

CORRESPONDENCE

Adjuvant radiotherapy for DCIS

Sir—The investigators of the European Organization for Research and Treatment of Cancer (EORTC) (Feb 12, p 528)¹ on breast-conserving surgery with or without radiation for treatment of ductal carcinoma in situ (DCIS) point out that if their finding that there is an increased rate of cancers in the contralateral breast in the surgery plus radiation group was truly radiation induced, it might well cancel out (and more) the clinical gains afforded by adjuvant radiotherapy.

There is convincing evidence that this apparent increase in contralateral breast cancer is unlikely to be radiation induced. Specifically, we have used data from the surveillance, epidemiology, and end results (SEER) tumour registry for a cohort analysis of 32 000 women with DCIS treated between 1973 and 1993, directly comparing second-cancer risk in the women who did, or did not, receive radiotherapy. This large number allows good statistical power to test the hypothesis that radiotherapy induces an increased rate of second cancer in patients with DCIS.

Details of the SEER DCIS subcohorts are shown in the table. For comparison, in the EORTC study, the mean age at DCIS diagnosis was 53 years and the mean follow-up was 4.3 years.

The techniques used to estimate the relative risk of second cancer in the radiation versus the no-radiation SEER DCIS subcohorts are described elsewhere.² The relative risks for radiation versus no radiation were estimated using Mantel-Haenszel

Poisson models, adjusting for age at, and calendar year of, DCIS diagnosis, and follow-up time.

For second malignancies in the contralateral breast, the adjusted relative risk for radiation versus no radiation was 0.98 (95% CI 0.80–1.19); when only long-term (>10 years) survivors are taken into account, the adjusted relative risk was 1.07 (0.54–2.12). For all second malignancies, the adjusted relative risk was 1.00 (0.85–1.18). None of the adjusted relative risks were significant.

These null results are consistent with the corresponding US study³ on DCIS treatment, in which no increase in contralateral breast cancers was observed in the radiotherapy group. The mean radiation doses to the contralateral breast are probably comparable in the EORTC¹ and US³ studies,⁴ in that wedge compensators were used in the EORTC protocol, and in the US protocol half-beam blocks and, optionally, wedges were used.

These null results are also consistent with estimates of radiation-induced breast cancer derived from studies of atom-bomb survivors.⁵ For example, a fractionated radiation dose of 2 Gy (an upper-end estimate of the average contralateral breast dose)⁴ to the breast of a white woman aged 55 years gives a predicted lifetime breast-cancer risk of 0.33%—a relative risk of 1.03 compared with the background lifetime risk of about 11%.

The increased cancer incidence in the contralateral breast reported in the radiation arm of the EORTC DCIS study is unlikely to be a consequence of radiation exposure to the contralateral breast, and is more likely to be an artifact of confounding variables. Any gains afforded by adjuvant radiotherapy in treating DCIS are unlikely to be ameliorated by an increase in second cancers.

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- 1 Julien J-P, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. *Lancet* 2000; **355**: 528–33.
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Sir—Jean-Pierre Julien and colleagues¹ observed that adjuvant radiotherapy after breast-conserving surgery for DCIS significantly reduced the incidence of local recurrence. Their results are comparable to those of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study. Furthermore, their definition of complete excision and clear margins (absence of malignant cells at the inked margins) was comparable to that of the NSABP B-17 trial. It is very likely that the benefits of radiotherapy in both studies reflect the effects of radiotherapy on residual disease. This hypothesis is consistent with the finding that most (90%) local recurrences occur in the index quadrant and the observation by Waldman and colleagues² that locally recurrent tumours were clonally related (81%) to the primary DCIS lesion. Therefore, complete local excision with adequate margins may negate the need for adjuvant radiotherapy.

However, the investigators did not present data on the margin width. There is a growing consensus that a minimum three-dimensional margin width of 10 mm is required to achieve an adequate local excision to avoid the need for radiotherapy. Faverly and colleagues³ showed that DCIS especially at low grade, after three-dimensional reconstruction of mastectomy specimens, was commonly multifocal and showed a discontinuous growth pattern. However, the gaps between foci rarely exceeded 10 mm.

	No radiotherapy	Radiotherapy
Patients with DCIS with known treatment and follow-up	26 390	5650
Mean follow-up (years)	6.7	4.2
Mean age at DCIS diagnosis (years)	58	57
Mean calendar year of DCIS diagnosis	1989	1992
Second cancers (all malignancies diagnosed >2 months after DCIS diagnosis)	1816	270
Second cancers in contralateral breast	868	129

Details of women in SEER tumour registry treated for DCIS

The observations by Silverstein and colleagues⁴ that radiotherapy did not significantly reduce the incidence of local recurrence when the margin width was 10 mm, or more, further support this view.

We acknowledge that margin-width measurements are difficult to make with accuracy, and extensive histopathological examination of the resected specimens are needed. However, true quadrantectomy is more likely to achieve adequate margins than conventional wide local excision.

In our centre, patients with DCIS who are suitable for breast-conservative surgery are treated by segmental mastectomy (or quadrantectomy) to achieve adequate margins and remove multifocal disease and morphologically normal tissue that harbours genetic and molecular alterations in the vicinity of the DCIS. We observed no local recurrence in a series of 54 patients treated by breast-conservative surgery without radiotherapy with a median follow up of 4 years.⁵ We offer further local excision or skin sparing mastectomy with immediate reconstruction to patients with tumours that have inadequate margins. Adjuvant radiotherapy is rarely offered to patients with inadequate tumour margins who decline further surgery.

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- 1 Julien J-P, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first result of the EORTC randomised phase III trial 10853. *Lancet* 2000; **355**: 528–33.
- 2 Waldman FM, De Vries S, Chew KL, et al. Chromosomal alterations in ductal carcinomas in situ and their in situ recurrences. *J Natl Cancer Inst* 2000; **92**: 313–20.
- 3 Faverly DR, Burgers L, Bult P, Holland R. Three-dimensional imaging of mammary carcinoma in situ: clinical implications. *Semin Diagn Pathol* 1994; **11**: 193–98.
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- 5 Mokbel K, Wells C, Carpenter R. Treatment of ductal carcinoma in situ. *N Engl J Med* 1999; **341**: 998–99.

