necessary to allow the patient's transfer elsewhere—for rehabilitation, for example.

In conclusion, the cornerstone of control of methicillin resistant *S aureus* is good infection control practice, as I stated in my review. Infection control teams wish to prevent and control the spread of any multiresistant organism as the antimicrobial armamentarium against these organisms is reduced. Additionally, the few available antibiotics tend to be expensive and may be toxic. Unfortunately, epidemic strains of methicillin resistant *S aureus* still exist, and unaffected hospitals should remain vigilant to prevent their arrival and spread.

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Managing the third stage of labour

Nausea is a fair price for preventing haemorrhage

EDITOR,—Susan J McDonald and colleagues conclude that there are "few advantages but several disadvantages for the routine use of oxytocin-ergometrine when prophylactic active management of the third stage of labour is practised."¹ The disadvantages were significantly higher rates of nausea, vomiting, and high blood pressure measured in the labour ward. The results suggested, however, that if women received oxytocin alone an additional 8-11 women per 1000 would experience a severe postpartum haemorrhage. This is roughly one patient a week in an average hospital with 5000 deliveries a year. Although this increased incidence did not reach significance, it might have done had more women been recruited to the trial, as suggested by the results of meta-analysis.²

As the authors point out, postpartum haemorrhage is an important cause of death both in Britain and, more particularly, in the Third World. As it is far more important than the transient side effects that did reach significance, I believe that the conclusion reported was misleading. Until further studies with increased doses of oxytocin prove it to be as effective as the combined oxytocin-ergometrine preparation at reducing the incidence of postpartum haemorrhage, my preference will not change.

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Oxytocin more stable in tropical climates

EDITOR,—Susan J McDonald and colleagues conclude that parenteral oxytocin is as effective as a combination of oxytocin and ergometrine in reducing the risk of postpartum haemorrhage when used routinely in the third stage of labour but that the combination is associated with nausea, vomiting, and increased blood pressure.¹ In selecting the most appropriate injectable oxytocic drug for developing countries additional arguments should be used, such as the stability in tropical climates and cost. The stability of these lifesaving drugs is crucial as a serious lack of the active ingredient in samples of ergometrine has been reported from several developing countries.²

As part of a systematic research programme by the World Health Organisation to reduce maternal mortality we have studied the stability of different injectable oxytocic drugs at various temperatures and in various light conditions. Ampoules of 11 brands of injectable ergometrine, methylegometrine, and oxytocin were stored in the dark at 4-8°C, 21-25°C, 30°C, 40°C, and 50°C and in daylight (but protected from direct sunlight) at room temperature (21-25°C). The amount of active ingredient was measured at 0, 0.5, 1, 2, 3, 6, and 12 months. When stored at 4-8°C in the dark all three drugs retained acceptable amounts of active ingredient (table). All three drugs, however, showed a gradual loss of the active ingredient over time, the decline being faster at higher temperatures. In addition, ergometrine and methylegometrine were both very unstable when exposed to light, with an average loss of 21% and 27%, respectively, of the active ingredient in one month (range 14-61%) and over 90% after one year. Short exposure (2-4 weeks) to temperatures of 40-50°C in the dark—which often occurs during transport in tropical countries—had no serious effect on any of the drugs. Full results have been reported.³

Active ingredient of injectable oxytocic drugs after one year of controlled storage (values are mean percentage of initial amount (95% confidence interval))

	Storage condition		
	Dark, 4-8°C	Dark, 30°C	Light, 21-25°C
Ergometrine	95 (90 to 100)	69 (56 to 83)	9 (2 to 15)
Methylegometrine	96 (92 to 100)	82 (69 to 94)	9 (0 to 22)
Oxytocin	101 (99 to 102)	86 (83 to 90)	93 (91 to 95)

Under tropical conditions of temperature and light, oxytocin is more stable than either ergometrine or methylegometrine. This is especially relevant as ampoules of oxytocic drugs are often kept in open trays ready for use in pharmacies and labour wards in developing countries. The non-profit world market prices of generic 0.5 mg ergometrine and 10 IU oxytocin are similar at around \$0.11 per phial. The better stability in tropical climates and equal cost are additional reasons why oxytocin is the drug of choice for routine use in active management of the third stage of labour in developing countries.

