ridiculous. To discover the incidence of Down's syndrome in this particular population, we need, of course, to know the total number of babies born to all 213 school fellows. The authors omit this vital piece of information, though the true incidence of Down's syndrome probably *is* higher than the expected one in 600, unless the 213 had a mean family size of >16·9.

A further confusion arises because the control group appears to be a mixture of some of the remaining normal babies born to schoolfellows and babies born to mothers from other schools, one of whom had Down's syndrome. It is necessary to decide whether to conduct *either* a case controlled study, in which mothers of Down's babies are compared with matched mothers of normal babies, *or* a cohort study, in which the incidence of Down's syndrome in one school is compared with that in another matched school over the same period, or perhaps in siblings of case mothers who attended different schools.

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SIR,—I am concerned with the manner in which Dr Patricia M E Sheehan and Professor Irene B Hillary justified the causal connection between factors reported in their paper (12 November, p 428). Cornfield and MacMahon and Pugh have shown that given information on the overall incidence of disease in a population one can find estimators of risks for different subgroups, which are based on retrospective data.[1 2] In the paper by Dr Sheehan and Professor Hillary, however, there is no proper reference to such methods, and what is more it is not at all clear what population the authors are referring to. Were they referring to all pregnancies to all mothers who had attended the school in the 1950s? If so, what about mothers at the school who had reported an illness similar to influenza but who had not given birth to a Down's syndrome child? Nor are we told on what basis the control group was selected.

Equipped with a clearer understanding of the population to which the authors are referring the reader could be supplied with a more realistic assessment of the probability of observing such a cluster of Down's syndrome babies by chance alone.

Clearly the authors have a medical responsibility to bring these observations to the reader's attention, but statistically speaking I feel the observations serve best as generators of hypotheses rather than as proof of causal connection.

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[1] Cornfield J. A statistical problem arising from retrospective studies. In: Neyman J, ed. *Proceedings of the third Berkeley symposium on mathematical statistics and probability*. Vol 4. Berkeley: University of California Press, 1956:135-48.
[2] MacMahon B, Pugh TF. *Epidemiology: principles and methods*. Boston: Little, Brown and Company, 1970: 274.

SIR,—Dr Patricia M E Sheehan and Professor Irene B Hillary claim to have detected a cluster of births of infants with Down's syndrome. They were born to women who, as girls, had all attended the same school in Ireland and who had produced a total of 26 children. The authors state that the incidence of six babies with Down's syndrome in a total of 26 is significantly higher than the accepted incidence of one in 600. But surely the relevant total is not 26. If we assume that the future fertility of the 213 other pupils attending the school at the same time was the same as that of the mothers in the study then the denominator is estimated at 219 (26/6). And the expected number of cases of Down's syndrome among them is 219 (26/6) (1/600)=1·58. The sum of the Poisson probabilities corresponding to six or more events when 1·58 are expected is slightly more than 0·005, or one in 200. As there are more than 200 schools of comparable size in Eire, it would not be surprising if—even by chance—a school should exist there with as many cases of Down's syndrome among the babies of its former pupils. The argument for clustering is not compelling.

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**The authors reply below.—ED, *BMJ*.

SIR,—It would seem that our statistical comment on six cases of Down's syndrome occurring in 26 pregnancies has caused great concern to the statisticians who have read our report, as most of our explanatory figures were omitted in an attempt to shorten our original long winded report.

The figure of 213 quoted represents the number of pupils in the affected school from September 1951 to June 1961, all of whom were contacted and asked for details of obstetric and other personal history. Of these, 107 were in the senior classes in 1957 (age range 12-18 years). These we would consider were the "at risk" group which included the six mothers of the Down's syndrome babies. Twenty two of these senior girls did not wish to cooperate. (Since publication of the report we have learnt that two of the girls who did not wish to cooperate had Down's syndrome babies who died. These were not included in our original report.) We obtained full details of obstetric history from 81 of the 107 women in the group at risk. Of these, 28 were unmarried and nulliparous and 53 were married, of whom six were infertile. No contraceptives were used by any of the group. The 47 fertile women had 119 pregnancies resulting in 121 normal babies (including two sets of twins). Other abnormalities and pregnancy wastage in this group were as follows: neonatal deaths due to congenital heart disease (two); spina bifida (two); miscarriages (three); spontaneous abortions (nine); cystic fibrosis (one). Thus 142 pregnancies were recorded in the group at risk. Six cases of Down's syndrome occurring in 142 pregnancies is an incidence of one in 24 and is therefore unlikely to have occurred by chance. Using the Z test, Z=13·5 (p=<0·001), which is highly significant.

Our controls (128) included younger and older pupils of the affected school (55), pupils of two other schools (49) (one where influenza had not occurred and the other where there had been influenza in late October 1957) and mothers (24) of similar age in the Down's Syndrome Association who were also tested initially for viral antibodies. Excluding this latter group, the total pregnancies among the 59 parous women in these control groups was 193, of which one was a Down's syndrome born to a 40 year old mother as a result of her fifth pregnancy.

