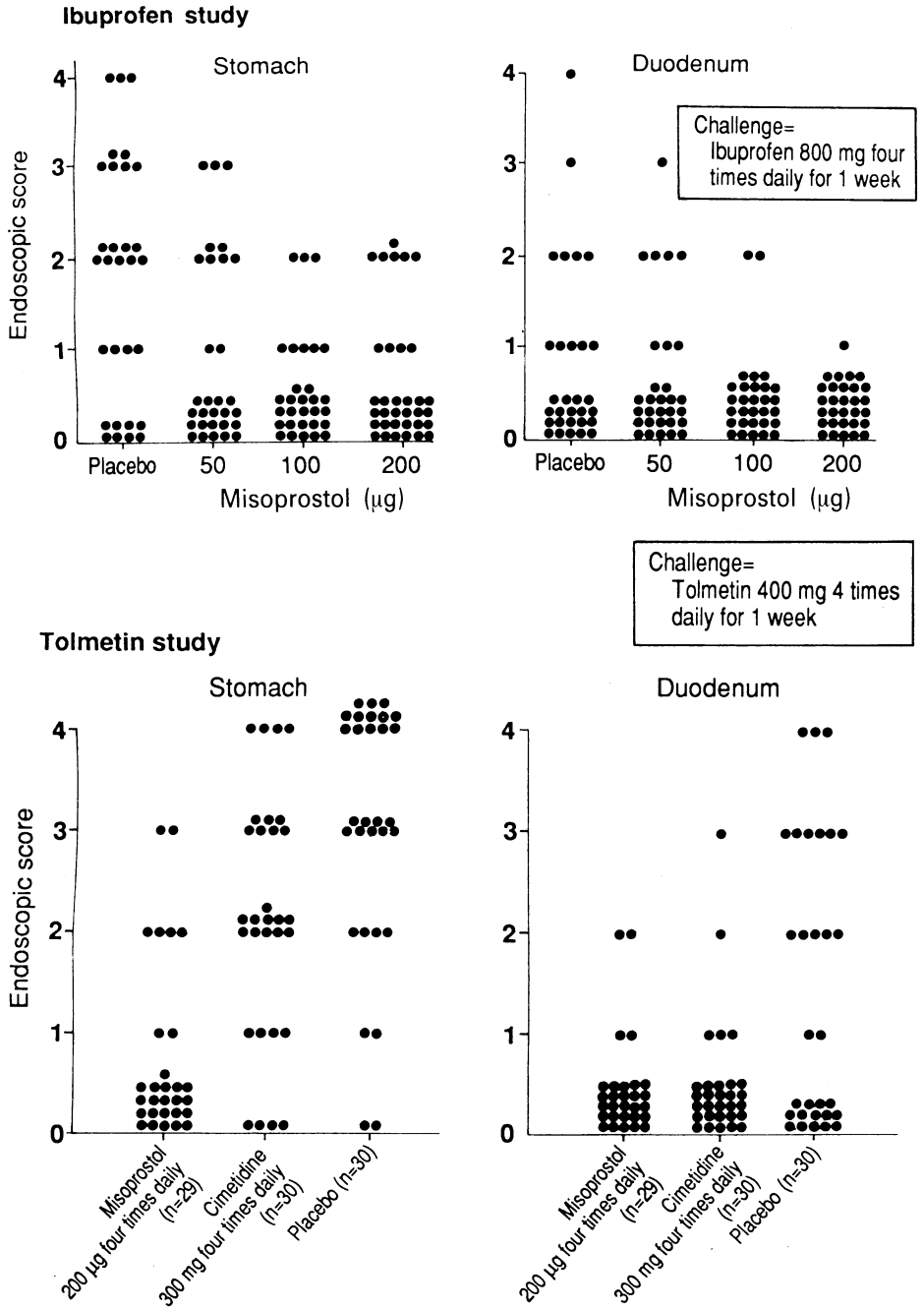
National Blood Transfusion Service,
Manchester M13 9LL

1 Tovey LAD. Haemolytic disease of the newborn and its prevention. *Br Med J* 1990;**300**:313-6. (3 February.)

NSAIDs and peptic ulcers

SIR,—I would like to suggest that the extrapolations that Dr C J Hawkey makes about how to prevent damage induced by non-steroidal anti-inflammatory drugs and the cost of such prevention are seriously flawed.[1]

The first point concerns the frequency of serious gastrointestinal events associated with non-steroidal anti-inflammatory drugs. Dr Hawkey makes no mention of the record linkage study by Beardon *et al*[2] in which the incidence of serious gastrointestinal events was compared in some 25 000 patients taking non-steroidal anti-inflammatory drugs and in age and sex matched controls. The sample size on which he based his projections regarding incidence of serious events associated with non-steroidal anti-inflammatory drugs in the general population was a case-control study of 230 patients.[3] The study by Beardon *et al* was not only controlled but was conducted in the Tayside region of Scotland and relevant to European practice. Furthermore, the yearly turnover of the population is low, in contrast to the American populations Dr Hawkey quoted. This point is important when looking for serious events as missing only a few may affect the results. The Tayside study clearly showed an age related effect and an incidence of



Endoscopic scores after one week's treatment with a non-steroidal anti-inflammatory drug ibuprofen and tolmetin with and without protective drugs in duodenum and stomach

morbidity 10 times the estimate to which Dr Hawkey referred—namely, up to 2·3% a year in those aged over 60. With the 10% mortality rate which is recognised for such gastrointestinal events, the Tayside figures would suggest an annual death rate of closer to 2000 than 200 and an admission rate of about 20 000 for the whole United Kingdom due to gastrointestinal events generated by non-steroidal anti-inflammatory drugs.

