Dr Andrew Wakefield MB BS FRCS FRCPath is an academic gastroenterologist. He graduated in Medicine from St Mary's Hospital (part of the University of London) in 1981, pursuing a career in gastrointestinal surgery with a particular interest in inflammatory bowel disease. He qualified as Fellow of the Royal College of Surgeons in 1985 and in 1996 was awarded a Wellcome Trust Travelling Fellowship to study small intestine transplantation in Toronto, Canada. Discoveries made during his work in Canada led him to return to the United Kingdom to pursue the study of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. In 1998, Dr Wakefield and his colleagues at the Royal Free Hospital in London reported a novel inflammatory bowel disease in children with developmental disorders such as autism; the condition later became known as autistic enterocolitis. He was awarded the Fellowship of the Royal College of Pathologists in 2001. Dr Wakefield is involved in many scientific research collaborations worldwide centring on the immunological, metabolical and pathological changes occurring in inflammatory bowel diseases such as autistic enterocolitis, links between intestinal disease and neurologic injury in children; and the possible relationship of these conditions to environmental causes, such as childhood vaccines. During the course of his work on childhood developmental disorders, Dr Wakefield was increasingly convinced of the need for a research oriented, integrated biomedical and educational approach to these disorders, in order to translate clinical benefits for affected children into measurable developmental progress; this is the driving aim of Thoughtful House Center for Children in Austin, Texas. He has published over 130 original scientific articles, book chapters and invited scientific commentaries.

That Paper

By Dr Andrew Wakefield MB BS FRCS FRCPath

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

On February 28th 1998, together with twelve colleagues published a **case-series** paper in *The Lancet*, a respected medical journal, as an *'Early Report'*[1]. The paper described the clinical findings in 12 children with an autistic spectrum disorder (ASD) occurring in association with a mild to moderate inflammation of the large intestine (colitis). This was accompanied by swelling of the lymph glands in the intestinal lining (lymphoid nodular hyperplasia), predominantly in the last part of the small intestine (terminal ileum). Contemporaneously, parents of 9 children associated onset of symptoms with MMR exposure, 8 of which were reported in the original paper (see also Child PH's story on following page). The significance of these findings has been overshadowed by misunderstanding, misrepresentation, and a concerted, systematic effort to discredit the work. This effort and specifically, the complaint of a freelance journalist and an intense political desire to subvert enquiry into issues of vaccine safety and legal redress for vaccine damage, culminated in the longest running and most expensive 'fitness to practice' case ever to come before the UK's medical regulator, the General Medical Council. At this point, the evidence is in and the outcome is awaited. Now, and only now, with all of the contemporaneous documentation available, is it timely to review both the original paper and its legacy.

Background

From the late 1980s my team at the Royal Free Medical School, the Inflammatory Bowel Disease Study Group, published extensively on possible causes and mechanisms of inflammatory bowel disease (e.g. Crohn's disease). This involved examination of a possible causal role for measles and measles vaccine. From May 1995, parents started contacting me with the story that their normally developing child had regressed into autism or an autism-like state, with onset in the majority of cases, soon after MMR vaccine. At around the same time, the children had developed chronic gastrointestinal GI symptoms similar to those described by Dr Lenny Gonzalez in the July 2009 edition of *The Autism File*[2]. Despite what were often debilitating intestinal symptoms, many indicative of abdominal pain, few of these children had undergone physical examination, let alone been investigated. Mention of the MMR vaccine had often alienated parents further from their child's healthcare providers. Many doctors put the onset of symptoms down to 'coincidence' and were content to leave it at that. Conversely, at the Royal Free a systematic plan of clinical care and research was designed in order to help affected children.

The first report on these children appeared in February 1998; the purpose of this series of articles is to review *The Lancet* paper for what it was, what it said and didn't say, and to examine the legacy of the paper in the light of subsequent events.

Study design

The Lancet paper – the first in a series of related papers – is a **case-series**: This is stated explicitly in the first line of the paper : *"… a consecutive series of children with chronic entero-colitis and regressive developmental disorder"*[1]. A typical example of how basic epidemiological textbooks define and describe a case-series is found in Hennekens and Buring[3]:

Child *PH's story, as originally told by his mother, did not cite MMR as the culprit. Eighteen months of normal development was followed by regression, giving rise to what several doctors labelled *'secondary autism'*. Loss of developmental milestones was accompanied by loss of co-ordination (he could no longer throw and catch a ball), his gait became, *"awkward and stiff like an old man"*, and he could no longer go from sitting to standing unaided. He lost the twenty words that he had gained and developed secondary faecal incontinence. At eighteen months of age, severe episodes of abdominal pain started that were associated with screaming and drawing his knees to his chest. He developed a pattern of chronic loose bowel motions with undigested food from two years of age. He went from the 97th centile for weight at one year of age to the 50th by two. His diet went from being varied to very restricted, consisting of refined carbohydrate and at least ten 200ml cartons of orange flavoured drink per day.

