

# CORRESPONDENCE

## Consequences of in-utero death in twin pregnancy

Sir—P O D Pharoah and Y Adi (May 6, p 1597)<sup>1</sup> conclude that “the live-birth co-twin of a fetus that died in utero is at an increased risk of cerebral impairment, the overall risk is 20% (95% CI 16–25). The gestational-age-specific prevalence of cerebral palsy after fetal death of the co-twin is much higher than that reported for the general twin population”.<sup>1</sup> These confidently stated conclusions are not justified by the data.

We do not dispute the 20% estimate of risk. However, it is not clear what increased risk the investigators refer to, or what comparisons are intended. The investigators start by comparing rates of cerebral palsy and other cerebral impairment in children surviving the in-utero death of a co-twin of the same and different sex. They acknowledge the potential confounding or distorting role of gestational age in the association of same-sex or different sex-twins and cerebral palsy. However, the reported significant difference in cerebral palsy rates in same-sex and different-sex twins is based on crude rates. We carried out a Mantel-Haenszel stratified analysis, controlling for gestational age using data from the paper. The adjusted difference in cerebral palsy in same-sex and different-sex twins was no longer significant ( $p=0.08$ ), nor were differences significant at any single gestational age-group ( $p$  all  $>0.28$ ). We also fail to see a significant difference in other cerebral impairment or in overall cerebral impairment.

Pharoah and Adi then shift tack and compare their results to the general twin population, suggesting that gestational-age-specific rates of cerebral palsy are higher among co-twins of an in-utero death. However, no comparable questionnaire was sent to controls, either singletons or twin pairs where both survived. Instead, the investigators cite lower cerebral palsy rates from a UK study by Williams and colleagues<sup>2</sup> but give no information on how the rate was estimated in the latter study or on the comparability of the design or questionnaires used in the two studies. Different rates from a Swedish study are discounted.<sup>3</sup> It seems that rates of cerebral palsy are heavily dependent on methods of ascertainment.

There is nothing in this study that shows, with any degree of certainty, that

same-sex surviving twins have higher rates of cerebral palsy than different-sex surviving twins, apart from what would be expected given their lower gestational age. Livebirths with a co-twin who died in-utero may have more cerebral palsy than twins where both survive, but this study was not designed to test this hypothesis and cannot do so. There is no significant difference between same-sex and different-sex twins in other cerebral impediments, and no comparison is made with rates of other cerebral impediments in any other population.

The scientific process aims to eliminate poor research, but there may be more reason to be rigorous before publishing work heralding bad news for vulnerable groups. Parents of surviving twins are in a complex emotional situation, and should be protected from news of poor prognoses based on flawed studies.

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- 1 Pharoah POD, Adi Y. Consequences of in-utero death in a twin pregnancy. *Lancet* 2000; 355: 1597–602.
- 2 Williams K, Hennessy E, Alberman E. Cerebral palsy: effects of twinning, birthweight, and gestational age. *Arch Dis Child* 1996; 75: F178–82.
- 3 Rydhström H, Ingermarsson I. Prognosis and long-term follow-up of a twin after antenatal death of the co-twin. *J Reprod Med* 1993; 38: 142–46.

Sir—Pharoah and Adi<sup>1</sup> use their data on twin pregnancies complicated by single intrauterine death to estimate that the risk of cerebral impairment in monozygotic co-twin survivors is 40–50%. This risk is twice as high as the previous estimate for cerebral damage of 24%.<sup>2</sup> In fact, their excess risk of cerebral palsy in same-sex co-twins compared with different-sex co-twins was only 77/1000, whereas cerebral impairment rates were similar. Correcting the risk to exclude the proportion of same-sex twins likely to be dichorionic ( $[\% \text{ of twins that are same-sex} = \text{about } 67\%] / [\% \text{ of twins that are monozygotic} = \text{about } 20\%]$ ), results in an attributable risk in monozygotic

survivors of single intrauterine death of 26%.

Pharoah and Adi then suggest that the mechanism of co-twin damage in monozygotic single survivors is uncertain. In contrast, numerous lines of evidence indicate that the mechanism is acute transfusion at the time of co-twin death, from the surviving twin into the dead twin, resulting in cerebral hypoperfusion. Fetal blood sampling studies<sup>2</sup> done shortly after death indicate anaemia in survivors. There is a comparable risk of co-twin death, also secondary to acute inter-twin transfusion. Also, cerebral lesions are not prevented by rapid delivery of the survivor. Acute transfusion seems predominantly mediated via large calibre arterioarterial anastomoses.<sup>3</sup> This is supported by modelling data in a computer simulation (<http://www.aspects.net/~fletcher> accessed Aug 7, 2000), which predicts a faster rate of development of hypotension in the presence of arterioarterial compared with arteriovenous anastomoses. Arterioarterial anastomoses are identified antenatally on ultrasound,<sup>4</sup> and could be used as a basis for targeting preventive strategies.

The vanishing twin hypothesis given by the investigators attributes a high proportion of cerebral palsy in singletons to unrecognised single intrauterine death in monozygotic twins in the first trimester. In support, they cite data showing a higher rate of fetal loss in monozygotic compared with dichorionic pregnancies;<sup>5</sup> however, these losses almost always occur in the second trimester. There are further difficulties with their theory. Internationally, and our own, experience with feticide of one monozygotic twin in the first trimester is that death of one twin is followed by death of the co-twin. Single intrauterine death in one monozygotic twin in the first trimester has not been reported with any frequency, and thus must be exceptionally rare. Also, children with unexplained cerebral palsy do not usually have major lesions on brain imaging. In contrast, major vascular insults to the brain in the first trimester have been linked with global lesions such as hydronephaly, while porencephaly and multicystic encephalomalacia are characteristic features in clinical series of

cerebral damage after single intrauterine death in monozygotic twins.

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- 1 Pharoah POD, Adi Y. Consequences of in-utero death in a twin pregnancy. *Lancet* 2000; **355**: 1597–602.
- 2 Nicolini U, Poblete A. Single intrauterine death in monozygotic twin pregnancies. *Ultrasound Obstet Gynecol* 1999; **14**: 297–301.
- 3 Bajoria R, Wee LY, Anwar S, Ward S. Outcome of twin pregnancies complicated by single intrauterine death in relation to vascular anatomy of the monozygotic placenta. *Hum Reprod* 1999; **14**: 2124–30.
- 4 Taylor MJO, Denbow ML, Tanawattanacharoen S, et al. Doppler detection of arterio-arterial anastomoses in monozygotic twins: feasibility and clinical application. *Hum Reprod* 2000; **15**: 1632–36.
- 5 Sebire NJ, Sniijders RJM, Hughes K, Sepulveda W, Nicolaidis KH. The hidden mortality of monozygotic twin pregnancies. *Br J Obstet Gynecol* 1997; **104**: 1203–07.