The second point concerns Dr Hawkey's interpretation of the data on protection against gastric and duodenal damage induced by non-steroidal anti-inflammatory drugs. The suggestion that an H_2 antagonist such as ranitidine should be used to prevent such duodenal damage (a use outside its licensed indications) and that misoprostol should be confined to protecting the gastric mucosa reflects a misunderstanding of clinical trial results. This confusion may arise from misinterpretation of the results from placebo controlled studies. The situation is perhaps best understood by comparing results obtained in the same individuals exposed to a non-steroidal anti-inflammatory drug alone and when given concomitant protective agents.

The figure shows results adapted from two studies, one showing a dose response for misoprostol coadministered with ibuprofen,[4] the other a comparison between tolmetin and placebo versus tolmetin and misoprostol or cimetidine.[5] The "dottogram" shows each individual's final endoscopic score after a week's non-steroidal anti-inflammatory drug treatment as a dot against the relevant endoscopic score on the ordinate (0=normal mucosa, 4=ulceration).

For ibuproten the authors considered, correctly from a statistical point of view, that even the lowest dose of misoprostol gave significantly better protection than placebo in the stomach, while only the highest doses were significantly better than placebo in the duodenum. Without the dottogram it would be justifiable to conclude that it is more difficult to protect the duodenum than the stomach, but the situation is the reverse. Damage in the placebo group was considerably greater in the stomach than in the duodenum, and this reduced baseline allowed small doses of misoprostol to show protection. In the duodenum damage was slight with a non-steroidal anti-inflammatory drug alone so a high dose would be needed to show any improvement over the duodenum's own physiological protective mechanisms.

The same picture is seen in the misoprostol/cimetidine study.[5] Damage was greatest in the stomach. An acid suppressant drug like cimetidine can show some protection in the duodenum identical to misoprostol, but in the stomach—where real protective efficacy is required—only misoprostol produced significant protection.

Consequently many of the questions that Dr Hawkey asks in his review are already answerable. Recent clinical studies with ranitidine confirm the above findings and show that the drug offers no protection in the stomach while providing some in the duodenum.[6,7] The differences between the findings of Graham *et al*[8] and Ehsanullah[7] are probably easily explicable. In the latter study the high incidence of duodenal ulcer was probably due to the recruitment of patients with a history of ulcer.

Studies such as the one by Graham *et al* and many earlier ones,[9] in which only patients without a history of ulcer were included, clearly show non-steroidal anti-inflammatory drug-induced damage to be predominantly gastric rather than duodenal, though some non-steroidal anti-inflammatory drugs may cause more duodenal than gastric damage through factors such as enteric coating. Nevertheless, that would still be a different situation from exacerbation of pre-existing peptic duodenal ulceration, the latter being a consequence of acid damage rather than prostaglandin deficiency.

In conclusion, it does not appear logical to give misoprostol and ranitidine when the former, which offers both acid inhibition and mucosal protection, can protect both the duodenum and the stomach. Taken in conjunction with the much higher morbidity figures quoted earlier, the cost effectiveness of a rational prophylactic policy using misoprostol alone may well prove to be a positive rather than a negative balance, especially when one considers what additional savings might be made by the cessation of ineffective "prophylactic regimens."

MICHAEL J SHIELD

GD Searle and Co Ltd,
High Wycombe,
Bucks HP12 4HL

1 Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. *Br Med J* 1990;**300**:278-84. (3 February.)
2 Beardon PHG, Brown SV, McDevitt DG. Gastrointestinal events in patients prescribed non-steroidal anti-inflammatory drugs: a controlled study using record linkage in Tayside. *Q J Med* 1989;**266**:497-505.
3 Somerville K, Faulkner G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet* 1986; i:462-4.
4 Lanza FL, Fakouhi D, Rubin A, *et al*. A double-blind placebo-controlled comparison of the efficacy and safety of 50, 100 and 200 μg of misoprostol QID in the prevention of ibuprofen-induced gastric and duodenal mucosal lesions and symptoms. *Am J Gastroenterol* 1989;**84**:633-6.
5 Lanza FL, Aspinall RL, Swabb EA, *et al*. Double-blind placebo-controlled endoscopic comparison of the mucosal protective effects of misoprostol versus cimetidine on tolmetin-induced mucosal injury to the stomach and duodenum. *Gastroenterology* 1988;**95**:289-94.
6 Robinson MG, Griffin JW, Bowers J, *et al*. Effect of ranitidine on gastroduodenal mucosal damage induced by nonsteroidal antiinflammatory drugs. *Dig Dis Sci* 1989;**34**:424-8.
7 Ehsanullah RSB, Page MC, Tildesley G, Wood JR. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. *Br Med J* 1988; **297**:1017-21.
8 Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. *Lancet* 1988;ii:1277-80.
9 Collins AJ, Davies J and Dixon ASTJ. A prospective endoscopic study of the effect of orudis and oruvail on the upper gastrointestinal tract in patients with osteoarthritis. *Br J Rheumatol* 1988;**27**:106-9.

SIR,—Dr C J Hawkey considerably underestimates both the number of deaths associated with use of non-steroidal anti-inflammatory drugs and the cost effectiveness of coprescribing an ulcer healing drug.[1]