Sir—The early results of the EORTC trial¹ confirmed the results of the similar NSABP B-17 trial.² Radiotherapy in this situation reduced significantly the risk of subsequent occurrences (invasive or non-invasive) in the irradiated breast. This is somewhat grudgingly conceded by Melvin Silverstein and Michael Lagios in their commentary.³ We would, however, take issue with two points they raise.

While it is true that quantitatively the B-17 trial reveals a unique finding of a 3.5-fold reduction in invasive local recurrences, qualitatively it is not unique: the EORTC trial reveals a similar effect of a significant two-fold reduction. If, as Silverstein and Lagios claim, other studies do not show this, they should acknowledge those studies were not randomised.

We share the commentators' concern over the incidence of contralateral cancers in the irradiated group, but it must be acknowledged that it certainly would be unique if these (contralateral) malignancies occurred as a consequence of the radiation in 4 years, a relatively short time.

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- 1 Julien J-P, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. *Lancet* 2000; **355**: 528–33.
- 2 Fisher B, Constantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993; **328**: 1581–86.
- 3 Silverstein MJ, Lagios MD. Benefits of irradiation for DCIS: a Pyrrhic victory. *Lancet* 2000; **355**: 510–11 (erratum appears in *Lancet* 2000; **355**: 1190).

Sir—The EORTC 10853 study¹ shows, like the NSABP B-17 study,² that post-operative radiotherapy for DCIS reduces both invasive and non-invasive recurrences in the ipsilateral breast. However unlike B-17, the EORTC study showed an increased number of contralateral breast events in the patients randomly allocated adjuvant radiation (8 vs 21; $p=0.01$). The investigators suggest that the increase might be a consequence of the radiation. We feel this is highly improbable given the short latency time, the low doses scattered to the contralateral breast, and the lack of such an effect in numerous studies where radiation has been used to treat invasive disease.³ Instead, we suggest that an uneven use of tamoxifen between the two experimental arms could explain the apparent difference. We would be interested to know whether the investigators have any information about the use of tamoxifen in their study population. Tamoxifen halves subsequent contralateral disease in patients with DCIS.⁴ There is a high level of public awareness of the benefits of adjuvant tamoxifen for invasive disease, particularly since the overview published in 1988.⁵ It is not unreasonable to speculate that tamoxifen has been used more

frequently (ie, by concerned family practitioners) in patients randomly assigned no additional adjuvant therapy.

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- 1 Julien J-P, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. *Lancet* 2000; **355**: 528–33.
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Authors' reply

Sir—Although some have described the benefits of breast irradiation for DCIS as a Pyrrhic victory, the results of the EORTC 10853 trial do, nevertheless, contribute to an advance in evidence-based medicine. For some time the only published randomised trial for DCIS was the B-17 study,¹ done by the NSABP, the results of which have not been universally reproducible. EORTC 10853 and NSABP B-17 had similar designs and showed that radiotherapy could reduce the risk of recurrence. However, the 3.5-fold reduction in invasive progression found in NSABP B-17 was not quantitatively confirmed. The increased incidence of contralateral cancers in the irradiated group, although probably a chance finding, does remain a concern. Since the carcinogenic effect of irradiation would be expected to occur many years after the event, we will closely monitor the participants to assess this phenomenon after longer follow-up. However, we agree with David Brenner and colleagues that the available evidence on radio-induced breast cancer makes a causal relation between irradiation and contralateral breast cancer unlikely. The use of tamoxifen was not recommended in the protocol. We requested information about any anticancer drugs given, and only incidentally the use of tamoxifen was mentioned. Tamoxifen use was balanced over the two treatment arms.

Kefah Mokbel and colleagues point out that other factors, such as the extent of local surgery and hence the width of DCIS-free margin, might play an important part in risk of local recurrence. We agree that there is a need for subgroups, which have a very low risk of recurrence and progression and so might be treated safely without irradiation, to be defined. Even more importantly, we feel that those patients with an unacceptably high risk of invasive progression after breast-conserving treatment for DCIS should be identified so that they can be offered mastectomy with immediate reconstruction to minimise their risk of subsequent metastatic disease. Many studies have attempted to identify risk factors for relapse but most are not randomised and suffer selection bias. The minimum free margin of 10 mm or more recommended by Silverstein and colleagues² has not been confirmed by any other study. Silverstein and colleagues have acknowledged that they have not proved their hypothesis that radiotherapy is of no benefit in patients with a margin width of 10 mm or more.³

The EORTC trial was designed to investigate the role of radiotherapy in breast-conserving treatment for DCIS. Because of the large scale of the trial, with 42 centres participating, it was not possible to assess margin status in all patients, despite an attempt to standardise pathological handling of specimens. Accurate measurement of margin width requires uniform work-up of the resected specimen including inking of margins, sectioning, and radiography of the lamellated specimen, and representative sampling of suspect areas and margins. The results of a central pathology review, including both clinical and pathological risk-factor analysis will soon be available.

Achieving complete local excision of a non-palpable DCIS is a technically difficult procedure and local recurrence often reflects failed complete excision. Radiotherapy has been proved to reduce risk of relapse and progression by one third in two randomised trials. Until randomised studies have confirmed that there are subgroups of patients who can be safely treated by local excision alone, the available evidence indicates that breast conservation for patients with DCIS should include complete local excision and breast irradiation.

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- 1 Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993; **328**: 1581–86.
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Antipsychotic drugs and risk of homicide

Sir—S W Mikhail and H G Kennedy (April 1, p 1189)¹ describe three patients charged with homicide while prescribed novel antipsychotics. Although reviews did not find an association between homicides by the mentally ill and non-compliance with medication, Mikhail and Kennedy believe that “it is premature to dispense with the use of depot neuroleptics in patients with a history of non-compliance or a risk of violence when psychotic”. In the cases presented some other points should be considered. The authors suggest that depot neuroleptics may improve compliance and decrease the relapse rate. This is hard to prove because none of the novel antipsychotics are yet available in depot form. Our study found no differences in 1-year relapse rates in schizophrenic patients treated with oral classical neuroleptics, depot forms, or the newer agents risperidone or clozapine.² All three patients had long duration of illness (from 20 months to 5 years) and were psychotic at time of discharge and at the time of homicide. Perhaps some had treatment-resistant schizophrenia. There are no data on previous clozapine trials in the patients presented. In treatment-resistant patients, clozapine is more effective than classical or other novel antipsychotics³ and reduces the risk of suicide.⁴ However, although suicide (self-injurious aggression) and homicide (aggression toward others) may have different mechanisms, it is reasonable to expect that clozapine might also reduce violence. This was confirmed in a recent study⁵ which found that clozapine has a specific antiaggressive effect that could not be explained by sedation or general antipsychotic effects.

