Help for parents after stillbirth

SIR,—Professor R W Beard and his colleagues (21 January, p 172) ask for comments and criticisms on the leaflet which they have designed for parents whose child is stillborn. Our comments are based on our recent experience of undertaking a review of all perinatal deaths in Leicestershire and interviewing in depth a sub-sample of these women in the months following the event.

Many mothers we have interviewed have commented that it was particularly valuable to discuss matters with someone who was not emotionally involved in the situation, as this gave them an opportunity, which they felt they needed, to be more open about their feelings. We feel that it would not be helpful for parents to read generalised descriptions of a highly personal grief, and in some cases such descriptions could have a harmful effect. Judging from our experience the parents need the opportunity to explore their own emotional reaction and to receive support in this.

It also seems likely that the sections of the proposed leaflet concerned with seeing and holding the baby and the funeral and burial arrangements are redundant, since such decisions need to be taken shortly after the death. We feel that these matters too are discussed more appropriately in the period immediately after delivery or following early neonatal death.

We also feel that there are considerable difficulties in producing a leaflet for distribution to parents from widely varying social and cultural backgrounds where the ability to read and understand the language in the leaflet may be limited. Certainly within our experience there would be a substantial number of parents who would not fully understand parts of the proposed leaflet.

At the present time many parents who suffer either a stillbirth or a neonatal death do not, as suggested by Ann Cartwright (4 February, p 298), receive the help they need. This is in part due to the fact that the training of doctors and nurses is largely inadequate in equipping them to discuss the effects and management of bereavement. We must therefore place increasing emphasis on the training of doctors and nurses to provide the necessary support for these parents. We must ensure, if we are to provide leaflets of the kind suggested, that these supplement good personal counselling and do not become the excuse that doctors and nurses use to explain the avoidance of personal discussion.

JACQUELINE HEWARD MICHAEL CLARKE
P B WOODCOCK JOHN MACVICAR
L F PHILLIPS JULIA FAULCONBRIDGE
A J WILLIAMS

University of Leicester Medical School

Salbutamol: lack of evidence of tumour induction in man

SIR,—Dr D Poynter and others (7 January, p 46) purport to place in perspective the finding of tumorigenicity in rats of the β -adrenoceptor stimulant salbutamol. This finding led the US Food and Drug Administration (FDA), on the advice of its Pulmonary, Allergy and Clinical Immunology Advisory Committee, to suspend further clinical testing of salbutamol and to request manufacturers of currently marketed β -stimulant bronchodilators and of those undergoing clinical

investigation to perform adequate animal studies to ascertain whether the tumorigenicity demonstrated with salbutamol (and two non-marketed β -stimulants) would also be evident with any of their compounds. In attempting to place the rat findings in perspective Dr Poynter and his colleagues make several unwarranted assumptions.

First I shall describe the actions of the FDA, which were not adequately explained by Dr Poynter and his colleagues. The tests required of the β -stimulant bronchodilator manufacturers are virtually identical with those performed by the Schering Corporation and Mead Johnson Inc on salbutamol and the two non-marketed compounds. The purpose of these tests is to determine whether tumorigenicity is a class-related or only a compound-related phenomenon. In this connection it should be noted that the FDA has required all manufacturers of β -adrenergic blocker drugs to perform tumorigenicity studies, using a protocol with as many common features as was feasible, because of a finding of tumorigenicity in some members of the class. These studies have shown that some β -adrenergic blockers are tumorigenic under the conditions of study and some are not, and as a result compounds demonstrating tumorigenic properties have been withdrawn from clinical studies. Similarly, the FDA has required class studies for the oral contraceptives and several have been removed from clinical use because of tumorigenicity in dogs.

The concern of the FDA and its advisory committee is not an isolated one. Following presentation by the FDA of the findings with salbutamol (and the other two investigational drugs) to the National Cancer Institute's Chemical Selection Working Group of the Chemical Carcinogenesis Bioassay Program the group nominated isoproterenol (isoprenaline), epinephrine (adrenaline), and ephedrine (with phenylephrine as a control for the β -adrenoceptor hypothesis of tumorigenicity) for testing under the bioassay program.

