Summary

Regressive autism, ileal-lymphoid nodular hyperplasia, measles virus, and MMR vaccine: summary of published studies offering evidence for linkages

David Thrower
Email: David.Throwerwarrington@ntlworld.com

Abstract

This note summarizes clinical evidence for the link between (1) autism and a novel form of inflammatory bowel disease; (2) inflammatory bowel disease and measles virus; and (3) measles virus and vaccination with MMR. Also some of the other wider safety concerns over MMR are considered.

Keywords: regressive autism, ileal-lymphoid nodular hyperplasia, measles virus, MMR vaccine

1. The link between autism and a novel form of inflammatory bowel disease

There is now ample evidence, confirmed by independent groups of researchers, of a link between regressive autism and a novel form of inflammatory bowel disease. Full publication references are at the end of these notes.

- The possible association between MMR vaccine, regressive autism and intestinal symptoms was first recounted by parents to Dr. Andrew Wakefield, a UK gastroenterologist at the Royal Free Hospital, London, in 1995. The first group of children presenting in this way to Wakefield and colleagues at the Royal Free were reported in The Lancet as a clinical case series in February 1998 [1]. Although the interpretation put on this paper at the time was the subject of intense controversy—particularly in the absence of corroborative clinical research by other researchers at that time - the strong evidence of a hitherto-unreported link between autism and a novel intestinal disease, ileal-lymphoid nodular hyperplasia, has not been disputed, and still stands as an important initial clue as to the causes of regressive autism.

- A group of researchers led by Horvath [2] subsequently independently reported in 1999 upon patients with autism who had gastrointestinal symptoms, including a study of 36 children with autism that found grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15 (42%) and chronic duodenitis in 24 (67%).

- Further research published in September 2000 [3] by Wakefield, Anthony *et al.* confirmed that ileal-lymphoid nodular hyperplasia (ILNH) was found in 54 out of 58 (93%) children with autism or other disorders (50 with autism, 5 Aspergers, 2 disintegrative disorder, one ADHD, one schizophrenia, one dyslexia), but only 5 out of 35 (14.3%) normal controls, pointing to a very strong ILNH-autism link.

- Research published in 2001 by Furlano, Anthony *et al.* [4] reported on ileocolonoscopy performed on 21 consecutively-evaluated children with autistic spectrum disorders and bowel symptoms, and made "blinded" comparisons with 8 children who had a histologically normal ileum and colon, plus 10 developmentally-normal children with ILNH, 15 with Crohn's Disease, and 14 with ulcerative colitis. The study confirmed a distinct lymphocytic colitis in the children with ASD, in which the epithelium appeared particularly affected, offering further corroboration for gut epithelial dysfunction in autism.

- Research reported in 2001 by Buie [5] reported that, as a result of over 400 gastrointestinal endoscopies with biopsies and evaluation of digestive enzyme function, on children with autism, he had found the presence of chronic inflammation of the intestinal tract, although the incidence was less frequent than in the Royal Free Hospital group of patients reported by Wakefield *et al.*, and that biopsy results indicated the presence of chronic inflammation of the digestive tracts, including esophagitis, gastritis and enterocolitis. Ileal lymphoid nodular hyperplasia, as first found by the Royal Free study, had been found in 15 of 89 children examined for it.

- A review [6] published in September 2002 by Wakefield, Anthony, Montgomery *et al.* noted that as early as 1986, a researcher named Soddy had noted that recurrent gastrointestinal upsets were a constant feature of autistic children, and that in a systematic analysis of an unselected population of 385 children on the autistic spectrum, clinically-significant gastrointestinal symptoms occurred in 46%, compared with 10% of 97 developmentally-normal controls, strongly suggesting a gastrointestinal-autism link. Mucosal lesions in the small and large intestine were consistent with an autoimmune pathology, and suggested the

doi: 10.1588/medver.2007.04.00156

possibility of an autoimmune response leading to cerebral damage.