We wish to emphasise that this study, which was started in 1974, was concerned only with looking for a possible infective cause in this closed community. The possible connection with radioactivity and therefore with Windscale could hardly be ignored in view of the coincidence in timing and the relevant information made available to us from the Meteorological Office's records.

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Role of radiation in aetiology of Down's syndrome

SIR,—Dr Patricia H E Sheehan and Professor Irene B Hillary (12 November, p 1428) have uncovered an interesting connection between six mothers who had children with Down's syndrome—namely, that they were all pupils at a small school in Dundalk during the 1950s. In October of 1957 an outbreak of "illness similar to influenza" occurred in the school. On 10 October 1957, there was a fire at Windscale, 120 miles away across the Irish Sea, leading to the release of certain radionuclides, notably ^{131}I, to the atmosphere. Extensive environmental measurements were made at the time, and Crabtree traced the path of the radioactive cloud over England and into Europe and Scandinavia.[1] The predominant movement was in a south easterly direction, away from Ireland. Stewart and Crooks measured ^{131}I levels in Belfast during the next few days, and the concentration of ^{131}I in air, integrated over time, was 6 pCi-days/m^3.[2] The comparable figure for London was 425 and for Brussels 49. The Irish meteorological reports referred to by Dr Sheehan and Professor Hillary were based on the total beta radioactivity in the air (not ^{131}I specifically), and in 1957 an appreciable proportion of this would be due to fallout from testing of atmospheric weapons, The daily levels would vary with weather conditions. There is no evidence that the Windscale fire made any appreciable contribution of radiation to the population of Dundalk or anywhere else in Ireland, and some evidence that it did not. Indeed, it seems that two of the most unexceptional features of school life in Dundalk in 1957 were influenza and the ambient level of radiation.

Whether radiation plays a part in the aetiology of Down's syndrome is not clear. It has been recognised for over 50 years that radiation is a potential cause of non-disjunction in chromosomes, and more recent experimental work in the mouse has shown that it can cause non-disjunction in mammalian oogenesis and spermatogenesis.[3 4] Epidemiological studies have been conducted among survivors of the atomic bombs, people living in Kerala, where the natural background radiation is very high, and retrospectively for mothers of Down's syndrome babies to examine the possible influence of diagnostic radiology. A recent exhaustive review could identify only four studies showing a positive effect.[5] It also quoted Uchida, who is author of two of the positive epidemiological studies and

much experimental work as stating "... it may still be premature to say with conviction that radiation as a cause of non-disjunction increases the frequency of 21-trisomy. However, it seems logical to avoid unnecessary exposure to mutagens that might add to the genetic burden of humans."

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1 Crabtree J. The travel and diffusion of the radioactive material emitted during the Windscale accident. *Quarterly Journal of the Royal Meteorological Society* 1959;**85**:362-70.
2 Stewart NG, Crooks RN. Long-range travel of the radioactive cloud from the accident at Windscale. *Nature* 1958;**182**:627-8.
3 Uchida IA, Lee CPV. Radiation-induced non-disjunction in mouse ocytes. *Nature* 1974;**250**:601-2.
4 Hansmann I, Probeck HD. The induction of non-disjunction of irradiation in mammalian oogenesis and spermatogenesis. *Mutat Res* 1979;**61**:69-76.
5 United Nations Scientific Committee on the Effects of Atomic Radiation. *Report*. New York: UN, 1982.

Stillbirth rates in the area around Windscale, 1949-81

SIR,—After the claims made recently in a television programme (12 November, p 1464) of an excess incidence of childhood cancers in some of the coastal villages close to Windscale (now known as Sellafield), we have examined stillbirth rates in the county district of Copeland (see fig 1). Before local government reorganisation in 1974 this district comprised the rural districts of Millom and Ennerdale and the municipal borough of Whitehaven.

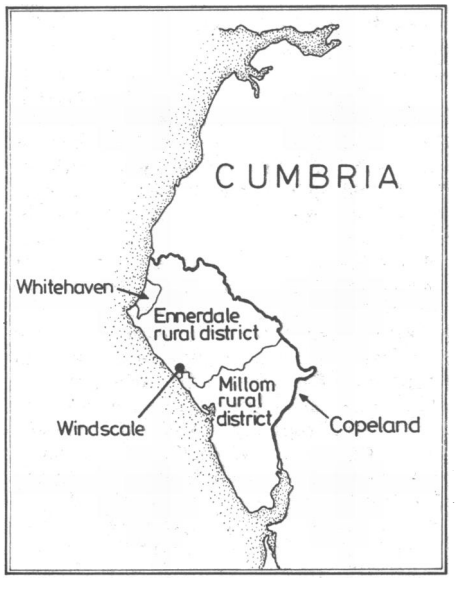

FIG 1—County district of Copeland.

The numbers of stillbirths and livebirths for these areas and for England and Wales were extracted from the annual reports of the Registrar General for the period 1949-81. Stillbirth rates were calculated per 1000 total births and annual rates are shown for England and Wales, together with a three point moving average of the annual rates for the area that is now the county district of Copeland (see fig 2).

There is no evidence of (*a*) any temporal effect on the stillbirth rates in Copeland that might have been associated with the 1957 fire, or (*b*) any positive association between stillbirth rates and the relatively large amounts of radioactive material released into the Irish sea in the 1960s.

