Dangers of ozone depletion

SIR,—The dangers of ozone depletion in the United Kingdom, particularly with regard to non-melanoma skin cancer, are probably much greater than estimated in the recent article on this topic by Fiona Godlee.¹ The figures given in the article suggest that non-melanoma skin cancer may rise by 8000 cases a year in Britain if there is a 10% reduction in total column ozone. This figure is based on current incidence figures from cancer registries, which are widely accepted as being gross underestimates.²

I recently suggested that the true incidence of non-melanoma skin cancer in England and Wales may be close to 100 000 cases a year.³ If this is true then, using a formula devised at the National Cancer Institute, Bethesda, Maryland,⁴ we might expect something like 35 000 extra non-melanoma skin cancers each year in England and Wales. Furthermore, there would probably be a relative increase in the potentially more dangerous squamous cell carcinoma compared with basal cell carcinoma.⁵ Of course, these figures should not be taken at their face value as it is difficult to give an exact percentage rise in skin cancers because predicting what changes may occur in holiday and clothing habits is impossible.⁶

The article therefore highlights the inadequacy of registration of skin cancer in the United Kingdom. Few attempts have been made to define the extent of the problem, and thus monitoring adequately any changes that may occur in the incidence of skin cancer is going to be impossible. As I have pointed out previously, there is an urgent need to review and improve registration of skin cancer throughout the United Kingdom.³

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Infection acquired from transplant donor

SIR,—Jérôme Babinet and colleagues report the transmission of *Plasmodium falciparum* by cardiac transplantation.¹ The diversity of infections after transplantation is increasing, and we report a new mechanism for transmission of the common cold.

A 37 year old woman with complex cyanotic congenital heart disease received a heart-lung transplant from a 14 year old girl who had died of meningitis of uncertain aetiology. In accordance with our routine practice, bronchial secretions and bronchoalveolar lavage specimens were taken from the donor airways for microbiological culture before transplantation. There was a mild polymorphonuclear cell infiltrate, and culture yielded both *Staphylococcus aureus* and rhinovirus. After an uneventful transplant procedure she was extubated within 24 hours.

On the fifth postoperative day she developed a temperature with coryzal symptoms and signs. There was no evidence of deterioration in chest radiographs or on blood gas analysis, and culture of bronchoalveolar lavage specimens yielded the rhinovirus identified previously. No evidence of

rejection was found on transbronchial biopsy, and her common cold resolved over the next four days with only symptomatic treatment. However, rhinovirus was identified in routine bronchoalveolar lavage samples for up to six weeks after transplantation.

Although infection acquired from the donor is a well recognised problem in pulmonary transplantation,² we believe that this is the first report of a new "exogenous" mechanism of spread of rhinovirus.

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Heart valve records falsified

SIR,—Clare Dyer reported on malfunctioning Björk-Shiley convexoconcave heart valves.¹ Shiley has sent data on the fracture of struts of the valves to specialists but not general practitioners. Prompt diagnosis of fractured struts and treatment may save lives and litigation. As the risk of valve replacement is currently much higher than that of strut fracture,² explanation is not recommended. Concern has been expressed about undue anxiety when asymptomatic patients are notified.

General practitioners have ultimate responsibility in the aftercare of those needing careful counselling. It is often they who have the most contact with the patients and families many years after implantation of the valve. It is vital that they should be equipped with sufficient knowledge to deal with the many questions surrounding this issue.

Tracing recipients of convexoconcave valves will be difficult. General practitioners should check records of patients taking anticoagulants or who had a heart valve implanted between 1979 and 1986. If the make of valve cannot be identified the implant surgeon should be contacted. Medic Alert, with a grant from Shiley, has launched an international implant registry to trace the estimated 4000 recipients in the United Kingdom through the medical profession. Recipients of Shiley valves will be offered free membership and information on future developments.

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Dundee coronary risk-disk

SIR,—Several people who read my article on the Dundee coronary risk-disk have written to me because they have been puzzled by their inability to relate the multiple logistic function formula for the five year risk of coronary heart disease, which always gives a probability below unity, to the Dundee risk score (shown in figure 1 and in the photograph of the disk), which runs from 1 to 50.¹ I

emphasised in the paper that this was a relative risk score, which therefore had no absolute units. Because of this I omitted to state that in the formula used for calculating the Dundee risk score the probability shown in the multiple logistic formula has been multiplied by 100, to the percentage risk over five years, as whole numbers are more manageable than decimals. I apologise for the inadequate explanation.

