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THE *LANCET* PAPER

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>
> (Wakefield et al 1998: 637)

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>
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Dr Wakefield's landmark paper, published in *The Lancet* on 28 February 1998, provided the missing link in the theory that MMR was responsible for the supposed 'autism epidemic'. That link was 'autistic enterocolitis' – a novel and distinctive form of inflammatory bowel disease found in children with autism and other developmental disorders. Dr Wakefield was the 'senior scientific investigator' in the Royal Free research team and the paper's lead author. A dozen co-authors included paediatric gastroenterologists Simon Murch and Mike Thomson, who did the colonoscopies, child psychiatrist Mark Berelowitz, and Professor John Walker-Smith, who was the 'senior clinical investigator'. Dr Wakefield and his colleagues believed they had made a discovery of historic significance; it was rumoured that some of them wondered aloud whether they might win a Nobel Prize or some similar recognition if their bold hypothesis was vindicated.

The paper was based on the investigation of 12 children, who were said to have been consecutively referred to Dr Wakefield's clinic at the Royal Free Hospital with a history of diarrhoea, abdominal pain, bloating, and food intolerance. The dozen included only one girl; in ten cases the diagnosis was autism or 'autistic spectrum dis-

order'; in two there was a suspicion of 'post-viral encephalitis'; and in one the diagnosis was uncertain between autism and 'disintegrative disorder'. Examination of the lining of the large and small intestine through a fibre-optic endoscope (ileo-colonoscopy) passed up the rectum (under sedation) revealed a distinctive pattern of inflammation (non-specific colitis) associated with enlarged lymph glands at the end of the small intestine (ileal lymphoid nodular hyperplasia). Microscopic examination of biopsy specimens confirmed chronic inflammatory changes. Furthermore, the authors reported that the parents of eight of the children believed that their behavioural symptoms, characterised as 'regression', began shortly after the MMR immunisation (on average after 6.3 days). They suggested that, in these children, the measles virus (present in an attenuated form in the MMR vaccine) might have produced bowel inflammation, allowing toxic peptides to 'leak' into the bloodstream and hence pass to the brain, causing autism.

The authors conceded that they had not proved a link between MMR and 'autistic enterocolitis'. However, they considered that the chronic inflammatory features they had identified in both the small and large bowels of these children 'may be' related to neuropsychiatric dysfunction. The interpretation offered in the summary at the head of the report, as quoted above, was that the authors had 'identified associated gastro-intestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers' (Wakefield et al 1998: 637). The only 'environmental trigger' identified in the report was MMR immunisation, which was linked by eight of the children's parents to the onset of their disturbed behaviour.

An acrimonious debate

There were two unusual aspects to the publication of the Wakefield paper and both contributed to the subsequent furore. The first was that it was accompanied by a critical commentary by Robert Chen and Frank DeStefano, two American vaccine specialists (Chen, DeStefano 1998). The second was that it was launched at press conference at the Royal Free Hospital. Let us look at these in turn.

As Richard Horton, editor of *The Lancet*, has indicated in his reflection on the 'acrimonious debate' that erupted following his decision to publish the Wakefield paper, he was well aware of its controversial character (Horton 2003: 207). The substance of Dr Wakefield's MMR–autism thesis had already been widely leaked and

The Lancet's peer reviewers had raised concerns about the study's methods and interpretations, as well as about the dangers of undermining public confidence in immunisations. Dr Horton insisted that the paper was revised to clarify that its authors had no proof that MMR caused autism, following which it was published under the label of 'early report' to 'highlight its preliminary nature' (Horton 2003: 208). Furthermore, he commissioned two US vaccine experts, Robert Chen and Frank DeStefano to write 'Vaccine adverse events: causal or coincidental?' – a brief but devastating critique of the Wakefield paper published in the same issue of *The Lancet* (Chen, De Stefano 1998).

Chen and DeStefano first indicated the excellent safety record of MMR in hundreds of millions of people worldwide over three decades. They questioned whether the newly identified syndrome of autistic enterocolitis could be considered clinically distinctive: 'no clear case-definition was presented, a necessary requirement of a true new clinical syndrome and an essential step for future research' (Chen, DeStefano 1998: 612). They emphasised that the authors had not confirmed the presence of vaccine virus in the tissues of their patients. They suggested that 'selection bias' might have resulted from the referral of children to the clinic of 'a group known to be specially interested in studying the relation of MMR vaccine with inflammatory bowel disease' (Chen, DeStefano 1998: 612). They noted that it is usually difficult to date precisely the onset of a syndrome such as autism, and wondered whether 'recall bias' may have resulted from parents attempting to relate the onset of their child's problems to an unusual event such as a coincidental vaccine reaction. They also pointed out that, although Dr Wakefield and his colleagues postulated that MMR might lead to inflammatory bowel disease, which, in turn, might cause autism, in almost all the cases reported in their paper behavioural changes preceded bowel symptoms. The time course of these pathological processes was also curious: in one case the effect of MMR on behaviour was evident within 24 hours – faster than any known process of infection-induced vasculitis (the underlying pathology postulated as the cause of 'autistic enterocolitis, a type of process that unfolds over several weeks).

