ISOLATED TESTICULAR RELAPSE AFTER BONE MARROW TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

SIR,—Total body irradiation (TBI) combined with chemotherapy prevents graft rejection in patients with acute leukaemia receiving bone marrow transplantation (BMT) from histocompatible donors.[1] TBI may also eradicate residual disease in sanctuary sites which drugs do not penetrate. We report two cases of null cell acute lymphoblastic leukaemia (ALL), grafted in remission in whom isolated testicular relapse developed following TBI.

Case 1

A 31-year-old man presented with a 3 week history of malaise in October, 1981. He had splenomegaly (3 cm), a haemoglobin value of 72 g/dl, a white cell count of 2.0×10^9/l and platelet count of 85×10^9/l. Null type ALL (CALLA negative) was diagnosed on bone marrow aspirate. Remission was rapidly achieved with the UKALL IX schedule, and he was given 18 Gy cranial prophylaxis together with a course of six intrathecal methotrexate treatments. In view of his poor prognosis he received a bone marrow graft from his histocompatible father. Following preparation with cyclophosphamide and TBI (9·5 Gy at a dose rate of 2·5 cGy/min) graft-versus-host disease developed. He also had a cord compression requiring laminectomy, following fibrosis caused by an extradural abscess from a lumbar puncture. 7 months after BMT a painless left testicular swelling developed, confirmed on biopsy to be due to a relapse of the leukaemia. At that time bone marrow and CSF were free of leukaemia. Despite left orchidectomy, irradiation of the remaining testis (24 Gy), and systemic chemotherapy, bone marrow relapse developed 8 weeks later, and the patient died of refractory leukaemia.

Case 2

A 19-year-old man presented in July, 1978, with a month's history of tiredness. He had axillary lymphadenopathy and lymphoblasts in the blood. Null cell type ALL was diagnosed on bone marrow examination. He was given COAP chemotherapy and CNS prophylaxis with irradiation and six intrathecal methotrexate treatments. In December, 1980, bone marrow relapse occurred but remission was reinduced. In view of the poor prognosis he was given a BMT from his histocompatible brother following preparing with cytosine, etoposide, methylprednisolone, daunorubicin, and TBI (9·5 Gy at a dose rate of 3·7 cGy/min in a single fraction). In October, 1982, an isolated testicular relapse developed, confirmed on wedge biopsy. After bilateral testicular irradiation (20 Gy) and systemic reinduction chemotherapy he remains well and in remission.

Thirty-three male patients have received BMT for ALL at this centre. All except three patients were transplanted in complete remission. Testicular involvement before BMT was assessed by clinical examination and no patients had signs suggestive of testicular infiltration.

Twelve of these patients have now relapsed, four with testicular involvement. Of these four patients, two had concomitant marrow relapse; one (case 1) had marrow relapse 8 weeks after treatment for isolated testicular relapse had been started and the other (case 2) remains well. Our own observations confirm the report of Cairo et al[2] that isolated testicular relapse may occur following BMT for ALL despite the use of TBI.

The results of salvage treatment for isolated testicular relapse are improving. Tiedemann et al treated eleven boys with isolated testicular relapse with testicular irradiation and full systemic reinduction.[3] Ten out of the eleven are alive and disease free. However, the results for isolated testicular relapse after BMT will probably be worse, as these patients have been heavily pretreated or belong to a poorer prognostic group. Our first patient fared badly despite intensive treatment.

The incidence of testicular relapse following bone marrow transplantation could be reduced either by bilateral testicular wedge biopsy before transplantation with testicular irradiation in positive cases or by routine prophylactic testicular irradiation at the time of BMT. However, negative testicular biopsies can be followed by overt disease[4] and surgical intervention could provide a portal of entry for infective organisms. We are, therefore, considering the use of additional testicular irradiation (12 Gy) for males before BMT. Although sterility will result, this can happen anyway after chemotherapy and TBI for ALL.[5] When possible, sperm storage should be offered to adults before induction chemotherapy.