#### Authors' reply

Sir—The Mantel-Haenszel stratified analysis done by Laura Rodrigues and colleagues may be correct but it is unwise to insist on the accepted level of significance and to consider cerebral palsy rates in isolation. We urged caution in interpreting the difference in cerebral palsy rates between same-sex and different-sex twins because discretion was sometimes exercised in registering sex when the stillborn baby was of indeterminate sex. However, in addition to the cerebral palsy rate, the infant mortality rate was also significantly higher in same-sex than in different-sex twins. Cerebral palsy is only part of a spectrum of cerebral impairment, and many of the infant deaths were attributable to cerebral impairment. If gestational age-specific rates of cerebral palsy and infant deaths are combined, Mantel-Haenszel stratified analysis to compare same-sex with different-sex twins gives a weighted odds ratio of 2.24 (95% CI 1.17–4.42;  $p=0.01$ ).

Misclassification could also have occurred in small growth-retarded stillborn babies, because a female fetus may have been wrongly registered as male. Although we reported instances where only twins were registered, in three instances the registrant had noted that it was part of a triplet or quadruplet pregnancy. Presumably those not registered were fetal deaths that had been expelled from the womb before 24 weeks of gestation. Registered twins may be of different sex but it cannot be assumed that both are from a dizygotic pregnancy.

Rodrigues and colleagues question the validity of the cerebral palsy rates

because no questionnaires were sent to controls. Studies in which cerebral palsy registers were examined have found that cerebral palsy rates in singletons were about two per 1000 infant survivors.<sup>1,2</sup> The cerebral palsy prevalence where both twins survived was 11.3 (95% CI 8.6–14.6) per 1000 infant survivors.<sup>2</sup> For Rodrigues to infer that the differences in these cerebral palsy rates from registers and those reported in our study could be due to a failure of ascertainment is not tenable.

We made no claim that the “other cerebral impairment” rates were significantly different in same-sex and different-sex twins. Our results were based on the general practitioners' (GPs) responses to the request for further observations about the child. All responses that could be construed as showing cerebral impairment were included in our report. The 20% estimate (table 3) of risk was obtained by including all twins.

Neil Sebire and colleagues ignore our proviso that an extreme assumption would be for all cerebral impairments in same-sex pairs to be among monozygotic twins. Only if this extreme assumption is met, is the estimate of cerebral impairment in monozygotic survivors as high as 40–50%.

We agree with Sebire and colleagues that the current view of the cause of co-twin damage in monozygotic single survivors is probably cerebral hypoperfusion. However, thromboembolisation has been postulated in earlier reports. We disagree that acute transfusion occurs necessarily at the time of the co-twin death. We have data (unpublished) that show same-sex compared with different-sex twins are at significantly increased risk of cerebral palsy even when both are born alive. The mechanism may be acute hypoperfusion but co-twin death is only an extreme example of the spectrum of damage that may affect either twin.

Sebire and colleagues are wrong to compare feticide with spontaneous death of a twin in their criticism of our vanishing twin hypothesis. From the Mersey Cerebral Palsy Register we found two cases with first trimester loss of a twin and cerebral palsy in the co-twin. And in May, 2000, a child being treated at the Walton Neurology Centre had perisylvian syndrome (pseudobulbar cerebral palsy) confirmed by magnetic resonance imaging. There had been loss of a co-twin in the first trimester.

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- 1 Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets and cerebral palsy births in Western Australia in the 1980s. *BMJ* 1993; **307**: 1239–43.
- 2 Pharoah POD, Cooke T. Cerebral palsy and multiple birth. *Arch Dis Child* 1996; **75**: F174–77.

## Cardiovascular disease in South Asians

Sir—Sonia Anand and colleagues (July 22, p 279)<sup>1</sup> report a rise in atherosclerosis in South Asians, as well as increased prevalence of glucose intolerance, raised total and LDL cholesterol and triglycerides, low HDL cholesterol, and high fibrinogen, lipoprotein (a), and plasminogen activator inhibitor. These features are classic for insulin resistance or metabolic syndrome,<sup>2</sup> which they do not mention.

Anand and colleagues state that these changes only partly explain the higher rates of cardiovascular disease among South Asians. The remainder of the explanation could be in the insulin resistance syndrome. The Quebec Heart Study,<sup>3</sup> showed that insulin resistance was an independent risk factor for coronary artery disease, probably because of its association with endothelial dysfunction. Albuminuria is a marker for endothelial dysfunction.<sup>4</sup> South Asians, even in non-obese people, have a higher frequency of insulin resistance.<sup>5</sup>

I believe that Anand and colleagues would find the complete explanation for the higher rates of cardiovascular disease among South Asians by measuring their fasting serum insulin concentrations and the ratio of urine albumin to creatinine.

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- 1 Anand SS, Salim Y, Vuksan V, et al. Differences in risk factors, atherosclerosis and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000; **356**: 279–84.
- 2 Reaven GM, Lithell H, Lundsberg L. Hypertension and associated metabolic abnormalities: the role of insulin resistance and sympathetic adrenal system. *N Engl J Med* 1996; **334**: 374–81.
- 3 Despres JP, Lamarche B, Mauriege P, Cuntin B, Dagenais GR, Moorjani S. Hyperinsulinaemia as an independent risk factor for ischaemic heart disease. *N Engl J Med* 1996; **334**: 952–57.
- 4 Mykkanen L, Haffner SM, Kuusisto J, Pyorala K, Laakso M. Microalbuminuria precedes the development of NIDDM. *Diabetes* 1994; **43**: 552–57.
- 5 Mather HM, Keen H. The Southall diabetes survey: prevalence of diabetes in Asians and Europeans. *BMJ* 1985; **291**: 1081–84.

## Testing for West Nile virus

Sir—Thomas Briese and colleagues (May 6, p 1614)<sup>1</sup> report that real-time PCR is a rapid and sensitive method for detecting West Nile virus, and that a positive test in cerebrospinal fluid correlates with a poor prognosis. We believe that proper statistical analysis and interpretation of the findings in their clinical and epidemiological context refute these conclusions.

Data from the 1999 New York outbreak of West Nile virus suggest that IgM-capture ELISA and plaque reduction neutralisation tests are more sensitive than real-time PCR. Standard reverse transcriptase PCR was not positive in sera or cerebrospinal fluid from any of the 62 patients confirmed by serologic tests; extensive use of the new real-time PCR method on cerebrospinal fluid samples from these and many other suspect cases identified no additional cases. Furthermore, preliminary data suggest that more than 30% of patients with serologically-confirmed infection were negative by real-time PCR.