In conclusion, Chen and DeStefano warned presciently that, if claims of adverse events resulting from vaccines were not properly substantiated, there was a danger that vaccine-safety concerns may 'snowball into societal tragedies when the media and the public confuse association with causality and shun immunisation' (Chen,

DeStefano 1998: 612). Many of these themes were taken up and expanded in subsequent letters to *The Lancet*.

In retrospect, Dr Horton conceded that the publication of Dr Wakefield's paper in *The Lancet* gave it 'more credibility than it deserved as evidence of a link between the MMR vaccine and the new syndrome' (Horton 2003: 209). Yet, while he defended his decision to publish the paper, he unreservedly admitted to 'a failure to manage the media reaction' – a failure that started with the now notorious Royal Free press conference.

The press conference was an extraordinary event. Journalists were treated to a special introductory video prepared by the Royal Free press office and the Dean of the Medical School, Professor Arie Zuckerman, himself a vaccine specialist, presided over the conference. (Professor Walker-Smith refused to attend, indicating that he disapproved of medical research being debated prematurely in the mass media. He has recalled that the only enthusiasm for the conference came from Dr Wakefield and his staunch ally Professor Roy Pounder, senior adult gastroenterologist at the hospital [Walker-Smith 2003: 241].)

Dr Wakefield seized the next day's headlines with his sensational recommendation that parents should reject the MMR immunisation and give their children each of the three components separately, 12 months apart (*The Times*, 27 February 1998, *Daily Telegraph*, 27 February 1998). This recommendation was not included in the *Lancet* paper and is in no way supported by it. Such a programme of vaccination has not been introduced anywhere in the world and there is no evidence to justify any particular interval between vaccinations. It was immediately repudiated by Professor Zuckerman and by the paediatricians in the Wakefield team. Dr Simon Murch, Dr Mike Thomson and Professor Walker-Smith subsequently wrote to *The Lancet* to disassociate themselves from Dr Wakefield's call for separate vaccines (Murch et al 1998). Not a single member of the team publicly endorsed Dr Wakefield's anti-MMR stand. Yet, as the press conference broke up in rancour, the campaign against MMR received its biggest boost so far.

Five years later Richard Horton was still smarting from the 'vituperative attack and personal rebuke' he experienced as a result of his decision to publish the Wakefield paper (Horton 2003: 213). Many critics complained that *The Lancet*'s process of peer review should have exposed the weaknesses of the paper and prevented its publication. Dr Horton insists that the role of peer review is not to judge the validity of a piece of research – that can only be verified by other

scientists – but to comment on the importance of the issue under investigation and on the design and execution of the study (Horton 2003: 213). He decided to publish Wakefield's paper, not because he believed it to be true, but because it raised an important question that required urgent verification. Dr Horton has argued the important principle that medical journals must uphold free expression in scientific debate even if this creates problems for public health. He maintains that to have refused to publish Wakefield would have been an act of censorship. But, as Chen and DeStefano and many others have pointed out, there were basic errors in design, execution, analysis and interpretation in the Wakefield paper. Dr Horton indicates elsewhere that, every year, *The Lancet* publishes 500 out of 10,000 papers that are submitted: this is not censorship but editorial judgement (Horton 2003: 307). Indeed, when Dr Wakefield submitted his follow-up paper, including a further 48 cases, Dr Horton exercised this discretion and rejected it (it was finally published in the *American Journal of Gastroenterology*; Wakefield et al 2000).

MMR and the Medical Research Council

Although the Royal Free press conference projected the MMR–autism debate onto the national stage, and Dr Wakefield gained a growing status among anti-immunisation campaigners and parents of autistic children, he made little headway in convincing his medical and scientific colleagues of his case. In March 1998, at the request of Sir Kenneth Calman, Chief Medical Officer, the Medical Research Council (MRC) convened an ad hoc group of 37 experts, drawn from the spheres of virology, gastroenterology, epidemiology, immunology, paediatrics and child psychiatry, to review the associations suggested by the Royal Free team between measles virus and MMR on the one hand, and between inflammatory bowel disease and autism on the other (MRC 1998). The group's meeting was chaired by the pathologist Professor Sir John Pattison (a veteran of the mad cow crisis); Dr Wakefield and epidemiologist Scott Montgomery (one of the Royal Free team) attended the meeting to present and discuss their case.

The group first considered the laboratory evidence produced by the Royal Free group for the hypothesis that measles virus caused inflammatory bowel disease and noted that 'the most sensitive molecular genetic techniques were negative in the hands of all groups' (see Chapter 9) (MRC 1998: 2). They emphasised that further studies 'must involve independent laboratories testing the

same specimens, using full controls and a range of techniques with agreed experimental protocols' (MRC 1998: 2). When considering the epidemiological evidence claimed to link viral infections and inflammatory bowel disease, the group found no correlation between measles or mumps infection alone and Crohn's disease and ulcerative colitis. The experts agreed that there was some correlation between the occurrence of measles and mumps infection within the same year and the later incidence of inflammatory bowel disease. However, they considered existing studies limited and recommended further examination by independent groups.

