Thus in Lothian about 250 children—the vast majority not infected with HIV—are likely to suffer the death of one or both parents due to disease related to HIV in the near future; this figure is probably an underestimate as it represents only the tested population. Although many of these children will be beyond their early years when their parents develop advanced disease, they will require much support and counselling. Research should focus on what happens to children when a parent infected with HIV dies and on the role of fostering and adoption services. In our experience it is often grandparents or other family members who bring up children when their HIV infected parents have died or are unable to cope: account needs to be taken of the pressure exerted within extended families in such cases. The care of healthy, dependent children due to suffer bereavement as a result of the HIV epidemic in Lothian should be addressed while the problem is still in its infancy.

PETER J M RONALD
J R ROBERTSON

Edinburgh Drug Addiction Study,
Edinburgh EH4 4PL

BRUCE M DUNCAN

Department of Public Health,
Lothian Health Board,
Edinburgh EH3 7QQ

AILEEN S THOMSON

Centre for HIV, AIDS, and Drug Studies,
City Hospital,
Edinburgh EH10 5SB

1 Robertson JR, Bucknall ABV, Welsby PD, Roberts JJK, Inglis JM, Peutherer JF, *et al.* Epidemic of AIDS related virus (HTLV-III/LAV) infection among intravenous drug abusers. *BMJ* 1986;**292**:527-9.
2 European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. *Lancet* 1992;**339**:1007-12.
3 Giaquinto C, Giacomet V, Pagliaro A, Ruga E, Cozzani S, D'Elia R, *et al.* Social care of children born to HIV infected parents. *Lancet* 1992;**339**:189-90.
4 Department of Health. *Consultation document. Children and HIV: guidance for local authorities.* London: DoH, 1992.
5 Communicable Diseases (Scotland) Unit. Human immunodeficiency virus type 1 (HIV-1). Quarterly report to 30 September 1991. *ANSWER—AIDS news supplement, CDS weekly report* 1991:42.

Trends in prenatal diagnosis of Down's syndrome

EDITOR,—David E Mutton and colleagues report their analysis of the national Down's syndrome register for 1989-91.[1] One of their main findings is the increasing importance of fetal ultrasonography in the prenatal diagnosis of fetal trisomy 21. Though I do not doubt the considerable advances made in certain ultrasound centres in Britain and the United States in the use of fetal ultrasonography as an adjunct to prenatal diagnosis of fetal trisomy 21, the evidence in the Down's syndrome register is only as good as the information provided to the cytogenetics centres from people requesting karyotyping.

In the past year I have identified two cases of trisomy 21 in our screening district for which the regional cytogenetics centre was advised that the reason for requesting karyotyping was a suspected anomaly seen on ultrasonography. Examination of the records of prenatal biochemical screening for these two cases showed that biochemical screening had been carried out and a report of an increased risk of Down's syndrome issued before the ultrasonography was done. To ascribe diagnosis of such cases solely to ultrasonography is thus incorrect as prior knowledge of the results of biochemical screening could lead to a bias in identifying cases by ultrasonography. If these examples are duplicated across Britain doubt may be cast on the finding of an increased effectiveness of fetal ultrasonography in the prenatal diagnosis of fetal trisomy 21.

The Down's syndrome register should consider classifying reasons for referral more precisely. It will become increasingly less likely that any one element (biochemical screening, maternal age, or ultrasonography) will be the sole reason for referral for karyotyping.

KEVIN SPENCER

Endocrine Unit,
Department of Clinical Biochemistry,
Oldchurch Hospital,
Romford,
Essex RM7 0BE

1 Mutton DE, Ide R, Alberman E, Bobrow M. Analysis of national register of Down's syndrome in England and Wales: trends in prenatal diagnosis, 1989-91. *BMJ* 1993;**306**:431-2. (13 February.)

Retinoblastoma in children of former residents of Seascale

EDITOR,—In 1990 three cases of retinoblastoma were reported in children whose mothers had spent part of their childhood in Seascale and whose maternal grandfathers had worked at Sellafield nuclear plant.[1] Subsequently a further two cases of retinoblastoma linked to Seascale came to light.[2] The common feature in these five cases is that the mother had been resident in Seascale at some time since the early 1950s, when the Sellafield nuclear plant came into operation.

We have estimated the size of the denominator population as an average of 31·4 births a year which, projected to a 41 year period (1950-90), gives 1287 births. Of the children born in Seascale 57% entered the village school; the others were assumed to have left the village. If the average age at school entry is 4·5 years this gives an outward migration rate of 12·5% a year (95% confidence interval 10·8% to 14·4%).

If it is assumed that the age structure of the inward flow and the outward flow is similar and that those who leave continue to reproduce at the same rate as those of a similar age who stay then an estimate of the number of births to women who leave can be made (table). Two methods of calculation are possible.