- A June 2002 presentation [7] by Krigsman to the U.S. Congressional Committee on Government Reform reported that a large percentage of his autistic patients suffered from chronic unexplained gastrointestinal symptoms. Of 43 patients, the majority had a clear history of developmental regression, after previous normal development, suffering gradual or precipitous decline between age 12 months and 18 months. Most regressive children also exhibited poor growth. Patients had undergone colonoscopy. Findings were that the lymphoid nodules of the terminal ileum were markedly enlarged, thus confirming the early work of the Royal Free team. Evaluation of biopsy specimens confirmed that 65% had colitis, 51% had active colitis, 40% had chronic colitis, 7% had eosinophilic colitis, 90% had lymphoid nodular hyperplasia of the terminal ileum, and 35% had neither active nor chronic nor eosinophilic colitis. Patterns of inflammation were patchy and unpredictable, but findings were similar and consistent from patient to patient within affected sub-groups.

- A November 2003 paper [8] published by Ashwood, Murch *et al.* reported on the examination of 52 affected autistic children, compared with 25 histologically-normal developmentally-normal controls and a further 54 histologically-inflamed but developmentally-normal controls. Analysis of intestinal biopsies in regressive-autistic children indicated a novel lymphocytic enterocolitis with autoimmune features, though the precise linkage between the finding and cognitive functions still remained unclear. The study concluded that it provided further evidence of a panenteric mucosal immunopathology in children with regressive autism, that is distinct from other previously-known inflammatory bowel diseases.

- An April 2004 paper [9] by Torrente, Anthony *et al.* identified, following earlier reports of lymphocytic colitis and small bowel enteropathy in children with regressive autism, that the gastritis in regressive autism was clearly distinct from that in Crohn's and other conditions, pointing to a distinctive form of gastritis being linked with regressive autism.

- A November 2004 paper [10] by Ashwood, Anthony *et al.* found that molecules (cytokines) produced by immune cells in the intestine, that cause or control inflammation, showed an abnormal pattern in autistic children compared with non-autistic children. The pattern was different to other forms of intestinal inflammation, and the disease resembled a longstanding viral disease of the intestine, not unlike the intestinal inflammation seen on patients with other viral infections such as HIV-associated enteropathy (intestinal disease) that often accompanies infection with HIV.

- A February 2005 paper [11] by Jyonouchi, Geng *et al.* further confirmed the original ileal-lymphoid nodular hyperplasia/regressive autism link first reported by the Wakefield team in 1998. The study again found evidence of marked inflammatory and immune abnormalities in children with autism associated with gastrointestinal symptoms.

- An April 2005 published letter [12] by Balzola, Barbon *et al*., entitled *Panenteric IBD-like disease in a patient with regressive autism shown for the first time by the Wireless Capsule Enteroscopy: another piece in the jigsaw of this gut/brain syndrome?*reported that a 28-year-old male with regressive autism, severe constipation, bloating, abdomen distension and symptoms of gastroesophageal reflux was examined. Gastroscopy under general anaesthesia revealed hemorrhagic gastritis with inflammatory pseudopolypsthat had reached the pylorum, with a pearl-necklace appearance, and a panenteric IBD-like disease consistent with previously-published descriptions of autistic enterocolitis was finally diagnosed. The wireless capsule images were the first to be obtained beyond the limits of the duodenum and terminal ileum, and demonstrated the potential for the entire bowel to be implicated in this inflammatory disease.

- A May 2005 study [13] by Balzola, Daniela *et al.* reported on 9 consecutive patients (range 7-30 years) with autism and chronic intestinal symptoms (abdominal pain, bloating, constipation and/or diahorrea). Routine blood and stool tests and gastroscopy and colonoscopy with multiple biopsies were performed under sedation, and wireless enteroscopy capsules were used in three of the adult patients. Gastroscopy revealed mucosal gastritis in 4 patients, esophagitis in 1 patient and duodenitis in 1 patient, and histological findings showed chronic inflammation of the stomach and duodenum in 6 patients, inconsistent with celiac disease. The authors reported that preliminary findings were strongly consistent with previous descriptions of autistic enterocolitis, and supported a not-coincidental occurrence. They showed for the first time a small-intestinal involvement, suggesting a pan-enteric localization of this new inflammatory bowel disease.