On autism, the group considered the *Lancet* paper and emphasised the point that autism commonly becomes apparent in the second year of life – at around the time children receive MMR. However, the group insisted, 'such coincidence does not imply a causal link'. They pointed out that, whatever the trends in the incidence of autism, they bore no relationship to the introduction of MMR. They considered that the proposed 'leaky bowel'/opioid excess mechanism was 'biologically implausible' (MRC 1998: 3). They further pointed out that the supposedly distinctive pattern of 'lymphoid nodular hyperplasia' identified by the Royal Free group was a common and benign condition in children. Finally, it was argued that the findings of abnormally low levels of some immunoglobulins (IgA) in four out of the twelve children was a simple error resulting from the use of adult normal ranges (when using appropriate paediatric ranges, only one child had a low IgA level) (Richmond, Goldblatt 1998).

After a day-long meeting the experts concluded that there was no current evidence linking MMR and autism. They thought that 'it would be surprising if the link had not been noted in other countries with good diagnostic facilities for autism where MMR has been widely given for many years' and suggested that 'further research on an international basis would settle this matter' (MRC 1998: 3). The expert group advised the Chief Medical Officer that there was no reason for a change in current MMR vaccination policy, as had been recommended by Dr Wakefield. However, they proposed more research on both inflammatory bowel disease and autism. These conclusions were sent in summary form to every doctor in the country in a letter from the Chief Medical Officer on 27 March (Calman 1998).

Dr Wakefield later complained that he felt he had been 'set up' at this meeting (Mills 2002: 17). He claimed that the 37 experts had all been 'picked by the government' and that he and Dr Montgomery

had had to face them 'alone'. He felt that a nine-hour meeting fell short of the detailed scrutiny he had hoped for.

Following the March 1998 meeting, the MRC set up an expert subgroup to steer and monitor research in inflammatory bowel disease and autism. This subgroup included leading figures in the relevant disciplines and it invited other specialists to attend particular meetings: these included Dr Wakefield, and his co-authors Professor John Walker-Smith and Dr Simon Murch. In its report in April 2000, the subgroup noted further evidence from the Royal Free group of 'a classic pan-colitis associated with severe constipation and immune dysregulation in a group of children with developmental disorders' (MRC 2000, Wakefield et al 2000).

This study compared a series of 60 'consecutive' cases of 'autistic enterocolitis' (including the orginal 12), with a control group of 37 developmentally normal children undergoing ileo-colonscopy. Given the controversy still raging around the *Lancet* paper, it was curious that the new study included no information about MMR or any other immunisation history. The study confirmed 'an endoscopically and histologically consistent pattern of ileo-colonic pathology' in 'a cohort of children with developmental disorders' (Wakefield et al 2000: 2294). It also recorded results of investigations suggesting minor immunological abnormalities. The authors described a subtle 'new variant' inflammatory bowel disease, lacking the specific features of either Crohn's disease or ulcerative colitis. They again drew attention to the association of this pattern of bowel disease with 'a developmental disorder that was associated with a clear history of regression' – a loss of skills after a year or more of normal development. They concluded that 'this syndrome [autistic enterocolitis] may reflect a subset of children with developmental disorders with distinct etiological and clinical features' (Wakefield et al 2000: 2294).

This study was open to the same charges of selection bias as the *Lancet* paper. It was also criticised on the grounds that the control group was not properly matched for age. Apart from providing a fuller picture of the supposed new syndrome of 'autistic enterocolitis', it added little to the continuing MMR–autism controversy. The MRC report concluded that 'the case for "autistic enterocolitis" had not been proven' (MRC 2000: 4). It commented that the Royal Free studies had been performed in a 'self-selected group of patients and the histological finding of ileal lymphoid-nodular hyperplasia may have been secondary to severe constipation' (MRC 2000: 4).

The subgroup concluded that, in the 18-month period following Dr Wakefield's *Lancet* paper, 'there had been no new evidence to

suggest a causal link between MMR and inflammatory bowel disease/autism' (MRC 2000: 5). It conceded that much remained unknown about these conditions and that MRC support for research in these areas, particularly inflammatory bowel disease, was weak. It made a series of specific recommendations for future research.

Testing the MMR–autism hypothesis

In the concluding 'discussion' section of their *Lancet* paper, Dr Wakefield and colleagues suggested that further investigations were needed to examine the syndrome of 'autistic enterocolitis' and 'its possible relation' to MMR (Wakefield et 1998: 641). They indicated two directions for further research. First, the authors observed that if there were a causal link between MMR vaccine and this syndrome 'a rising incidence might be anticipated after the introduction of this vaccine in the UK in 1988'. They considered that published evidence was inadequate to answer this question, inviting further epidemiological research to clarify it. Second, they reported that 'virological studies' (presumably those later reported by the team headed by Professor John O'Leary in Dublin, Ireland) were 'underway'. Let us now examine the outcome of attempts to substantiate the MMR autism hypothesis through researches in these areas.

