These results confirm the efficacy of ibuprofen,[1] but do not conform to the supposition of Bärtsch and colleagues that high-altitude headache might respond to stimulation of 5-HT_1 receptors by sumatriptan.[2] Either their hypothesis is wrong or different trial conditions are responsible for the contrary results. In contrast to our investigation the experiment of Bärtsch and colleagues was not controlled and therefore a placebo effect cannot be excluded. On the other hand, their patients suffered from longer lasting and more severe headache than those in our experiment. Based on the speculation that severe headache causes an impaired blood-brain barrier, a central site of action of sumatriptan could explain the different effects observed.[4] If sumatriptan acts peripherally, we should have detected this. It remains to be seen whether a new 5-HT_1 receptor agonist that penetrates the blood-brain barrier more easily than sumatriptan will be effective also for the treatment of less severe altitude headache.[5]

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Ibuprofen treatment of patent ductus arteriosus

SIR—In preterm infants patent ductus arteriosus (PDA) is a common problem that leads to increased morbidity and mortality. Conventional treatment with intravenous indomethacin causes a decline in cerebral perfusion, reduced mitochondrial oxygenation, and disruption of cerebrovascular control.[1,2] The risk of ischaemic injury after indomethacin led a recent reviewer to stress the importance of research into alternative drugs for use in newborn infants.[3]

The action of indomethacin on PDA is mediated by inhibition of prostaglandin synthesis, but the deleterious cerebral effects appear to be due to a different mechanism which may be unique to indomethacin.[4] We have therefore studied the cerebral effects of a different prostaglandin synthesis inhibitor, ibuprofen, in preterm infants born between 23 and 28 (median 26) weeks postconceptional age.

The study compared the effects of ibuprofen 5 mg/kg (n=12) or 10 mg/kg (n=6), with indomethacin 0·1 mg/kg (n=15). The drugs were infused intravenously over 15 minutes during therapy for echocardiographically proven PDA. Near infrared spectroscopy (NIRO 500, Hammamatsu Photonics KK) was used to observe the effect of treatment on cerebral perfusion, indicated by changes in cerebral blood volume (CBV), and cerebral mitochondrial oxygenation, determined by the change in concentration of oxidised cytochrome aa_3 ($[CytO_2]$). In six cases receiving ibuprofen and four indomethacin, the response of CBV to changes in arterial carbon dioxide tension (CBVR) was also measured as an index of dynamic cerebrovascular control.

High and low doses of ibuprofen produced similar results, with no significant change being detected: the median (25th to 75th centiles) change in CBV was 0 (0·1 to −0·1) mL/100 g; and in $[CytO_2]$, 0 (0 to −0·1) μmol/L. CBVR was 0·13 (0·10 to 0·21) mL 100 g^{-1} kPa^{-1} before and 0·16 (0·09 to 0·17) after treatment. Control injections of indomethacin, on the other hand, induced significant falls in all variables similar to those seen in previous studies: the change in CBV was −0·4 (−0·3 to −0·5) mL/100 g; and in $[CytO_2]$, −0·2 (0 to −0·5) μmol/L. CBVR fell from 0·17 (0·13 to 0·19) mL 100 g^{-1} kPa^{-1} before treatment to 0·06 (0·05 to 0·07). The cerebral effects of ibuprofen and indomethacin were significantly different (Kruskal-Wallis analysis of variance with Dunn's multiple comparison test, $p<0·001$). However, there was no apparent difference in rate of PDA closure: both indomethacin and ibuprofen induced closure of the PDA in 57% of treated infants.

Unlike indomethacin, ibuprofen appears to induce closure of PDA without imparing cerebral haemodynamics and oxygenation. These results suggest that indomethacin may not be the best available drug for treating PDA in sick preterm infants. They are also relevant to researchers investigating the prophylactic administration of prostaglandin synthase inhibitors to prevent periventricular haemorrhage.

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Cutaneous dysplastic naevi: risk factor for uveal melanoma

SIR—Many studies have looked at the phenotypic features of individuals who are prone to develop cutaneous melanoma.[1,2] One of the main factors in melanoma risk assessment is the presence of dysplastic naevi (clinically atypical moles).[3]

Risk factors for uveal melanoma are less well defined, though Tucker et al[4] observed that exposure to sunlight increases the odds of intraocular malignant melanoma, and atypical naevi are more common in uveal melanoma patients than in controls.[5]

We have assessed the presence of dysplastic naevi among 75 consecutive uveal melanoma patients (36 women, 39 men; mean age 45·4 years) and 86 consecutive cutaneous melanoma patients (47 women, 39 men; 47·3 years). Controls were recruited from among patients referred to other clinics (78 women, 65 men; 46·2 years).