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ORAL CONTRACEPTIVES AND RHEUMATOID ARTHRITIS

SIR,—In the June 11 *Lancet* (p 1299) Dr Linos and colleagues report a case-control study in which they did not find an association between oral contraaceptives (OC) and rheumatoid arthritis (RA); a finding which contrasts with evidence from the Mayo Clinic,[6] the Royal College of General Practitioners study,[7] and ourselves.[8]

In our case-control study[8] we set limits on the age of women who were enrolled—namely, aged 25–54 in 1980 and diagnosed between 1960 and 1979. This ensured that the women were premenopausal at a time in which they could have been OC users. Linos et al used only a lower age limit (age 16 at time of diagnosis) and enrolled women diagnosed between 1960 and 1974. Thus, they also included the 70-year old who was diagnosed with RA in 1962. This woman will never have used OC. The inclusion of such non-informative cases will tend to dilute the odds ratio towards unity and decrease the statistical power of the study.

The information about OC use was, in our study, directly obtained from cases and controls and in exactly the same manner. We did not rely upon existing records since different clinicians at different clinics have varying interest in routinely recording past use of OC. Linos et al offer no information about the diagnostic categories included in their control group. It is thus difficult to judge whether cases and controls were seen at the same outpatient or inpatient clinics by physicians with a similar interest in recording OC use.

Linos et al did not define the "onset of rheumatism". We ourselves tried to do this by calculating the approximate date of the first visit to the general practitioner for rheumatic complaints. It is not clear whether the date of diagnosis at the Mayo Clinic coincides with the first diagnosis (or suspected diagnosis) of the disease. If not, this could bias the results since we have noted the tendency of RA patients in the Netherlands to take up "the pill" after RA has been diagnosed.[9]

Linos et al did not exclude cases and controls with contraindications for "pill use". Inclusions and exclusions in case

control studies should be as rigid as they have to be in clinical trials.[5] We did exclude all patients with possible contraindications for OC use: this did not, as Linos et al suppose, result in proportionally more exclusions of cases.

Linos et al only report relative risks, which makes it difficult to get a feeling for their data. For example, a rough indication of what proportion of cases and controls ever used OCs or were current users, or the publication of their main result as a table of case-control triplets, could give an insight into the statistical power of this study, and into the amount of "missing data".

We agree with the closing comment in Linos and colleagues' paper: "the presumed protective effect of OC on RA has not yet been established".

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DANGER OF GAS WATER HEATERS

SIR,—The attention paid in British newspapers to deaths of holidaymakers in Portugal caused by carbon monoxide (CO) poisoning prompts us to draw attention to accidents caused by gas water heaters in Copenhagen. Within 2 months there were four accidents where nine people died from CO poisoning caused by prolonged use of poorly maintained gas water heaters. The deaths included a mother and her four children. The following two case-reports and the survey they led to illustrate the health hazard associated with gas water heaters.[1-3]

A 2-year-old girl was admitted after an akinetic seizure. After her family had had a bath, she had started crying and then collapsed; on admission she was drowsy, with an ataxic gait. She fully recovered in a few hours and was discharged without the seizure having been explained. 3 weeks later she was readmitted after a similar episode, this time with a temperature of 38·8°C and right-sided hyperreflexia. Again she completely recovered and was discharged. At an outpatient visit some weeks later, her mother reported a further seizure that morning; she suspected that the seizures were caused by the gas water heater. The child's COHb value 2 h after the most recent seizure was 16%. The gas board found that the water heater produced high levels of CO when in use. Further questioning revealed that an elder sister had had recurrent headache and vomiting for some months and that the mother often had headaches.