- Also in 2005, a further paper [14] by Wakefield, Ashwood et al was published, assessing ileocolonic lymphoid nodular hyperplasia in ASD and normal control children. Some 148 consecutive children with ASD, with gastrointestinal symptoms, were investigated by ileocolonoscopy, with 74 ASD children and 23 normal controls undergoing upper gastrointestinal endoscopy. The presence of lymphoid nodular hyperplasia was significantly greater in ASD children compared with controls, in the ileum (129 out of 144, compared with 8 out of 27 controls), and in the colon (88 out of 148, compared with 7 out of 30 controls). Comparative percentages were 90% vs 30% and 59% vs 23%. This was whether or not controls had co-existent colonic inflammation. The severity of ILNH was significantly greater in ASD children compared with controls, with moderate-to-severe ILNH present in 98 out of 144 ASD children compared with 4 out of 27 controls; percentages were 68% and 15%. On histopathological examination, hyperplasic lym-

doi: 10.1588/medver.2007.04.00156

phoid follicles were significantly more prevalent in the ileum of ASD children (84 out of 138, or 61%) compared with normal controls (2 out of 23, or 9%). The data thus further corroborated the finding that ileal lymphoid nodular hyperplasia is a significant pathological finding in autistic children.

- Additionally in 2005, a study [15] was published by Gonzalez, Lopez *et al.*, seeking evidence of immunological alterations in 68 autistic children ages 22 months to 11 years and presenting with digestive systems, and examining biopsies from their digestive tracts. Endoscopies and colosopies were undertaken, with biopsies of the esophagus, stomach, duodenum and colon, with verification of presence of inflammation, eosiophil infiltration, lymphoid nodular hyperplasia and CD-4 and CD-8 cells. The results were that lymphoid nodular hyperplasia was discovered in 2/68 esophagus, 6/68 stomachs, 8/68 duodenums and 36/68 (53%) of colons. Eosiophil infiltration with more than 20 eosiphils per field were found in 3/68 eosphagus, 1/68 stomach, 8/68 duodenum and 24/68 (35%) colons. Inflammatory reactions were found in 56/68 (82%) esophogitis, 64/68 (94%) gastritis, and all (100%) presented with duodenitis and colitis. CD-4/CD-8 relationship existed of >3 in 42/68 (62%) and <1 in 16/68. The authors concluded that the children presented immunological and immunohistochemical alterations of the biopsies of their digestive tracts, and that there was a significant finding of lymphoid nodular hyperplasia, eosiophilinfiltration, and that prevalence of greater CD-4 than CD-8 cells in the inflammation of the intestinal wall demonstrated in favour of a Th2 type allergic reaction.

Taken together, the above now provide very convincing evidence from a number of wholly-independent groups of researchers of a link between the novel inflammatory bowel disease of ileal lymphoid nodular hyperplasia and regressive autism.

2. The link between inflammatory bowel disease and measles virus

These autism/inflammatory bowel disease findings were followed by findings that linked the novel form of inflammatory bowel disease with persistent measles virus in the gut of affected children:

- A paper [16] by Uhlmann, Sheils et al, noting that measles virus nucleoprotein (N antigen) had been detected in association with follicular dendritic cells (FDC) in patients, and seeking molecular confirmation of this result, found that :solution phase RT PCR yielded specific measles virus N gene amplification in affected children (10/10), and identified distinct measles virus genome in FDC reactive follicular centres by in-cell RNA amplification. None of the normal controls showed any evidence of measles virus genome. The data highlighted a possible causal link between measles virus infection and ileo-colonic lymphoid nodular hyperplasia in affected children

- A paper [17] presented in the year 2000 by Singh to the US House of Representatives Committee on Government Reform reported a hyperimmune response to the measles virus, with an association between measles virus antibody levels and incidence of brain autoantibody.

- An April 2000 paper [18] presented by O'Leary to the Committee on Government Reform reported the investigation whether measles virus was present n the gut biopsies of autistic children, and if so, where and how much. The paper reported that the biopsies of 24 out of 25 (96%) of the autistic children examined were positive for measles virus, and that amongst normal (non-autistic) controls, only 1 out of 15 children (6.6%) were positive, strongly suggesting a connection between measles virus and autism.