In its responsibility for vaccine safety, the Medicines Control Agency commissioned an epidemiological study to investigate the question of whether there was an increase in cases of autism in Britain following the introduction of MMR. Dr Wakefield's challenge to analyse any rise in incidence was taken up by Professor Brent Taylor, community paediatrician at the Royal Free Hospital, and a team including vaccine specialist Dr Elizabeth Miller and Open University statistician Dr Paddy Farrington. Their results were published in *The Lancet* in June 1999 (Taylor et al 1999a).

They identified all known children with an autistic spectrum disorder born between 1979 and 1998 in eight North Thames health districts – 498 children in all – and studied their medical and vaccination records. They found that:

- although the number of cases of autism had increased steadily since 1979, there was no sudden 'step-up' or change in the trend line after the introduction of MMR in 1988;
- there was no difference in age at diagnosis between the cases vaccinated before 18 months of age, after 18 months of age, and those never vaccinated;

- there was no clustering of developmental regression in the months after vaccination.

They concluded that 'our analyses do not support a causal association between MMR vaccine and autism' (Taylor et al 1999a: 2026).

The authors themselves acknowledged two limitations of their study. They could not verify the diagnoses of autism in all cases and they may have missed some cases. They relied on clinical notes of variable quality and many did not contain systematic or regularly updated information, which would have allowed independent validation of diagnosis. Despite making 'substantial efforts' to identify all cases, they may have missed some children who were not known to local health or education authorities. However, it is unlikely that these factors significantly affected the overall results.

In a letter to *The Lancet*, Dr Wakefield criticised the Taylor study on three grounds (Wakefield 1999). He claimed that the statistical methodology used ('case-series') was inappropriate to detect temporal associations between vaccination and conditions, such as autism, characterised by an insidious onset and delay in diagnosis. On the contrary, the authors replied, this method was particularly suitable for this sort of study, which has a good record of revealing rare adverse effects (Taylor et al 1999b). Dr Wakefield's second objection focused on the authors' judgement that one finding – that of a marginally significant raised incidence of parental concern between 0 and 5 months after MMR – was a statistical artefact. The authors claimed that one such finding (out of 14) might have been expected by chance, and that it could be explained by 'the combined effect of approximate recording of parental concern at 18 months and a peak in MMR vaccinations at 13 months'. Finally, Dr Wakefield made the accusation that the authors had 'failed to declare' the fact that some of the children in the study may have received MMR as a result of a catch-up campaign. The authors' rebuttal was that these children had been identified and that in all cases in which the age of first parental concern was recorded, it preceded vaccination.

If epidemiological studies failed to support the MMR autism hypothesis, what about the virological studies? During 2002 two papers based on studies of intestinal biopsies on Dr Wakefield's 'autistic enterocolitis' patients by a team lead by Professor John O'Leary in Dublin were published.

In the first paper, published in February, the researchers claimed to have identified fragments of the measles virus in intestinal tissues

of 75 out of 91 children with inflammatory bowel disease and developmental disorder (Uhlmann et al 2002). However, this study did not indicate whether the children had had measles or MMR. The authors did not indicate whether they had found whole measles virus, whether of wild or vaccine strain, or any other viruses, such as mumps and rubella. Many commentators wondered whether inadvertent sample contamination or some other technical error with the notoriously difficult reverse transcriptase polymerase chain reaction assays might explain these results (Afzal et al 2003). The study was also criticised on the grounds that the controls were not matched for age or time since vaccination. Others observed that, even if these findings were confirmed and replicated, the presence of measles virus fragments in the gut would not prove that they caused either inflammatory bowel disease or autism.

In response to the controversy generated by his paper, Professor O'Leary issued a statement insisting that he had 'not set out to investigate the role of MMR in the development of either bowel disease or developmental disorder, and no conclusions about such a role could, or should be, drawn from our findings' (O'Leary 2002a).

In a presentation in June 2002 to a US congressional committee Dr Wakefield claimed that a new study, due to be published by Professor O'Leary, had confirmed that the measles virus present 'in the diseased intestinal tissues of children with regressive autism' was indeed derived from the MMR vaccine (Wakefield 2002a). For Dr Wakefield, these studies constituted 'a key piece of evidence in the examination of the relationship between MMR vaccine and regressive autism'. Professor O'Leary, however, promptly rejected Dr Wakefield's interpretation of his work, insisting that it 'in no way establishes any link between the MMR vaccine and autism'. (O'Leary 2002b). Indeed, he strongly recommended that parents should give their children MMR[1].

An abstract (summary) of the new O'Leary study was duly presented at the annual meeting of the Pathological Society of Great Britain and Ireland in Dublin in July 2002. This was a pilot study designed to discover whether the measles virus RNA found in the

1 It is interesting to note that Professor O'Leary's repudiation of the claims, made on his behalf by Dr Wakefield and his supporters, has never been acknowledged by the anti-MMR campaigners, who continue to cite O'Leary's research in support of the MMR–autism thesis, in explicit defiance of his statements to the contrary.

guts of children in the earlier study originated in wild measles or from immunisation. The paper described a technique for discriminating between two closely related genome sequences, which the authors claimed could distinguish between wild and vaccine strain measles (by identifying a single nucleotide at position 7901 of the genetic code of the wild measles virus). They found vaccine-strain measles virus in the gut biopsies of 12 children with inflammatory bowel disease and development disorder (and confirmed wild measles strain in brain specimens of three patients with SSPE – a rare complication of measles). They concluded that 'this pilot study corroborates our earlier findings of an association between the presence of measles virus and gut abnormalities in children with developmental disorder, and indicates the origins of the virus to be vaccine strain' (Shiels et al 2002).