Even Briese and colleagues' own data do not support their conclusion about real-time PCR. Of the four survivors with serologically confirmed West Nile virus infection, only one was positive by the new method. Extrapolation of this finding to the 1999 outbreak, in which only seven of 62 patients with West Nile virus died, suggests that real-time PCR would not have detected the disease in 41 of the 55 survivors.

The conclusion that positive real-time PCR correlates with death or severe prognosis is also unsubstantiated. All four patients who died had a positive test, compared with only one of four who survived, but this difference is within the limits of chance ( $p=0.14$ ). More importantly, our own data show that these cerebrospinal fluid samples were obtained late in the course of illness. Although Briese and colleagues report no correlation between PCR results and duration of illness, the median time between onset and sample collection was 19 days for PCR-positive patients, compared with only 3 days for PCR-negative patients. Indeed for three of the four fatal cases, specimens were obtained at necropsy. The presence of detectable RNA in postmortem samples cannot be interpreted as prognostic of death.

Our data suggest that the single most important risk factor for severity of illness and death from West Nile virus in the 1999 outbreak was

advanced age.<sup>2,3</sup> Briese and colleagues did not account for age. Had they done so, they would have noted that age older than 75 years correlated with prognosis.

Although real-time PCR is a promising rapid diagnostic test, the best screen for West Nile virus infection remains serological testing for antibody. IgM capture ELISA is simple and inexpensive to use, requires 2 days to complete, and unlike PCR, is sensitive for sera and cerebrospinal fluid. Real-time PCR is still a research tool that requires expensive equipment.

Unfortunately, Briese and co-workers' report was widely cited and misrepresented in the US press: national public radio reported that the test would allow physicians to institute successful early treatment of infection (this despite the fact that no specific antiviral treatment currently exists). Real-time PCR must be assessed more fully, not just in the laboratory, but together with clinical and epidemiological data which can shed light on its true value. We hope that physicians will not be misled, but will recognise that the diagnosis of West Nile virus infection currently relies mainly on serological testing.

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- 1 Briese T, Glass WG, Lipkin WI. Detection of West Nile virus sequences in cerebrospinal fluid. *Lancet* 2000; **355**: 1614–15.
- 2 CDC. Update: West Nile-like virus Encephalitis—New York, 1999. *MMWR Morb Mortal Wkly Rep* 1999; **48**: 890–92.
- 3 CDC. Update: West Nile virus encephalitis—New York, 1999. *MMWR Morb Mortal Wkly Rep* 1999; **48**: 944–55.

### Authors' reply

Sir—We agree with Annie Fine and colleagues that real-time PCR is not as sensitive as serology for detection of West Nile virus infection. We reported that some seropositive patients were PCR negative. Thus, we do not propose real-time PCR as a screening tool for epidemiology. Nonetheless, whether our assay (50–100 molecules sensitivity) is as insensitive as the one used by Fine and colleagues is not clear.

Samples submitted for PCR analysis should be treated differently than those used for serology. One set of cerebrospinal fluid samples sent to us for analysis had been heated to 56°C and shipped cross country at room temperature. A subset was PCR

negative. We also saw an adverse impact of such treatment on viral RNA standards. We wonder whether suboptimal sample treatment might have confounded Fine and colleagues' results as well.

As molecular microbiology becomes mainstream and samples are appropriately processed, we anticipate an improved success rate for PCR and related methods. Real-time PCR is not just a research tool, it is being incorporated in many hospitals and some instruments cost less than \$30 000. Any tool that facilitates rapid specific recognition of a causative agent is an important advance.

Although age is an important prognostic variable in West Nile virus encephalitis, not all infected older individuals succumbed. Thus, whether older individuals with non-fatal outcomes are more likely to be free of detectable viral sequences in their cerebrospinal fluid needs to be assessed. If we incorporate the corrections of Fine and colleagues, we have a median of 17 days for PCR-positive and 3 days for PCR-negative samples compared with their 19 days and 3 days, respectively. We believe the differential prognostic potential of finding antibodies or viral sequences in cerebrospinal fluid or blood relative to the duration of illness is unclear until the course of the disease and its associated clinical parameters have been charted through targeted studies. We agree that larger studies comparing sensitivity and specificity of serologic and real-time PCR analyses of blood and cerebrospinal fluid for diagnosis and prognosis, in conjunction with clinical and epidemiological data, are required to determine the relative value of these tests.

We are not as pessimistic about the prospects for treatment of West Nile virus infection. There are intriguing in-vitro results with the nucleoside analogues ribavirin and pyrazofurin;<sup>1</sup> the hormone dehydro-epiandrosterone seems to promote survival in mice infected with West Nile virus;<sup>2</sup> and burgeoning interest in West Nile encephalitis is attracting federal and industry investments in antiviral research and pathogenesis. It is ironic that as we are writing this letter, ribavirin is in human use for West Nile virus encephalitis.

Finally, unless journalists submit copy to authors of scientific papers for review it is unreasonable to hold authors responsible for the accuracy of media reports.

Lanciotti and Roehrig of the Centers for Disease Control and Prevention provided all clinical and sample information, and reviewed and approved the manuscript.

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- Jordan I, Briese T, Fischer N, Lau JYN, Lipkin WI. Ribavirin inhibits West Nile virus replication and cytopathic effect in neural cells. *J Infect Dis* 2000 (in press).
- Ben-Nathan D, Lachmi B, Lustig S, Feuerstein G. Protection by dehydroepiandrosterone in mice infected with viral encephalitis. *Arch Virol* 1991; 120: 263: 236–71.

## Digital arterial occlusive disease

Sir—D Dingli and colleagues (July 22, p 312)<sup>1</sup> describe the development of acute digital arterial occlusive disease with human parvovirus B19 infection. We previously reported an association between B19 and acute coagulopathy in a woman aged 46 years with critical digital ischaemia.<sup>2</sup>

Our patient presented with a similar non-specific malaise and a short history of digital ischaemia in the hands. Empirical treatment with the intravenous prostaglandin analogue Ilomedin (Schering), heparin, warfarin, and broad-spectrum antibiotics did not improve digital perfusion. Subsequent doppler studies confirmed widespread arterial and venous thromboses. Other presenting features included abnormal liver-function tests ( $\gamma$ GT and alkaline phosphatase) and thrombocytopenia. Echocardiography showed non-specific mild thickening of the anterior mitral leaflet, not judged to be a source of emboli.

As in Dingli and colleagues' patient, a full coagulation screen was negative except for borderline concentrations of IgG antibodies to cardiolipin. IgM titres were unmeasurable because of background binding.) Titres of antibodies to B19 showed seroconversion from IgM to IgG during the acute illness and PCR on blood samples obtained in the early stages of admission showed B19 parvoviraemia. Once parvoviraemia was diagnosed, intravenous immunoglobulin was given and digital ischaemia improved steadily over the next 3 weeks.