- A February 2002 paper [19] by Uhlmann, Wakefield, O'Leary et al investigated the presence of persistent measles virus in the intestinal tissue of 91 autistic patients with new-variant inflammatory bowel disease (ileal-lymphoid nodular hyperplasia, or ILNH). Patient samples were provided by the Royal Free Hospital, London. The patients were ages 3-14, and 77 out of 91 were male. There were 70 developmentally-normal controls ages 0-17 years, 47 out of 70 being boys. Of these, 19 had normal ileal biopsies, 13 had mild non-specific chronic inflammatory changes, 3 had ILNH and had been investigated for abdominal pain, 8 had Crohn's Disease, one had ulcerative colitis, and 26 had undergone appendicectomy for abdominal pain including appendicitis. The results were that 75 out of 91 patients with a histologically-confirmed diagnosis of ileal-lymphoid nodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue, compared with 5 out of 70 controls. Using TaqMan RT-PCR techniques, 70 out of 91 affected children were positive for measles virus, compared with 4 out of 70 controls. Of the controls, measles virus was not detected in normal children or children with isolated ileal-lymphoid nodular hyperplasia. However, 4 out of 26 appendicectomy samples harboured measles virus genome; the study suggested that the prevalence of measles virus in the general population warranted further investigation. The study concluded that the data confirmed an association between the presence of gut pathology and of measles virus in children with developmental disorder. The study did not exclude the presence of alternative infections to measles virus.

- A February 2004 paper [20] presented by Singh to the U.S. Institute of Medicine, Washington DC, measured antibodies in autistic children to five viruses, measles, mumps, rubella, CMV and human herpes virus 6. Researchers found that the antibody level of the measles virus alone, and not the other four, was significantly higher in autistic children than in normal children. The research also found a correlation between measles antibody and brain autoimmunity, which was marked by myelin basic protein antibodies. The two markers correlated in over 90% of the autistic children tested for them, suggesting a causal link between measles virus and autoimmunity in autism. The serology to other

doi: 10.1588/medver.2007.04.00156

viruses and other brain autoantibodies did not show this correlation. This suggested a temporal link of measles virus in the etiology of autism.

An early-report presentation by Walker, Hepner et al, at the International Meeting for Autism Research, Montreal, June 2006, reported that PCR analysis on terminal ileum biopsy tissue from an initial 82 patients found 70 (85%) positive for measles virus f-gene amplicon. These preliminary results confirm earlier findings of measles virus RNA in the terminal ileum. Full publication of this study is anticipated.

The above studies provide significant evidence for a link between measles virus and ileal lymphoid nodular hyperplasia, with the latter's earlier-demonstrated onward link with regressive autism.

3. The link between measles virus and vaccination with MMR

- A July 2002 paper [21] presented by O'Leary reported that the strain of measles virus used in MMR had been detected in the gut tissue of 12 autistic children. Medical histories had indicated that each of the children had developed autism after the date of receipt of MMR, and none had exhibited outward signs of measles infection before becoming autistic

- An April 2000 study [22] by Kawashima, Takayuki et al confirmed that, amongst 8 patients with Crohn's Disease, 3 patients with ulcerative colitis and 9 patients with autistic enterocolitis, and 8 children who were either healthy or who had SSPE, SLE or HIV-1, 1 out of 8 patients with CD, 1 out of 3 patients with UC and 3 out of 9 patients with autism were positive for measles virus. Controls were all negative. The sequences from patients with CD shared the characteristics of wild-strain measles virus. The sequences from patients with UC and from patients with autism were consistent with vaccine strain measles virus. These results were consistent with patients' medical histories, and point to a connection between autism and vaccine-strain measles virus.

- A May 2002 paper [23] by Singh, Nelson, Jensen and Bradstreet found that a significant percentage of autistic children examined had antibodies to myelin basic protein (up to 88% positive) and to MMR (up to 65% positive). Normal children did not exhibit these antibodies. The analysis of paired samples (serum and cerebral spinal fluid from 7 autistic children also revealed a high degree of serological association between MMR and myelin basic protein. Some 50% of CSF had MMR antibodies, 86% of CSF had MBP antibodies, 75% of sera had MMR antibodies and 100% of sera had MBP antibodies. Therefore there was a strong correlation between MMR antibodies and myelin basic protein antibodies. By using monoclonal antibodies, the authors characterized that the MMR antibodies were due to the measles sub-unit, but not to the mumps or rubella sub-units, of MMR. In the light of this, the authors suggested that in some cases of autism, MMR might cause autoimmunity, and it might be doing so by bringing on an atypical measles infection that manifests neurological symptoms.