Minimising the risk of violence it is probably not only a question of depot versus oral drug. The clinician should also try to find an antipsychotic that will strongly reduce or abolish the psychopathological symptoms and has a demonstrated antiaggressive effect. Clozapine may be an appropriate drug in this respect.

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Acquired syphilitic retinitis and HIV

Sir—Stephanie Young and colleagues (March 18, p 984)¹ highlight the importance of keeping in mind syphilis as a cause of retinitis in patients with HIV-1. The patient they present had acute reduction of visual acuity and red eye, which are pointers to possible involvement of the posterior segment rather than it being a case of simple conjunctivitis. Such suspicion would have facilitated an early diagnosis and treatment.

It is established that infectious uveomeningeal syndromes like syphilis, tuberculosis, and infections with fungi, cytomegalovirus, varicella zoster virus, and herpes simplex virus are common in patients positive for HIV-1 or with AIDS. These uveomeningeal syndromes share involvement of retina, uveal tract (iris, ciliary body, and choroid), and brain.² In some of these cases, the presentation may be with visual loss and there may be a relatively symptomless pleocytosis evident from cerebrospinal fluid investigations. In others, neurological abnormalities may be the presenting symptom with symptomless ocular features.²

The case described by Young and colleagues shows that a venereal disease research laboratory blood test should

be included in the routine work-up of a uveitis–retinitis syndrome, especially in a clinical setting, where there is a history of HIV-1 infection or AIDS-related complex.

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Pneumocystis carinii pneumonia in Malawian children

Sir—Stephen Graham and colleagues (Jan 29, p 369)¹ report findings from Malawi of 333 children who were investigated for severe pneumonia. In 114 of the children who died there was no confirmed cause of illness. The limited availability of diagnostic facilities in resource-poor countries such as Malawi is well recognised. However, other investigative work-up would have been helpful in coming to a proper diagnosis in this group. Lung aspirates would have provided useful additional diagnostic information, particularly in children who did not have radiological evidence of interstitial emphysema or hyperinflation. It is surprising that with such a high prevalence of HIV infection in their population, in none of these children with severe pneumonia was pulmonary tuberculosis diagnosed by Ziehl-Neelsen stain or isolation. Furthermore, the incidence of *Streptococcus pneumoniae* pneumonia was also strikingly low. The risk of tuberculosis and invasive pneumococcal disease in HIV-infected individuals is known to be several-fold higher than in non-HIV-infected individuals. It would seem that other infective agents were not rigorously investigated.

Study of lung aspirates have been shown to improve the number of diagnoses made in children with severe pneumonia and peripheral consolidation by about 50%. If lung aspirates had been taken by Graham and colleagues for selected individuals, either before or after death, a more comprehensive picture of the infective agents involved would have been drawn.

Several studies have shown the superiority of lung aspirate over blood

culture for the aetiological diagnosis of childhood pneumonia.² In a study of the aetiological agents in community-acquired pneumonia,³ lung aspirates provided evidence of microbial aetiology in 65% of 55 patients with pneumonia whose disease aetiology could not be defined by conventional methods. In this study, lung aspirates confirmed 44% of the 54 diagnoses made by conventional methods, including infection with *Mycoplasma pneumoniae*, *S pneumoniae*, *Chlamydia pneumoniae*, *Pneumocystis carinii*, and *Mycobacterium tuberculosis*. The incorporation of lung-aspirate study into the diagnostic work-up changed the ranking and the spectrum of micro-organisms established by conventional methods.

The investigators did not report on the nutritional status of these children and its possible influence on disease incidence and outcome. Participants were not investigated for respiratory syncytial virus (RSV) or other viruses and so *P carinii* infection may have been clinically over-diagnosed, since hyperinflation and hypoxaemia may be common to both conditions. Although the primary objective of the review was to address morbidity from *P carinii*, these other agents could have contributed to morbidity and mortality.

The limitations of available therapy is appreciated, but it is difficult to conceive that the bioavailability of cotrimoxazole after oral administration or intramuscular chloramphenicol will be similar to parenteral cotrimoxazole or intravenous chloramphenicol administration in these severely hypoxaemic and possibly poorly perfused children.

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- 1 Graham SM, Mtitimila EI, Kamanga HS, Walsh AL, Hart AC, Molyneux ME. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *Lancet* 2000; 355: 369–73.
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Authors' reply

Sir—We agree with many of Steven Obaro's comments and did refer to most of them in our paper. Lung aspiration would have increased the diagnostic yield of bacterial

pneumonia and probably that of *P carinii* pneumonia (PCP) as well. The low incidence of pneumococcal pneumonia is likely to reflect poor sensitivity of blood culture as a diagnostic technique, rather than actual incidence. We therefore presented the data as a report of PCP and the impact of HIV infection on outcome. Patients with bacterial pneumonia, even if an underestimate, were useful for comparison to describe the clinical presentation of PCP. We stated that intravenous cotrimoxazole is not available. We acknowledged that the study group was likely to represent the most severe spectrum of community-acquired pneumonia, which could select for a higher prevalence of PCP and HIV.

