Complexities of equitable drug availability

Sir—Nathan Ford and colleagues (Feb 14, p 560)[1] present a fascinating account of the legal complexities surrounding access to patented medicines in the developing world, describing events that led up to a judgment by the Thai Central Intellectual Property and Trade Court to allow generic manufacture of the antiretroviral compound, didanosine. The dedication, energy, and determination of the groups involved is both moving and inspiring.

Events described in this Viewpoint article relate to a legal dispute and are, therefore, adversarial in character. A review based on the positions taken in such a dispute, irrespective of the rights and wrongs of this particular case, might not provide an optimum basis for informed discussion of the complex issues that need to be solved to ensure equitable access to healthcare on a worldwide scale. In particular, the generalisation suggested in the title that commercial interests might be a force essentially inimical to public health is misleading and unjust. The development of new medicines depends on research undertaken in academic and industrial settings, both of which to varying degrees have commercial interests to consider.

Most new drugs are discovered and developed by the pharmaceutical industry, a contribution to public health that is substantial by any measure; didanosine, the drug at the heart of the dispute outlined in the article, is exceptional in that workers at the National Institutes for Health, funded by the US government, discovered it. Given this role, presentation of the US government as an opponent to improving public health in Thailand seems at best an oversimplification.

Rapid globalisation, occurring in the past few decades, has vastly improved means of communication and travel coupled with an equally rapid propensity for the spread of infectious disease. The establishment of a global framework for political and commercial interaction has not kept pace with these events. Failure to achieve progress at the World Trade Organization talks in Cancun, Mexico, in 2003, underlines this. Once the finger-pointing and blaming for this failure are dealt with, serious work will be needed to move forward. In the context of global access to drugs, the process of drug development from basic research to equitable distribution, and contributions made at all levels need to be considered.

The article by Ford and colleagues makes compelling reading and hopefully the outcome of the dispute it describes will provide benefit for patients with HIV in Thailand. Ford and colleagues focus on the complex issues surrounding access to medicines, reflecting the interests for which their employers campaign in an advert on the rear cover of *The Lancet* (Feb 21, 2004), and help to identify some of the issues that need to be resolved to achieve equitable drug availability worldwide. However, a more balanced consideration of the issues than can be conveyed in the description of an adversarial legal dispute is needed to make substantial progress. Contributions made by governments, academia, and industry to the overall process of drug development and distribution need to be recognised.

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1 Ford N, Wilson D, Bunjumnong O, von Schoen Angerer T. The role of civil society in protecting health over commercial interests: lessons from Thailand. *Lancet* 2004; **363:** 560–63.

MMR—responding to retraction

Sir—Almost 6 years have passed since AJW disclosed in a letter published in *The Lancet*[1] that he was undertaking a pilot study on behalf of the Legal Aid Board (later to become the Legal Services Commission), a study that sought to examine the merits of parental claims of an association between their children's exposure to the measles, mumps, and rubella (MMR) vaccine and subsequent autistic regression and intestinal symptoms. He wrote on May 2, 1998, 3 months after the original paper: "Only one author (AJW) has agreed to help evaluate a small number of these children on behalf of the Legal Aid Board."

There was no attempt at any stage to conceal the fact that the viral study was ongoing before the publication of the paper in *The Lancet* in 1998. Almost 6 years have passed during which *The Lancet* and our co-authors have had the opportunity to seek further details and consider their position with respect to perceived conflicts of interest. We read the absence of any comment as implying tacit acknowledgment of lack of such conflict, as stated by AJW at the time. *The Lancet* requires that the funding source for a study be declared; our report conformed to this requirement since there was no external funding for the work relevant to this report. *The Lancet* disclosure policy also required that the authors declare anything that would embarrass an author if it were to emerge after publication. This is, of course, a subjective definition and we can confirm that this is not an issue which causes us embarrassment; we are, however, dismayed by the way in which events have been misrepresented.