Some of those concerned wanted to program their own electronic calculators to derive both the Dundee score and the rank. Although the rank follows an S shaped curve (shown in figure 1), it does not trace a simple mathematical formula—it traces the population distribution of the score in 10 000 men and women. Our own IBM compatible computer program has a "look up" table, 100 lines long, to emulate the relation between the two non-linear concentric scales on the disk; this is too much for many calculators. Despite the greater versatility and four figure precision of electronic digital microcomputers a dedicated mechanical analogue calculator such as the disk can still score on simplicity.

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Risk factors in Alzheimer's disease

SIR,—The editorial on risk factors in Alzheimer's disease by L J Whalley¹ outlined the results of a collaborative study on the epidemiology of the disease.² Age, sex, and family history emerged as significant risk factors and were duly noted. The editorial did not, however, mention head trauma. In the same European study a history of head trauma was found in 3.35% of cases.³ Subsequent meta-analysis confirmed head trauma as a significant factor in 2.2% of all cases of Alzheimer's disease.⁴ To place this in context, the autosomal genetic defect is responsible for less than 1% of cases.⁵ Thus the editorial omitted to discuss the risk factor currently identified as causing the largest number of cases of the disease.

Our own investigations indicate that repetitive head trauma as suffered by boxers can lead to a disease process with a molecular pathology indistinguishable from that of Alzheimer's disease.⁶ This also applies to some long term survivors of a single incident of head trauma.⁷ More recently we have shown that about a quarter of patients with severe head trauma show formation of β amyloid plaques (a critical pathological feature of Alzheimer's disease).⁸ This complements reports that mutations within the gene coding for the β amyloid precursor protein may be the cause of some familial cases of Alzheimer's disease.⁹ The critical factor in both the genetic and the head injury studies is the disturbance of the precursor protein metabolism, and it has been proposed that the mismetabolism of this protein may cause the disease.⁸ Experiments on mice expressing engineered gene constructs support this hypothesis.⁹

Thus, rather than the presumed complex pathogenesis discussed in the editorial, the pathogenic event is seductively simple. The over-expression of precursor protein and its subsequent mismetabolism are at the heart of Alzheimer's disease. Preliminary evidence indicates that some vascular disorders may also operate in the same way.¹⁰

If mismetabolism of the precursor protein does prove to be the central pathogenic event underlying Alzheimer's disease, irrespective of the causative

factors, we suggest that this has two profound implications: firstly, risk factors in the disease will be defined as those that alter expression of the precursor protein gene, and, secondly, effective treatments of Alzheimer's disease will be those targeted at modulating expression of the precursor protein gene.

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Chemotherapy in advanced ovarian cancer

SIR,—The Advanced Ovarian Cancer Trialists Group performed an overview of randomised trials of chemotherapy in advanced ovarian cancer.¹ I have questions about their conclusion favouring platinum chemotherapy.

They categorised 45 trials into five groups, and many of the trials seem to have had arms that could be included in more than one group. However, there are only four trials in two different groups, and only one trial in three groups. If a trial had an arm that could fit into two groups it should be used twice, and this should be done consistently, to increase the power of the study's findings. The median survivals approximated from the graphs (figs 1, 3, 5, 7, and 9) are 14 months for both arms in group I, 16 and 18 months in group II, 16 and 18 months in group III, 19 and 21 months in group IV, and 22 and 24 months in group V. Some of the difference in the median survival of apparently similar arms may be due to the exclusion of valid subgroups. This increased median survival from group I to group V may simply be due to stage creep, the Will Rogers phenomenon.²

The authors found no significant difference between combinations with and without platinum (comparison III) and also state that there is no evidence that non-platinum drug combinations are superior to non-platinum single agents (comparison I). A reasonable conclusion from these two statements is that there is no clear evidence that platinum based treatment is more effective than a single or non-platinum agent. The reason for stating that "immediate platinum based treatment was better than non-platinum based treatment" is not obvious as the confidence intervals of the relevant curves (figs 1, 3, and 5) show that treatment without a platinum based agent gave equal results.