- An earlier 1999 paper [24] by Bitnun has previously and independently confirmed the presence of measles virus in the brain tissue of a previously-healthy child following exposure to MMR, when the child had no history of wild measles infection.

- A February 2004 paper [25] by Bradstreet, O'Leary, Sheils et al to the US Institute of Medicine, and subsequently published later that year, reported that three children with regressive autism had undergone cerebrospinal fluid assessment, including for measles virus. All three had had concomitant onset of gastrointestinal symptoms and had already had measles virus genomic RNA detected in biopsies of ileal-lymphoid nodular hyperplasia. None of the cases nor non-autistic controls had any history of measles exposure other than possibly via MMR. Serum and cerebrospinal fluid samples were also evaluated for antibodies to measles virus and myelin basic protein. The result was that measles virus f-gene was present in the cerebrospinal fluid of all three autistic cases but not in non-autistic controls. Further, serum anti-myelin basic protein autoantibodies were detected in all children with autistic encephalopathy. Anti-MBP and measles virus antibodies were detected in the CSF of two cases, but the third had neither. The study concluded that the findings were consistent with a measles-virus etiology for autistic encephalopathy, indicating the possibility of a virally-driven cerebral immunopathology in some cases of regressive autism. The virus genome found in the autistic children was "exclusively consistent with vaccine strain".

- A May 2006 study [26] by Wakefield, Stott, and Limb investigated the hypothesis of whether or not a dose-response effect of measles-containing vaccine on intestinal pathology existed. If such an effect existed, this would constitute evidence of a causal association. In the study, children with normal early development and autistic-like developmental regression were divided into two groups: some 23 re-exposed children, i.e., those who had received more than one dose of a measles-containing vaccine (MCV), and 23 children who had received only one dose of MCV. The groups were matched for sex, age and time that had elapsed from first exposure to time of endoscopy. Comparisons made included secondary gastrointestinal (GI) and related physical symptoms,, and "observer-blinded" scores of endoscopic and histological disease. The results were that re-exposed children scored significantly higher than only-once-exposed for secondary physical symptoms, including incontinence, presence of severe ileal-lymphoid nodular hyperplasia, the number of bi-

doi: 10.1588/medver.2007.04.00156

opsies with epithelial damage, and number of children with acute inflammation. Markers of acute inflammation include number of children affected, and proportion of biopsies affect. The conclusion of the study was that the data confirmed a re-challenge effect (i.e. a double-hit effect) of measles-containing vaccines on symptoms, and also confirmed a biological gradient effect upon intestinal pathology. These findings thus link exposure to measles-containing vaccines to autistic-like regression and enterocolitis. (Note: it was stated in April 2001 by the Vaccine Safety Committee of the US Institute of Medicine that in the context of MMR and autism "challenge re-challenge would constitute strong evidence of an association.")

Taken together, with the Walker, Hepner *et al.* study, the above points to MMR as the means by which measles virus enters and persists in the gut, leading to ileal-lymphoid nodular hyperplasia, and in turn leading to regressive autism. The evidence to fully explain the complete causational mechanism by which this occurs is still emerging, and clearly requires further urgent research.

The intestinal disease has the features of a viral disease. Measles virus is known to infect the intestine, and produces the features described originally by Wakefield and colleagues in 1998

All the findings described in the 1998 Lancet report by the Wakefield team—including the discovery of a possible new type of inflammatory bowel disease—have therefore been subsequently independently confirmed by other researchers in the US, in Italy and in Venezuela.

The studies suggest that in some children, brain damage leading to autism may be secondary to, or occur in parallel with, a disease in the intestine, and that vaccine strain measles virus has become the prime suspect in this complex investigation.

The findings to date have important implications for our understanding and treatment of the complex disorder of regressive autism.

4. Wider safety concerns over MMR

It is also instructive to examine the original, and any subsequent, safety studies of MMR.

- An authoritative independent review by the Cochrane Collaboration [27] of the safety studies of MMR vaccine concluded that "the design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate". It further confirmed that neither before nor after the introduction of the MMR vaccine were proper safety trials carried out.