Estimate of number of children born 1950-90 whose mothers had lived in Seascale at some time since 1950

Method and migration rate (%)	No of births		
	Outside Seascale	In Seascale	Total
Method A			
10·8	2850	1287	4137
12·5	3299	1287	4586
14·4	3800	1287	5087
Method B			
10·8	2518	1287	3805
12·5	2914	1287	4201
14·4	3357	1287	4644

Method A assumes that women who leave in any one year will produce a×b children a year thereafter, where a=average number of children born in Seascale per year and b=the migration rate. The number born from 1950 to 1990 is obtained by summing over all years—that is, a×b (sum of 0·5 to 40·5). This will be an overestimate, however, as some of the births will be grandchildren, not children, of Seascale residents.

Method B corrects for this overestimate by using the average age at which women give birth, which in England and Wales between 1950 and 1990 was 27·1 years.[5] The women who leave Seascale in 1950 will produce approximately a×b×27 children, as will those who leave in 1951, and so on for 14 years. But then the number will reduce. An estimate is given by:

$$(a\times b\times 27\times 14)+(a\times b\ (\text{sum of } 0{\cdot}5 \text{ to } 26{\cdot}5))$$

The total number of births (table) is in the region of 4000-5000. Retinoblastoma occurs in 1 in 20 000 live births, and the expectation in 5000 children is 0·25 case. Five cases is a 20-fold increase (6·4 to 46·4; p,0·0001).

There is a considerable increase in retinoblastoma in children whose mothers have lived in Seascale during the period of operation of the Sellafield nuclear plant. A longitudinal health study of this population is required to see if the incidence of other childhood cancers is increased.

J A MORRIS

Lancaster Moor Hospital,
Lancaster LA1 3JR

R BUTLER
R FLOWERDEW
A C GATRELL

Geography Department,
Lancaster University,
Lancaster LA1 4YW

1 Morris JA, Edwards JM, Buckler J. Retinoblastoma in grandchildren of workers at Sellafield nuclear plant. *BMJ* 1990;**301**:1257.
2 Morris JA, Buckler J. Retinoblastoma linked to Seascale. *BMJ* 1991;**302**:112-3.
3 Gardner MJ, Hall AJ, Downes S, Terrell JD. Follow up study of children born elsewhere but attending schools in Seascale, west Cumbria (schools cohort). *BMJ* 1987;**295**:819-22.
4 Gardner MJ, Hall AJ, Downes S, Terrell JD. Follow up study of children born to mothers resident in Seascale, west Cumbria (birth cohort). *BMJ* 1987;**295**:822-7.
5 Office of Population Censuses and Surveys. *Birth statistics.* London: HMSO, 1989.

Persistent glue ear in children

EDITOR,—The *Effective Health Care* bulletin No 4 on the management of persistent glue ear in children[1] has caused controversy.[2] As there is considerable clinical uncertainty and variation in practice in this condition such debate is to be welcomed. Some clarification of points raised might, however, be useful.

Carl Watson seems to have misread the bulletin in a few places.[2] We do not report that 22% of all tonsillectomies for glue ear in Yorkshire were done as day case procedures but that 22% of tonsillectomies carried out as single procedures were. This represents only two cases in 1990-1, and all costings were based on the assumption that tonsillectomies took place as inpatient procedures. Altogether 471 tonsillectomies were performed for glue ear, all but nine of which were performed with other operations such as adenoidectomy. What is more worthy of comment is the high number of tonsillectomies for this cause, given the evidence that tonsillectomy does not enhance the effectiveness of either adenoidectomy or insertion of grommets in improving hearing.[1]

The bulletin's conclusion is based on a comprehensive review of all the studies, and the stated beneficial effects of some surgery for some children took into account the positive results from a study by Gates *et al.*[3] We drew particular attention to three studies because they reported a level of hearing loss which can be more objectively compared between studies and is a major clinically relevant end point. Our observations about possible problems with using the contralateral ear as a control were made as a contribution to debate and were not used as a basis for excluding any studies from consideration or inclusion.

H B Whittet and colleagues make the valid point that hearing loss is not the only important outcome measure.[4] We argued (paragraph J.2) that broader outcome measures that are more sensitive to potential disability should be included in future research and audit. Nevertheless, we take issue with some of the indications for treatment that they mention. None of the 19 randomised controlled trials used otalgia or recurrent acute otitis media as an outcome measure and so there is little scientific evidence that surgery benefits children with these conditions, especially when the high proportion who experience severe or persistent discharge after insertion of grommets is considered.

