

# CORRESPONDENCE

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## MMR and autism: the debate continues

Sir—Simon Murch has previously made an important contribution towards treating children with regressive autism and bowel problems, and so it is vital to respond to his letter (Nov 1, p 1498)<sup>1</sup> with hard fact rather than emotion.

The evidence to support his claim that there is no link between the measles, mumps, and rubella (MMR) vaccine and regressive autism comes from a large number of studies, too numerous to comprehensively reference here. But all of these studies have only been epidemiological. Perhaps the most interesting was the study by Kaye and colleagues,<sup>2</sup> which showed that autism in the UK had increased seven-fold between 1988 (the year MMR was introduced in the UK) and 1999. That study explained the increase away as possibly being “due to increased awareness of the condition among parents and general practitioners, changing diagnostic criteria or environmental factors”, although the authors offered no evidence to support this speculation. There is thus *prima facie* evidence of an underlying real increase in autism in the UK since 1988.

Careful review of the numerous epidemiological studies (how many of MMR’s defenders have personally taken the time to read them all carefully and test the methods and conclusions of each to destruction?) exposes each one as flawed, with unsupported assertions, questionable hypotheses, and overstated outcomes. For example, studies based on the UK General Practice Research Database are utterly reliant on the relevance of that database to an affected child’s detailed bowel condition and developmental history. This is clearly a heroic assumption on an industrial scale. Few such children have undergone ileocolonoscopy or had tissue samples analysed. And none of the epidemiological studies distinguished between regressive autism and other autism—a crucial failure.

Another epidemiological study<sup>3</sup>—the only one to look at records of actual damaged children—published in support of MMR’s safety, was that by the UK Committee on Safety of

Medicines. This study, based on records of several hundred UK children obtained from lawyers, was so weak that it was forced to admit that “it was impossible to prove or refute the suggested associations between MMR vaccine and autism or inflammatory bowel disease because of the nature of the information [made available to the study]”. No children were clinically examined, and no parents interviewed.

There also have been no clinical studies of damaged children with regressive autism that firmly refute Andrew Wakefield’s hypothesis of an association between MMR and regressive autism. Are these epidemiological studies Murch’s sole evidence of MMR’s safety?

We now turn to studies that offer some background support to the ground-floor level of Wakefield’s hypothesis (again, note that he has never claimed that MMR causes all autism, only a subset of cases). Several studies have been published, or papers presented, that indeed strongly suggest that Wakefield’s hypothesis of a link between gut pathology and regressive autism is correct. Among these is a paper by Timothy Buie.<sup>4</sup> Buie found evidence of chronic inflammation of the intestinal tract among autistic children he examined, with ileal lymphoid nodular hyperplasia (ILNH) in 15 of 89 children. Buie concluded that the children “are ill, in distress and pain, and not just mentally, neurologically dysfunctional”. His findings thus support at least some link between a disorder of the gastrointestinal tract and some cases of autism. No contrary published evidence to refute Buie’s work has been offered or presented to date.

A paper by Arthur Krigsman<sup>5</sup> noted his finding that a large proportion of his autistic patients had chronic unexplained gastrointestinal symptoms. In his assessment of 40 children, 90% had lymphoid nodular hyperplasia of the terminal ileum. Most of the cohort had a clear history of developmental regression, with a precipitous or gradual decline at age 12–18 months after earlier normal development. Again, no evidence to refute Krigsman has since been offered.

These findings, together with those of Wakefield and his co-authors—including Murch—strongly suggest a link between ILNH and regressive autism. The numerous defenders of MMR’s safety might at least wish to acknowledge—or provide clinical evidence to contradict—this vital first stage in the unfolding story of regressive autism’s cause.

The most up-to-date figures available from the US Individuals with Disabilities Education Act (State-sourced) database confirm that children and young people aged 6–21 years with autism, in full-time education, have increased from 12 222 in 1992–93 to 118 602 in 2002–03, a deeply-troubling increase. It emphasises the huge and rapidly-rising cost to the community of autism, in all its forms, and the importance of making real progress in tracing its causes.

Child health is not just about measles, or vaccine take-up rates. In the UK, a dozen suspected measles cases is a media headline. A thousand cases of autism go unnoticed, unrecorded, and unreported, yet their lifelong physical and economic effect is vastly greater. It is vital that the medical community now recognises the importance of the pioneering work of Wakefield, Buie, Krigsman, and other co-workers, accepts that there is a *prima facie* connection between ILNH and regressive autism, and conducts the most urgent research as to its potential causal pathways. It is an extreme understatement to emphasise that there is much at stake.

I am the parent of an autistic child.

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- 1 Murch S. Separating inflammation from speculation in autism. *Lancet* 2003; **362**: 1498.
- 2 Kaye JA, del Mar Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 2001; **322**: 460–63.
- 3 UK Committee on Safety of Medicines. Report of the Working Party on MMR Vaccine. London: Committee on Safety of Medicines, 1999.

- 4 Buie T. Initial autism research findings at Harvard, Massachusetts. Presented at Oasis 2001 Conference for Autism. Portland, Oregon, USA: November, 2001. <http://www.autismnwaf.com/harvardproject2.htm> (accessed Jan 20, 2004)
- 5 Krigsman A. Testimony by Dr Arthur Krigsman MD before the Committee on Government Reform. Presented to US Congressional Committee on Government Reform's hearing, The Status of Research into Vaccine Safety and Autism. Washington DC: Congressional Committee on Government Reform, 2002.