- A more recent review [28] from the same organization identified that safety studies for the single measles vaccine were better than those conducted for MMR: "We found only limited evidence of safety of MMR compared to the single component vaccines, that had a low risk of bias". The authors of the Cochrane reviews were highly critical of the safety studies of MMR, which they stated "need to be improved." Cochrane mentioned a specific concern that safety studies followed up the children involved for no more than three weeks, except for one study that lasted just six weeks.

- Concern over MMR's safety has been expressed [29] by a key former scientific adviser to the U.K. licensing authorities. Dr Peter Fletcher, former Principal Medical Officer in the (then) U.K. Medicines Division, who was medical assessor to the Committee on Safety of Medicines, commented: "Evidence on safety was very thin," and "Too few children were followed for a sufficient time… Big numbers were necessary, and computerised databases were already in place to permit this, but it was not done… Caution should have ruled the day… There should have been strong encouragement to conduct a 12-month observational study on 10,000 to 15,000 children (this was not done)… The granting of a product licence was premature."

- A year-2000 review [30] by Wakefield & Montgomery examined early safety studies of MMR, by Buynak et al 1969, Stokes et al 1971, Minekawa et al 1974, Schwartz et al 1975, Crawford and Gremillion 1981, and Miller et al 1987. The Buynak study identified viral "interference", but the follow-up period was only 12 days. The Stokes study revealed persistent gastrointestinal problems in the US trial children, but the follow-up was only 28 days. Stokes compared 228 MMR children with 106 unvaccinated controls. Data, from Philadelphia and Costa Rica and San Salvador, was merged - a major methodological error. Gastroenteritis was found to be significantly more common in the Philadelphia vaccinees (24%) compared with the unvaccinated Philadelphia controls (5.6%). No significant difference was found between the vaccinated and the unvaccinated in Costa Rica and San Salvador because of high ambient levels of gastroenteritis anyway (50% in vaccinees, 44% in controls). Combining all the data masked these instructive differences. There was also significant "unrelated" illness in 39% of Philadelphia vaccinees (otitis, allergy, viral infection, abdominal pain), compared with 12.2% in controls. The potential relevance of this was not seen at time. The Minekawa study confirmed viral interference. The follow-up period was only 15 days. The Schwartz study also merged its data, so provided insufficient insight, and again follow-up was only 21 days. The study looked at two different populations: 282 children in Ohio and 926 children in Santo Domingo, Dominican Republic. Again, the merging of data from different countries was a serious error. No data was provided to permit analysis of adverse events. Crawford and Gremillion's study of USAF recruits confirmed viral interference, but the follow-up period was only 19 days. Some 512 vaccinees were compared with 835 unvaccinated controls. The study noted increased fever and diarrhoea in those that received measles and rubella vaccines simultaneously. But the potential effect of trivalent vaccine was only seen as additive instead of potentially synergistic—a key point. The Eddes study (a small U.K. study) in 1991 compared reactions to MMR

doi: 10.1588/medver.2007.04.00156

with monovalent measles vaccine. High rates of gastrointestinal disorders (41.9% and 37.8%) were found, but the authors dismissed these as normal background illness. The Dr. Elizabeth Miller study noted that diarrhoea was common (26% of vaccinees), but the follow-up again was only 21 days. This was a major missed opportunity to follow up a large cohort. The Stokes, Schwartz, Miller and Eddes studies were therefore all too small or too superficial to pick up uncommon adverse events. The Plesner *et al.* study of gait disturbance following MMR (Acta Paediatrica, 2000;89:58–63) confirmed an association, and indicated that more severe cerebellar ataxias following MMR may be associated with residual cognitive deficits.

Cochrane was forced to conclude that "the safety record of MMR is probably best attested by its almost universal use." Or to put it another way, "the best evidence of MMR's safety we can find is the fact that it is being widely used"—hardly a scientific test of a product's actual safety, particularly when the evidence of problems is through a hitherto-unsuspected link between MMR and autism, that would not have been monitored prior to 1998.

References

[1] Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M *et al.* Inflammatory Bowel Disease Study Group. Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive development disorder in children. Lancet 1998 Feb. 28;351(9103):637–41.

[2] Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. J Pediatr 1999 Nov.;135(5):559–63.

