

Wakefield's "autistic enterocolitis" under the microscope

Andrew Wakefield's claims for a new bowel condition in autistic children have been largely overlooked in the furore over MMR vaccination. **Brian Deer** reports

Twelve years ago, a now infamous and retracted paper appeared in the *Lancet*¹ and launched a health scare. In it, researchers at the Royal Free medical school in London reported on 12 children with developmental disorders, and linked their problems to MMR (measles, mumps, and rubella) vaccination.

It was the proposed link between the vaccine and "regressive" autism that caught the headlines and sparked alarm. But the paper also claimed to have discovered a new gut pathology, reported in 11 of the 12 children, which the lead author, Andrew Wakefield, an academic gastroenterologist, would dub "autistic enterocolitis." "Researchers at the Royal Free Hospital School of Medicine may have discovered a new syndrome in children involving a new inflammatory bowel disease and autism," the institution announced in a press release in February 1998.² "Their paper . . . also suggests that in a number of cases the onset of behavioural symptoms was associated with MMR vaccination."

Six years later, the vaccine link was dropped when 10 of the paper's 13 authors retracted this claim³ in the wake of my investigation for the *Sunday Times*.⁴ And in February the entire paper was retracted,⁵ after a General Medical Council panel decided that Wakefield was "dishonest" and "unethical."⁶

Not a lot was said during the GMC hearing about "autistic enterocolitis," which Wakefield continues to insist is real. In 2005 he established a private clinic in Austin, Texas, focusing on researching and treating this "syndrome." And, although he resigned his post there after the GMC verdict, patients have been drawn from throughout America, and even the United Kingdom.

"We continually find inflammatory bowel disease that is different from Crohn's disease and ulcerative colitis," explains a doctor on the

clinic's website.⁷ "This was initially named 'autistic enterocolitis' by Dr Wakefield because of the unique pattern of inflammation." The *Lancet*, too, stood by this claim despite distancing itself from other aspects of the paper. "I do believe there was, and remains, validity to the connection between bowel disease and autism, which does need further investigation," the journal's editor, Richard Horton told the BBC in February 2004.⁸

Dr Horton was speaking two days after I had presented him with the first findings of my now six year investigation for the *Sunday Times* that led to the GMC's charges.⁴ Three weeks later came the paper's partial retraction.

Inflammatory evidence

So what survives of "autistic enterocolitis" after Wakefield's disgrace and the paper's retraction? The answer requires an understanding of Wakefield's mission, which was to discover precisely such a disease. Two years before the paper was published he was hired by a solicitor to help launch a speculative lawsuit against drug companies that manufactured MMR vaccine. And the instrument of their attack was to find what he called at the time "a new syndrome"⁶ of bowel and brain disease caused by vaccines.

"In contrast to the IBD cases, which have a prima face [sic] gastrointestinal pathology, chil-

dren with enteritis/disintegrative disorder form part of a new syndrome," said Wakefield and the lawyer in a confidential submission for legal aid funding for the project in June 1996, before any of the 12 children in the paper had been investigated. "Nonetheless, the evidence is undeniably

in favour of a specific vaccine induced pathology."⁹

But when the children were brought in to the Royal Free for ileocolonoscopy, between July 1996 and February 1997, a snag in Wakefield's project emerged. The hospital's pathology service repeatedly judged colonic biopsy samples to be unexceptional, and thought bowel disease was a possibility in only one child.

In almost all cases, histopathologists reported a typical mix of cell types and numbers in the biopsy specimens. "Large bowel-type mucosa within normal histological limits,"

said, for example, the report for child 3 in the series. "No evidence of architectural distortion or increase in inflammatory cells in the lamina propria," said child 4's.

The lead pathologist for the Wakefield project, and an author of the now retracted paper, was Susan Davies, now at Addenbrooke's Hospital, Cambridge. At weekly meetings with paediatricians, the unexceptional results were confirmed.