Should it transpire that tumorigenicity of the β -stimulant bronchodilators is a class-related phenomenon, perhaps due to an effect on β -adrenoceptors, as hypothesised by Dr Poynter and his colleagues, then all members of the class would be treated equally and information about the animal findings would be placed in the labelling for all of the β -stimulant bronchodilators. Since it is by no means certain that such is the case, however, in our opinion it would be a disservice to the public to allow marketing of a compound which is a demonstrated tumorigen when other compounds are available which have not been implicated to date. If salbutamol were a compound with significant advantages over all other available β -stimulant bronchodilators, then the benefit-risk considerations would permit marketing at this point in time. Such advantages, however, have not yet been shown.

In their discussion of the implications of the finding of mesovarian leiomyomas in rats Dr Poynter and his colleagues dismiss the finding in a manner which is simplistic. They assume that a specific animal tumour can be directly extrapolated to another species, in this case the human, when it is well known that tumorigenic compounds may produce tumours in different locations in different species. Having made their extrapolation, however, they then assume that because there has been no reported increase in the incidence of mesovarian leiomyomas in women, and in particular women treated with various β -stimulant bronchodilators, these drugs are free of the potential for causing such tumours. Dr Poynter and his colleagues assume that, in the absence of any inkling of a possible association between such tumours and the use of the β -stimulants, physicians would nevertheless have recognised an association. The chances of such an association being detected by a practising physician are extremely limited and it would require either epidemiological studies to determine whether an association exists or the astuteness of a Baum who, having heard of two cases of benign hepatomas within close proximity in time, searched for

additional cases and suggested an association between oral contraceptive use and hepatomas.¹ Not to detract from her astuteness, it should be pointed out that an association between a steroid and adenomatous lesions of the liver was a less difficult one of which to conceive than would be that of β -stimulant bronchodilators and mesovarian leiomyomas. Should there be evidence of tumorigenicity in the studies to be conducted by the National Cancer Institute with the older bronchodilators, serious consideration would need to be given to the conduct of epidemiological studies to attempt to determine whether there is an increased risk of tumours in humans.

Finally, Dr Poynter and his associates are comforted by the fact that there was no evidence of malignancy in the rat mesovarian leiomyomas. Whereas some comfort can be taken from this finding in that salbutamol appears to be a weak tumorigen, it has been demonstrated repeatedly that tumorigens are capable of inducing both benign and malignant lesions under appropriate conditions and oncology experts are reluctant to conclude that any tumorigenic compound will be restricted in its activity to the induction of benign tumours.

Although it may very well be that the findings with the β -adrenoceptor stimulants are species-specific (Dr Poynter and his colleagues indicate that there were no tumorigenic findings in salbutamol-treated mice), this will never be known with certainty. Some years ago a pharmaceutical industry colleague of theirs stated: "Unfortunately, some toxic manifestations are species-specific, occurring perhaps in only one animal species while absent in others. Nevertheless, in our present state of knowledge, prudence requires that man should be considered equivalent to the least favoured species" (his italics).²

MARION J FINKEL
Associate Director for
New Drug Evaluation,
Bureau of Drugs

Department of Health Education
and Welfare,
Public Health Service,
Food and Drug Administration,
Rockville, Maryland

¹ Baum, J K, *et al*, *Lancet*, 1973, **2**, 926.

² Bogue, J Y, *Pharmaceutical Journal*, 1962, **188**, 27.

The water story

SIR,—Your recent leading article entitled "Progress in the water story" (4 February, p 264) evokes the response, "Whither?" It is disappointing that in summarising 20 years of epidemiological study into the relationship between heart disease mortality and the concentration of calcium in drinking water many significant papers should receive no mention. Heyden¹ reviewed the work in this subject and drew very different conclusions from yours—perhaps because of differences in the samples of papers considered. For example, you mention (without reference) a study of communities which changed the calcium concentrations of their water supplies but not community studies matched for socioenvironmental variables other than drinking water calcium (for example, Allwright *et al*²) or comparing cases and controls within one community (for example, Comstock³). These studies, using respected epidemiological techniques to reduce the effect of confounding variables, failed to show any association between water calcium and heart disease mortality.

Another surprising omission was the work of British pioneers in the present controversy. Morris *et al*⁴ showed that the "unexplained" association between drinking water calcium