However, an immediate response to this study from the WHO collaborating centre for measles in the UK challenged the validity of the technique used by O'Leary's team. This indicated that the method used was not able to distinguish between wild and vaccine strains (it could result in several wild strains being incorrectly classified as vaccine strains). 'Consequently', it concluded, 'the technique described does not reliably discriminate between wild and vaccine measles virus' (Brown et al 2002). When presented with this information at the US congressional hearings on autism, Dr Wakefield accepted that if this method could not reliably make distinguish the two different forms of measles, then the conclusion drawn by the paper was not justified. The first piece of evidence promising some support to the hypothesis advanced by Dr Wakefield in 1998 was thus discredited even before publication.

MMR safety

In January 2001 Dr Wakefield adopted a radically different tack in the campaign against MMR. He now turned to the field of public health and vaccination policy, questioning whether appropriate safety procedures had been followed when MMR was introduced into Britain in the late 1980s. In a paper written with his Royal Free colleague, epidemiologist Scott Montgomery, Dr Wakefield claimed that the trials carried out on MMR before it was licensed in Britain involved monitoring children for side effects for only 28 days (Wakefield, Montgomery 2000). They also claimed that the authorities had not taken account of the problems of 'viral interference' arising from using the combined MMR vaccine and that early

studies had missed or ignored evidence of gastro-intestinal side effects of MMR.

Entitled 'MMR vaccine: through a glass, darkly'[2] the Wakefield and Montgomery paper provoked a storm of controversy.

It was published in the *Adverse Drug Reactions and Toxicological Reviews*, a highly specialist (and now defunct) journal with a regular readership estimated at around 300. The editors of this journal, anticipating a critical response to the article, published it together with the comments of four reviewers. (Critics subsequently pointed out that, although the reviewers were distinguished in their own fields, they did not include a vaccine specialist.) The most significant comment came from Dr Peter Fletcher, a former head of the Committee on Safety of Medicines, who substantially endorsed the case made by Wakefield and Montgomery and concluded with the damning judgement that 'the granting of a produce licence [for MMR] was premature' (Fletcher 2001: 289). In the subsequent discussion, another supporter of the anti-MMR campaign emerged: Dr Stephen Dealler, consultant microbiologist at Burnley General Hospital in Lancashire (Dealler 2001). A veteran of the BSE/CJD controversy, in which he emerged as a protégé of Professor Richard Lacey (whose maverick reputation appeared to be enhanced when the nightmare scenario he had long predicted came, at least in part, to pass), Dr Dealler had now become a supporter of Dr Wakefield's theory of autism (see Fitzpatrick 1998: 45–8). He had already published a comprehensive endorsement of unorthodox biomedical approaches to autism on the Internet (Dealler 1999).

Recognising that his most recent paper might not otherwise attract public attention, Dr Wakefield launched the article at a press conference and released copies of the paper to the mainstream media before either public health authorities or doctors involved in giving vaccinations had a chance to read it. Another stormy press conference guaranteed a blaze of publicity (Abbasi 2001).

The Wakefield/Montgomery paper prompted forceful rebuttals from vaccine authorities. On behalf of the Medicines Control Agency, Arlett and Bryan insisted that the MMR trials had followed up children for between six and nine weeks (and, in some studies, for longer) (Arlett, Bryan 2001). They accused Wakefield and

2 The title is derived from the epistles of St Paul: 'For now we see through a glass, darkly; but then face to face: now I know in part; but then shall I know even as I am known' (Corinthians I; 13:12).

Montgomery of errors of statistics and interpretation of key surveys, and claimed that they had missed or ignored other important studies. A scathing review from the Public Health Laboratory Service (now the Health Protection Agency) concluded that 'overall, we find this paper lacking in a coherent scientific rationale, selective in the reporting and interpretation of other work and statistically invalid' (Miller, Andrews 2001). Paediatric vaccine specialists dismissed the concerns raised by Wakefield and Montgomery as 'idiosyncratic' and questioned the authors' tactics in presenting their paper to the popular press before most clinicians had a chance to read it in a peer-reviewed journal (Elliman, Bedford, 2001).

Two distinct issues were confused in the discussion of 'interference' (Arlett, Bryan 2001, Wakefield, Montgomery 2001). One is the question of whether there is a higher incidence of adverse reactions with the combined vaccine, compared with vaccines given separately. Contrary to Dr Wakefield's claims, the consensus emerging from a number of studies is that there is not (Halsey 2001). For the MCA, Arlett and Bryan insisted that there was no convincing evidence of either chronic gastro-intestinal problems or autism resulting from MMR (Arlett, Bryan 2001). The second is the question of 'immunological interference': does giving three antigens together lead to a diminished antibody response to each one? According to the review by the American Academy of Pediatrics, 'although early studies showed the potential for some interference between these vaccine viruses as indicated by reduction in the mean antibody response to one or more of the components in the combined vaccines, adjusting the titres of the vaccine viruses resulted in similar responses for the combined and separate administration of these vaccines' (Halsey 2001: 25). Arlett and Bryan pointed out that, in 30 studies of the combined MMR vaccine before its introduction in Britain, no problems of interference had been identified. Furthermore, the effectiveness of post-licensing surveillance had been confirmed by its success in identifying, as a rare adverse reaction, ITP (idiopathic thrombocytopenic purpura – a rash associated with a blood abnormality, which usually resolves spontaneously) at a rate of one in 24,000 cases (Miller 2001).