PETER MACDIARMID/GETTY IMAGES

Andrew Wakefield was hired by a solicitor to help launch a lawsuit against MMR manufacturers. This was based on a “new syndrome” of bowel and brain disease caused by vaccines



JUSTIN SUTCLIFFE/REX

The Royal Free Hospital's pathology service repeatedly judged the biopsy samples to be unexceptional and thought bowel disease was a possibility in only one child



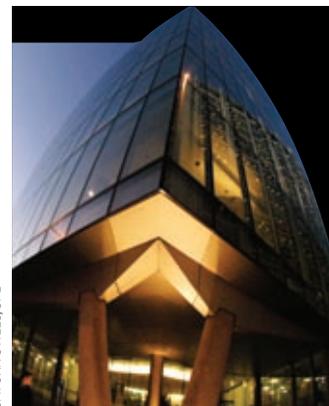
DAVID PEARSON/LAMY

The proposed link between the MMR vaccine and autism caught the headlines rather than the new gut pathology dubbed “autistic enterocolitis”



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The pathology reports that formed the basis of the *Lancet* paper were not a major focus for the GMC panel, which branded Wakefield as “dishonest”



MARK THOMAS

For four of the 12 she made additional notes recording the position more bluntly: “no abnormality detected.”

The biopsy slides are no longer available, according to one of the paper’s authors, Professor Amar Dhillon, but the GMC obtained all but one of the hospital pathology reports, and for the missing case I obtained the discharge summary. I passed the summary and reports to specialists for their reaction. They concluded that most of the 11 children reported as having non-specific colitis in the *Lancet* paper had been reported by the Royal Free as having normal pathology. “In the present reports and patients, overall, it is my impression that 8 of the 11 [for whom pathology reports were available] were normal.” Karel Geboes, a professor in the gastrointestinal pathology unit of the Catholic University of Leuven, Belgium, told me. “Based on the reports it seems that [the remaining] three showed focal active colitis (of unclear significance). The significance of focal active colitis has been studied in adults and children by Greenson et al from Ann Arbor, and they showed that the risk for a chronic condition is low.”

The Royal Free service did occasionally report inflammation—for example, in child 1. Although two colonic biopsy specimens were “within normal histological limits,” one from this child’s caecum showed neutrophils and cryptitis with “incipient crypt abscess formation.” But Ingvar Bjarnason, of King’s College London, a gastroenterologist with extensive paediatric experience, told me that such “caecal cryptitis” may be a normal phenomenon. “I would not call this colitis in the way gastroenterologists or histopathologists usually use the term.”

That term, however, was repeatedly used in the *Lancet* paper. Eleven of the 12 children were said to have “non-specific colitis”: a clinically significant inflammation of the large bowel. In all 11, it was said to be “chronic,” while in four it was

reported as both “acute and chronic.”

With swollen glands in the terminal ileum (widely regarded as a benign¹⁰ or normal¹¹ finding in children), this “colitis”—which was even cited in the retracted paper’s title—was Wakefield’s new disease. And yet the colitis was apparently invisible to the Royal Free’s pathology service.

In fact the service identified findings suggestive of possible inflammatory bowel disease in only one of the 12 children. “The mild patchy generalised increase in inflammatory cells with lymphoid aggregates and follicles is not very specific but could be in keeping with low grade quiescent inflammatory bowel disease,” it reported for child 2. But this inflammation resolved after two months’ enteral feeding with a product now marketed as Modulen. A repeat ileocolonoscopy found no abnormality, and a food intolerance was diagnosed.

Mismatch

So how did the mismatches occur? On the one hand official pathology reports, which were presented to clinicians with the biopsy slides, showed almost nothing of importance in the colon. And on the other, a peer reviewed paper gave a headline finding of “non-specific colitis” in 11 of 12. The pathology reports were not a major focus for the GMC panel, but Wakefield and his co-accused, John Walker-Smith and Simon Murch, were occasionally asked about them.

