Second, we now know that despite what seemed to be an increase in issues related to brain damage when the original trial reported, the longer-term study shows that CNEP might, if anything, be kinder on the brain. The paediatric community now has to decide whether CNEP has a place in the care of these babies or whether everything has moved on.

Third, we can now see the headlines about baby deaths in perspective. They were lurid and misleading and in making such headlines the mass media did not do anyone a good service; it created unnecessary anxiety and did nothing to further the research that might save lives in the future.

Finally, we should acknowledge the parents. Assistance from Mr and Mrs Henshall is acknowledged in Telford and colleagues' paper.[4] Many of the parents who gave evidence to the review met each other regularly because their children attended the same special-care nursery. It is not surprising that parents with that burden to bear would want answers even when there are none. I am pleased that one outcome of our review is that we now know that CNEP did no more damage than any other treatment that might have been used to try and help these infants. Hopefully, if we can get research governance right, we can look forward to constructive partnerships between clinicians and parents that could help us find other important answers.

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I declare that I have no conflict of interest.

1 NHS Executive West Midlands Regional Office. Report of a review of the research framework in North Staffordshire Hospital NHS Trust NHS Executive West Midlands Regional Office, May 8, 2000: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4005415&chk=/CUYME (accessed March 28, 2006).
2 Hey E, Chalmers I. Are any of the criticisms of the CNEP trial true? *Lancet* 2006; **367:** 1032–33.
3 UK Department of Health. An organisation with a memory—report of an expert group on learning from adverse events in the NHS chaired by the Chief Medical Officer. June 13, 2000: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4065083&chk=PARoiF (accessed March 23, 2006).
4 Telford K, Waters L, Vyas H, Manktelow BN, Draper ES, Marlow N. Outcome after neonatal continuous negative-pressure ventilation: follow-up assessment. *Lancet* 2006; **367:** 1080–85.

How specific are therapeutic monoclonal antibodies?

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The tragic events at Northwick Park, Middlesex, UK, in which six participants in a phase I clinical trial of the monoclonal antibody TGN1412 became seriously ill on March 13–14, forcefully remind us of the potency of the compounds that modern biotechnology can provide. While the exact cause of the unexpected reactions continues to be investigated, it would be well to pause and consider a founding principle of the widespread use of monoclonal antibodies—that they are exquisitely specific. It is all too easy to accept the potentially dangerous concept that monoclonal antibodies are harmless proteins that are highly specific and safe therapeutic agents binding only one specific molecular target.[1–3]

Monoclonal antibodies are key elements of much of modern medicine. Indeed, many sophisticated diagnostic tests that are now taken for granted are based on these remarkable molecules. However, even in the in-vitro tests, cross-reactive binding to substances other than the test substance is often seen. Such unwanted binding occurs even though reactions take place under optimum conditions, in very simple controlled environments, with a relatively simple sample. Molecularly, monoclonal antibodies are compromises selected because they bind their target antigens extremely well, but they do not express the exact lock-and-key fit so beloved by textbooks. They can, and do, bind to molecules other than their intended target.

The situation becomes even more intricate when antibodies are used therapeutically in a more complicated environment, the human body. Here, we are concerned not only with unwanted, and possibly damaging, cross-reactivity with normal tissues, but also with localisation away from the target due to the body's efficient sequestration mechanisms and by persistence in the circulation. A further major complication is the distribution of the targeted antigen itself. Few, if any, therapeutic antibodies currently target molecules that are totally disease-specific.[4,5] For instance, overexpressed cellular receptors used as targets in cancer therapy are often present, albeit at lower concentrations, on normal cells.[3–5] When all these factors are taken into account, it is unsurprising that truly cancer-specific tumour antigens are thought to be virtually unattainable.[5] All these

influences cause non-specific binding and lead to potential side-effects, which are then amplified by the simple fact that there is much more normal tissue than tumour in an individual with cancer. These issues are important whether the antibody is a physiological antagonist, agonist, or toxic-load carrier.

Despite these often ignored problems, therapeutic monoclonal antibodies have great potential to target and cure many conditions. Several valuable therapeutic antibodies have been produced.[5-7] However, even with the outstanding anticancer agent, trastuzumab, there is some concern about unwanted targeting of cardiac tissues in a few patients.[8]

Despite the targeting problems, many important technical advances have been made. Much of the emphasis has been placed on humanising antibodies so they are not regarded as foreign by, and thus rapidly removed from, the body.[3-7] However, these advances still require the antibodies to have exquisite targeting specificity within the body.

While the search continues for the elusive target antigens that are truly specific to cancer cells, there is a need to develop other ways of increasing the probability that an antibody will find its target. One way is to attempt to make the antibodies more regionally specific, such that they do not bind and cause damage to tissues within normal regions of the body. Some investigators have resorted to physical methods such as isolated-limb perfusion,[9] others have developed photodynamic therapy agents,[10] in which antibodies are labelled with molecules that only become active on illumination. Antibody-directed enzyme prodrug treatments have also been designed to limit damage to healthy tissues.[7] Our approach to this problem has been to increase the effective functional specificity of the antibodies by making their activity light-dependent.[11] Through this approach, we can achieve control of when, and more importantly where, an antibody is active, reducing unwanted binding and potentially damaging side-effects. Such technology should allow many previously produced anticancer antibodies, discarded because they were not specific enough in vivo, to be turned into important clinical products.

As monoclonal antibodies are more widely used clinically, and at various stages of disease, increasingly close focus will be applied to their side-effects. It would be an appalling tragedy if the very potency of monoclonal antibody therapies,[7] possibly demonstrated so forcefully by recent events, was the feature which hindered, or even prevented, the rapid future development of these extremely valuable drugs.

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Computer artwork of antibodies and cell

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1 Smith KA, Nelson PN, Warren P, Anstley SJ, Murray PG, Greenman J. Demystified . . . recombinant antibodies. *J Clin Pathol* 2004; **57**: 912–17.
2 Stockwin LH, Holmes S. Antibodies as therapeutic agents: vive la renaissance! *Expert Opin Biol Ther* 2003; **3**: 1133–52.
3 Bodey B, Bodey B Jr, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents. *Curr Pharm Des* 2000; **6**: 261–76.
4 Christiansen J, Rajasekaran AK. Biological impediments to monoclonal antibody-based cancer immunotherapy. *Mol Cancer Ther* 2004; **3**: 1493–501.
5 Morrow KJ Jr. Challenges remain for antibody products. *Genet Eng News* 2005; **25:** 1–19.
6 Brekke OH, Sandlie I. Therapeutic antibodies for human diseases at the dawn of the twenty-first century. *Nat Rev Drug Discov* 2003; **2:** 52–62.
7 Schrama D, Reisfeld RA, Becker JC. Antibody targeted drugs as cancer therapeutics. *Nat Rev Drug Discov* 2006; **5:** 147–59.
8 Levine MN. Trastuzumab cardiac side effects: only time will tell. *J Clin Oncol* 2005; **23:** 7777–76.
9 Thompson JF, de Wilt JH. Isolated limb perfusion in the management of patients with recurrent limb melanoma: an important but limited role. *Ann Surg Oncol* 2001; **8:** 564–65.
10 Dolmans DEJDJ, Fukumura D, Jain RK. Photodynamic therapy for cancer. *Nat Rev Cancer* 2003; **3:** 380–87.
11 Self CH, Thompson S. Light activatable antibodies: models for remotely activatable proteins. *Nat Med* 1996; **2:** 817–20.