What Child PH's mother did not tell us in 1996 was that, contemporaneously, **she too had linked her son's problems to MMR vaccine**. Our description of this child in *The Lancet* faithfully reiterated the onset of symptoms following an episode of otitis media as his mother had reported and made no mention of the MMR. The reason for this discordance in the narrative provides a valuable lesson: the reaction of successive doctors to the suggestion that MMR might have been involved ranged from patronisingly dismissive to outright hostile. Mentioning the vaccine was beginning to negatively impact their ability to get help for their son. By the time they came to the Royal Free Hospital the father had urged his wife not to mention the MMR again, to avoid discrimination by doctors who considered her to be *crazy*.

So it was that a potentially important element of the clinical history in this child had been corrupted by the arrogance of those who knew better.

*Initials have been changed.

*"Case-series studies **describe** the experience of a single patient or a **group of patients** with a **similar diagnosis**. These types of study, in which typically an astute clinician identifies **an unusual feature of a disease** or a patient's history, may lead to **formulation of a new hypothesis** ... At that time an analytic study (most frequently using a case-control approach), can* [then] *be done to investigate possible causal factors."*

Myths: *The Lancet* paper

- **was funded by the Legal Aid Board (LAB)**[4]

  False – Not one penny of LAB money was spent on *The Lancet* paper. An LAB grant was provided for a separate viral detection study. This study, completed in 1999, does disclose the source of funding. *The Lancet* paper had been submitted for publication before the LAB grant was even available to be spent.

- **my involvement as a medical expert was kept 'secret'**[5]

  False – At least one year before publication, my senior co-authors[6], the Head of Department and the Dean of the Medical School[7], and the CEO of the hospital were informed by me. This fact was also reported in the national press 15 months prior to publication[8].

- **children were 'sourced' by lawyers to sue vaccine manufacturers**[5]

  False – Children were referred, evaluated, and investigated on the basis of their clinical symptoms alone, following referral from the child's physician[9].

- **children were litigants**[10]

  False – At the time of their referral to the Royal Free – the time material to their inclusion in The Lancet paper – none of the children were litigants .

- **I had an undisclosed conflict of interest**[11]

  False – *The Lancet's* disclosure policy at that time was followed to the letter. Documentary evidence confirms that the editorial staff of *The Lancet* were fully aware that I was working as an expert on MMR litigation well in advance of the paper's publication[12].

- **did not have Ethics Committee (EC) approval**[5]

  False – The research element of the paper that required such an approval – detailed systematic analysis of children's intestinal biopsies – was covered by the necessary EC approval[13].

- **I 'fixed' data and misreported clinical findings**[14]

  False – There is absolutely no basis in fact for this claim and it has been exposed as false[15].

- **findings have not been independently replicated**[12]

  False – The key findings of LNH and colitis in ASD children have been independently confirmed in 5 different countries[16].

- **has been retracted by most of the authors**[17]

  False – 11 of 13 authors issued a retraction of an interpretation [that MMR vaccine causes autism]. This interpretation is not provided in the paper. While it remains a possibility, a possibility cannot be retracted.

- **the work is discredited**[18]

  False – Those attemping to discredit the work have relied upon the myths above. The findings described in the paper are novel and important[19].

The legacy of *The Lancet* paper

The first demonstration of intestinal pathology in ASD

GI symptoms are common in children with autism and these symptoms are frequently associated with intestinal inflammation.

Treatment of GI inflammation may lead to symptomatic improvement in both GI and behavioural symptoms[21].

The first demonstration of abnormal vitamin B12 metabolism in ASD

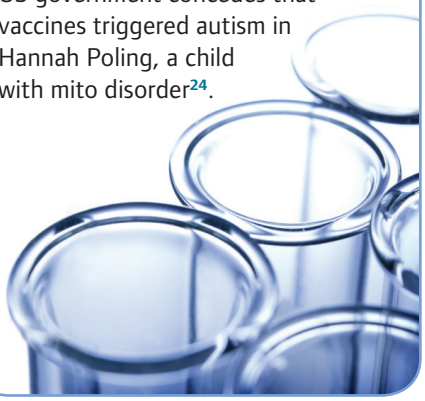
Now the subject of major clinical and research activities in autism, ranging from study of genetic differences in B12/folate metabolism to treatment with active forms of B12.