The findings of widespread arterial and venous thrombosis, thrombocytopenia, marantic-type mitral-valve changes and borderline titres of antibodies to phospholipid led us to postulate that an acquired antibody to phospholipid could be a possible

thrombotic cause in our patient. Antibodies to cardiolipin after parvovirus B19 infection, which may not always be detectable by conventional assays, are a potential factor.<sup>3</sup>

Our patient's subsequent clinical outcome was good. After 1 year, she had developed strongly positive IgM and IgG antibodies to cardiolipin. Our experience supports the assertion by Dingli and co-workers that acute B19 infection merits consideration in the differential diagnosis of critical ischaemia. Evolution of crossreacting antibodies to phospholipid should be considered as a possible pathological factor in this clinical context. Intravenous immunoglobulin might be useful because of its effective clearance of B19 parvoviraemia in immunosuppressed individuals and may have clinical efficacy in B19-associated vasculitis.<sup>4,5</sup>

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- Dingli D, Pfenzenmaier DH, Arromdee F, et al. Severe digital arterial occlusive disease and acute parvovirus B19 infection. *Lancet* 2000; 356: 312–14.
- Linton SM, Jackson R, Pritchard MH, et al. Acute parvovirus B19 infection and coagulopathy. *Rev Med Microbiol* 1999; 10: 19–25.
- Loizou S, Cazabon JK, Walport MJ, et al. Similarities of specificity and cofactor dependence in serum antiphospholipid antibodies from patients with human parvovirus B19 infection and from those with systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 103–08.
- Frickhofen N, Young NS. Persistent parvovirus B19 infection in humans. *Microb Pathog* 1989; 7: 319–27.
- Finkel TH, Torork TJ, Ferguson PJ, et al. Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? *Lancet* 1994; 343: 1255–58.

## Intra-arterial thrombolysis for hyperacute stroke

Sir—Philip A Barber and colleagues (May 13, p 1670)<sup>1</sup> report a new quantitative computed tomography scoring system introduced for detecting early ischaemic changes after ischaemic stroke. Since the approval of intravenous recombinant tissue plasminogen activator for acute ischaemic strokes, much interest has been generated about the use of thrombolytic therapy.

We treated ten patients with intra-arterial urokinase within 3 h of stroke. All ten had a history of atrial fibrillation. In eight of the ten patients, successful recanalisation was seen

within 6 h of ictus. Five had a good outcome, three had a poor outcome, and two died. All deaths were associated with the presence of internal carotid occlusion. We tried to apply the computed tomography scoring system (ASPECTS) described by Barber and colleagues to these ten patients. The initial scans were taken between 20 min and 90 min of ictus. Two experienced neurosurgeons (HN, SF) assessed the initial scans in the absence of other clinical information.

The sides of the affected hemisphere were correctly identified by both neurosurgeons, but the ASPECTS values were inconsistent between observers in three of the ten patients. Furthermore, the two patients who died from symptomatic intracerebral haemorrhage after thrombolysis had high ASPECTS values (8 and 9).

Early ischaemic changes on computed tomography might depend on the degree to which the local cerebral blood flow has decreased, and the duration of profound ischaemia. We wonder whether the early ischaemic changes were too subtle to be detected within 1 h of ictus. In elderly patients who have brain atrophy, early focal brain swelling could hardly be discerned, especially when the scans were taken within 1 h of ictus. Did Barber and colleagues find any correlation between the presence of early ischaemic changes and the length of time that the scan was taken after ictus? Intra-arterial thrombolysis could result in a higher rate of recanalisation than intravenous administration, but postfibrinolytic haemorrhagic transformation occurred in seven of the ten patients in our series. Symptomatic haemorrhage occurred in two patients who had high ASPECTS values.

The ASPECTS scoring system is simple and may be able to predict the outcome after intravenous thrombolytic therapy. To predict the increased risk of symptomatic haemorrhagic transformation after intra-arterial fibrinolysis, other methods such as local cerebral blood flow studies and diffusion-weighted magnetic resonance imaging, might be needed. Barber and colleagues also showed that serum glucose (>10 mmol/L) was a significant predictor of symptomatic haemorrhagic transformation. Normalisation of serum glucose and subsequent fibrinolytic therapy might be promising. A poor outcome or death is associated with failure to recanalise or with excessive brain oedema, or symptomatic haemorrhagic trans-

formation after reperfusion. The optimum prophylaxis for ischaemic stroke therefore remains rapid recanalisation while preserving endothelial integrity.

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- 1 Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000; **355**: 1670–74.

#### Authors' reply

Sir—Hiroshi Nawashiro and Shinji Fukui raise several important issues about why some stroke patients respond to thrombolytic therapy and others do not, some of whom seem to be harmed by it.

ASPECTS was developed because there were concerns about the reliable detection of early ischaemia on computed tomography and of its importance to functional outcome and the risk of symptomatic intracerebral haemorrhage in ischaemic stroke patients treated with intravenous thrombolytic therapy. ASPECTS was simple and reliable for stroke neurologists, radiology residents, and experienced neuroradiologists to use. We were able to detect early ischaemia in 75% of baseline scans with ASPECTS. In addition, the values predicted functional outcome and symptomatic intracerebral haemorrhage following intravenous tissue plasminogen activator.

The first point to make about Nawashiro and Fukui's findings is that their baseline computed tomography scans were done very early after symptom onset. Ischaemia would, therefore, have been difficult to detect. Only 20% of scans in the ASPECTS study were done within this time frame. The depth and extent of ischaemia becomes important, especially when attempting to salvage tissue. Imaging quality is of critical importance, with 5 mm cuts and optimum window levelling. The duration from computed tomography to treatment and the time of eventual recanalisation is also essential. Our study, which used immediate intravenous treatment, suggested that the risk of symptomatic haemorrhage was related to the extent of ischaemia—nine of ten patients with symptomatic intracerebral haemorrhage and ASPECTS scores of 7 or less. Although intra-arterial thrombolysis might result in higher rates of recanalisation than intravenous

therapy, it is slower to institute and post-treatment haemorrhagic transformation may be higher. This was the case in the intra-arterial PROACT II trial<sup>1</sup> in which the observed rate of symptomatic intracerebral haemorrhage in the treatment group was 10% and that of haemorrhagic transformation was 35%. The longer the delay after computed tomography, the less reliable the scan is. Time is brain!

Although other imaging methods, such as positron emission tomography and perfusion and diffusion-weighted magnetic resonance imaging are developing a more advanced understanding of acute stroke, these techniques have not yet been shown to help clinical decision making, although they show the evolution of the pathological process. We would, however, support the initiative of organising detailed clinical studies that may provide pathophysiological clues to the mechanisms of deterioration and therapeutic complications such as reperfusion injury and haemorrhagic transformation.