We decided not to carry out diagnostic lung aspiration for many reasons. Background evidence and clinical experience suggested that PCP would be common.¹ There is a significant risk of air leaks after invasive lung procedures in children with PCP.² Many children were severely hypoxic on admission and there were limited facilities to manage a potentially fatal complication. Chest radiography can assist in selection of patients for aspiration—ie, the risk of air leak from aspiration of segmental or lobar consolidation is minimal. In our circumstances, this approach would often have resulted in an unacceptable delay before starting of antibiotics. Further, there were no available radiological data from the region that might have assisted us in being selective and we were unwilling to assume that the pattern would be similar to that reported from USA and Europe. Necropsy evidence shows that mixed pulmonary infection is common in HIV-infected African children, and one of the children in our study with confirmed PCP also had *Haemophilus influenzae* isolated from blood.

Our study highlights the need for data that describe the incidence and aetiology of acute and chronic pneumonia in HIV-infected African children.³ We hope that it provides useful background data for future studies of pneumonia aetiology in HIV-infected African children that include lung aspiration. We mentioned the possibility of clinical overlap of RSV infection with PCP and reported RSV in an earlier study in Malawian children.¹ A study in Botswana identified RSV in 12.5% of HIV-seropositive children at necropsy.⁴ Obaro may not be correct to assume that because HIV infection

increases susceptibility to tuberculosis then tuberculosis is common in HIV-infected African infants.⁵

Children infected with HIV were not significantly more malnourished than HIV-uninfected children (mean WAZ score -1.55 vs -1.36 ; $p=0.46$). Similarly, children with confirmed PCP were not significantly more malnourished than the rest of the study group (mean WAZ score -1.58 vs -1.46 for not PCP; $p=0.72$) and tended to be less malnourished than those with bacterial pneumonia (mean WAZ -1.81 ; $p=0.35$). Our impression is that PCP is the first clinical indicator of HIV infection and that these infants are often not emaciated.

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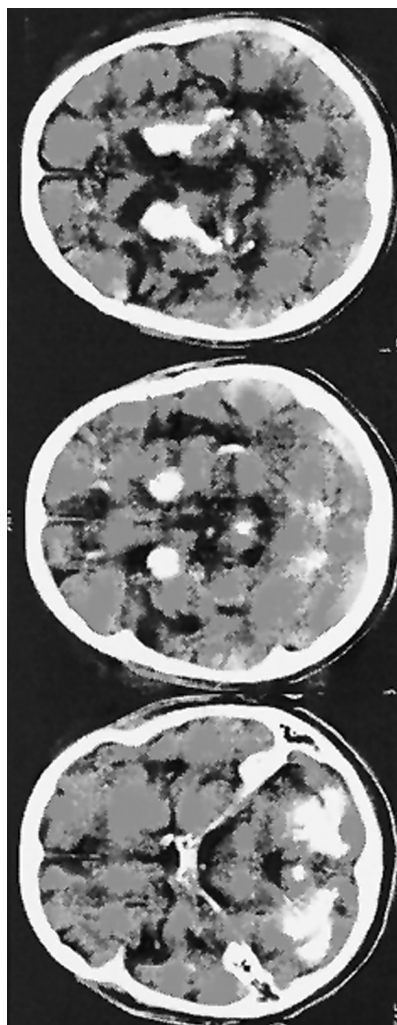
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Reversible dementia due to coexisting disease

Sir—F Formiga and colleagues (April 1, p 1154)¹ report on reversible dementia in a woman aged 89 years who was diagnosed as having normal-pressure hydrocephalus and hypercalcaemia, which was a result of primary hyperparathyroidism. We have had experience with another parathyroid-related partially reversible form of dementia.

A woman aged 66 years was admitted to hospital with progressive mental disorder, inability to walk, and finally stupor. She could not cooperate enough for the mini-mental state examination (MMSE) to be done. No focal neurological signs were present. Her cardiopulmonar



CT brain scan of woman aged 66 years

Extensive calcifications (white) can be seen in the cerebellum, mid-brain, and basal ganglia as a result of delayed (43 years) postsurgical hypoparathyroidism.

condition was stable. Emergency laboratory tests showed hypercalcaemia (4.3 mmol/L [normal 2.1 – 2.5]), slightly low potassium concentrations (3.1 mmol/L [3.5 – 5.0]), and impaired renal function (creatinine 2.3 mg/dL [<1.1]). Full blood count, glucose, liver function tests, vitamin B12, folic acid, chest radiograph, 12-lead electrocardiogram, and cerebrospinal fluid were all normal. Thyroid function was normal; the patient was on substitution thyroxine because of goitre-prompted thyroidectomy 43 years previously. Parathyroid hormone was decreased (3.7 pg/L [10 – 50]). A computed-tomography scan (figure) showed extensive brain calcifications consistent with Fahr's syndrome. After immediate dialysis and intensive care, marked improvement was observed. Further inquiries revealed that the patient had been treated repeatedly for hypocalcaemic episodes, leading to

calcium carbonate (900 mg daily) and dihydrotachysterol (1.5 mg daily) administration 2 months before admission.

Brain calcifications and neurological and mental disorders can be observed in hypoparathyroidism² and also in hyperparathyroidism³ and often appear many years after disease onset.⁴ The calcification mechanism is yet unclear. Pathologically, influence on the small deep vessels is assumed to lead to a type of vascular dementia.² Animal experiments have shown a destructive cascade in pathology with initial activation of glutamate receptors, induction of excitotoxic neurodegenerative processes, formation of cytoplasmic filaments, and deposition of biological apatites and aluminosilicates. But it is unclear whether these findings are applicable to human beings.⁵ In hypoparathyroidism, however, prompt treatment with calcium and vitamin D may prevent development of calcification⁴ and probably of the related neuropsychological changes.² Unfortunately our patient's secondary hypoparathyroidism was not diagnosed until nearly 43 years after thyroidectomy.

The patient now has an MMSE score of 23 and a Barthel index of 70. In this patient reversible hypercalcaemic dementia was not a result of hyperparathyroidism, but of hypoparathyroidism with drug overdose. When caring for patients with dementia and hypercalcaemia, primary hyperparathyroidism and hypoparathyroidism should be considered.