The first study to report a re-challenge effect of a measles containing vaccine (MCV)

Follow up indicates that intestinal inflammation is significantly worse in re-challenge ASD children than children receiving only one measles-containing vaccine (MCV)[22].

First study to seek evidence of a mitochondrial disorder by measurement of lactate: pyruvate in cerebrospinal fluid

Mito disorders appear to be common in ASD children and may be acquired. US government concedes that vaccines triggered autism in Hannah Poling, a child with mito disorder[24].



The crucial design feature which differentiates the **case-series** from other designs is its lack of requirement to select participants on the basis of either the exposure (e.g. MMR) or the outcome of interest (e.g. autism). A case-series does not require – and should not employ – strict inclusion or exclusion criteria. Rather, it should function to observe similar presentations in groups of patients that appear to share other common features, in order to raise hypotheses that later may be tested in the appropriate study design framework (e.g. a **case-control** study).

The Lancet paper does exactly what is required of a case-series. It states immediately what the report sets out to do: no particular developmental disorder was stated, no particular features or timing of onset were required, no particular initial exposure was necessary, no specific outcome was predicted, and no causal association was claimed.

Of note, we have been criticised for not having controls in the study; that is, developmentally normal children included for the purpose of comparison. While controls are not usually part of a case-series, we went beyond what would normally be required and *did* include controls – 19 age-matched children (5 for microscopic examination of tissues and 14 for measurement of urinary methylmalonic acid [MMA]). This would have been evident upon a proper reading of the paper.

Finally, Hennekens and Buring[3] make the crucial point that the purpose of a case-series is to **generate new hypotheses** about potential causation. It is **not** designed to investigate possible causality. *The Lancet* paper was hypothesis generating; it stimulated a series of subsequent papers – rarely if ever acknowledged by critics – that confirmed and characterised the bowel disease as novel, relatively frequent and potentially treatable and tested ideas about causation[19]. Among the critics there has been some confusion on this point which is evident, for example, in a widely quoted analysis of the paper by Professor Trisha Greenhalgh[20], which raises and attempts to answer a series of questions, including:

Was the research hypothesis clearly stated?

She observes that, *"The paper does not state a research hypothesis at all"*. This is quite true. Case-series studies are neither required nor expected to do so. Having established that there was no hypothesis, Professor Greenhalgh goes on to pose the ridiculous question:

Was this design an appropriate way to test the research hypothesis?

She concludes that the study design was not an appropriate way to test *"the research hypothesis"*. However, since she has already identified the fact that no hypothesis was stated, it rather begs the question as to which hypothesis the study was not designed to test. It soon becomes clear, that it was **her** hypothesis that the study did not test. Her conclusion that *"the study design was incapable of proving the [MMR] link one way or the other"* is of course, entirely accurate as we had already indicated in the paper on p641, para 2, lines 1 and 2[1]:

> *"We did not prove an association between measles, mumps and rubella vaccine and the syndrome described ...,"*

and para 5, lines 4-6:

> *Further investigations are needed to examine this syndrome and its possible relation to the vaccine."*

Professor Greenhalgh ventures even further off course when she asks:

Were the study's conclusions supported by the data?

It is not clear whether Professor Greenhalgh is referring to the **authors'** conclusions – i.e. that the data do not demonstrate a causal link between the disorder and MMR exposure and that further research is required, or whether she is asking if the data support her own hypothesis. In the

former case, the data clearly support our conclusions. Not surprisingly, they do not support Professor Greenhalgh's hypothesis – that MMR causes the syndrome described. She continues:

If the answer to [the question above] is no, would a more robust study design have been practically possible to test the study's main hypothesis?

Having inserted her own hypothesis, Professor Greenhalgh answers her question with a resounding "yes". That she **does** appear satisfied on the basis of what can only be described as a complete misunderstanding of *The Lancet* study's design, is cause for concern. In turn, failure of the Department of Health (whose website directed people via the National Health Service Executive to her analysis) to appreciate the potential impact of this deeply flawed document on the perceptions of many thousands of worried parents, is alarming.