For the present, we think ASPECTS greatly assists the clinician in making individual treatment decisions about the use of intravenous thrombolysis for acute stroke.

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- 1 Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischaemic stroke. The PROACT II study: a randomised controlled trial. *JAMA* 1999; **282**: 2003–11.

### Pumpless extracorporeal lung assist

Sir—Michael Reng and colleagues (July 15, p 219)<sup>1</sup> reported their successful use of a pumpless extracorporeal assist system in adult respiratory distress syndrome. They were able to improve oxygenation with this device in eight of ten patients. The difference, however, was not significant compared with pump-driven lung assist and the increase in partial pressure/fractional concentration of oxygen (paO<sub>2</sub>/FiO<sub>2</sub>) averaged only 14.9% (range 0.5–39.6). Seven patients survived. They conclude that this survival is because of this very marginal improvement of oxy-

genation. The basic problem in the use of pumpless extracorporeal support in hypoxaemic pulmonary failure is to achieve a substantial improvement in oxygenation without impairment of haemodynamics. Pumpless extra-corporeal support requires additional cardiac output to drive the extracorporeal circuit.

The extracorporeal device in the Reng study was driven by 16–37% of cardiac output. Nevertheless, only small increments in catecholamine treatment were necessary to stabilise the patients' haemodynamic conditions. We doubt very much that this new device is really able to improve the outcome of patients with acute respiratory distress syndrome. We know that there is no real evidence for the value of extracorporeal membrane oxygenation (ECMO) in these patients either, but looking at differences in oxygenation index, ECMO is much more efficient.<sup>2</sup> We used an arteriovenous pumpless system with a mini oxygenator (Jostra, Hirrlingen, Germany) 5 years ago in two children aged 3 years with contraindications for ECMO. In these two patients, 20% of cardiac output was drawn for the extracorporeal device and catecholamine requirements increased greatly. The paO<sub>2</sub> in the femoral vein was always above 600 mg Hg (postoxygenerator), but we could neither reduce ventilatory support nor see any increase of arterial oxygen saturations in either patient.<sup>3</sup>

We recommend caution on interpreting the usefulness of pumpless arteriovenous extracorporeal oxygenation in severe hypoxaemic respiratory failure (paO<sub>2</sub>/FiO<sub>2</sub><100), since the improvement in oxygenation is slight, but haemodynamic instability is likely.

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- 1 Reng M, Philip A, Kaiser M, Pfeifer M, Grüne S, Schölmerich J. Pumpless extracorporeal lung assist and adult respiratory distress syndrome. *Lancet* 2000; **356**: 219–21.
- 2 Lewandowski K, Rossaint R, Pappert D, et al. High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. *Int Care Med* 1997; **23**: 819–35.
- 3 Möller JC, Schaible TF, Reiss I, Kohl M. Die kontinuierliche pumpenfreie arteriovenöse Oxygenierung ist keine sinnvolle Therapie bei schwerem pädiatrischen Lungenversagen. *Mtschr Kinderheilkd* 1997; **145**: S110.

## Breast carcinoma in young patients

Sir—Stephan Aebi and colleagues (May 27, p 1869)<sup>1</sup> did a combined analysis of different clinical trials of patients with breast cancer who received adjuvant cyclophosphamide-methotrexate-fluorouracil (CMF) therapy after surgery, and confirmed data<sup>2</sup> that indicated that women under the age of 35 with early breast cancer fared substantially worse than women of age 35 or more. Surprisingly, in the younger women, oestrogen-receptor positivity was found to be associated with the worst prognosis. In the study by Aebi and colleagues, the response of young women with breast cancer to adjuvant post-surgical therapy was not addressed because of the lack of an untreated control group. Indeed, although most randomised clinical trials give a definitive answer regarding the usefulness of a particular therapy, when the patient series is not large enough, such as in breast carcinoma in very young women, the actual benefit of the therapy for low-frequency subsets of patients cannot be defined.

We analysed the overall survival of patients with breast cancer who had undergone surgery at the Istituto Nazionale Tumori, Milan, Italy during 1968–96 (1117 women), when chemotherapy was not available for post-surgical use, and 1978–79 (859 women), when CMF adjuvant therapy was given after surgery. Survival analysis of the two series indicated an improvement in the series of patients who received adjuvant chemotherapy, with a 10-year survival of 67% when compared with 59% in the

patients who received no adjuvant chemotherapy (data not shown). Comparison of the two series according to patient age indicated that the younger patients benefited the most, with a 31% improved 10-year survival as compared with only 6% improvement in the older patients (figure). Analysis of survival according to age at diagnosis showed that young age (<35 years) was a factor of poor prognosis in the first series (32% 10-year survival *vs* 61% in patients 35 years and over), while in the second, the adjuvant treatment seems to minimise the age-dependent poor prognosis—ie, the 10-year survival was 63% in the under 35 years group and 67% in the 35 years and more group.

One interpretation of these results is that young women benefit more than older women from early diagnosis. However, this explanation seems quite unlikely since the frequency of tumours in patients under 35 years did not differ significantly in the two series (5.1% in the first series *vs* 6.1% in the second). Or, it might be that younger patients respond better to adjuvant chemotherapy than do older patients. Indeed, chemotherapy is well known to be more effective in tumours with high proliferative rates, the type of tumour frequently seen in younger patients.<sup>3</sup> The improved survival found by Aebi and colleagues in the oestrogen-receptor-negative subset of young patients with breast carcinoma treated with CMF might likewise be a result of a particular effectiveness of the therapy in these tumours, since oestrogen-receptor-negative tumours frequently have a higher proliferative rate than hormone-receptor positive tumours.<sup>4</sup> On the other hand, a higher proliferative rate in tumours from young patients cannot by itself explain such a good response to therapy; other factors associated with the young age such as interference with hormones and growth factors are likely to be involved.

Further studies are needed to fully explain the age-dependency of the responsiveness to chemotherapy in patients with breast cancer.

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- 1 Aebi S, Gelber S, Castiglione-Gertsch M, et al. Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? *Lancet* 2000; **355**: 1869–74.
- 2 de la Rochefordiere A, Asselain B, Campana F, et al. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993; **341**: 1039–43.

- 3 Nixon AJ, Neuberg D, Hayes DF, et al. Relationship of patient age to pathological features of the tumour and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 1994; **12**: 888–94.
- 4 Remvikos Y, Magdelenat H, Durollaux B. Genetic evolution of breast cancers. III; age-dependent variations in the correlations between biological indicators of prognosis. *Br Can Res Treat* 1995; **34**: 25–33.