Logically then, patients could be treated with a regimen such as oral chlorambucil, with com-

bination treatment being reserved for subsequent relapse as no difference in survival has been shown. Oral chlorambucil is well tolerated and can be taken as an outpatient and is cheaper than intravenous platinum based regimens. With platinum added into the cost of treatment as second line treatment there would still be advantages in terms of both cost and quality of life. This must be included as an arm in future trials.

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SIR,—We agree with many of D J Cruickshank's comments¹ on our overview of randomised clinical trials of chemotherapy in advanced ovarian cancer.² He emphasises that in the past clinical practice has been unduly influenced by small, inconclusive trials.

It is true that in the absence of any randomised trials incorporating an untreated control group there is no direct evidence that chemotherapy is beneficial in advanced ovarian cancer. Given the widespread routine use of chemotherapy, however, it would not currently be possible to conduct such a trial. Nevertheless, we are carrying out a trial in early stage disease in which patients are randomised to receive immediate or deferred adjuvant platinum based chemotherapy. This will run concurrently with another trial comparing carboplatin alone with cyclophosphamide, doxorubicin, and cisplatin in advanced disease. Although we agree that quality of life studies are extremely important, these can be placed in context only by accurate estimates of survival. Both of these two trials are "large simple trials," and within their flexible framework interested groups can incorporate assessment of quality of life. Indeed, one such study is already planned.

The trial comparing carboplatin with cyclophosphamide, doxorubicin, and cisplatin shows that we are interested in quality as well as quantity of survival. Although we do not agree that the regimen of cyclophosphamide, doxorubicin, and cisplatin is highly toxic, as some of the severe side effects can be controlled with modern antiemetic agents, it is less pleasant treatment than carboplatin alone. As existing information suggests that platinum based combinations² and, in particular, cyclophosphamide, doxorubicin, and cisplatin³ may improve survival, however, it is necessary to establish whether this is indeed so and the magnitude of any possible effect of treatment. Only then can we consider a reliable cost-benefit analysis of the treatments, including survival, toxicity, and quality of life. Studies of patients' attitudes have shown that they are willing to accept more aggressive treatments in return for very moderate survival benefits.⁴

As there is little reliable information on major prognostic factors in advanced disease the suggested "prognosis oriented treatment strategy" is not feasible at this time. We do, however, believe that further study is required and plan to investigate many prognostic factors when we update the overview next year.

Finally, power calculations were omitted from the article for reasons of space; they are stated clearly in the trial protocols. For the trial comparing carboplatin alone with cyclophosphamide, doxorubicin, and cisplatin in advanced disease, assuming a five year survival of 20%, 2000 patients would enable us to detect a 6% absolute or 30% relative improvement at five years (5% significance

level, 90% power). For the trial comparing immediate and deferred adjuvant platinum based chemotherapy in early disease, assuming a five year survival of 60%, 2000 patients would enable us to detect an absolute difference of 7% with the same significance level and power.

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Intravenous magnesium in suspected acute myocardial infarction

SIR,—In their overview of trials of intravenous magnesium salts in acute myocardial infarction Koon K Teo and colleagues point out¹ that the largest published study (the first Leicester trial) reported only those deaths occurring during the 24 hours for which magnesium sulphate or saline was infused.² We have now completed a long term follow up of the patients randomised in that study, which took place between October 1983 and May 1984. By using hospital and general practice records and the NHS Central Register we have obtained survival data on 96% of the patients at one year and 92% at five years. We have analysed the groups as randomised; the initial report was confined to those in whom myocardial infarction was subsequently confirmed.

The mortality odds ratio and its 95% confidence interval (magnesium:placebo) were 0.64 (0.31 to 1.33) at 28 days after randomisation, 0.77 (0.42 to 1.41) at one year, and 0.77 (0.47 to 1.26) at five years. If the 28 day data are used to recalculate the typical odds ratio for all seven studies included in the overview the point estimate is 0.52 (0.33 to 0.80), marginally nearer the null value but still suggesting that intravenous magnesium has a substantial protective effect.

Recruitment of about 2400 patients to the second Leicester study is due to be completed in February. The fourth international study of infarct survival, which examines an essentially identical magnesium regimen in a factorial design, has already enrolled over 5000 patients. A clear answer on this intriguing issue is therefore likely to be available before long.

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Urinary incontinence

SIR,—Though it is laudable to try to provide and evaluate conservative management of incontinence economically in the community, we think that