continued speculation based on such small numbers seems inappropriate.

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1 Kinlen LJ. Can paternal preconceptional radiation account for the increases of leukaemia and non-Hodgkin's lymphoma in Seascale? *BMJ* 1993;306:1718-21. (26 June.)
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Research must continue

EDITOR,—L J Kinlen's study further elucidates the controversy surrounding preconceptional radiation and its potential effect on the increase in leukaemia and non-Hodgkin's lymphoma in Seascale.[1] While I agree that the study shows a significant excess of both these diseases (which is not restricted to young people who were born in Seascale) and that a high level of paternal preconceptional radiation cannot by itself explain the excess among young people in the parish, I remain unconvinced that such radiation can therefore be exonerated.

If the definition for the exposure categories of external radiation in the fathers was widened to include doses above 50 mSv then a re-examination of the information set out in table III clearly indicates that of the eight residents of Seascale aged under 25 who were also born there and had leukaemia or non-Hodgkin's lymphoma, six had fathers whose radiation exposure was ≥ 50 mSv. Table IV shows that five of the six cases born in Seascale had fathers whose preconceptional radiation exposure was ≥ 50 mSv, compared with only one of the five born elsewhere. This disproportion cannot be ignored. On the basis of what is known about the likely genotoxic effects of even small doses of ionising radiation, restricting the analysis to a cut off point of 100 mSv seems unnecessarily arbitrary in terms of a potential for causing chromosomal damage to primitive germinal epithelium—especially for small repeated doses over time, which might tax cellular repair mechanisms. Biological plausibility, the application of sound logic, and use of simple as well as more complex statistical analyses all have a place in the final assessment of causal inference in the epidemiology of cancer.

Sadly, Martin Gardner is not able to enter into the debate. I know he would have done so energetically. Most people agree that, after further elucidation, there may not be a single dominant cause for the excesses shown, but nevertheless we must not be lulled into false reassurance by the convenient appeal of an apparent outright exclusion of one of them; the real reason(s) for the causal association may lie just beneath the surface of easy recognition if we are prepared to acknowledge it. The research, study, and analysis must continue.

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1 Kinlen LJ. Can paternal preconceptional radiation account for the increase of leukaemia and non-Hodgkin's lymphoma in Seascale? *BMJ* 1993;306:1718-21. (26 June.)

Author's reply

EDITOR,—It is not clear which aspect of my data Pat Doyle and Eve Roman consider to be sparse. It cannot, surely, be the absolute number of cases of leukaemia and non-Hodgkin's lymphoma that show no association with high levels of paternal preconceptional radiation: this would mean overlooking the fact that these cases represent a significant excess or, for that matter, exceed the number in the original study with this association. If they mean the quality of the data on radiation this would be an odd comment as it is the same as in the original study.[1]

The data were not, as they state, standardised for age but were tabulated in detail as observed and expected numbers by calendar period and five year age group. I agree that the difference in age with respect to place of birth is interesting, particularly as this also applies to the cases near Dounreay.[2] It would be consistent with these excesses having an infective basis, the lack of cases in older locally born children reflecting the fewer susceptible subjects—because of their exposure at younger ages than was possible among the incomers. This and other factors are discussed elsewhere.[2]

I too am participating in continuing studies of the children of nuclear workers.[3] The last question about such children emphasised by Doyle and Roman, however, is only part of the larger question of why there is an excess of leukaemia near certain nuclear sites, for this is clearly not restricted to the children of the workers. A recent study in rural Scotland including the Dounreay area shows how easily excesses might be incorrectly attributed to the nuclear industry if the effects of population mixing and the North Sea oil industry are ignored.[2]

My paper was concerned only with the question that formed its title. Gardner *et al* stated that if high levels of paternal preconceptional radiation caused childhood leukaemia "then the reported geographical excess [in Seascale] could effectively be explained."[1] I simply showed that it could not be. The opposite impression had resulted from the exclusion of cases in people born outside Seascale, a group (incorrectly) regarded as showing no excess.

The hypothesis was based, therefore, on an association present only in a subgroup of the excess cases that had prompted the study, making it less striking than many had previously thought. The pitfalls of subgroup analyses are well known. To invoke two separate causes for different subgroups offends the principle of scientific parsimony and needs strong justification.

I did not attempt in my paper to weigh the totality of the evidence relating to the possible effects of paternal preconceptional irradiation and did not claim, as C A Veys implies, that "such radiation can therefore be exonerated." The new finding does, however, accord better with the three tests of Gardner's hypothesis that have failed to support it[3-5] than with the hypothesis itself.