Notwithstanding Professor Greenhalgh's follies, one should never underestimate the importance of the case-series as a starting point for medical discovery. It is the tried and tested mode of the description of human disease syndromes, including Kanner's autism, Asperger's syndrome, and Heller's disease (disintegrative disorder). One final word on the matter endorses this perspective:

> *"Clinical situations in which a case report or case-series is an appropriate type of study include the following: a doctor notices that two babies born in his hospital have absent limbs (phocomelia). Both mothers had taken a new drug (thalidomide) in early pregnancy. The doctor wishes to alert his colleagues worldwide to the possibility of drug related damage as quickly as possible (McBride, in The Lancet 1961). Anyone who thinks 'quick and dirty' case reports are never scientifically justified should remember this example."*

And the source of this invaluable piece of advice? Dr Trisha Greenhalgh, author of 'How to Read a Paper'[24].

Coincidence

Coincidence – often the first resort of sceptical physicians – refers, in this context, to the chance occurrence of autistic symptoms being identified in the second year of life, at around the same time as MMR is given. Regularly advanced as an explanation for the parents' story, coincidence is a conclusion of last resort – one that should be arrived at, only after diagnostic due diligence has excluded alternative causes for neurological deterioration in a child. Meticulous attention should be paid to the parental history and the practice of claiming 'coincidence' without first excluding possible causes has no place in clinical medicine. Where an infection such as herpes simplex or Epstein-Barr virus ('mono') has preceded autistic regression, the medical literature shows that extensive testing has been undertaken, the cause identified, and the child treated accordingly[25]. In contrast, when MMR vaccination has preceded autistic regression little, if any, attempt has been made to investigate children appropriately. The case of Bailey Banks is one of those rare instances where this has been done and for whom the US vaccine court ruled that MMR caused his ASD[26]. Bailey's MRI, performed 16 days post-MMR for encephalopathy, revealed abnormalities of brain myelin, consistent with acute disseminated encephalomyelitis (ADEM), an autoimmune brain inflammation that can follow measles or a measles vaccine. The lesson is that every attempt should be made to evaluate children during the course of their regression since, in the case of ADEM, abnormalities of brain myelin may be transient and not evident, therefore, on an MRI performed two years after exposure. The fact that the parents of *The Lancet* children described loss of faecal and/or urinary continence in four cases and ataxia (clumsiness) in six – the latter being a reported adverse reaction to MMR vaccine[27] – is more than enough indication for thorough neurological work up. The history of regression with loss of acquired skills in a previously normal or near normal child should ring alarm bells and initiate a systematic approach to differential diagnosis. It was with this in mind that Professor Walker-Smith, one of the world's leading paediatric gastroenterologists and senior author of *The Lancet* paper wrote in 1997:

> *"[These children] have not had the level of investigation which we would regard as adequate for a child presenting with such a devastating condition."*[28]

Despite evident neurological symptoms, despite the proximity of onset to a viral exposure, and despite additional physical symptoms such as pain and diarrhoea, a diagnosis of autism trumped the need for anything but minimal investigation by "mainstream" autism practitioners for the majority of these children.

Coincidence and re-challenge**

Where a child with regressive autism has received more than one dose of a measles-containing vaccine (MCV), exacerbation of existing symptoms and/or recurrence of transient symptoms associated with the first dose, is frequently reported. Properly documented, the Institute of Medicine's Vaccine Safety Committee accepts the 're-challenge' effect as evidence of causation[29]. In order to examine this in the setting of MMR and *autistic enterocolitis* and to overcome the concern about parental recall of events that may have occurred many years before, we conducted a study comparing the severity of intestinal inflammation between children once vaccinated and those twice vaccinated with an MCV with the hypothesis that the disease should be more severe in those twice exposed if the disease were caused by the vaccine[22]. There was a significantly higher prevalence of active chronic colitis (involving pus-forming cells) in those children given an MMR or MR booster compared with those receiving only one dose, supporting a causal association.

Diligent science

The quest for precision can become a hostage to fortune, as the microscopic analysis of *The Lancet* children's tissues was to prove. There are few people in the world with Professor Walker-Smith's knowledge of the microscopic appearances of inflammatory disease of the intestine in children. So it was that, in the absence of a paediatric pathologist expert in this field at the Royal Free, Professor Walker-Smith conducted a weekly review of his patients' tissues, and identified the fact that disease was being missed in some children. In order to reduce this risk and to standardise the reporting of the ASD children's biopsies, all tissues were subsequently examined by a single senior pathologist with expertise in bowel disease. His findings were recorded on a specially designed chart to document specific features of tissue damage[30]. This record formed the basis of what was subsequently reported in *The Lancet*. Few case-series go to this level of precision.