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Early diagnosis of invasive aspergillosis

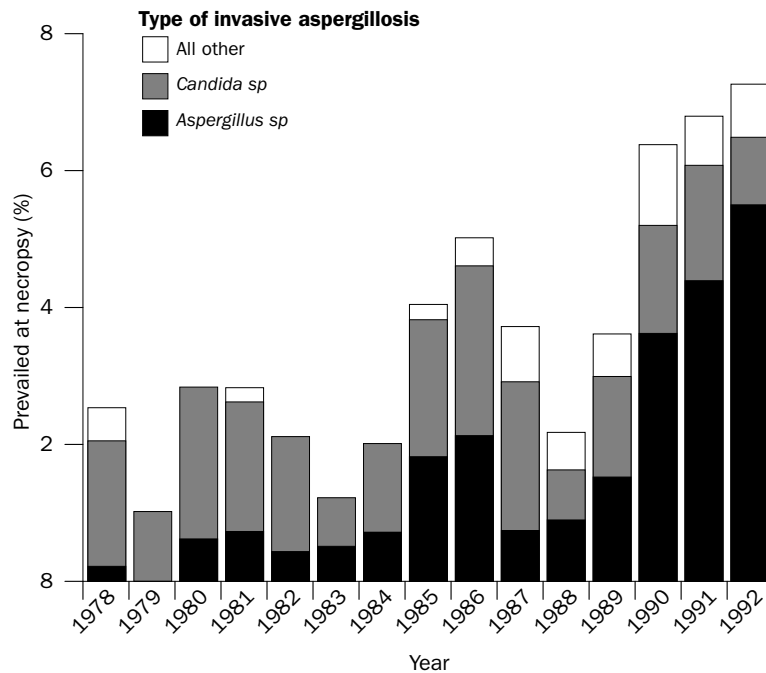
Sir—In his Feb 5 commentary¹ on invasive aspergillosis, David Denning refers to a study of Maertens and colleagues,² in which a prospective screening for circulating galactomannan by a sandwich ELISA (Platelia Aspergillus, Sanofi Diagnostics Pasteur, Marnes la Coquette, France) for patients with haematological disorders at high risk for invasive aspergillosis was assessed. The manufacturer of this assay recommends that the optical density (OD) index is calculated for the samples by dividing the OD value of each serum by the OD of a control serum (threshold serum) and to consider an index of 1.5 and above a positive test, an index of 1–1.5 a grey zone result, and an index of less than 1 a negative test. Maertens and colleagues deviated from the manufacturer's recommendation and defined an index of 1.0 and more as positive and an index of less than 1.0 as negative. Moreover, a result was considered true positive in this study when two consecutive samples for that patient tested positive, including retesting of the first sample. This approach was shown to be very sensitive and specific compared with the gold standard (necropsy and culture from necropsy specimens).

In Denning's commentary there is the statement concerning the study of Maertens and colleagues, that "a positive result is defined as positive samples collected on two different days and having OD values of more than 1.0". Denning has confused OD and OD index. The correct statement should be: . . . and having OD indices of 1.0 and more. This difference is clinically important. The OD of the threshold serum is in the range 0.3–0.8. This means, for example, that an OD of 0.9 can correspond to an OD index of more than 1.0—ie, an OD of 0.9 can represent a positive result.

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- 1 Denning DW. Early diagnosis of invasive aspergillosis. *Lancet* 2000; **355**: 423–24.
- 2 Maertens J, Verhaegen J, Demuyneck H, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis. *J Clin Microbiol* 1999; **37**: 3223–28.



Prevalence of invasive aspergillosis at necropsy at J W Goethe University Hospital, Frankfurt, Germany

Author's reply

Sir—The comments of D H Forster and colleagues are helpful and constructive. The correction they point out is important and represents an important subtle deviation from the manufacturer's recommendation on interpretation. However, as I pointed out in my commentary, cut-off values and utility of the test in other patient groups and samples have yet to be defined, and this should not be prejudged.

After publication of the commentary, Andreas Groll informed me that in the final years of the necropsy survey he and colleagues did,¹ most of the increase in cases of fungal infection was a result of invasive aspergillosis (figure). Early diagnosis remains a priority.

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- 1 Groll AH, Shah PM, Mentzel C, Schneider M, Just-Neubling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996; **33**: 23–32.

Sir—David Denning rightly states¹ that a high index of suspicion is required for the diagnosis of aspergillosis. One risk factor for aspergillosis he omitted to mention was proximity to areas of building.

In the Kaplan Medical Centre, Rehovot, Israel, we have encountered three cases of aspergillosis in

3 months. All these cases were detected in patients with neutropenia who were admitted to the Internal Medicine Departments, on the southern side of the hospital. During this period, a new building was being constructed.

A woman aged 71 years was diagnosed in September, 1998, with an acute undifferentiated leukaemia. She had been diagnosed with polycythaemia rubra vera in 1990, and since then had received treatment with hydroxyurea in a dose of 1–2 g a day. After the diagnosis of leukaemia, treatment was started with cyclophosphamide, oncovin, arabinoside C, and prednisone. She subsequently developed pancytopenia and concomitantly sinusitis with swelling of the left eye. Surgical debridement was done and aspergillosis was found to be present. Despite treatment with amphotericin her condition deteriorated and she died.

3 weeks later a man aged 58 years was admitted to hospital for peripheral-stem-cell transplantation as treatment for chronic lymphocytic leukaemia that he had suffered from for 8 years. He received the CBV protocol and was pancytopenic when he developed a herpes zoster rash, which responded to treatment with aciclovir. Subsequently, while still neutropenic, he developed a fever and piperacillin and amikacin treatment was started, and when the fever persisted, vancomycin was added.

While febrile he developed tinnitus and sinusitis was found on computed tomography scan. In addition, there were lung infiltrates. Culture of secretions from the nose and histological examination showed the presence of aspergillus. Treatment with amphotericin was started and the patient made a complete recovery.

3 weeks later a man aged 59 years was admitted to hospital with relapse of acute myeloid leukaemia. After repeat chemotherapy, he was in the neutropenic phase when he became febrile. Aspergillus flavus was isolated from blood cultures and he responded to treatment with amphotericin. He was discharged home but died from complications of the leukaemia several months later.