“What I wondered about was whether or not it seemed strange that 11 children would have the same diagnosis,” said Wendy Golding, a lay member of the panel, to Walker-Smith in August 2008. “They’ve come in with different issues, but they’ve got the same diagnosis.”

“That, of course, is the heart of the matter,” replied the Royal Free’s former professor of paediatric gastroenterology. “This is why we published in the *Lancet*, because there was this remarkable

homogeneity between the findings. There was a remarkable similarity, as you are rightly saying.”

“But you’ve changed what was actually diagnosed to what you wanted it to be.”

“I’ve certainly not changed it to what I wanted them to be, in any way,” Walker-Smith hit back. “I mean there are changes, but I’ve suggested that these changes are not dramatic. It’s just a way of looking at it. There were changes but not dramatic.”

These changes—from normal to abnormal, or from healthy to diseased—had also raised concern in the mind of at least one of the paper’s authors. In September 2007, Davies, the lead histopathologist for the Wakefield project, was examined at length before the panel. “When you were given a draft of the *Lancet* paper, did you read it?” she was asked by Sally Smith QC, for the doctors’ regulator.

“Yes,” Davies replied.

“What was your overall view of the terminology used in relation to the histology findings in the *Lancet* paper, just when you read the paper?”

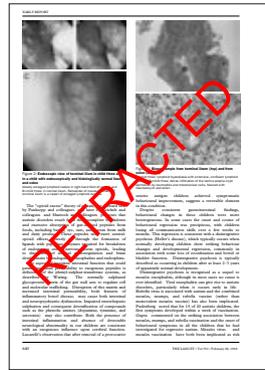
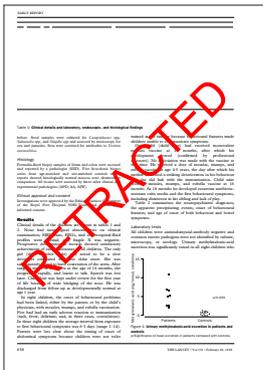
“I was somewhat concerned with the use of the word colitis.”

“First of all, what did you understand that word to mean?”

“I personally use that terminology, ‘colitis,’ when I see active inflammation, or a pattern of changes which suggest a specific diagnosis, and it was not my impression that the children coming through in the spasmodic way that they had, I [sic] had formulated some distinct pattern warranting that terminology.”

Second look

Davies said her doubts about the draft paper were assuaged by three doctors in the medical school. Before publication, they had performed a “formalised review,” re-examining the slides “in minute detail.”



“The [original] histopathology reports would have been generated by myself and everyone else in a normal work context, where you do not necessarily have protected time to look very, very closely, as you would with a formalised review,” she explained.

That account has been corroborated by two other authors: Wakefield and Dhillon, now a professor at the Royal Free and University College Medical School. In statements over the years, both have said that this second look was blinded, and also controlled by healthy samples said to have been supplied by another London hospital.

“It was decided that the senior consultant histopathologist with expertise in intestinal disease (Dr Dhillon) should review all biopsies from autistic children, and that pathology should be graded on a pro forma (or grading sheet) designed by him,” Wakefield said last March, in a now suspended complaint¹² to the UK Press Complaints Commission about one of my *Sunday Times* reports.¹³

But no second look was pre-specified in the project’s protocol.¹⁴ It was mentioned in the paper. The paper’s Patients and Methods section contains a 51 word paragraph describing the histology methods. “Formalin-fixed biopsy samples of ileum and colon were assessed and reported by a pathologist (SED),” this explains. “All tissues were assessed by three other clinical and experimental pathologists (APD, AA, AJW).” The initials refer to Susan Davies, Amar Dhillon, Andrew Anthony (then a junior, now a professor), and Andrew Wakefield. This apparent concurrence of four pathologists gave strength to the finding of a new bowel disease. But there is no suggestion in the paper that the second assessment caused findings to be substituted or changed, and since the paper’s publication, Wakefield has insisted that it was merely a clinical case series, not research.