In the subsequent discussion about the safety of MMR a number of issues arose (although none shed much light on the MMR autism hypothesis). One set of concerns – promoted at first by the wider anti-immunisation movement – focused on the withdrawal in Britain in 1992 of two brands of MMR that used a mumps component derived from the Urabe strain of the virus. In 1988, before the intro-

duction of MMR in Britain, a study in Canada and the UK reported the occurrence of aseptic meningitis following immunisation with the Urabe strain mumps vaccine, at a rate of between one in 100,000 to one in 250,000. Given that this rate of meningitis was much lower than that occurring with natural mumps (which MMR had been shown to prevent) it was preferable to proceed with the introduction of MMR. Furthermore, it was not, at that time, clear that any alternative vaccine was safer. However, although passive surveillance procedures showed a very low risk, a more intensive study in 1992 in the Nottingham area revealed a higher incidence of aseptic meningitis – at a rate of one in 3,000 – following MMR (Miller et al 1993). Accordingly, the vaccine authorities decided to switch to using only brands of MMR containing the Jeryl Lynn strain of mumps (which had not been linked to cases of meningitis). In response to continuing claims of government perfidy in introducing MMR including Urabe (on the grounds that it was known to cause aseptic meningitis in rare cases), it has been pointed out that, if Jeryl Lynn had not been available, it would still have been preferable to carry on with MMR include Urabe as the benefit from reducing the risk of mumps far exceeded the risk of vaccine-related meningitis.

Another controversy arose from official attempts to promote studies of MMR safety in general as evidence against claims that it caused autism. The most popular study in this regard comes from Finland – a country that introduced a two-dose MMR programme in 1982 and now claims to have virtually eradicated these three diseases. Long-term population-based passive surveillance studies found that no cases of developmental regression had been reported as resulting from MMR in 1.8 million children (Peltola et al 1998, Patja et al 2000). It is true, however, that because people in Finland had no reason to suspect that MMR might be associated with autism, they would be unlikely to report it as an adverse reaction. Dr Fletcher, among many others, was critical of the government's use of such 'negative studies as absolute evidence of safety'. Nevertheless, the large-scale, long-term, comprehensive and prospective character of these studies make them strong evidence for the safety of MMR in general (Bandolier 2002).

In response to studies of this type, which failed to substantiate the claims of anti-MMR campaigners, they retorted that 'absence of evidence is not the same as evidence of absence' (Aitken 2001b) – meaning that just because a particular study does not turn up evidence for the MMR–autism link does not prove that there is no link. (This epithet became something of a mantra.) But two things may be

said in response to this. The first is that, as stated in the MCA reply to Wakefield's paper, 'it is not that there is no evidence, but that there is evidence and it does not show an association' (Arlett, Bryan 2001: 44). The second is that, if you have looked hard enough for a particular sort of evidence and have failed to find it, the sensible conclusion must be that it is not there and that it is time to think again and look elsewhere. This is how Professor Vivian Moses responded to similar demands for absolute assurances of the safety of genetically modified food products:

> Since we can judge present and future safety only on the basis of past experience, an absence of evidence of harm is precisely the only evidence we can ever expect to accumulate for the absence of harm.
>
> (Moses 2002: 2)

Alternatively, one can continue to demand that the rest of the world proves that there is no link, or one can delude oneself that the evidence really is there, if only the rest of the world could see it.

The most curious feature of the 'through a glass, darkly' paper is that it has no direct relevance to the MMR–autism link. Even if it were true that pre-licensing surveillance of MMR had been inadequate, this would not advance Dr Wakefield's claim that MMR was causing 'autistic enterocolitis' and thus contributing to an epidemic of autism. It is strange that, at a time when he was under intense pressure to substantiate this hypothesis, Dr Wakefield chose to turn aside from his own sphere of expertise (gastroenterology) to enter fields (public health and vaccination policy) in which he had no previous experience. However, a close reading of the concluding section of the paper suggests that Dr Wakefield's strategy was that, if the safety of MMR in general could be put in doubt, the credibility of any particular risk attributed to the vaccine would be raised.

Confident of finding a resonance in an increasingly risk-averse climate, Dr Wakefield invoked the 'precautionary principle' popularised by the environmentalist movement:

> Surely, when a medical intervention is intended for universal use, particularly in healthy infants, there is almost no limit to the vigilance that should be exercised.
>
> (Wakefield, Montgomery 2000: 277)

With a reference to 'healthy infants' that was guaranteed to appeal

to the popular press, Dr Wakefield proposed an extreme level of caution that would deter any preventive or therapeutic intervention. In truth, there must *always* be a limit to vigilance: otherwise we allow the danger against which we are vigilant to become oppressive.