There is a well-described association between building renovations and aspergillus infection. An increase in the recovery of *Aspergillus flavus* from respiratory specimens has been reported during a period of several months in 1977.² 86% of the patients with positive cultures were located adjacent to a building construction site. The increased incidence of positive air samples during periods of building renovation has been shown to be prevented by the use of high-efficiency particulate air filtration and laminar air flow.³ Denning's suggestion to run a galactomannan test on high-risk patients being treated by haematologists is most appropriate. There is a report from Germany of an increase in the incidence of positive aspergillus galactomannan antigenaemia in a bone-marrow-transplantation ward, that ranged from 20.9% in the year with major building activities to 0% in the year without.⁴

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Mycobacterium tuberculosis transmission and HIV status

Sir—Marcos Espinal and co-workers (Jan 22, p 275)¹ provide evidence that HIV-positive patients with tuberculosis are less likely than HIV-negative patients to transmit *Mycobacterium tuberculosis* infection to contacts. This article sheds light on the debated subject of infectiousness of HIV-associated tuberculosis. However, the immune status of the HIV-positive patients is a crucial issue not focused on by Espinal et al. Features of HIV-associated tuberculosis are known to change according to the patient's immune deterioration.²

Clinical and pathological findings in tuberculosis developing in HIV-positive patients with a relative conserved immune status (represented by CD4+ T-cell count) are virtually indistinguishable from those seen in tuberculosis in HIV-negative individuals. However, by contrast, knowledge of tuberculosis acquired in non-HIV individuals may not apply to the most severely immunosuppressed AIDS patients, in whom the clinical and pathological picture is often atypical. Opinions differ on the infectious potential of these patients. Pulmonary evidence of a greater than usual number of viable bacilli interspersed in poorly competent and unspecific tissue reactions³ suggested a potential for greater infectiousness. In some hospital settings transmission of *M tuberculosis* infection and disease from AIDS patients to health-care workers was significantly more likely than in comparable HIV-negative settings.⁴ On the other hand, the immunodeficiency-related tendency to a higher bacillary count seems to be counterbalanced by a lower ability to generate open lesions (the ones accounting for infectiousness) in the respiratory tract.⁵

In Espinal and colleagues' report, might the reduced infectiousness be attributable to the fraction of most immunosuppressed patients rather than being a characteristic of all HIV-positive tuberculous individuals? Weakened cough (suggested by the authors as an explanation for the reduced infectiousness) seems to be clinically reasonable only in very compromised HIV-positive patients.

The issue has clinical and epidemiological implications too. The belief that all HIV-positive patients with tuberculosis, rather than just a proportion of them, are potentially less

infectious could lead to underestimates of the risk in many settings.

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- 1 Espinal EA, Pérez EN, Báez J, et al. Infectiousness of *Mycobacterium tuberculosis* in HIV-1-infected patients with tuberculosis: a prospective study. *Lancet* 2000; **355**: 275–80.
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Sir—Marcos Espinal and colleagues¹ report that HIV-1-infected tuberculosis patients are less likely than HIV-1-negative tuberculosis patients to transmit *M tuberculosis* to close contacts. They conclude that current policy on tuberculosis contact tracing does not need to be adjusted for the presence of HIV. Espinal et al cite our conference abstract (later published²) in which we specifically avoided publishing tuberculosis infection data because it is so difficult to interpret tuberculin test results among contacts among whom there is a significant level of BCG vaccine coverage or an appreciable prevalence of HIV infection, or both. Under such conditions a positive second tuberculin test, when the first was negative, is difficult to interpret since it may be due to recent tuberculous infection or a booster effect among BCG-vaccinated individuals or those infected with *M tuberculosis* who did not respond to the first test because of depressed immunity due to HIV.

We found 36 cases of tuberculosis (7.9%) among 456 contacts of 124 HIV-infected smear-positive patients but only 24 (3.8%) among 624 contacts of 124 HIV-seronegative smear-positive patients ($p=0.004$). The 97 HIV-infected cases who were intravenous drug users generated 34 secondary cases; the 27 patients in other HIV transmission groups generated only two secondary cases

($p=0.03$). We concluded that, in Barcelona, HIV-infected, smear-positive patients transmit tuberculosis more often because intravenous drug abuse favours non-compliance with treatment and delays diagnosis.²

In the Dominican Republic, Espinal et al found similar percentages of tuberculosis among contacts of HIV-infected tuberculosis patients and among contacts of patients who were HIV seronegative, but the HIV transmission pattern in their patients must differ from ours. If the Dominican study had been restricted to smear-positive individuals and if the true meaning of a second test being positive could be determined, the difference in tuberculosis infection rates might not have been significant.

In our opinion, in the tracing of contacts of an HIV-infected tuberculosis patient, intravenous drug use must be taken into account—as should the possibility that contacts are themselves HIV infected with the consequent obligation to be much stricter in the tracing of contacts (including broadening of circles of contact and increases in primary and secondary chemoprophylaxis).³⁻⁵

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- 1 Espinal MA, Pérez EN, Báez J, et al. Infectiousness of *Mycobacterium tuberculosis* in HIV-1-infected patients with tuberculosis: a prospective study. *Lancet* 2000; **355**: 275–80.
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Authors' reply

Sir—The infectiousness of patients with pulmonary tuberculosis determines the rate of secondary cases. From a public health point of view, if the clinical and pathological findings of the disease in HIV-infected and HIV-negative patients are indistinguishable there should be no difference in infectiousness. Therefore the policy

on household contact tracing of HIV-infected patients need not be changed. Nor need policy if HIV-infected patients are less likely to transmit *M tuberculosis*, as suggested by our study. Policy might have to change if such patients are more infectious. We cannot rule out the hypothesis put forward by Stefano Bonora and colleagues as a potential cause of increased infectiousness. However, the study they cite was only 16 HIV-positive cases and household contacts were not investigated.¹ Although we did not assess CD4-cell counts, evidence from Botswana shows that HIV-infected patients with lower CD4-cell counts may be less infectious than patients in earlier stages of AIDS.²

Some studies showing increased transmission of *M tuberculosis* by HIV-infected patients are likely to have been influenced by the nature of the study population. In injection drug users, if tuberculosis is not addressed promptly, a higher rate of secondary cases is likely, as suggested by Caylà and colleagues³—but it is the lack of proper tuberculosis control measures that take into account the needs and social status of this population that is responsible for the higher rate, not HIV. When Caylà et al excluded injection drug users, the proportion of tuberculosis cases generated by HIV-infected cases was lower (though not significantly so) than that generated by HIV-negative patients (2.4% vs 3.8%).