In the hands of someone determined to discredit the work, however, discrepancies between the routine clinical report (which may have come, for example, from a pathologist with an interest in brain disease or gynaecological pathology) and the standardised expert analysis, were falsely reported in the national media as 'fixing' of the data. I was specifically accused of this[31], although I had no part in scoring the

Re-challenge with a measles vaccine

Child RT* was monitored closely in his first year due to wide bridging of his nose. He was discharged from follow up as developmentally and physically normal by 15 months of age. He later received a single measles vaccine following which he stopped 'cruising' around furniture and regressed to crawling. His learning plateaued and by 20 months, he had lost words and soon thereafter, stopped talking altogether.

General ill health developed in his second year with ear, chest, and throat infections, and diarrhoea with abdominal pain. According to his mother's story, two weeks following an MMR vaccine, at 4.5 years of age, he *"disappeared"* and *"lost all skills and communication"*. Whereas at 10 months of age he was able to build a tower of bricks, his play skills declined to the point that, *"now he [was] lost as to what to do with them."* In addition, he became clumsy, started head banging, and developed repetitive behaviours. He lost his self-help skills such that, whereas before the MMR booster he could feed himself with a spoon, afterwards he could no longer even hold a cup.

The history of Child RT's GI problems is also instructive. His records state: *"The diarrhoea became a problem at between 1-1½ years of age* [after his single measles vaccine] … *it generally contains undigested food. His diarrhoea became significantly worse from 4½ years of age* [after his MMR] …" Failure to thrive, a cardinal sign of paediatric inflammatory bowel disease, was evident from the GP's records; he was reported to be *"dropping off centile charts"*. This failure to thrive continued and took another downturn at the same time his diarrhoea worsened, when he was noted to have dropped from the 9th to the 2nd centile for weight.

Further examination of MMR re-challenge is currently underway.
*Initials have been changed.

Did they read the paper?

Dr Ari Brown MD

Spokesperson for the American Academy of Pediatrics and the Immunization Action Coalition

"This flawed study concluded that the rise in autism was related to giving the combination vaccine of measles-mumps-rubella (MMR)."[31]

Professor Sir Michael Rutter FRS

Expert prosecution witness GMC, expert witness on behalf of MMR vaccine manufacturers

"Publication of a study claiming a causal relationship between measles mumps and rubella (MMR) vaccine and autism spectrum disorders (ASD) sparked a heated debate ..."[32]

Professor Eric Fombonne

Expert witness on behalf of MMR vaccine manufacturers

"Recent reports claim to have identified another variant of autism (called 'autistic enterocolitis') in children referred to a gastroenterology department. The hypothesis has involved 3 separate claims: 1) that a new phenotype of autism associated with developmental regression and gastro-intestinal symptoms has emerged as a consequence of measles-mumps-rubella vaccination ..."[33]

reviews. It is notable that despite five years of investigation by the GMC no charge of scientific fraud has been made against any of the defendants. The allegation of fraud was made by Brian Deer, the same freelancer who had initiated the GMC enquiry, continuing his litany of false allegations. There is no evidence at all that the data had been 'fixed' as was alleged and the newspaper in question has failed to produce any, despite a request to do so from the Press Complaints Commission. Paradoxically, the price paid for diligent science has been a headline proclaiming fraud. No doubt the intended goal – to reinforce the false belief that the work is discredited – has worked for some.

The damage done

The damage done to my reputation and that of my colleagues, and the personal price for pursuing a valid scientific question while putting the patients' interests above all others, is trivial compared with the impact of these falsehoods on the children's access to appropriate and necessary care. My experience is intended as a cynical example to discourage others. As a consequence, many physicians in the UK and US will not 'risk' providing the care that is due to these children. There is a pervasive and openly stated bias against funding and publication of this work, and I have been excluded from presenting at meetings on the instructions of the sponsoring pharmaceutical company. It has been an effective exercise in public relations and selling newspapers. But it will fail. It will fail because nature cannot be deceived.

It has always been a privilege working with these children and their families. It is my hope that before too long the tide will turn and that, in addition, my teacher and mentor Professor Sir Stanley Peart FRS will come to realise that I have never forsaken his instruction.

In the next edition of *The Autism File*, Dr Wakefield continues his analysis of 'That Paper' and its legacy.

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