The second patient was a 2½-year-old boy. After his family had had a bath, the boy suddenly became unconscious and had convulsions for 1–2 min. He regained consciousness after half an hour. Although his temperature on admission was 36·5°C, febrile convulsions were diagnosed. At a follow-up visit it came to light that his elder brother had had frequent bouts of vomiting and that his mother had had headache, nausea, dizziness, and fatigue during the winter and had once fainted briefly. With the first case in mind CO poisoning was suspected. CO values in the kitchen, with the gas water heater on and the kitchen door closed, were 0·02% after 10 min and 0·10% after 30 min.

In an age group where febrile convulsions and other kinds of seizure are common, seizures as a presenting symptom make diagnosis difficult. Fever, as in the first child, has been described as a symptom of CO poisoning.[4] Symptoms of less severe CO poisoning are vague and include headache, nausea, vomiting, and fatigue. Where several family members are affected, these symptoms can easily be misdiagnosed as a viral infection.

To find out how frequently gas water heaters produced high levels of CO, we did a survey, in cooperation with the Danish Governmental Institute for Gas Safety. We examined 124 homes with gas water heaters fitted without flues. 122 were in the kitchen and 43 were connected to the bath as well. 20 (16%) produced CO in excess of the recommended safety threshold (0·1% CO emitted); values ranged from 0·3% to 5·7% with a median of 1·0%. All 20 heaters were poorly maintained with dirty burners. In 4 of the 20 households we measured CO levels after the gas water heater had been on for 10 min. With levels of CO in the emission of 0·5%, 1·5%, 1·5%, and 4·5%, the concentrations in the middle of the kitchen were 0·10%, 0·09%, 0·20% and 0·18%, respectively. 0·1% CO can produce unconsciousness after an hour of exposure and 0·2% after a few minutes.[5]

Since 1981 all new heaters in Denmark have had to be installed with a flue. Most old gas water heaters in use remain without flues. Our survey resulted in a campaign through television and radio and by letters in which householders were told about the potential dangers of gas water heaters and about the importance of maintenance. The Government is now considering compulsory yearly maintenance and a proposal that all old heaters should, by 1990, be equipped with a flue to the outside.

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SCREENING FOR HYPERCHOLESTEROLAEMIA ON BLOOD-SPOTTED FILTERPAPER

SIR,—Many metabolic disorders are now screened in the neonatal period and successfully treated. However, for hypercholesterolaemia, and for type IIa especially, there is no method for mass screening before xanthomatosis, atherosclerosis, or myocardial infarction develop, although methods of treatment have been reported.[1-4]

We have developed a new method to screen serum cholesterol levels from the blood-spotted filterpapers which are now widely used for Guthrie tests.

Whole or capillary blood is spotted on filterpaper ('PKU-roshi', Toyoroshi KK, Japan) over an area more than 11 mm in diameter from which two 5 mm diameter discs are punched out. The two discs are put in a test tube (12×105 mm) and 2 ml of chloroform-methanol (2:1) solvent is added. The test tube is capped with aluminium foil, stirred by electric mixer for a few seconds, and allowed to stand at room temperature. The two discs are then removed with a long needle. Each test tube is allowed to stand at room temperature. The solvent evaporates completely in 24 h. Dried lipids containing cholesterol remain in the bottom.

2 ml of 'Determiner TC5', a cholesterol determining reagent in commercially available kits (Kyowa Medix KK, Japan) containing cholesterol esterase, cholesterol oxidase, peroxidase, and 4-aminoantipyrine, is added to the test tube. The reaction mixture is stirred, incubated at 37°C, and measured after 5 min for optical density at 500 nm(OD_{500}), representing the amount of cholesterol extracted from the discs. A cholesterol solution (300 mg/dl) was diluted and used as standard.

Serum cholesterol levels measured by autoanalyser (with determiner TC5 reagent) and OD_{500} values on simultaneously obtained blood samples were analysed in 160 children and 2 patients with familial hypercholesterolaemia type IIa. The results (figure) demonstrate good correlation between OD_{500} and serum cholesterol ($r=0·60$, $p<0·001$). The serum cholesterol (in mg/dl) can be calculated from the formula: $OD_{500}\times 1·54\times 1000-93·0$.

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