Despite this, at a time when the nation was in the grip of a multiplicity of millennial anxieties, Dr Wakefield readily found the highest authority for his precautionary approach:

> As the last Minister for Health, the Hon. Frank Dobson said recently, in the context of another medical intervention, "if there is even a hypothetical risk [of harm] and a safer alternative exists, we should use it"
>
> (Wakefield, Montgomery 2000: 279)

As a 'precautionary measure' to prevent possible transmission of variant CJD in February 1998, Mr Dobson had insisted that albumen (derived from blood products) used as a stabiliser in some vaccines should be imported from countries not affected by BSE. If the Minister for Health himself could use a hypothetical risk to justify introducing an alternative, then so could Dr Wakefield. He argued, 'for MMR', in relation to autism and inflammatory bowel disease, 'a significant index of suspicion exists without adequate evidence of safety' (Wakefield, Montgomery 2000: 279).

Although Dr Wakefield had not clearly established either that there was 'a significant index of suspicion' about MMR or that its safety record was inadequate, his case appeared to be strengthened by coupling these two dubious propositions together. 'If the risk of chronic immune-mediated disease is increased by concurrent exposure to the component viruses of MMR, either in their natural or vaccine form' (a conditional clause that remained unvalidated), then, Dr Wakefield triumphantly concluded, by giving the vaccines separately 'we have the ability to artificially dissociate these exposures, and the possible associated risks' (Wakefield, Montgomery 2000: 279). By disparaging the safety record of MMR and inflating unsubstantiated risks, Dr Wakefield may not have advanced the MMR–autism thesis, but he had given a powerful boost to the demand for separate vaccines.

Moving the goalposts

> If these researchers are able to prove cause and effect between immunisation and the described syndrome, they

> should do so straight away. If they are unable to do so they should publicly set the matter straight lest the health of our nation's children suffers.
>
> (Lindley, Milla 1998)

This challenge to Wakefield and his colleagues was issued by two senior gastroenterologists at Great Ormond Street Hospital for Children in immediate response to the *Lancet* paper in February 1998. Five years later Wakefield and his colleagues had still neither proven their hypothesis, nor withdrawn it.

In response to the failure of research in the two areas recommended in the *Lancet* paper – epidemiology and virology – to substantiate his hypothesis, Dr Wakefield continued to support the campaign against MMR, while redefining his case for its causative role in autism. At the outset, the concept of MMR-induced 'autistic enterocolitis' was advanced to explain a dramatic increase in the incidence of autism (the 'autism epidemic'). Before long, however, a close temporal association between MMR and the onset of behavioural regression – at first regarded as a significant indicator of causation – was relaxed and then abandoned. When epidemiological studies still failed to substantiate a link, Dr Wakefield hypothesised that MMR caused 'autistic enterocolitis' in a subset of children, rendered vulnerable by a combination of genetic and environmental factors (including food allergy, antibiotic use, ear infection, multiple concurrent vaccine exposure, a strong family history of atopic and auto-immune disease, and exposure to mercury) (Wakefield 2001b). (This list of possible cofactors in the aetiology of autism – familiar from our account of unorthodox biomedical approaches to autism – reflects Dr Wakefield's growing reliance on parent activists and anti-immunisation campaigners.)

In a response to a Danish epidemiological study (published in the *New England Journal of Medicine* in November 2002) that failed to show any link between MMR and autism, Dr Wakefield argued that this subset may be 'no more than 10 per cent of diagnoses' (Madsen et al 2002, Wakefield 2002b). In a subsequent letter to the journal, Dr Wakefield appeared to give up on epidemiology, arguing that the effect of the number and complexity of cofactors was 'to reduce statistical power to the extent that such studies fail to offer any convincing evidence either way' (Wakefield 2002b). Or as he put it in a newspaper interview in March 2003, 'retrospective studies like this are meaningless' (Phillips 2003: 43). But it was retrospective

studies such as this that Wakefield specifically invited in his *Lancet* paper.

The end result of this process of shifting the goalposts is that MMR, once blamed for producing an autism epidemic, is now said to be a factor in causing autism in a number of cases too small to discern by epidemiological methods. If this is so, how can MMR have caused autism in more than 1,000 cases currently pursuing compensation under the leadership of Richard Barr (with expert medical advice from Dr Wakefield)? We know that such methods of study are capable of detecting rare adverse effects of immunisation, such as ITP at a rate of one in 32,000 vaccinations (around 20 cases a year), so detecting a subset the size of 10 per cent of all cases of autism should be fairly straightforward.

Given the failure of epidemiology to confirm his hypothesis, Dr Wakefield has counter-posed the need for clinical studies – a call loyally echoed by his anti-MMR campaign followers. But populations are made up of individuals: if an effect of MMR – a vaccine administered at a population level – cannot be discerned at a population level, then it does not exist. Furthermore, Dr Wakefield's attempts to substantiate his hypothesis at a clinical level, in collaboration with Professor O'Leary, have also failed to bear fruit.