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Reduction in haemorrhage is a major advantage

EDITOR,—Susan J McDonald and colleagues make recommendations about the most effective oxytocic agent in the management of the third stage of labour.¹ We are surprised at their conclusion that a potential 1% reduction in severe postpartum haemorrhage is of minimal advantage compared with the "serious" disadvantages of vomiting and a rise in blood pressure. As their observed rate of severe postpartum haemorrhage was 4%, a 1% reduction is in effect a 25% reduction in the overall incidence. We consider this to be a major advantage, especially in the developing world, compared with the "non-serious," albeit unpleasant, disadvantages of vomiting and changes in blood pressure of uncertain adverse clinical effect.

The interpretation of the data remains subjective. We think that it is worth detecting a true reduction of 1% in the incidence of severe postpartum haemorrhage in view of the contribution of postpartum haemorrhage to maternal mortality globally. This would have required a sample size of 8300, so we would have recommended the extension of the McDonald and colleagues' trial. The reduction of postpartum haemorrhage deemed to be clinically important remains arbitrary.

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Deciding who should have thrombolysis

EDITOR,—K S Channer¹ and other correspondents seem to misunderstand the results of clinical trials of thrombolytic agents. In 17 000 patients in the second international study of infarct survival (ISIS-2) the odds of dying were reduced by 25% by streptokinase compared with placebo (figure).³ With such large numbers the confidence intervals, which indicate where the "true" result is to be found with 95% certainty, are narrow.

The reduction in odds was greater than average for those with ST elevation in the presenting electrocardiogram and less than average for those without ST elevation. The confidence intervals did not include unity for either group, so a significant

Odds ratios and 95% confidence intervals for death within 35 days after streptokinase or placebo in patients with or without ST elevation in second international study of infarct survival

reduction in mortality was shown for both groups. Subdivision of these two groups into seven electrocardiographic categories resulted in widening of the confidence intervals, so that significance was lost for all categories except those with anterior ST elevation. Nevertheless, in each category except ST depression mortality was lower with streptokinase than with placebo, and the wide confidence intervals in those with ST depression mean that benefit in that subgroup is not precluded; indeed, benefit was seen when streptokinase was given with aspirin.

Subgroup analysis, by reducing group size, carries the risk of perpetrating a type II error—the conclusion that two treatments are equivalent when they are not. It may be a grievous mistake if, as a result of such a conclusion, patients are not given the benefit of the doubt but receive the inferior treatment.

To decide whether patients are likely to benefit from thrombolytic treatment one should consider whether they would have met the inclusion criteria for any of the trials of thrombolysis. If they are suspected of having acute myocardial infarction and would have been eligible for the second international study of infarct survival the odds of their dying would be reduced by 25% with streptokinase—a little more if they had ST elevation and a little less if they had other electrocardiographic abnormalities.

In the face of the overwhelming evidence of benefit for suspected acute myocardial infarction that has been obtained from large clinical trials,¹ it is perverse for Channer to suggest that thrombolytic treatment should be withheld from an eligible patient on the basis of speculation about the pathogenesis of the acute coronary syndrome in a small minority of patients.

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The Gardner hypothesis

Found wanting

EDITOR,—In 1990 Gardner *et al* identified an association between paternal preconceptional irradiation and childhood leukaemia and non-Hodgkin's lymphoma in a subpopulation of workers at Sellafield living in west Cumbria.¹ The Gardner hypothesis asserted that this association might be causal. In her editorial Hazel Inskip cites a series of studies that have been conducted to test the hypothesis.² Perhaps the most telling of these is the recently published work of Parker *et al*, which tested the Gardner theory in the whole of the population from which it was derived.³ This study, along with the others described by Inskip, have failed to support the hypothesis of paternal preconceptional irradiation, as Inskip acknowledges.

Also mentioned is the possibility that paternal preconceptional irradiation might be a marker for some other occupational exposure. Although these other occupational factors should more properly be seen as confounders of the original study, some people have raised them to the status of surrogate Gardner hypotheses. Now these too have been tested by the Health and Safety Executive's recent study and found not to support a Gardner-type theory.⁴ We work as chief medical officers in the nuclear industry, and our first duty is to keep employees fully informed of the risks of working in

the industry. We have been cautious not to express any view until the science base has been overwhelming in the clarity of the opinion that it offers.

