When DMARDs fail to control rheumatoid arthritis patients need biological treatments, such as tumour necrosis factor inhibitors. These are both highly effective and expensive (£8000-£10 000/patient/year). Treating all patients with biologicals is clearly unaffordable. However, undertreating inflammatory arthritis also has high personal and societal costs. When biologicals were first introduced, large numbers of patients had very active disease. Times have now changed and clinical remission is achievable. In most of western Europe and North America biologicals can be used when patients have failed DMARDs and have ongoing active disease. Existing NICE guidelines mean that in the UK many patients with active arthritis do not fulfil the eligibility criteria to receive evidence based biological treatment. The UK should adopt more universal Western criteria.[12]

Limiting access to effective treatments is never defensible, whether based on UK postcodes or European country. The final priority is to make remission a UK quality standard when treating inflammatory arthritis. The challenge for rheumatologists, regulators, and commissioners is to ensure that patients get the treatment they need to achieve long term remission in ways that are deliverable and affordable.

Modern intensive treatments enable many patients with inflammatory arthritis to achieve sustained remission. Ailsa Bosworth's personal story, which shows what can be achieved in the face of personal adversity, highlights the limitations of treating arthritis too little and too late.[3] General practitioners, specialists, and healthcare commissioners must work together to ensure that patients receive both early and effective care.

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Wakefield's article linking MMR vaccine and autism was fraudulent

Clear evidence of falsification of data should now close the door on this damaging vaccine scare

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"Science is at once the most questioning and . . . sceptical of activities and also the most trusting," said Arnold Relman, former editor of the *New England Journal of Medicine*, in 1989. "It is intensely sceptical about the possibility of error, but totally trusting about the possibility of fraud."[1] Never has this been truer than of the 1998 *Lancet* paper that implied a link between the measles, mumps, and rubella (MMR) vaccine and a "new syndrome" of autism and bowel disease.

Authored by Andrew Wakefield and 12 others, the paper's scientific limitations were clear when it appeared in 1998.[2 3] As the ensuing vaccine scare took off, critics quickly pointed out that the paper was a small case series with no controls, linked three common conditions, and relied on parental recall and beliefs.[4] Over the following decade, epidemiological studies consistently found no evidence of a link between the MMR vaccine and autism.[5-8] By the time the paper was finally retracted 12 years later,[9] after forensic dissection at the General Medical Council's (GMC) longest ever fitness to practise hearing,[10] few people could deny that it was fatally flawed both scientifically and ethically. But it has taken the diligent scepticism of one man, standing outside medicine and science, to show that the paper was in fact an elaborate fraud.

In a series of articles starting this week, and seven years after first looking into the MMR scare, journalist Brian Deer now shows the extent of Wakefield's fraud and how it was perpetrated. Drawing on interviews, documents, and data

made public at the GMC hearings, Deer shows how Wakefield altered numerous facts about the patients' medical histories in order to support his claim to have identified a new syndrome; how his institution, the Royal Free Hospital and Medical School in London, supported him as he sought to exploit the ensuing MMR scare for financial gain; and how key players failed to investigate thoroughly in the public interest when Deer first raised his concerns.[11]

Deer published his first investigation into Wakefield's paper in 2004.[12] This uncovered the possibility of research fraud, unethical treatment of children, and Wakefield's conflict of interest through his involvement with a lawsuit against manufacturers of the MMR vaccine. Building on these findings, the GMC launched its own proceedings that focused on whether the research was ethical. But while the disciplinary panel was examining the children's medical records in public, Deer compared them with what was published in the *Lancet*. His focus was now on whether the research was true.

The Office of Research Integrity in the United States defines fraud as fabrication, falsification, or plagiarism.[13] Deer unearthed clear evidence of falsification. He found that not one of the 12 cases reported in the 1998 *Lancet* paper was free of misrepresentation or undisclosed alteration, and that in no single case could the medical records be fully reconciled with the descriptions, diagnoses, or histories published in the journal.