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1 Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in west Cumbria. *BMJ* 1990;300:423-9.
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Epidemiology of childhood leukaemia

EDITOR,—L J Kinlen *et al* have shown that some rural areas that experience rapid population growth have a higher than expected mortality from childhood leukaemia and that this could be linked to a rare response to a common infection under unusual patterns of population mixing.[1] Population movement into areas that were previously sparsely populated may produce a large pool of susceptible subjects with low herd immunity to common infections, and any resulting epidemic could increase the incidence of childhood leukaemia.

Overall, in England and Wales rural areas have been found to carry a slightly greater risk of childhood leukaemia than urban areas (1·09:1).[2] Less is known about the variation in the incidence of childhood leukaemia among other types of geographical area. The Leukaemia Research Fund's data collection survey provided information on the incidence of acute lymphoblastic leukaemia in 0-14 year olds during 1984-8 for 145 local authority districts of England and Wales.[3] These were categorised according to the national classification of residential neighbourhoods, which groups together districts with similar socioeconomic and demographic features based on variables in the 1981 census.[4]

Ratio of observed to expected numbers of cases of acute lymphoblastic leukaemia in childhood in 145 districts of England and Wales 1984-8

Classification of local authority district	Observed: expected cases	Observed: expected cases adjusted for social class	No of cases
Service centres and cities	0·69	0·73	59
Traditional manufacturing towns	1·06	1·11	66
Mixed towns and country areas	1·09	1·13	171
High status areas	0·94	0·85	34
Resort and retirement areas	1·10	1·00	27
More rural areas	1·11	1·05	81

*According to national classification of residential neighbourhoods.

The ratio of observed to expected cases standardised for age and sex showed a significant deficit of childhood acute lymphoblastic leukaemia in the large urban service centres and cities (observed:expected = 0·69, p = 0·008; table). This could reflect the concentration of more socially deprived populations in cities as childhood leukaemia occurs more commonly in areas of higher social class.[2] The deficit remains, however, after social class is controlled for (observed: expected = 0·737, p = 0·022). None of the other results were significant at the 0·05 level. The deficit was absent from other urban areas such as traditional manufacturing towns and mixed town and country districts with some industry.

It seems that a relative protective effect against childhood acute lymphoblastic leukaemia is being seen in major cities compared with smaller urban centres as well as more rural areas. The large cities and service centres have well mixed populations, with a greater than average transient population of young people, high rates of daily commuting, and high densities.[4] Modelling of epidemic patterns of common infections[5] can show that large cities are likely to have fairly stable endemic levels of most common infections, and large pools of susceptible subjects are unlikely to develop. Epidemic outbreaks affecting large proportions of the population over short times are less likely than in other areas. The observed deficit in large urban centres could therefore lend support to the infection hypothesis of childhood leukaemia.

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1 Kinlen LJ, Clarke K, Hudson C. Evidence from population mixing in British new towns 1946-85 of an infective basis for childhood leukaemia. *Lancet* 1990;**366**:577-82.
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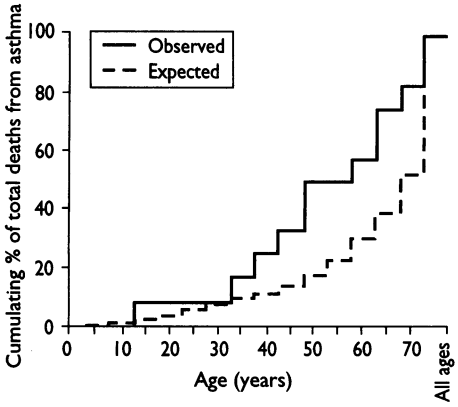
Bronchodilator treatment in asthma

EDITOR,—Win Castle and colleagues have now provided data that were missing from their report on the safety of salmeterol in the large British postmarketing surveillance study[1]—namely, the ages of patients at death.[2] They suggest that, given the range of ages, the only appropriate statistic to use is overall mortality.[2] Failure to analyse by age, however, obscures the important observation that the proportion of younger people among those dying of asthma during salmeterol treatment seems to have increased.

We have compared the data reported from the salmeterol study[1,2] with mortality data for England and Wales for 1988, 1989, and 1990 provided by the Office of Population Censuses and Surveys; we have assumed that the age distribution of the study population was similar to that of the wider asthmatic population. Half of the patients treated with salmeterol who died were aged under 50 compared with only 18% of patients in national statistics, and three quarters were under 65 compared with only 39% in national statistics. The figure shows the observed cumulating proportion of deaths by five year age group among those who died while being treated with salmeterol[2] compared with the expected cumulating proportion of deaths by age calculated from national statistics.