Hypotheses are useful only as a stimulus to work and must be discarded if found wanting. If the jury is truly still out on the Gardner hypothesis then it is still out on the link between smoking and cancer. In our view the link between smoking and cancer has stood the test of time, but Gardner's hypothesis has not and should be set aside. It remains to be seen if other theories such as those of Kinlen can explain the Seascale cluster.⁵ One fact that 10 years of costly research has determined is that, whatever does explain the cluster, it is not paternal preconceptional irradiation.

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Cancer not linked to radiation or chemicals

EDITOR,—In her editorial on the Gardner hypothesis Hazel Inskip¹ refers to the Health and Safety Executive's recently published study of childhood cancer in the children of workers at Sellafield.² She makes the point that this and other evidence now shows little support for a direct causal association between paternal preconceptional irradiation and leukaemia. She goes on to mention an alternative suggestion—put forward by Gardner—"that some other exposure (for which to date there are few clues), such as to chemicals or internal exposure to radionuclides, might be responsible" but does not say that the Health and Safety Executive's study addressed such alternatives.

In that study we examined case and control fathers' assessed potential for exposure to a range of chemicals, their assessed and measured exposure to radiation from internal radionuclides, and their recorded involvement in contamination incidents. None of these factors explained the different patterns of incidence of leukaemia and non-Hodgkin's lymphoma between Seascale and elsewhere or the association between preconceptional irradiation and leukaemia and non-Hodgkin's lymphoma in Seascale. There was also no overall association between fathers' internal radiation dose and leukaemia and non-Hodgkin's lymphoma (or other cancers) in their children. This was true both for total internal dose and for the dose due to α emitters. There was a strong positive association between fathers' assessed potential exposure to tritium and leukaemia and non-Hodgkin's lymphoma in their children, but this association was not borne out by the data on measured exposure to tritium.

Inskip also refers to other cancers in young people in Seascale and the possible role of the Sellafield plant in their occurrence. The Health

and Safety Executive's study found no positive association between any of the workplace factors examined and the occurrence before the age of 25 of cancers other than leukaemia and non-Hodgkin's lymphoma in the children of male workers at Sellafield. Nor did it find any evidence of a role for population mixing in this regard, in contrast to the finding of a possible role for this postulated mechanism in the occurrence of leukaemia and non-Hodgkin's lymphoma in Seascale.

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Old infective theory discredited

EDITOR,—The review by Hazel Inskip of evidence relating to the Gardner hypothesis¹ refers to resurrection of an infective theory to offset anomalies in the epidemiological evidence on which the hypothesis rests and to explain the clustering of leukaemia cases round Seascale and some other locations. Kinlen and others have proposed that the congregation of previously separate communities to form new towns may raise the incidence of leukaemia by facilitating transmission of infective agents.^{2,3}

Those who have worked in cancer research for the past 50 years or so will know that the infective theory of human cancer causation became a global obsession for many years after the 1930s. Our Imperial Cancer Research Fund, under three successive directors, was exclusively dedicated to a general infective theory of malignant disease. The British Empire Cancer Campaign allocated a substantial portion of its resources to a hunt for viruses that caused cancer and, year after year, promised its supporters imminent prevention of leukaemia by immunisation. The National Cancer Institute of the United States set up a large institute dedicated to the isolation and characterisation of viruses causing human cancer (by the early 1980s the building was used as a warehouse). This worldwide, protracted, and costly crusade failed to prove an infective cause for any human malignant disease.

Leukaemia and Hodgkin's disease have always been the prime suspects, and clustering of cases evidently continues to sustain wistful believers of the infective theory. It does not seem a wise scientific policy to respond to deficiencies of evidence for the Gardner hypothesis by reinstating an infective theory that has been so intensively explored and decisively discredited. The Gardner hypothesis rests on the well established facts that ionising radiation does induce genetic mutations and that such mutations may be manifested by somatic disease in progeny.

Finally, if the infective theory came to vie with the Gardner hypothesis in the courts damages might be sought from industry on the grounds that the risk of childhood leukaemia had been increased by the creation of new towns for the purpose of advancing large projects.

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