Sir—Aebi and colleagues<sup>1</sup> identify patients with breast cancer under age 35 years as candidates for additional therapy. However, they do not mention a sub-group within this age group that certainly accounts for a part of their poor survival characteristics—women who have had a recent pregnancy shortly before diagnosis.

We have reported<sup>2</sup> that in women aged 20–29 years, pregnancy within the 4 years before the diagnosis of breast cancer, was associated with a significant decrease in survival compared with women who have never been pregnant. For example, after adjustment for tumour size and the number of positive nodes, the relative risk of dying of breast cancer was 1.88 (95% CI 0.88–3.98) for the patients who had given birth in the 12 months preceding the diagnosis.

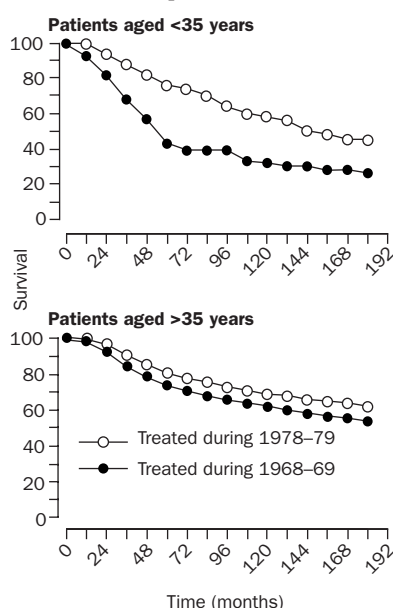
In a subsequent report, Kroman and colleagues<sup>3</sup> observed that for women under age 45 years, a diagnosis of breast cancer less than 2 years after giving birth, was associated with a particularly poor survival compared with women who had given birth 6 years or more earlier. They had an adjusted relative risk of 1.58 (1.24–2.02). Olson and colleagues<sup>4</sup> have also reported women of less than age 45 years who, having given birth within 2 years before the diagnosis of breast cancer, were at increased risk of dying compared with nulliparous women. Their adjusted relative risk was 3.1 (1.8–5.4).

Additional or more intense therapy for women younger than 35 years is particularly pertinent for patients who have had a pregnancy before diagnosis.

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- 1 Aebi S, Gelber S, Castiglione-Gertsch M, et al. Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? *Lancet* 2000; **355**: 1869–74.
- 2 Guinee VF, Olsson H, Moller T, et al. Effect of pregnancy on prognosis for young women with breast cancer. *Lancet* 1994; **343**: 1587–89.
- 3 Kroman N, Wohlfahrt J, Andersen KW, et al. Time since childbirth and prognosis in primary breast cancer: population based study. *BMJ* 1997; **315**: 851–55.
- 4 Olson SH, Zauber AG, Tang J, et al. Relation of time since last birth and parity to survival of young women with breast cancer. *Epidemiology* 1998; **9**: 669–71.



**Survival of patients with breast carcinoma according to age at diagnosis**

## NICE and drugs for multiple sclerosis

Sir—In a press release issued on June 20, 2000, the Chairman of the UK National Institute of Clinical Excellence (NICE), expressed the Appraisal Committee's view that the "modest clinical benefit" of  $\beta$ -interferon and glatiramer acetate for multiple sclerosis (MS) is outweighed by their cost. As an international observer with day-to-day experience of these drugs in clinical practice, I am both puzzled and disappointed by this provisional opinion. Many health authorities (including the European Medicines Evaluation Agency) and reimbursement agencies throughout the world have reviewed the same data and concluded that interferons are effective and safe.

Several controlled clinical trials have shown significant benefits from  $\beta$ -interferon therapy in patients with relapsing MS.<sup>1-4</sup> The most comprehensive data on longer-term outcomes are derived from the Prevention of Relapses and Disability by Interferon  $\beta$ -1a Subcutaneously in Multiple Sclerosis (PRISMS) study,<sup>1</sup> the 4 year results of which have been presented.<sup>5</sup> The results of this double-blind, multicentre study show highly significant treatment advantages of interferon  $\beta$ -1a over placebo, sustained over 4 years and covering clinical endpoints and measures of underlying disease activity taken by magnetic resonance imaging (MRI). Maximum benefit, including impact on progression of disability, was achieved with the higher dose of  $\beta$ -interferon, (44  $\mu$ g three times a week). Time to disability progression was almost doubled (24 months *vs* 42 months,  $p < 0.05$ ).<sup>5</sup> Long-term, such a delay is likely to have a clear effect on quality of life.

Relapses of MS are often severe, disabling, and distressing and may require admission to hospital. Over the 4 years of the PRISMS study, patients treated with interferon  $\beta$ -1a (44  $\mu$ g three times a week), had 43% fewer relapses than those treated with placebo for the first 2 years of the study (0.74 *vs* 1.3 relapses per year,  $p < 0.0001$ ).<sup>5</sup> MRI showed a highly significant reduction in new lesion activity and disease burden ( $p = 0.0001$ ). A significant and sustained reduction in relapses, and the delay in disability progression should not be trivialised by calling it a minor clinical benefit. From the patient's point of view the benefits of interferon- $\beta$  in relapsing MS are both major and long-term.

It seems both ironic and tragic that the UK, with its first class pharmaceutical and biotechnology industry, would first ration and then withhold the only proven drug treatment for relapsing MS. The international community of researchers and clinicians involved in MS is astonished that the number of patients (3%) receiving  $\beta$ -interferon in the UK is so low compared with other developed countries (12–16% in France, Germany, and North America).

On the basis of the wealth of clinical data supporting the use of disease-modifying drugs in MS, I suggest that the provisional recommendations should be modified and this therapy be made available to patients with MS who would benefit through the National Health Service.

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- 1 PRISMS Study Group. Randomised, double-blind, placebo-controlled study of interferon  $\beta$ -1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; **352**: 1498–504.
- 2 IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicentre, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43**: 655–61.
- 3 The IFNB Multiple Sclerosis Study Group, the University of British Columbia MD/MRI Analysis group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomised controlled trial. *Neurology* 1995; **45**: 1277–85.
- 4 Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; **39**: 285–94.
- 5 Freedman MS, and the PRISMS Study Group. PRISMS 4-year results: evidence of clinical dose effect of interferon beta-1a in relapsing MS [abstr]. AAN 2000, San Diego, LBN 001.

## Jehovah's Witness blood policy

Sir—Spurred by David Sharp's July 1 commentary,<sup>1</sup> I would like to provide insight into the publicity over Jehovah's Witness' statements to the press about their blood policy. I write as a former Jehovah's Witness who spent 30 years in this religion, from birth, but who left 20 years ago.