Conflict of interest is created when involvement in one project potentially could, or actively does, interfere with the objective and dispassionate assessment of the processes or outcomes of another project. We cannot accept that the knowledge that affected children were later to pursue litigation, following their clinical referral and investigation, influenced the content or tone of the 1998 paper which was a description of a possible new syndrome in the classical mode. We emphasise that this was not a scientific paper but a clinical report. The laboratory support funded by Legal Aid for a separate viral detection study had no bearing on the original paper. No Legal Aid money was used in the preparation of the 1998 paper, and the viral study could not then and indeed, does not now, influence the "objective and dispassionate assessment" of the veracity of the original paper, which we reiterate simply reported a novel clinical syndrome. There was no conflict of interest. When the viral study is published, the Legal Aid Board (now Legal Services Commission) funding will be duly acknowledged.

Various claims were made by agents of the *Sunday Times* of Feb 22, 2004, against those of us involved in the *Lancet* 1998 report. These claims included inappropriate patient referral, inappropriate use of Legal Aid funding, lack of ethics approval, unmerited clinical investigation, and keeping secret for 6 years the involvement of the Legal Aid Board in a separate study. All of these claims have been investigated and we know they are unfounded and vigorously deny them.

It is worth reiterating that all of the first 12 children reported in the *Lancet* study were referred to the Royal Free Hospital exclusively for the investigation of their intestinal symptoms at a time when none was involved in Legal Aid litigation. Their pathological findings were interpreted and reported by clinicians who could have had no knowledge of any future legal claim. The report itself was a description of the history as reported to us, and the relevant clinical findings. No claim of a causal association with MMR was ever made. The opinion on choice of single vaccines pending scientific resolution of

any possible association, expressed by AJW at the press briefing, was based not on the findings in these children alone, but on a detailed investigation of the history of MMR vaccine and its safety. AJW's opinion, then and now, has been restated in Jefferson and colleagues' subsequent 2003 Cochrane Review[2]—ie, that "the design and reporting of safety outcomes in MMR vaccine safety studies, both pre- and post-marketing, are largely inadequate", and furthermore, that Jefferson and colleagues "found limited evidence of safety of MMR compared to its single-component vaccines from low risk of bias studies". Nonetheless we regret the furore and polarisation of opinion that ensued from that press briefing for which AJW bears some responsibility.

Richard Horton is reported to have stated that he would not have published the paper, had he known about the MMR litigation. As reported, this clearly has major implications for the valid scientific investigation and reporting of possible iatrogenic injury in patients who may also be seeking legal redress. It is notable that subsequent to the aforementioned Legal Aid pilot study, other university-based studies have been funded by the Legal Services Commission, and reported in the *British Medical Journal*.[3]

On March 6, 2004, some of our ex-colleagues issued a "retraction of an interpretation", not a retraction of the factual content of the paper, as widely inferred. Since no interpretation of the possible MMR/autism link was offered in the original 1998 *Lancet* report, other than to state that the data did not constitute evidence of an association and suggest that further research was required, it is difficult to know quite what has been retracted, particularly in light of Richard Horton's current plea for further research funding for autism, a plea that we welcome wholeheartedly.

Let us be clear that parents reported gastrointestinal symptoms in their children that many medical professionals denied and refused to investigate. Some parents were referred to social services and false claims of Munchausen's syndrome by proxy were levied. The parents were right; their children have an inflammatory intestinal disease. The medical profession was wrong, in some cases shamefully so. In light of this lesson it is imperative that rather than relying on endless reviews of epidemiological data which fail to even address the original hypothesis,[4] parental claims should be taken seriously and their children should be investigated on an individual basis.

More than 6 years on, the original *Lancet* report should be viewed in the context of the emerging laboratory and clinical evidence of intestinal pathology,[5–10] measles virus persistence in diseased tissues,[11,12] and abnormal measles immunity[13–15] in this specific subset of children with autistic spectrum disorder. It would be inappropriate to interpret the events of the past month as exonerating MMR vaccine as a possible cause of autism.