Observed cumulating proportion of deaths from asthma by five year age group in subjects dying of asthma during salmeterol treatment[1,2] compared with expected cumulating proportion derived from national statistics for England and Wales 1988-90

Comparative risks of death should be calculated from the prevalence of asthma in each age group (which is not known) and the number of subjects in each age group exposed to salmeterol in the surveillance study (which Castle and colleagues presumably do know). In the absence of these data, the calculations above provide the only means of relating actual mortality to expected mortality; they leave us with the concern that salmeterol seems to increase the risk of death among younger people.

We remain surprised that five of the 14 deaths from asthma reported by Castle and colleagues occurred in hospital. The statement that these patients "were not found to have had unusual features" is singularly uninformative. Death from asthma should be exceedingly rare once a patient is in hospital; again we question whether these subjects had attacks resistant to usual treatment. How many of these subjects were using salmeterol?

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1 Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;**306**:1034-7. (17 April.)
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High dose inotropic support in septic shock

EDITOR,—We endorse most of J D Edwards's recommendations on the management of septic shock.[1] We cannot, however, agree with the statement that treatment directed at attaining high levels of oxygen delivery and oxygen consumption has been well validated. Two of the studies quoted to support this contention were not controlled,[2,3] and the third showed an improvement in survival only when the groups were redefined so that one consisted of control and protocol patients who achieved a high cardiac index ($>4{\cdot}5$ l/min/m^2) while the other comprised all those who failed to achieve this value.[4]

Although high levels of oxygen delivery and oxygen consumption are clearly associated with survival from critical illness, there are no convincing data to suggest that the aggressive use of inotropic support in an attempt to achieve values of these variables seen in survivors improves outcome in septic shock. Rather—provided volume replacement is adequate, blood pressure is maintained, and inotropes are used appropriately to achieve a normal cardiac output—the observed relation may simply reflect the physiological reserve and the severity of the insult. Indeed, the use of high dose inotropic support may be associated with worsening of the maldistribution of flow, cardiac arrhythmias, and myocardial ischaemia.[5] Until the results of prospective randomised controlled trials analysed according to intention to treat are published the value of high dose inotropic support remains uncertain.

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1 Edwards JD. Management of septic shock. *BMJ* 1993;**306**: 1661-4. (19 June.)
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Contraceptives and the selected drugs list

EDITOR,—Contraceptives are among the 10 categories of drugs to be added to the selected drugs list. Both the editorial and the correspondence on the selected list failed to emphasise the consequences of a reduction in choice for women needing contraception.[1,2] Many people argue that a reduction in the range of contraceptives would lead to more women stopping taking them and more unwanted pregnancies. The most widely used reversible method of contraception in Britain, and the one with the most scope for a reduction in prescribing costs, is the combined contraceptive pill, with prices ranging from 60p to £2.40 for a 21 day course. While one particular brand may be suitable for many users, some women need an alternative preparation to obtain safe contraception that is free of side effects.

We have investigated the prevalence of changes in the brand prescribed in our family planning and well woman centre in Edinburgh. The records of the first 2000 new patients to register in 1988 were analysed to determine the number of changes of brand of combined pill that occurred over the subsequent five years and the reasons for the change. A total of 1536 women attended for advice on contraception, 73% of whom used the pill at some time during the five years. Altogether 699 women used only one brand of pill and 417 changed their brand at least once (105 women switched brands twice and 60 switched brands three times or more). Where a reason for change was recorded (n = 670) breakthrough bleeding was the commonest (132 women). Some 40 changed brands on the advice of the doctor. Forty one women were known to have had a termination of pregnancy during the period of the study: 35 of these terminations occurred in the women who changed their pill at least once.

Clearly, an appreciable proportion of women will try a different pill in an attempt to overcome troublesome side effects. Women who have difficulty in finding an acceptable method seem to be at greater risk of an unwanted pregnancy. A reduction in the choice of available pills would reduce the chance of some women finding an acceptable one. Sixteen of the brands of combined pill currently available cost under £1 for 21 days; retaining these would result in a fairly large selected list. We believe not only that there must be choice but that the choice must include the modern, third generation pills containing progestogen, which may be safer and more effective.

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1 Bateman DN. The selected list. *BMJ* 1993;**306**:1141-2. (1 May.)
2 Correspondence. Limiting the drugs list. *BMJ* 1993;**306**:1687-8. (19 June.)

Cimetidine and weight loss

EDITOR,—P Mangtani and P Seed raise three questions[1] about our study of cimetidine and weight loss.[2] They suggest that inclusion of the non-compliant patients would have resulted in a significant difference in weight loss between the placebo and cimetidine groups. Analysis of our trial by intention to treat did not, however, change the outcome or the conclusions. Furthermore, the small number of non-compliant patients and the about average weight loss of these patients could not explain the average increase in weight during the third week of the study as suggested.[1]

Mangtani and Seed also suggest that the