Atypical naevi were found in greater proportions of the uveal melanoma (17 of 75) and of cutaneous melanoma (19 of 86) groups than in the control group (9 of 143). The relative risks of uveal melanoma and cutaneous melanoma were 4·36 (95% CI 1·84–10·4) and 4·22 (1·81–9·84), respectively.

These results suggest that subjects with dysplastic naevi are at similar risks of the development of uveal melanoma and cutaneous melanoma, and that both dermatological and ophthalmological follow-up is indicated.

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CD44v6 and CD44v3 expression in ulcerative colitis and Crohn's disease

SIR—Rosenberg and colleagues (May 13, p 1205) report comparative expression of the v6 and v3 variants of CD44 in ulcerative colitis, Crohn's disease, and normal epithelium. They describe immunohistochemical expression of CD44v6 in 23 of 25 patients with ulcerative colitis (with intensity of immunostaining increasing with the severity of inflammation), in three of 18 with Crohn's colitis, and in none of 22 with normal large bowel mucosa. Similarly there was CD44v3 expression in all 16 patients with ulcerative colitis as opposed to two of 11 with Crohn's colitis and none of 17 controls. They argue that such a consistent disease-specific pattern of expression may indicate a role for these molecules in the pathogenesis of ulcerative colitis. We agree that a large body of evidence points to immune dysfunction as an important factor in ulcerative colitis. Expression of those molecules on epithelial cells that have corresponding ligands on lymphocytes may be the first step in the initiation of immune-mediated destruction by allowing lymphocyte-epithelial adhesion. There are, however, several points that we feel need further clarification.

First, the same group, using the same antibodies, reported weak but unequivocal expression of CD44v6 and CD44v3 in both formalin-fixed and frozen tissue from various normal epithelia, including that of large bowel.[1] We have also shown CD44v6 expression in normal large bowel epithelium. How do they reconcile this observation with their current finding of no such expression of either of these molecules in normal large bowel? Second, could the fact that the intensity of immunostaining increased with the severity of inflammation represent a disease-specific event rather than a primary pathogenetic event? Third, they report that nine of 10 patients with dysplasia were positive for CD44v6. Was this positivity in the presence of associated inflammation? If immune surveillance of neoplastic tissue exists, one would expect downregulation of those molecules involved in the immune response.

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Authors' reply

SIR—Ilyas and colleagues ask three questions. The first addresses differences in the interpretation of weak positive staining for CD44v3 and CD44v6 in large bowel biopsy specimens, which may be semantic. In questioning discrepancies between reports of weak staining with CD44 antibodies they identify the difficulty of comparing subjective evaluations in different immunohistochemical studies. Uncertainty about negative staining and degrees of positivity can be reduced by including contemporaneous controls which are treated and analysed identically to the disease samples, use of a clearly described scoring system, and by ensuring that observers are blinded to the clinical diagnoses. Although these steps provide some degree of objectivity within a single study, comparisons of levels of staining between studies are subject to numerous errors, especially in the absence of a standardised scoring system.

In our study we included biopsy specimens from healthy controls and treated them identically to those from patients. In the Patients and Methods section of our report, we describe the scoring system that we used in reporting our biopsy results, all of which were scored by observers blinded to the clinical diagnoses. Fox et al,[1] describe "weak focal reactivity" with antibodies to CD44v3 and CD44v6 on normal colorectal biopsy specimens, but do not describe the scoring system used in reporting their results. The "weak focal reactivity" described by Fox et al corresponds to "patchy weak staining on fewer than 25% of crypt epithelial cells per sample" graded as "negative" in our study.

We agree that the correlation between the intensity of immunostaining and severity of inflammation in ulcerative colitis may represent a disease-specific epiphenomenon. However, CD44 v3 and v6 antibodies will still be of great value in differentiating ulcerative colitis from other forms of colonic inflammation if this observation proves to be disease specific.

In the patients with dysplasia associated with ulcerative colitis all the biopsy specimens showed mild to moderate inflammation. It is our subjective impression that the pattern of staining for CD44v6 in these specimens was more focal than that seen in non-dysplastic samples, in line with the suggestion that dysplastic cells are evading immune surveillance. However, this observation needs verification.

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1 Fox SB, Fawcett J, Jackson DG, et al. Normal human tissues, in addition to some tumours, express multiple different CD44 isoforms. *Cancer Res* 1994; **54:** 4539–46.

Swabaholics?

SIR—Liauw and Archer (June 24, p 1648) state that there is no function to the use of alcohol-soaked swabs and that they should therefore be abandoned. I have personally carried out a single-user trial of my own use of alcohol swabs and find that there are occasions when they are useful. It is well known that some patients have good veins whereas others are very difficult to bleed. If veins are prominent and easy to see, I would agree with the assertion that there is very little purpose in the use of alcohol swabs; however, when the patients has bad veins, I find that alcohol swabs are invaluable because they act as a lubricant which makes palpation to find a suitable target more effective.

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