Like John Marshall and Anthony A Narula, we would like to see improved access to high quality audiological and otolaryngological assessment.[5] By ignoring the complex natural course,[1] however, they mistakenly assume that, because waiting times are often considerable, children who present with effusion have had glue ear for some time and will continue to do so without treatment. Watchful waiting is more likely to establish persistence and reduce the unacceptably high dry tap rates reported in several of the studies reviewed.

TREVOR SHELDON
NICK FREEMANTLE

Effective Health Care,
School of Public Health,
University of Leeds,
Leeds LS2 9LN

1 The treatment of persistent glue ear in children. *Effective Health Care* 1992;No 4.
2 Watson C. Persistent glue ear in children. *BMJ* 1993;**306**:454. (13 February.)
3 Gates GA, Avergy CA, Prihoda TJ, Cooper JC. Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. *N Engl J Med* 1987;**317**: 1444-51.
4 Whittet HB, Marks N, Heyworth T, Parker R. Persistent glue ear in children. *BMJ* 1993;**306**:454. (13 February.)
5 Marshall J, Narula AA. Persistent glue ear in children. *BMJ* 1993;**306**:454. (13 February.)

Tumour markers and primary site of cancer

EDITOR,—A R Gamble and colleagues[1] aimed to identify the primary site of metastatic cancer using tumour marker immunoreactivity in the hope that this will reduce the number of investigations in patients with often a very limited life span. However, their article states that "investigative mastectomy could be considered for women with normal mammograms who present with axillary node disease when antibody reactivity supports a primary tumour in the breast." According to their results, in 10 out of 16 patients with breast as the predicted primary site the prediction was incorrect. Normal results on breast examination and the mammogram would make a breast primary even less likely. Breasts are not just appendages which can be removed to provide the histology department with a tissue diagnosis.

ANJA PINHORN

St George's Hospital,
London SW17 0QT

1 Gamble AR, Bell JA, Ronan JE, Pearson D, Ellis IO. Use of tumour marker immunoreactivity to identify primary site of metastatic cancer. *BMJ* 1993;**306**:295-8. (30 January.)

Pre-emptive analgesia

EDITOR,—Dudley J Bush mentions the conflicting evidence for the existence of pre-emptive analgesia and suggests that differences in surgical procedure and anaesthetic may explain this.[1] The noxious stimulation used in animal studies (chemical and thermal) is also suggested to be inadequate and given as reason why these studies often lend support to pre-emptive analgesia. Recent studies have shown that rapid molecular events occur in the spinal cord after noxious peripheral stimulation and may explain why pre-emptive analgesia is often difficult to show.

Hunt *et al* showed that brief noxious but generally not other stimulation will lead to the rapid expression of the *c*-fos gene in Rexed layers I, II, and V of the spinal cord.[2] These changes may last many hours, and thermal stimulation especially gives rise to a particularly complex and longlasting expression of the gene. Fos protein dimerises with Jun protein to bind the AP1 binding site on DNA. The gene for pre-pro-dynorphin (PPD) has the AP1 binding site and fos has been shown to colocalise with dynorphin. Models of acute pain and inflammation have been associated with increased production of dynorphin and dynorphin applied directly to the spinal cord causes hyperalgesia.[3] Furthermore, changes in immunoreactivity of fos can be correlated with the severity of the disease state in an arthritic model. On the basis of these findings a model can be suggested to explain how noxious stimulation can lead to induction of *c*-fos and give rise to the neurophysiological and behavioural changes seen in pain states.

Attempting to block the expression of *c*-fos is extraordinarily difficult. Morphine given preemptively in an acute pain model will block the induction of *c*-fos in a dose dependent manner, however, even with relatively high doses there is still a basal level of *c*-fos induction with noxious stimulation.[4] Though MK-801, the *N*-methyl-D-aspartic acid (NMDA) antagonist, blocks central sensitisation and "windup," it does not stop the expression of *c*-fos in a noxious stimulation model.[5] There is also evidence that previous "low level" noxious stimulation may have a priming effect, allowing further minor noxious stimulation to cause dramatic *c*-fos induction. This may have implications for the effectiveness of pre-emptive analgesia in surgery for previously painful conditions.

We agree with Bush that the persistence of afferent stimulation after the pre-emptive analgesia has "worn off" may allow a barrage of nervous impulses which will induce *c*-fos and so minimise the beneficial effect of the technique. Research into *c*-fos and other related genes (known as immediate early genes) as markers of noxious stimulation in the nervous system can increase understanding of the basis of both acute and chronic pain state.