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1 Wakefield AJ. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 1356.
2 Jefferson T, Price D, Demicheli V, et al. Unintended events following immunization with MMR: a systematic review. *Vaccine* 2003; **21:** 3954-60.
3 Paul A, Cunningham J, Dhanesha U, Ballard M, Thompson J, Marsh J. Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *BMJ* 1999; **319:** 807–11.
4 Wakefield AJ, Montgomery SM. Autism, viral infection and measles-mumps-rubella vaccination. *Isr Med Assoc J* 1999; **1:** 183–87.
5 Wakefield AJ, Anthony A, Murch SH, et al. Enterocolitis in children with developmental disorders. *Am J Gastroenterol* 2000; **95:** 2285–95.
6 Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatrics* 1999; **135:** 559–63.
7 Furlano R, Anthony A, Day R, et al. Quantitative immunohistochemistry shows colonic epithelial pathology and γδ-T cell infiltration in autistic enterocolitis. *J Pediatrics* 2001; **138:** 366–72.
8 Torrente F, Machado N, Ashwood P, et al. Enteropathy with T cell infiltration and epithelial IgG deposition in autism. *Mol Psych* 2002; **7:** 375–82.
9 Horvath K, Perman A. Autistic disorder and gastrointestinal disease. *Curr Opin Pediatr* 2002; **14:** 583–87.
10 Ashwood P, Murch SH, Anthony A, et al. Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J Clin Immunol* 2003; **23:** 504–17.
11 Uhlmann V, Martin CM, Shiels O, et al. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *Mol Pathol* 2002; **55:** 84–90.
12 Sheils O, Smyth P, Martin C, O'Leary JJ. Development of an 'allelic discrimination' type assay to differentiate between the strain origins of measles virus detected in intestinal tissue of children with ileocolonic lymphonodular hyperplasia and concomitant developmental disorder. *J Pathol* 2002; **198** (suppl)**:** 5A.
13 Singh VK, Lin SX, Yang VC. Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. *Clin Immunol Immunopathol* 1998; **89:** 105–08.
14 Singh VK, Lin SX, Newell E., Nelson C. Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism. *J Biomed Sci* 2002; **9:** 359–64.
15 Singh VK, Jensen RL. Elevated levels of measles antibodies in children with autism. *Pediatr Neurol* 2003; **28:** 292–94.

Editor's reply

We do not accept Andrew Wakefield and colleagues' interpretation of the letter published in *The Lancet* on May 2, 1998,[1] which was, in any event, only published 3 months after the original 1998 *Lancet* paper. This letter was written in response to a letter from Dr A Rouse,[2] published in the same issue. Dr Rouse's letter raised concerns about whether children investigated in the 1998 paper had been referred to the authors by the Society for the Autistically Handicapped, and simply mentioned that his concerns arose out of a fact sheet produced by a firm of solicitors.

Although the letter made it clear that Dr Wakefield "has agreed to help evaluate" some children for the Legal Aid Board, it does not indicate that in fact such work had been commissioned and was being undertaken well before the 1998 paper was published. The natural and ordinary meaning to be drawn from Dr Wakefield's letter at the time was that following the publication of the 1998 paper he had agreed to complete evaluations of children reported in the 1998 paper for the Legal Aid Board. We understood the letter to mean that, although Dr Wakefield agreed to undertake an evaluation for the Legal Aid Board, the evaluation had not taken place before the 1998 paper's publication.

In the light of this, and Dr Wakefield's express statement that no conflict of interest existed, we had no reason to investigate the position further, until the editors were notified for the first time that Dr Wakefield's relationship with the Legal Aid Board predated the publication of the 1998 paper by some considerable time.

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1 Wakefield AJ. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 1356.
2 Rouse A. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 1356.

DEPARTMENT OF ERROR

Hughes RAC. Treatment of Guillain-Barré syndrome with corticosteroids: lack of benefit? Lancet *2004;* ***363:*** *181*—In this Commentary (Jan 17), the last sentence of paragraph two should have read: "Meta-analysis of the two intravenous methylprednisolone trials alone shows 0·17 (–0·06 to 0·39) more improvement in the corticosteroid than the placebo-treated patients, which is still not significant."