Who perpetrated this fraud? There is no doubt that it was Wakefield. Is it possible that he was wrong, but not dishonest: that he was so incompetent that he was unable to fairly describe the project, or to report even one of the 12 children's cases accurately? No. A great deal of thought and effort must have gone into drafting the paper to achieve the results he wanted: the discrepancies all led in one direction; misreporting was gross. Moreover, although the scale of the GMC's 217 day hearing precluded additional charges focused directly on the fraud, the panel found him guilty of dishonesty concerning the study's admissions criteria, its funding by the Legal Aid Board, and his statements about it afterwards.[14]

Furthermore, Wakefield has been given ample opportunity either to replicate the paper's findings, or to say he was mistaken. He has declined to do either. He refused to join 10 of his coauthors in retracting the paper's interpretation in 2004,[15] and has repeatedly denied doing anything wrong at all. Instead, although now disgraced and stripped of his clinical and academic credentials, he continues to push his views.[16]

Meanwhile the damage to public health continues, fuelled by unbalanced media reporting and an ineffective response from government, researchers, journals, and the medical profession.[17 18] Although vaccination rates in the United Kingdom have recovered slightly from their 80% low in 2003-4,[19] they are still below the 95% level recommended by the World Health Organization to ensure herd immunity. In 2008, for the first time in 14 years, measles was declared endemic in England and Wales.[20] Hundreds of thousands of children in the UK are currently unprotected as a result of the scare, and the battle to restore parents' trust in the vaccine is ongoing.

Any effect of the scare on the incidence of mumps

TEK IMAGE/SPL

remains in question. In epidemics in the UK, the US, and the Netherlands, peak prevalence was in 18-24 year olds, of whom 70-88% had been immunised with at least one dose of the MMR vaccine.[21 22] Any consequence of a fall in uptake after 1998 may not become apparent until the cohorts of children affected reach adolescence. One clue comes from an outbreak in a school in Essen, Germany, attended by children whose parents were opposed to vaccinations. Of the 71 children infected with mumps, 68 had not been immunised.[23]

But perhaps as important as the scare's effect on infectious disease is the energy, emotion, and money that have been diverted away from efforts to understand the real causes of autism and how to help children and families who live with it.[24]

There are hard lessons for many in this highly damaging saga. Firstly, for the coauthors. The GMC panel was clear that it was Wakefield alone who wrote the final version of the paper. His coauthors seem to have been unaware of what he was doing under the cover of their names and reputations. As the GMC panel heard, they did not even know which child was which in the paper's patient anonymised text and tables. However, this does not absolve them. Although only two (John Walker-Smith and Simon Murch) were charged by the GMC, and only one, the paper's senior author Walker-Smith, was found guilty of misconduct, they all failed in their duties as authors. The satisfaction of adding to one's CV must never detract from the responsibility to ensure that one has been neither party to nor duped by a fraud. This means that coauthors will have to check the source data of studies more thoroughly than many do at present—or alternatively describe in a contributor's statement precisely which bits of the source data they take responsibility for.

Secondly, research ethics committees should not only scrutinise proposals but have systems to check that what is done is what was permitted (with an audit trail for any changes) and work to a governance procedure that can impose sanctions where an eventual publication proves this was not the case. Finally, there are lessons for the Royal Free Hospital, the *Lancet*, and the wider scientific commu-

nity. These will be considered in forthcoming articles.

What of Wakefield's other publications? In light of this new information their veracity must be questioned. Past experience tells us that research misconduct is rarely isolated behaviour.[25] Over the years, the *BMJ* and its sister journals *Gut* and *Archives of Disease in Childhood* have published a number of articles, including letters and abstracts, by Wakefield and colleagues. We have written to the vice provost of UCL, John Tooke, who now has responsibility for Wakefield's former institution, to ask for an investigation into all of his work to decide whether any more papers should be retracted.

The *Lancet* paper has of course been retracted, but for far narrower misconduct than is now apparent. The retraction statement cites the GMC's findings that the patients were not consecutively referred and the study did not have ethical approval, leaving the door open for those who want to continue to believe that the science, flawed though it always was, still stands. We hope that declaring the paper a fraud will close that door for good.

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