We disagree with Caylà and colleagues' review that data on infection among contacts should not be presented and discussed in the presence of high BCG coverage. The effect of BCG on skin-test results is usually strongest in the first 2 years after vaccination and wanes thereafter.⁴ Furthermore, in our multivariate analysis excluding children less than 2 years of age (in the Dominican Republic BCG is given at birth), BCG had no significant effect on skin-test positivity. Furthermore, when we excluded anergic and BCG-vaccinated contacts, only 22% of household contacts of HIV-infected index cases converted their tuberculin skin test compared with 29% of household contacts of HIV-negative index cases. Only 57 of the 803 household contacts evaluated were contacts of smear-negative index cases, and when these were excluded no changes were observed.

Most HIV infections in less-developed countries are not related to intravenous drug use. Our recommendations were intended for less-developed countries, where the

management of tuberculosis and HIV infection differs from that in the industrialised world. We still believe that contact tracing in less-developed countries does not need to be revised on the basis of the prevalence of HIV infection.

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The ovary: cysts, screening, and tamoxifen

Sir—Timothy Crayford and colleagues (March 25, p 1060)¹ describe a long-term follow-up of 5479 symptom-free women, who entered, between 1981 and 1987, a transabdominal ultrasonographic screening trial for ovarian cancer. The age range of the women was 34–93 years. The investigators conclude that removal of persistent ovarian cysts was not associated with a decrease in the proportion of expected deaths from ovarian cancer relative to other cancers. However, new studies to screen for ovarian cancer are, and will be, ongoing.

The incidence of women from the general population presenting with ovarian cysts as a result of the use of the oestrogen receptor modulator tamoxifen, may change over the next years. Tamoxifen is currently administered, apart from in metastatic cancer, as 5-year adjuvant treatment with or without chemotherapy in patients with premenopausal and postmenopausal breast cancer. In addition, tamoxifen has been approved in the USA for the prevention of the breast cancer in women at high risk of developing the disease. At least in the USA, this will greatly increase the number of healthy women using tamoxifen.

Tamoxifen is a non-steroidal anti-oestrogen, and the effects on

endometrium and ovary depend on the ambient oestradiol concentration. Tamoxifen, although developed as a contraceptive, was shown in 1971 to induce ovulations. In patients with breast cancer as well as in a breast-cancer prevention study, several investigators reported the occurrence of ovarian cysts.²⁻⁴ We showed that ovarian cyst development during tamoxifen was associated with high serum oestradiol concentrations, younger age, and absence of high-dose chemotherapy pretreatment.² Women who retained a menstrual cycle after chemotherapy had an 81% chance of developing cysts.² Patients with cysts had strikingly high concentrations of oestradiol (1.95 [range 0.17–4.8] nmol/L). Therefore, although ovarian cysts during administration of tamoxifen have been described during menopause,⁴ they seem to occur predominantly in postmenopausal women.^{2,3}

Women with a family history of breast cancer will have an increased chance to receive tamoxifen for prevention or as treatment. However, these women may have an increased risk of developing ovarian cancer and will therefore undergo regular transvaginal ultrasonography. When cysts are observed in premenopausal women, they may be solely tamoxifen induced and therefore a harmless and temporary phenomenon. On the other hand, the fact that tamoxifen can induce ovulations and thus, theoretically, might increase the chance of developing ovarian cancer should keep clinicians alert. Future ovarian cancer prevention trials will have to register co-medication and family history.

Crayford and colleagues showed that resection of benign ovarian cysts was not of additive value. Resection will therefore result in undesirable morbidity. In case of a diagnostic dilemma in premenopausal tamoxifen users with persistent ovarian cysts, one might consider to use, temporarily, a leuteinising-hormone-releasing hormone analogue to suppress ovarian function and check for disappearance of the cysts, as described by Cohen and colleagues.⁵ Because the behaviour of ovarian cysts in tamoxifen users in the long-term is unknown, it will be important to include tamoxifen users in future observation trials and assess what happens to their ovaries.

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The global burden of disease disability weights

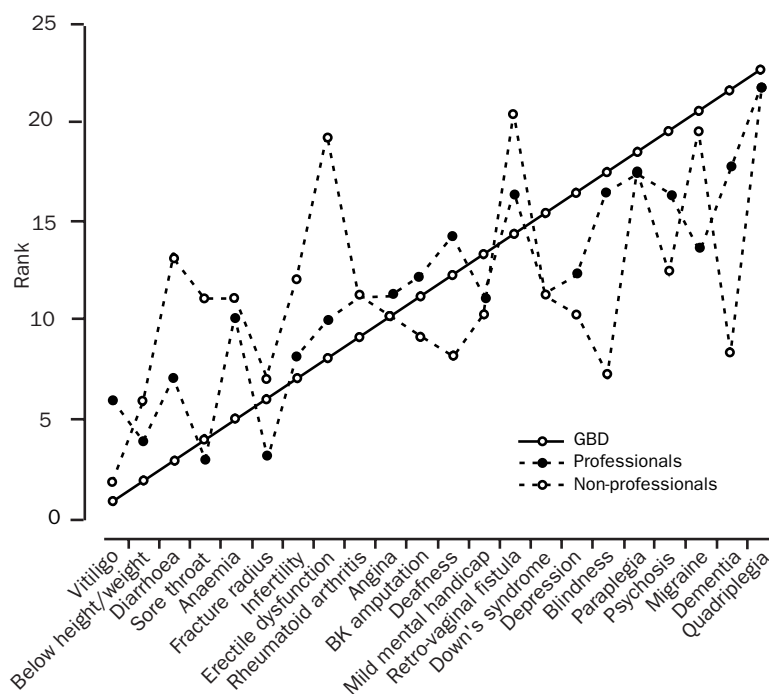
Sir—The universal applicability of disability weights has been debated within *The Lancet*.¹⁻³ As part of the Zimbabwe National Burden of Disease study, we attempted to validate the disability weights used by Murray⁴ in the calculation of disability adjusted life years (DALYs). In Zimbabwe there is a large differential in income and education between the average person and the educated elite. We hypothesised that the ranking of severity of different disabilities by Zimbabwean health professionals

would correlate highly with the global burden of disease (GBD) ranks and that the correlation with the ranking of non-professional Zimbabweans would be much lower.