And how bad was this “colitis,” such that the hospital’s pathology service didn’t spot it as the children came through?

As for the histological grades produced in any second review the published paper includes nothing of these. In any case, specialists I’ve consulted say that grading sheets are research tools and don’t generate clinical diagnoses such as colitis. Applying such terminology is a clinical decision: somebody must make a judgment. Moreover, in 1997, the British Society of Gastroenterology said that “inflammation requiring further investigation” to reach “a specific disease category” should be called “inflammation—unclassified.”¹⁵ Not colitis. Would the *Lancet* have published on just “inflammation—unclassified”? Would any claim of a new syndrome have sounded credible? And how many peer reviewers would have felt comfortable approving the paper if they had known that the hospital pathology service reported biopsy specimens as largely normal, but they were then subjected to an unplanned second look and reinterpreted?

The response from one of the *Lancet*’s peer reviewers of the Wakefield paper was “no”: he wouldn’t have felt comfortable. “I’m surprised the GMC didn’t make more of this,” said David Candy, paediatric gastroenterologist at St Richard’s Hospital, Chichester, who reviewed the paper in 1997. “That’s an example of really naughty doing—to exclude the original pathology findings.” And how bad was this “colitis,” such that the hospital’s pathology service didn’t spot it as the children came through? Walker-Smith told the GMC panel that he had “concerns” about the service and its ability to detect inflammation. Yet inflammatory indices that were not reported in the *Lancet* paper, including serum C reactive protein concentrations and other blood tests, were almost all within normal ranges for the 12 children.⁶ And as an alternative explanation for any inflammation that was present, nearly all of the children had constipation with megarectum¹⁶ (unreported in the paper), which specialists say can cause cellular changes.

Through a senior member of the Royal Free medical school, I asked to speak to Dhillon. He declined, but gave a statement to the GMC: “I did not write the histology section of the paper and I cannot remember whether I made any amendments to the draft,” explaining that his role was to grade biopsy inflammation with roman numerals on a grading sheet. “I do not know if any other histopathologists undertook the same review exercise with the slides as me, and I did not see their observations.

“The person who wrote up the histological findings may have looked at the observations which I provided to Dr Wakefield. The person writing the research paper may have translated the roman numeral scores which I may have used into something readable.”

Question of interpretation

So who translated these scores on the grading sheet into findings of “non-specific colitis” in the paper? Dhillon says it wasn’t him. He says he would like to see the slides again, but they are missing from the Royal Free laboratory. “He [Dhillon], Andrew Anthony, and Wakefield all looked at them,” I was told, on Dhillon’s behalf, by a senior member of staff at the Royal Free. “Andy [Wakefield] then synthesised their results into what appeared in the paper.”

Anthony, however, was a junior at the time, so couldn’t have shouldered the responsibility. And Wakefield isn’t a pathologist—he trained as a surgeon before joining the Royal Free as a researcher. So how the Roman numerical scores, histopathological gradings for a variety of sites in the colon, became the “colitis” findings might, under such circumstances, be anybody’s guess.

However, in his complaint against me to the Press Complaints Commission, Wakefield last year offered a glimpse into how this happened. He gave a detailed explanation for child 8—the only girl in the *Lancet* series. This 3 year old’s clinical notes said: “Histology normal.” The pathology service reported three large bowel biopsy specimens: “All pieces of normal colonic-type mucosa containing occasional lymphoid aggregates,” a consultant reported. “Minimal

inflammatory changes. May be result of operative artefact.”

Wakefield wrote: “When the biopsies were reviewed and scored by experts in bowel pathology—namely, Drs Dhillon and Anthony—these doctors determined that there was mild inflammation in the caecum, ascending colon, and rectum,” he said. “This was correctly reported as non-specific colitis in the *Lancet*.” In other words, it looks like it was Wakefield who translated the scores.