Since 1961 all Jehovah's Witnesses have known that they risk exclusion if they do not toe the Watchtower Society's line on blood.<sup>2</sup> Since 1981

Jehovah's Witnesses have known how they are expected to view and treat those who are excluded and those who choose to disassociate themselves.<sup>3</sup> Jehovah's Witnesses worldwide went through those magazines at their study meetings, paragraph by paragraph.

There was an important change to this policy in April, 1999, yet rank and file members appear to have learned of it only through media reporting this summer. The Society said accepting blood was no longer grounds for exclusion<sup>4</sup> and succeeded in placating the media by saying they had written to all elders in 1999, advising them of this change in regulations. Elders who participate in hospital liaison on behalf of Jehovah's Witnesses needing blood were included in this notification. But can the Society offer any proof that Jehovah's Witnesses will know about the freedom from fear of expulsion before they require blood? Or do elders wait till they hear of a Jehovah's Witness in hospital before advising them? What if the Jehovah's Witness dies before they can tell them? Why has the Society not yet spelled out this important change in their official magazine?

If, as I fear, Jehovah's Witnesses in general are being kept in the dark about partial release from sanctions, could the Society be culpable for the deaths of Jehovah's Witnesses refusing blood since April, 1999? Would not some of those people have changed their minds about refusing blood had they known they could avoid exclusion by later repenting of their acceptance in a moment of weakness?<sup>3</sup> This freedom from sanctions, however, is shallow, because if they do not repent, they will then be viewed as having dissociated themselves. Until all fear has been removed from Jehovah's Witnesses they continue to be sanctioned and cannot be said to be making up their own minds on this issue.

From 1961 members have never been free to make up their own minds on this issue because of fear of punishment from the Society and fear of punishment from God. Both fears remain despite anything the Society has said. Jehovah's Witnesses need to face up to this situation, but how can they when they are not being released from this man-made fear?

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- 1 Sharp D. Jehovah's Witnesses' blood policy. *Lancet* 2000; **356**: 8.
- 2 *The Watchtower*, Jan 15, 1961: 63–64.
- 3 *The Watchtower*, Sep 15, 1981: 17, 22–24.
- 4 Gledhill R. *The Times*, June 14, 2000: 3.

Sir—In response to R M Yate and colleagues' (July 1, p 69)<sup>1</sup> discussion of medicolegal issues in emergency treatment of Jehovah's Witnesses, we present our experience of managing such a patient in the accident and emergency department.

A girl aged 12 years was brought to our department after a lorry had run over her lower abdomen and pelvis. The child also had a head injury with an expanding haematoma over the right frontoparietal area of the scalp. Advanced trauma life support series of radiographs showed major pelvic disruption (later confirmed by a computed tomographic scan). Although initially stable, the child soon started developing the signs of hypovolaemic shock. The need for an urgent blood transfusion became essential for survival. Three separate clinicians explained the situation to the patient and the parents, who were Jehovah's Witnesses. Unfortunately consent for blood transfusion was not given. We did not judge the child as Gillick competent<sup>2</sup> because of the head injury. While a court order was awaited, the parents gave consent for the blood transfusion to go ahead and the child's life was saved.

On the basis of the medicolegal precedent presented by Yate and colleagues and our experience, two questions arise. What are the implications for clinicians who judge a seriously injured individual as being Gillick competent—but a court later rules to the contrary? What is the appropriate action if a seriously injured minor who is a Jehovah's Witness needs an immediate blood transfusion and there is insufficient time to wait for a court order?

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- 1 Yate RM, Milling MAP, McFadzean W. Treatment without consent: a medicolegal precedent. *Lancet* 2000; **356**: 69.
- 2 Kennedy I, Grubb A. The three stages of childhood. In: *Principals of medical law*. Oxford: Oxford University Press, 1998: 203–05.

Sir—R M Yate and colleagues<sup>1</sup> are wrong to suggest that the courts in the UK have power to over-ride the wishes of adults who have led a sheltered life. The High Court has such power only over children. This power is derived from the State's *parens patriae* role—ie, the State acting as parent. In situations where a competent minor refuses treatment, the courts can over-ride that decision. But the State has no comparable power over adults—even

incompetent adults. This was recognised by the House of Lords in the adult sterilisation case of *Re F* in 1990.<sup>2</sup> As for competent adults, their right to refuse treatment for reasons that are rational or irrational, or for no reason, is settled law.<sup>3,4</sup> If adults lack capacity, they may be treated in their best interests. It is, however, wrong to suggest that someone who has led a cloistered existence lacks capacity as a result.

The Human Rights Act 1998 comes into force on Oct 2, 2000, and incorporates the European Convention on Human Rights into English law. This may result in the State's *parens patriae* power over minors being curtailed. Competent minors wishing to refuse treatment can then involve the protection of Articles 5, 8, and 9 of the Convention (right to liberty and security of person; right to respect for private and family life; freedom of thought and conscience). These Articles would also protect adults wishing to refuse unwanted treatment.

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- 1 Yate RM, Milling MAP, McFadzean W. Treatment without consent. *Lancet* 2000; **356**: 69.
- 2 *Re F* (Mental Patient: Sterilisation [1990]) AC 1.
- 3 *Sidaway v Bethlem Royal Hospital* [1985] AC 871.
- 4 *St Georges' Healthcare NHS Trust v F* [1999] Fam 26.

## Ethics of mass STD treatment

Sir—Heiner Grosskurth and colleagues (June 3, p 1981)<sup>1</sup> conclude their review of the divergent results of the Mwanza and Rakai trials with a call for trials of single or multiple rounds of mass treatment for sexually transmitted diseases (STD). Such a call is disingenuous, given the negative findings of the Rakai trial and, furthermore, ignores those who believe mass treatment will have an adverse effect on public health.<sup>2</sup> In addition, there is the unexplained increase in HIV-1 incidence over time in Rakai, which we suggest is related to increased unsafe sexual behaviour in the face of a biomedical intervention.<sup>3</sup> An increase in STD prevalence was seen in Mwanza,<sup>4</sup> probably for the same reason. Again, an uncomfortable fact is conveniently overlooked.

We have argued elsewhere that trials of biomedical interventions should take place in cohorts of stable HIV-1

discordant couples before they are extended to the general population.<sup>3</sup> This approach applies to HIV-vaccine trials, mass STD treatment, antiretroviral treatments, and circumcision. At the XIII International AIDS Conference in Durban, there was much discussion about the latter. Circumcision of the male partner seems to be protective for male-female and female-male heterosexual HIV-1 transmission, but only in discordant couples.<sup>5</sup> Those working in Africa need to be more strident in resisting those who suggest mass biomedical interventions, while becoming supportive of biomedical interventions in discordant couples.