Focus-group discussions were used to determine the ranking of the 22-descriptor conditions that form the basis of the GBD weights. The first group consisted of 56 residents of a high-density suburb in Harare (mean age 31.8 [SD 0.9] years; 22 men, 34 women). 12 Zimbabwean health professionals comprised the other group (mean age 34.0 [2.6] years; six men, six women). The descriptor vignettes were translated into Shona for the non-professional respondents.

The results of the ranking exercises are shown in the figure. Spearman's ρ was 0.912 between the GBD and Zimbabwean professionals, 0.341 ($p=0.121$) between GBD and the non-professionals and 0.315 ($p=0.153$) between the Zimbabwean professionals and non-professionals.

The 22 conditions were then grouped together in seven condition clusters related to physical, sensory, cognitive, disfiguring, and reproductive disabilities, pain, and diarrhoea. Anaemia was included as a reproductive issue as the vignette states that it takes place during pregnancy. There was a difference of less than three in the mean ranks assigned by the GBD and by the non-professionals to disfiguring conditions,



Mean ranking of the 22 GBD indicator conditions by groups of medical professionals (n=12) and non-professionals (n=58)

pain, or physical disabilities. However, there was a difference of six or seven in the mean ranks of reproductive disabilities (Zimbabwe higher), cognitive and sensory disorders (GBD higher). Diarrhoea was ranked 13 (compared with rank 3 in the GBD weights) because it was associated with HIV.

It would seem that the GBD values represent those of an international elite of health workers. These findings contrast with Üstün¹ who reports a significant correlation between informant groupings from different socioeconomic backgrounds. However, the African sample is small and includes 15 informants from one African country, of which six are non-professionals.

The Shona people define themselves in terms of the group and their health or illness is actualised within that context. This is in striking contrast to western individualism and emphasis on self-determination and independence. Infertility, for example, is regarded as a serious disability as it threatens collective survival and renders the individual incapable of playing his or her part effectively in the collective process. Blindness has a lower ranking because it is confined to the individual and is neither life threatening nor a threat to the collective. Discussion of the cultural interpretations of abnormal cognitive states is beyond the scope of this letter, but traditional religious beliefs resulted in relatively low weights being assigned to these conditions.

It seems that it is extremely difficult to generate weights that are universally applicable. It might be useful to use the GBD weights for international comparison. However, countries should examine the values of their own citizens before these weights are used as a basis for resource allocation. We suggest that the greater the divergence of the local culture from the individualist western world-view, the less likely that the GBD weights will be applicable.

This study was made possible by the Zimbabwe National Burden of Disease Study, funded by the Danish International Development Agency (DANIDA) and the Department for International Development (DFID).

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Attitudes to compulsory admission in psychiatry

Sir—In their Feb 19 commentary,¹ Frank Farnham and David James discuss reasons why patients with psychiatric disorders tend to reject hospital admission, which in turn leads to a high rate of compulsory admissions in the UK. Personal autonomy and freedom are highly valued in Western societies. Legislation, therefore, strongly restricts health-care measures that endanger these values—eg, compulsory admission to hospital. Findings of a representative survey we have done in Switzerland (n=1737; age 16–76 years, living in a private household) seem to contrast with the outstanding societal position of individual rights. We assessed² the public attitude to mental illness, psychiatric treatment, and the psychiatric services involved. Further, interviewees were asked whether they are in favour of compulsory admission in case of mental illness. We found that the general population and people with mental disorders who had had treatment experience, as well as their relatives, were mostly in favour of compulsory hospital admission (table). Within those subsamples, similar levels of acceptance were found, even if people with psychiatric treatment experience were further differentiated into therapy with or without medication.

We suppose that there is a societal consensus that to exist in society there is a necessity to occasionally use coercive measures. Even people with treatment experience share this understanding, which shows that their attitude and sensitivity with respect to compulsory admission do not differ from the general population. Furthermore, attitude is clearly dependent on the respondent's concrete situation: the interviewees selected for our survey were living in a private household. People with severe mental illness but not currently in inpatient treatment should have been included. Not being an inpatient facilitates having a positive attitude towards compulsory admission.

We assume that patients find the experience of hospital admission mostly traumatic because of the adverse

Characteristics	Compulsory admission		p
	Agreement (n=1244, 73%)	Disagreement (n=452, 27%)	
Own treatment experience			
No	1054 (73%)	385 (27%)	..
Yes (total)	190 (74%)	67 (26%)	0.82
Without medication	79 (73%)	30 (27%)	0.86
With medication	111 (75%)	37 (25%)	0.65
Family member is a patient			
No	754 (73%)	284 (27%)	..
Yes	484 (74%)	169 (26%)	0.50

Various kinds of treatment experience correlated with agreement or disagreement to compulsory admission

treatment conditions and the stigma associated with mental illness.³ Individuals with mental disorders might be able to hide their illness as long as it is not treated within hospital. But when admitted to hospital for treatment they are much more likely to be identified as mentally ill. Each hospital admission increases the risk of identification, ostracism from society, devaluation, and demoralisation of sufferers, their families, and even their caregivers.⁴

Our results and the arguments by Farnham and James show that the attitude patients have is multi-dimensionally determined. Individual experience, societal background, as well as the patient's concrete situation sway attitudes to compulsory admission. As such, improvement of environmental and treatment conditions in psychiatric services, as well as fighting the stigma of mental illness, would be the most effective way to help people who have mental illness.

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DEPARTMENT OF ERROR

Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial—In this Article by Lorenz von Seidlein and colleagues (Jan 29, p 352), the 50 mg artesunate tablets used in the study contained artesunic acid and not sodium artesunate, as stated in the Background section of the Summary and in the fourth paragraph of the Introduction.