Sir—I too write as a co-author of the *Lancet* paper of 1998 referred to by Simon Murch in his letter.<sup>1</sup> Statements in this letter cannot be allowed to pass without comment. There is a growing body of scientific evidence to show a relation between the measles, mumps, and rubella (MMR) vaccine, enterocolitis, ileocolonic lymphoid nodular hyperplasia, and autism.

The histologically unique condition ileocolonic lymphoid nodular hyperplasia, which is not a normal variant,<sup>2,3</sup> is associated with a diffuse enterocolitis. There are significant immunological and inflammatory abnormalities specific to this condition.<sup>4-12</sup>

There is evidence that affected children absorb undigested peptides with opioid properties,<sup>13</sup> and that the most powerful of these opioids are derived from casein and gluten. Exclusion of casein and gluten from the diet has proven beneficial effects on autistic children's behaviour.<sup>14</sup>

Evidence of persistent measles virus infection in the gut has been identified.<sup>15,16</sup> The virus identified in most of these children was shown to be consistent with the measles virus RNA from the MMR vaccine.<sup>17</sup> These children also have measles virus RNA in the blood, which is also consistent with that of the MMR strain.<sup>16</sup> Measles virus RNA has also been detected in the spinal fluid of 19 of 28 children with regressive autism and bowel disease and in one of 37 control samples (unpublished data).

Much is made of the epidemiological studies that have failed to show an association between MMR and autism. However, these studies are open to serious criticism.<sup>18,19</sup>

Murch was a co-author on 11 of the 17 peer-reviewed publications and presentations that I cite. These present a step-by-step cascade of evidence starting with the recognition of the clinical condition, followed by the pathology of the gut disease, the immunological and inflammatory abnormalities, the identification of measles RNA in the gut, blood, and cerebrospinal fluid, and subsequent identification of this RNA as being consistent with MMR virus.

I am an adult neurologist, not a paediatrician, not a gastroenterologist, and not an immunologist. Even so, taking a dispassionate and wide view of the published and unpublished information, I think there is increasingly compelling evidence for a causative link between the MMR vaccine, a unique gastrointestinal disease, and regressive autism.

I examined the original cohort of children, and they had no physical neurological abnormalities. I have recently seen one of them again. His behaviour is much worse, at times being uncontrollable. He has developed epilepsy and bilateral extensor plantar responses.

The problem now is to identify the numbers of children involved, and the susceptibility factors. In the meantime, consideration should be given to offering children single-injection measles vaccinations.

I am a trustee of the charity Visceral, which supports research into inflammatory bowel disease and autism

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For references, see <http://image.thelancet.com/extras/03cor12097webref.pdf>

#### Author's reply

Sir—David Thrower and Peter Harvey raise issues about my letter, which I wrote because I was angered by a report of life-threatening measles in immunocompromised children,<sup>1</sup> an increasingly common group now at particular risk due to low uptake of the measles, mumps, and rubella (MMR) vaccine. I have no financial interest, and the views expressed are my own. I concur with parts of both letters, agreeing that we and others have identified gut pathology in autistic children, and that there should be more research. Both letters however miss my central point, which was emphasised in the title. A subtle form of intestinal inflammation has been confirmed, but this does not mean that MMR is the cause of either this lesion or of autism. That some regulatory authorities ridiculed all aspects of these studies is unfortunate because it has allowed confirmation of the intestinal lesion to be appropriated by the anti-MMR lobby. I know that Buie and Krigsman have replicated our findings, and suggest that controversy over the existence of this lesion will be settled when they publish in peer-reviewed journals. Such publication is needed to establish autism as a proper area for paediatric gastroenterologists: the criticism we receive when presenting our work is that it has not been replicated.

The distinct issues of inflammation and causation must be examined separately, and not conflated, as attempted in both letters. Both demonstrate misunderstanding of our findings; therefore I should clarify what we have described. First, the lesion is not histologically unique, and features are relatively non-specific without special staining, although distinct from classic inflammatory bowel disease.<sup>2</sup> Second, ileal lymphoid nodular hyperplasia (ILNH) is a frequent, although not invariable, finding. Follicles are sometimes strikingly large, but this finding is neither specific nor diagnostic, since ILNH is increasingly recognised in children with food allergies.<sup>3</sup> Further immunological characterisation, by comparison with ILNH due to other causes, is thus required before any conclusions can be drawn about specificity. Third, the abnormal circulating lymphocyte subsets mentioned by Harvey<sup>4</sup> also overlap with our findings in food allergy.<sup>3</sup> Harvey overstates our findings to suggest a degree of specificity that I and my fellow clinicians, who have actually seen and investigated these children, do not seek to claim.

Our extensive immunohistochemical characterisation, by comparison with numerous controls, provides much stronger evidence to suggest a unique lesion. We found increased infiltration of CD8+ T cells in colon, duodenum, and stomach.<sup>6-8</sup> Their distribution is important because these cells cluster around the epithelium at each site studied. Although a viral cause should be considered for any CD8-dominated lesion, the periepithelial distribution of these cells is not consistent with any suggestion that this lesion might be driven by persistent measles infection. To my knowledge, no epithelial localisation of measles has been seen in any child by any technique at any level in the gut. Some of the features might be consistent with a low-grade autoimmune response to an epithelial determinant,<sup>7,8</sup> but this is by no means proven, and requires further study. Work should also continue into the disordered gut motility seen in so many of these children,<sup>9</sup> and I hope that this department will continue to contribute.

Harvey's contention that detectable RNA represents persistent measles infection is premature. Koch's postulates remain unfulfilled—ileal follicles from several children were cultured with measles-susceptible Vero cells, and not one transmitted infection. John O'Leary has shown the presence of fragments of measles RNA using the highly sensitive TaqMan PCR technique.<sup>10</sup> He has spoken in