space is traversed (this has a value of between 60 ml in the short pathways and 300 ml in the long pathways) carbon monoxide mixes according to the laws of diffusion with the lung volume.

The quantity of carbon monoxide produced by a cigarette is determined by (*a*) the temperature at the burning tip, which is a function of the inspiratory profile, (*b*) the ventilation of the paper and (*c*) the puff volume. The retention of carbon monoxide by the pulmonary circulation depends on the post puff inspiratory volume and the dwell time in the alveoli. The machine smoked yield of carbon monoxide is a poor indicator of inspired carbon monoxide and is a lesser indicator of retention so that its use as an objective measure of inhalation leaves much to be desired, as it omits the most important determinant, that of dwell time. If all other variables were identical a smoker with a dwell time of 3 seconds would have about one half of the carboxyhaemoglobin concentration of one with a dwell time of 6 seconds.

Particles behave in a different way, being carried into the lungs by convective flow, while diffusion plays almost no part and dead space has no meaning. Thus any indicator for particulate behaviour cannot properly be gaseous, and this is a real problem in assessing the retention of smoke particles. Dwell time plays a lesser part in particle deposition, the major reason for deposition being impaction on bronchial walls, which is a function of convective gas velocity. This in no way invalidates the point that inhalation may produce different patterns of particulate deposition but does deny the use of carbon monoxide levels as an index of such deposition and the verdict on the paper must be "not proved."

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Effect of stopping smoking after unstable angina and myocardial infarction

SIR,—Dr Leslie E Daly and others (30 July, p 324) reported mortality in a study population of 498 men divided into three groups: non-smokers at entry who remained non-smokers; smokers at entry who continued to smoke; and smokers at entry who stated two years after the first episode that they had stopped smoking. If reliable conclusions about the effects of smoking are to be drawn from comparisons between such groups all groups should be as similar as possible with respect to all pertinent factors except for the variable under test, cigarette smoking. In fact, continuing smokers differed from those who gave up smoking with respect to exercise; non-smokers showed various differences from smokers. As Dr Seltzer infers (29 October, p 1301) and Dr Daly and his colleagues concede (29 October, p 1302), non-smokers and smokers were not even matched for the severity of the initial attack. The requirements for valid scientific inference are not met in this or many other comparable studies.

An important risk factor for ischaemic heart disease is genetic predisposition, which is not readily controlled in epidemiological studies. As Dr Seltzer hints, randomisation is one way of achieving this desirable objective. In such a study smokers satisfying certain entry criteria are allocated randomly to one of two groups: the "intervention" group, which is subjected by the investigator to intensive pressure to give up smoking; and the "normal care" or control group, which is not subjected to such pressure. Randomisation of a suitably large population of selected smokers will ensure that the two groups are as well matched as possible for all pertinent factors, known or unknown, genetic and environmental. One randomised controlled trial of antismoking advice, uncomplicated by other forms of intervention, has been carried out in this country by Professor Rose and his colleagues, and the results of a 10 year follow up have been published.[1] In the intervention group of 714 men 123 deaths (17%) were reported; in the normal care group of 731 men 128 deaths (17·5%) occurred. The small difference is, of course, non-significant, its 95% confidence limits being −22% to +23%.[1] The main theoretical misgiving about randomised trials is that the pressures on the intervention group to give up smoking might result in other changes—for example, of diet or psychological stress—that could render that group dissimilar from the group receiving normal care.

Another method that controls for the effects of genetic predisposition and defeats the bias of self selection—but avoids the pressures of intervention—is the analysis of temporal (secular) trends in the levels of smoking and of ischaemic heart disease in a large and effectively closed population, such as that of England and Wales. Fortunately, the complications normally associated with secular changes in diagnostic practice and other causal or prophylactic agents can in this instance be overcome, and analysis shows that the association between smoking and fatal ischaemic heart disease has no appreciable causal component.[2]

For these several reasons the conclusion of Dr Daly and his colleagues "that stopping smoking is the most effective single action in the management of patients with coronary heart disease" must be questioned.

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[1] Rose G, Hamilton PJS, Colwell L, Shipley MA. A randomised controlled trial of anti-smoking advice: 10-year results. *J Epidemiol Community Health* 1982;**36**:102-8.
[2] Burch PRJ. Ischaemic heart disease: epidemiology, risk factors and cause. *Cardiovasc Res* 1980;**14**: 307-38.

**The authors reply below.—ED, *BMJ*.

SIR,—We accept fully the theoretical arguments for a randomised trial of stopping smoking after myocardial infarction. Indeed, were it ethically defensible or practically possible we would advocate such an approach. As it is, we have to make the best use we can of observational studies.

Dr Burch suggests that valid scientific inferences cannot be made in our study because we did not correct for possible confounding variables. Adjustment for such variables is required only when aetiological conclusions are to be made in the comparison of two or more groups. Our paper concentrated mainly on the 374 patients who were smokers at entry into the study, the basic comparison being between those who stopped smoking and those who continued to smoke.

A careful search for possible confounders in the comparison between those who stopped and those who continued smoking was made and the analysis was presented separately for three severity groups. Of all the other factors examined, exercise was the only one significantly associated with continuing or stopping smoking. Exercise experience, however, cannot explain the observed difference in mortality between the two groups as it was not itself related to mortality and thus cannot be a confounder of the association. This was stated in our paper.

We fully accept that the third group in our paper—the initial non-smokers—was indeed different from the group of initial smokers. In fact we pointed out that such differences may have contributed to their relatively poor survival. We did not correct for these factors as the comparison with non-smokers was not a major part of our paper and it is important to note that their adverse prognosis compared with those who stopped smoking was to be expected because of their higher prevalence of risk factors other than smoking, including hypertension and a higher mean age. To present mortality in non-smokers corrected for these factors would distort the de facto situation.

Dr Burch raises the possibility that the mortality difference between those who stopped and those who continued smoking could be due to unmeasured confounding variables, such as a genetic predisposition. The high relative risk of 2·4 between those who continued smoking and those who stopped is most unlikely to be due to the existence of an unmeasured confounder.[1] To explain the results on a genetic basis would require a strong genetic influence on cessation of cigarette smoking, an unlikely hypothesis. For this reason we consider it most unlikely that one or more unidentified factors explained the observed difference in mortality between those who stopped smoking and those who continued. We consider that our study confirms the importance of stopping smoking after myocardial infarction.

Dr Burch referred to the papers by Rose *et al* and Burch. Both these papers deal with primary prevention and are irrelevant to our study of secondary prevention.

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[1] Cornfield J, Haenszel W, Hammond EC, Lilienfeld AM, Shimkin BM, Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some questions. *Journal of the National Cancer Institute* 1959;**22**:173-203.

An unusual cluster of babies with Down's syndrome

SIR,—Dr Patricia M E Sheehan and Professor Irene B Hillary contacted all 213 pupils who attended the same school in the 1950s (a remarkable achievement) and found a total of six babies with Down's syndrome born to six ex-pupils. These six mothers had had a total of 26 babies.

The authors state that this gives an incidence of six cases of Down's syndrome in a total of 26 pregnancies. I have heard that you can prove anything with statistics, but this is

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