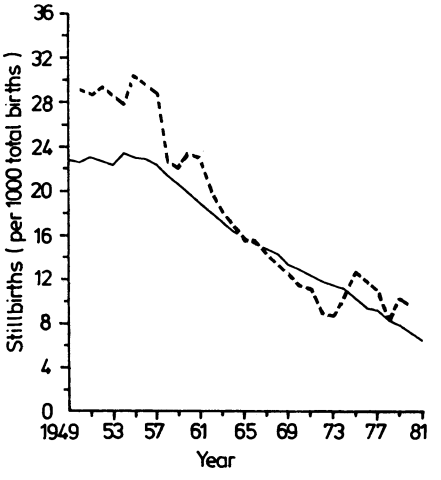

FIG 2—Stillbirth rates per 1000 total births by calendar year. ——— England and Wales, - - - - Copeland 1974-81, rural districts of Millom and Ennerdale and municipal borough of Whitehaven 1949-73 (three point moving average).

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Antibiotic resistance in Serratia marcescens

SIR,—We wish to add our experience to that reported by Dr D A Lewis and others (3 December, p 1701). We have recently isolated two cultures of *Serratia marcescens* from blood from two babies on the neonatal intensive care unit who subsequently died. Both cultures were of identical sero and phage type and were resistant to netilmicin (minimum inhibitory concentration 32 mg/l) but sensitive to gentamicin (minimum inhibitory concentration 1 mg/l). Both babies had received netilmicin.

The first baby, who had cystic fibrosis, died after a chest infection at the age of 4 weeks; a *Klebsiella pneumoniae* was also isolated from the terminal blood culture. The second baby, a premature triplet with an intraventricular haemorrhage, was progressing well but collapsed suddenly at the age of 2 weeks, was given penicillin and netilmicin empirically, but did not respond. *S marcescems* only was isolated from the blood culture taken one day before death, which occurred five days after *S marcescens* was isolated from the first baby. The two *S marcescens* isolates, both serotype 0:14, had the sensitivity pattern of strains isolated in the Bristol outbreak. All previous cultures from both babies, including cerebrospinal fluid and blood cultures, were sterile or had contained normal flora only.

A thorough survey of the environment, equipment, babies, and hands of medical and nursing staff showed only a washbasin contaminated with a non-typable netilmicin sensitive strain of *S marcescens*. Up to this time netilmicin was the first choice aminoglycoside used in the unit; after these incidents gentamicin was substituted.

It is perhaps inevitable that many babies in neonatal intensive care units are treated with broad spectrum antimicrobial agents whenever the possibility of infection arises and that such lavish use of agents selects resistant bacteria. Previously, the use of gentamicin has selected organisms that are resistant to gentamicin, but many are sensitive to other aminoglycosides, such as netilmicin. Now that the converse would appear to be true, however, the possibility that netilmicin should generally supersede gentamicin needs careful consideration. We believe that gentamicin is still the aminoglycoside of choice with other agents kept in reserve. The question of differential toxicity among the aminoglycosides is not yet settled.

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SIR,—We should like to qualify Dr J Douglas Sleigh's comments (3 December, p 1651) on the nature of the acetyltransferase AAC(6′) gene which conferred resistance to netilmicin and moderate resistance to amikacin in isolates from the Bristol outbreak (3 December, p 1701).

Dr Sleigh states that, although aminoglycoside resistance in serratia is commonly mediated by plasmids that are transferable, in this instance the resistance was due to mutation (chromosomal mutation implied) and was not transferable. It is true that we have been unable to transfer netilmicin resistance from our isolates to *Escherichia coli* K_{12} and the evidence suggests that the gene is chromosomally located, but it has not necessarily arisen by simple mutation of the serratia chromosome. It is more likely that the resistance determinant has been added to the chromosome by transposition (an event that results in the insertion of discrete pieces of DNA randomly into bacterial genomes). Because transposons may be inserted randomly into genomes they have been called "jumping genes" and have great potential for dissemination of antibiotic resistance among clinically important bacteria.

A transposon coding for several resistances including amikacin and netilmicin, mediated by AAC(6′), has recently been described.[1] This was isolated from a plasmid of the incompatibility group F11, which is a group of plasmids the host range of which includes *Serratia marcescens*.[2] By analogy with the behaviour of other drug resistance transposons such as TnA (the ampicillin resistance transposon)[3] we believe that the netilmicin resistance genes on the chromosome of our strain of *S marcescens* may have been acquired from a plasmid and we are currently investigating this idea.

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1 Meyer JF, Nies BA, Wiedemann B. Amikacin resistance mediated by a multiresistance transposon (Tn *2424*). *J Bacteriol* 1983;**155**:755-60.
2 Hedges RW, Rodriguez-Lemoine V, Datta N. R factors from Serratia marcescens. *J Gen Microbiol* 1975;**86**:88-92.
3 Bennett PM, Richmond MH. Translocation of a discrete piece of DNA carrying an amp gene between replicons in Esch coli. *J Bacteriol* 1976; **126**:1-6.