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- 1 Grosskurth H, Gray R, Hayes R, et al. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet* 2000; **355**: 1981–87.
- 2 Mathys F, Boelaert M. Preventing HIV: lessons from Mwanza and Rakai. *Lancet* 1999; **353**: 1523.
- 3 Hudson CP, Smith AN. Mwanza, Rakai, and the design of HIV vaccine trials. *Int J Infect Dis* 2000 (in press).
- 4 Habbema JDF, de Vlas SJ. Impact of improved treatment of sexually transmitted disease on HIV infection. *Lancet* 1995; **346**: 1157–58.
- 5 Gray R, Wawer M, Sewankambo N, et al. HIV incidence associated with male circumcision. XIII International AIDS Conference, Durban, July 9–14, 2000 (abstr MoOrC193).

Sir—Stephanie Clark in her July 15 news item (p 225),<sup>1</sup> states that “. . . all the speakers agreed that randomised controlled trials examining the effect of male circumcision on HIV transmission are needed”. However, the people who spoke in favour of randomised controlled trials did not represent everybody's views.

Most available data show a protective effect of male circumcision against HIV infection, but are mainly from studies not specifically designed to look at this association. Most used self-reports to establish circumcision status.<sup>2</sup> More importantly, researchers have used multivariate regression techniques to control for the strong association of circumcision status with religion and ethnic group but disagree about the extent to which residual confounding may still be present. Confounding was illustrated by some data presented at the conference,<sup>3</sup> but in some areas the evidence is convincing enough to merit action.

The strength of the protective effect of male circumcision varies between populations.<sup>4</sup> We find it hard to see how randomised controlled trials will help to resolve this issue, unless a series of trials are done in different populations with different rates of HIV infection and sexually transmitted diseases. We question the feasibility of randomised controlled trials. The best approach would probably be to do a community intervention trial. The intervention will not be male circumcision but promotion of male circumcision. Suitable duration and cost of such studies is unclear. Even more fundamental, however, is the implied change in culture if male circumcision is introduced. Such intervention with far reaching consequences can be justified only if there is evidence of beneficial effects, and if such evidence exists there should be no need for randomised controlled trials.

We propose that only in populations with high rates of HIV/AIDS and good evidence for a protective effect of male circumcision against HIV infection, acceptability and feasibility studies should be done.<sup>5</sup> If results are positive, a programme should be designed to promote sexual health, of which male circumcision and penile hygiene should be components. Such a programme needs to be carefully assessed. Observational studies should be done, including genital examination to assess circumcision status, in areas where evidence is in doubt.

The HIV and AIDS epidemics in parts of sub-Saharan Africa are devastating and more needs to be done to reduce the spread of HIV. We cannot afford to always postpone the large-scale implementation of interventions against the spread of HIV infection until we have gold standard evidence from randomised controlled trials that they work. We need to use all available evidence to guide a wide range of interventions, and, above all, we should use common sense.

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1 Clark S. Male circumcision could help protect against HIV infection. *Lancet* 2000; **356**: 225.

2 Urassa M, Todd J, Boerma JT, Hayes R, Isongo R. Male circumcision and susceptibility to HIV infection among men in Tanzania. *AIDS* 1997; **11**: 73–80.

- 3 Gray R, Wawer MJ, Sewankambo NK, et al. HIV incidence associated with male circumcision in a population-based cohort, and HIV acquisition/transmission associated with male circumcision and viral load in discordant couples: Rakai, Uganda. Presented at the XIIIth International AIDS Conference, Durban July 9–14, 2000 (abstr MoOrC193).
- 4 Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* 2000 (in press).
- 5 Bailey R, Muga R, Poulussen T. Trial intervention introducing male circumcision to reduce HIV/STD infections in Nyanza province, Kenya: baseline results. Presented at the XIIIth International AIDS Conference, Durban July 9–14, 2000 (abstr MoOrC196).

## On education and training

Sir—The accompanying panel is a distillation of views and prejudices accumulated over some 55 years since I did an honours degree in physiology with Samson Wright. My views have not changed much in the past 25 years or so and I approach my BBD so it seems appropriate to go public.

The panel has been used by others.<sup>1</sup> I trust that with the help of a little thought the meaning of the terms will be clear. I believe that most educators (really trainers) would assert and believe that they subscribe to the entries in the panel but their professed understanding is token—to mix a metaphor—and only skin deep. With this short piece I hope to encourage some of these misguided educators to search for better insight and to see through the jargon of their educationalist clichés. To the minority, those true educators, who do understand and sympathise I hope to encourage them to know there are others out there.

### Views and prejudices about education and training

Education	Training
Intrinsically valuable	Practically useful
Broad, not complete	Circumscribed, complete
Open ended	Closed ended
Promotes further growth	Inhibits further growth
Responsible to the student	Responsible to the community
University objectives	Professional objectives
University not responsible for licence	Professional responsible for licence
Difficulty to teach/learn	Easy to teach/learn
Difficult to examine	Easy to examine

At present there seems to be a thrust toward utilitarianism (training) throughout education, particularly higher education, at the level both of tactics and strategy. In medicine at the tactical level there has been an explosion of new curricula (new pathways), which purport to broaden the educational basis but too often get side-tracked into pedagogical gimmickry. The criterion of a student's success is still qualification, as defined by passing an exam. But qualification for what? In most jurisdictions a further period of residency or specialty training is required. In internal medicine it is my experience that these programmes, with their minuscule provision for general experience, may make the specialist deeper as it makes the doctor in him, or her, more shallow.

Then, in the grand strategy of high education, I find that the promotion of places of higher education to university status to be plain silly. Look to France and Germany.

In closing, I must emphasise that I am not advocating the separation of institutions dedicated to education from those devoted to training, although history and tradition indicate that some such distinction is both inevitable and desirable. Let me stick to what I know best. There is no place better than the ward or the clinic to blend the two provided that students are not blunted by their worry about some banal examination using multiple choice questions and the teacher/trainer's overdeveloped indulgent instinct for self-replication.

I thank Dr C B Mueller for his criticism.

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1 McManus IC. Examining the educated and the trained. *Lancet* 1995; **i**: 1151–53.

## DEPARTMENT OF ERROR

*Global health policy*—In this Correspondence letter by Gunnar Kvåle (Aug 19, p 680), the first sentence of the second paragraph on page 681 should be, “It is a well documented fact that infectious diseases represent the greatest disease burden for the poor of the world, and that the interventions available for this group of diseases are more cost-effective than those for many chronic diseases”.

*Debate continues on end-of-life issues*—In this News item by Sarah Ramsay (March 4, p 811), the third sentence of the first paragraph should be, “The coordinator of the working group on euthanasia for the Dutch Medical Association, Eric van Wijlick, told *The Lancet* he was aware that there are technical difficulties in [physician-assisted suicide], but the Association does have a policy on how to tackle this problem. It recommends use of the guidelines issued by the Royal Dutch Association of Pharmacy”.