Unfortunately, instead of accepting the failure to prove their hypothesis, and – in the interests of public health withdrawing it, Wakefield and his supporters have doggedly and dogmatically continued to proclaim their conviction that MMR causes autism in some children, in defiance of all evidence to the contrary.

As the anti-MMR campaign found itself on the defensive, its supporters mounted increasingly personal attacks on critics of the Wakefield position. Brent Taylor and Elizabeth Miller, whose epidemiological work provided the most powerful defence of MMR, came in for particular vilification. In response to their 1999 paper, for example, Allergy-induced Autism issued a scurrilous denunciation of these authors, accusing them of 'a cynical attempt to disguise the truth' and of perpetrating 'a scandalous public dupe of BSE proportions' (AiA 1999). It demanded the resignation of 'all key members of the study group' insisting that such an 'attempt to justify health policy by using inadequate research as propaganda is reprehensible'. The criticisms of the Taylor study made by AiA were the same as those made by Dr Wakefield in a slightly more restrained letter to *The Lancet*. In his testimony to the US senate committee hearing in April 2000, Dr Wakefield claimed that the Taylor paper was the subject of a 'highly critical' debate at the Royal Statistical

Society in London, which concluded that the 'study design was wrong' (Wakefield, Montgomery 2000). In fact no such debate took place and the Royal Statistical Society came to no conclusion about the design or validity of the study. This study was described by the US Institute of Medicine's immunisation safety review as 'the most extensive epidemiological study and the strongest published evidence against the hypothesis that MMR causes ASD [austistic spectrum disorder]' (Institute of Medicine 2001: 44).

As the debate became increasingly polarised, Wakefield and his supporters resorted to impugning the motives of critics of the campaign against MMR by alleging conflicts of interest arising from their links with vaccine manufacturers. Two distinct issues thereby became confused.

First, as a result of the class action against the manufacturers of MMR, the pharmaceutical companies concerned were obliged to seek expert advice from the small pool of specialists in the relevant disciplines. These specialists received fees for their services, in the same way that expert witnesses for the plaintiffs received fees from the Legal Aid funds secured by Richard Barr and his team. Though payments should be disclosed where there is any question of a conflict of interests, the notion that the receipt of such fees implies a loss of professional discretion and integrity is both absurd and offensive. Given the low profile of pharmaceutical companies in paediatrics or autism, it is highly unlikely that any of these specialists would have become 'drug company advisors' if it were not for the activities of the anti-MMR campaign.

Second, paediatricians or immunologists who are engaged in research or clinical trials of vaccines are obliged to do this work in collaboration with pharmaceutical companies, since virtually all vaccines are manufactured by such companies. It is standard practice that researchers are excluded from investing for personal gain in companies sponsoring their research. However, although they may not gain personally, professional success is to some extent dependent upon generating research funding, so it is legitimate to declare this interest. According to Adam Finn, professor of paediatrics at the University of Bristol, such declarations should be interpreted as a qualification to give a well-informed opinion, 'as anyone unable to declare such competing interests is unlikely to have had any direct experience of using new vaccines in children' (Finn 2002: 733). However, in the rancorous climate generated by the MMR controversy, anti-MMR campaigners have presented such declarations of interest – available on easily accessible official websites – as though

they were investigative journalists uncovering conspiracy and corruption. Although the implication that everybody is governed by the most venal motives is widely held in modern society, it is corrosive of any kind of civilised discourse.

Populist jibes against the drug companies are a recurrent theme among campaigners against all forms of immunisation. No doubt the pharmaceutical corporations, like all capitalist enterprises, are more concerned about their profitability than the welfare of their consumers. There are many areas in which they can be legitimately accused of profiteering, disease-mongering and sharp practice (see Moynihan et al 2002). Yet the provision of vaccines, a relatively low-volume and low-profit sector, is not one of them. Indeed it is an area characterised by low investment and declining innovation, partly as a result of the climate of risk aversion and litigiousness, particularly in the USA (Galambos 1999). In August 2003 a report by the US Institute of Medicine complained of supply problems resulting from the declining number of vaccine manufacturers and urged the government to subsidise vaccine costs (Institute of Medicine 2003). The report noted the relatively small size of the vaccine market in the USA and the fact that vaccines accounted for only 1.5% of global pharmaceutical sales. Companies complained that their return on investment was small and there was little incentive towards research and development. In a contribution to a conference on vaccination in the USA in October 2003, Richard Gallagher, editor of *The Scientist*, noted that 'vaccinations are unattractive targets for industry, under-appreciated from the public health perspective, underfunded by basic research organisations, and treated with suspicion by the public' (Gallagher 2003). He commented on the 'malign influence' of three groups – anti-vaccination lobbyists (whose 'ignorant' websites included contributions from 'health nuts, conspiracy theorists and misguided physicians'), journalists (who wrote 'badly-researched and poorly-argued scare stories') and lawyers. At the same conference, vaccine specialist Neil Halsey noted that class action lawsuits led to large damage awards and complained that the courts provided a forum for 'junk science' in the guise of expert testimony (*The Daily News*, 27 October 2003).