Pathology textbooks and journal reviews, however, make it clear that this interpretation was unorthodox to say the least.¹⁷⁻¹⁹ Minimal or mild inflammatory changes, of themselves, shouldn't be reported as colitis. Johns Hopkins pathologist Elizabeth Montgomery explains the point in her 2005 textbook. “The diagnosis of colitis requires evidence of injury to the epithelium, and not simply a mild increase in the amount of inflammatory cells within the lamina propria.”²⁰

No such injury (apart from a bit of architectural distortion) was reported for nearly all of the children.

So is autistic enterocolitis just a normal finding in biopsy specimens from autistic children? Wakefield says “no”: the disease is real. But recent analyses of faecal calprotectin (a marker for possible inflammatory bowel disease) and stool patterns in autistic children have failed to find any distinctive inflammation.^{21 22} And an expert literature review, while stressing a need for better gastrointestinal services, hasn't identified anything special in autistic patients.²³

Meanwhile, the disease born of a deal with a solicitor was last year hammered in a lawsuit. Throwing out a claim for vaccine damage from a patient at Wakefield's Texas clinic, a US judge said that not only has the “autistic enterocolitis theory not been accepted into gastroenterology textbooks, but that theory, and Dr Wakefield's role in its development, have been strongly criticised as constituting defective or fraudulent science.”²⁴

So what should we make of all this? Now the *Lancet* paper is retracted, its findings don't officially exist. And, if Dhillon is right in saying the slides can't be found, the ultimate proof is missing. All we have are the pathology reports, which independent specialists seem to agree are largely unremarkable. “They wanted this bad,” commented Tom MacDonald, dean of research at Barts and the London School of Medicine and coauthor of *Immunology and Diseases of the Gut*.²⁵ “If I was the referee and the routine pathologists reported that 8/11 were within normal limits, or had trivial changes, but this was then revised by other people to 11/12 having non-specific colitis, then I would just tell the editor to reject the paper.”

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Competing interests: BD undertook the *Sunday Times* investigation which led to the GMC hearing and retraction of the *Lancet* paper.

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MMR vaccination

A doc2doc poll asked, “Should children be denied access to school if they haven't had the MMR vaccine?” Some participants left comments (<http://tiny.cc/7318v>).

tnolan thinks that compulsory vaccination is “not a bad idea—but would middle class vaccine suspicious folk put up with it?”

Daxx disagrees: “No. This is yet another example of the increasingly paternalistic attitude taken by the medical profession towards the general community.”

audreyb reminds us what happens elsewhere in the world: “It's amazing how fast parents who have previously refused the vaccine bring their children to be immunised when they find that their children won't be able to go into school in their new Australian or US home if they haven't been vaccinated. Then we get demands for an immediate nurse appointment as they are flying out the next day.”

Neil G is clear that “Parents who want to send their kids to publicly funded schools ought also to have to abide by public policies in respect of health.”

A related discussion on doc2doc deals with the *Lancet's* retraction of Wakefield's MMR paper (<http://tiny.cc/1su6c>).

Helenj says: “Talk about closing the stable door after the horse has bolted. Given how thoroughly Andrew Wakefield has been dressed down by the General Medical Council, there's no way the *Lancet* could stand by the paper. On the other hand, there is an argument for the *Lancet* not having retracted the paper earlier: the article was a case study of 12 children and on the surface isn't particularly dodgy.”

Andrew Morrice thinks that: “Wakefield was caught because he made a great deal of his findings and attacked the UK vaccination programme, which is staunchly defended by most doctors. How much more dodgy nonsense is there gently swilling about in our literature, quoted and built on as fact? If it takes 12 years and one of the most spectacular GMC cases ever to get a paper retracted, I'd say an awful lot.”



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