R MUNGIANI

University Department of Anaesthesia,
School of Clinical Medicine,
Cambridge CB2 2QQ

STEPHEN HUNT

Division of Neurobiology,
Laboratory of Molecular Biology,
Medical Research Council Centre,
Cambridge CB2 2QH

1 Bush DJ. Pre-emptive analgesia. *BMJ* 1993;**306**:285-6. (30 January.)
2 Hunt SP, Pini A, Evan G. Induction of c-fos like protein in spinal cord neurons following sensory stimulation. *Nature* 1987;**328**: 632-4.
3 Dubner R, Ruda MA. Activity dependant neuronal plasticity following tissue injury and inflammation. *TINS* 1992;**15**: 96-103.
4 Presley RW, Menetrey D, Levine JD, Basbaum AI. Systemic morphine suppresses noxious stimulus-evoked fos protein-like immunoreactivity in the rat spinal cord. *J Neuroscience* 1990; **10**:323-35.
5 Wisden W, Errington ML, Williams S. Differential expression of immediate early genes in the hippocampus and spinal cord. *Neuron* 1990;**4**:603-14.

Inheritance of chronic inflammatory bowel disease

EDITOR,—Marianne Orholm and colleagues have reported an investigation into the mode of inheritance of chronic inflammatory bowel disease.[1] They performed a *mixed* model analysis by fitting several mathematical models to the segregation of ulcerative colitis and Crohn's disease in a series of Danish families. The authors proposed a dominant gene model for ulcerative colitis and suggested a recessive gene model for Crohn's disease to explain the evident familial clustering in these conditions.

Ten years ago, the *mixed* model was extended with the incorporation of transmission probabilities, which allows the formal testing of mendelian segregation proportions.[2] This *unified* model was introduced to prevent false detection of major gene inheritance. For example, McGuffin and Huckle showed in a *mixed* model analysis that attendance at medical school was adequately fitted by a recessive major gene model; however, this intriguing hypothesis was rejected when transmission probabilities were rigorously tested.[3] Contemporary computer programs for complex segregation analysis allow such tests of mendelian segregation, and I urge caution in interpreting these results pending a full analysis under the *unified* model.

The Danish group has previously commented on the familial occurrence of inflammatory bowel disease and reported empiric recurrence risks for first and second degree relatives of probands with either ulcerative colitis or Crohn's disease.[4] Risch has shown how the pattern of recurrence risks in various classes of relatives can elucidate the mode of inheritance of a trait.[5] The reported recurrence risk ratios (λ_R), which are defined by the risk to a relative of class R (K_R) divided by the population prevalence (K_p), fit a multifactorial model better than a monogenic model for both ulcerative colitis and Crohn's disease (see table; note that recurrence risks corrected for sex and age are not available to permit rigorous analysis of these data). The authors support this finding with their observation that the recurrence risk ratio for first degree relatives in families with two affected members is greater than that found among the relative of single probands (18·1 *v* 8). This increase in risk is a cardinal feature of a multifactorial trait.

Models of chronic inflammatory bowel disease

	Ulcerative colitis (population prevalence 161/100 000)		Crohn's disease (population prevalence 55/100 000)	
Class of relative	First degree	Second degree	First degree	Second degree
Prevalence (per 100 000) in R degree relatives (K_R)*	1522	264	569	156
Recurrence risk ratio (λ_R (=K_R/K_p))	9·6	1·6	10·3	2·8
Predicted by a multifactorial model (λ_R)	9·0	3·0	10·2	3·2
Predicted by a monogenic model (λ_R)	7·4	4·2	8·6	4·8

*Population prevalences (K_p) and prevalences in first and second degree relatives are drawn from Orholm *et al*.[5]

In view of these concerns over the mode of inheritance of chronic inflammatory bowel disease, attempts to map susceptibility loci should be analysed by a robust linkage test (for example, affected pedigree member of "sib pair" test) so as to minimise false positive claims of linkage.

MARTIN FARRALL

MRC Molecular Medicine Group,
Royal Postgraduate Medical School,
London W12 0NN

1 Orholm M, Iselius L, Sørensen TIA, Munkholm P, Langholz E, Binder V. Investigation of inheritance of chronic inflammatory bowel diseases by complex segregation analysis. *BMJ* 1993; **306**:20-4. (2 January.)
2 Lalouel J-M, Rao DC, Morton NE, Elston RC. A unified model for complex segregation analysis. *Am J Hum Genet* 1983;**35**: 816-26.
3 McGuffin P, Huckle P. Simulation of mendelism revisited: the recessive gene for attending medical school. *Am J Hum Genet* 1990;**46**:994-9.
4 Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TIA, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;**324**:84-8.
5 Risch N. Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet* 1990;**46**:222-8.

BCG vaccination and health care workers

EDITOR,—K M Citron discusses BCG vaccination against tuberculosis and asserts that vaccination of hospital staff may become increasingly important.[1] Under French regulations BCG vaccination is compulsory for hospital employees. I report on