[3] Wakefield AJ, Anthony A, Murch SH, Thomson M, Montgomery SM, Davies S *et al.* Enterocolitis in children with developmental disorders. Am J Gastroenterol 2000 Sep.;95(9):2285–95.

[4] Furlano RI, Anthony A, Day R, Brown A, McGarvey L, Thomson MA *et al.* Colonic CD8 and T-cell infiltration with epithelial damage in children with autism, Journal of Pediatrics 2001;138(3):366–72

[5] Buie T. Paper presented to the Oasis 2001 Conference for Autism, Portland, Oregon, November 2001.

[6] Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH. Inflammatory bowel disease Study Group. Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. Aliment Pharmacol Ther, 2002 Apr.; 16(4):663–74.

[7] Presentation by Krigsman to the U.S. Congressional Committee on Government Reform's June 2002 hearing, The Status of Research into Vaccine Safety and Autism, held in Washington DC.

[8] Ashwood P, Anthony A, Pellicer AA, Torrente F, Walker-Smith JA, Wakefield AJ. Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. J Clin Immunol 2003 Nov. 6;23(6):504–17.

[9] Torrente F, Anthony A, Heuschkel RB, Thomson MA, Ashwood P, Murch SH. Focal-enhanced gastritis in regressive autism, with features distinct from Crohn's and Helicobacter Pylori gastritis. Am J Gastroenterol 2004 Apr.;99(4):598–605.

[10] Ashwood P, Anthony A, Torrente F, Wakefield AJ. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter-regulatory interleukin-10. J Clin Immunol 2004 Nov.;24(6):664–73.

[11] Jyonouchi H, Geng L, Ruby A, Zimmerman-Bier B. Dysregulated innate immune responses in young children with autistic spectrum disorders: their relationship in gastrointestinal symptoms and dietary intervention., Neuropsychobiology 2005 Mar.;51(2):77–85.

[12] Balzola F, Barbon V, Repici A, Rizzetto M, Clauser D, Gandione M, Sapino A. Panenteric IBD-like disease in a patient with regressive autism shown for the first time by the wireless capsule enteroscopy: another piece in the jigsaw of this gut-brain syndrome? Am J Gastroenterol 2005; 100(4):979–81.

[13] Balzola F, Daniela C, Repici A, Barbon V, Sapino A, Barbera C, Calvo PL, Gandione M, Rigardetto R, Rizzetto M. Autistic enterocolitis: confirmation of a new inflammatory bowel disease in an Italian cohort of patients. Gastroenterology 2005:128(Suppl. 2):A-303.

[14] Wakefield AJ, Ashwood P, Limb K, Anthony A. The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. Eur J Gastroenterol Hepatol 2005 Aug.;17(8):827–36.

[15] González L, López K, Martinez M, Navarro D, Negrón L, Rodriguez R *et al.* Endoscopic and histological characteristics of the digestive mucosa in autistic children with gastrointestinal symptoms. Preliminary report. G.E.N. Suplemento Especial de Pediatria, 2005;1:41–7.

[16] Uhlmann V, Martin C., Sheils O, O'Leary J. Measles virus in reactive lympho-nodular hyperplasia and ileo-colitis of children. J Pathol 2000; 190(suppl):33A.

[17] Singh VK. University of Michigan College of Pharmacy, to the U.S. House of Representatives Committee on Government Reform, Washington DC, 2000.

[18] Paper presented by Professor John O'Leary, Dublin Women's Hospital, to the U.S. House of Representatives Committee on Government Reform, Washington DC, April 2000.

[19] Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. Mol Path 2002 Apr.;55(2):84–90.

[20] Singh VK. Department of Biology Center for Integrated Biosystems, Utah State University, Logan, Autism, Vaccines and Immune Reactions, presented to the Institute of Medicine, Washington DC, February 2004

[21] Paper presented by O'Leary, Coombe Women's Hospital and Trinity College Dublin to the Pathological Society of Great Britain and Ireland, July 2002.

[22] Kawashima H, Takayuki M, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A. Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. Digestive Diseases & Science, 2000 Apr.;45(4):723–9.

[23] Singh VK, Nelson C. Abnormal measles serology and autoimmunity in autistic children. Journal of Allergy and Clinical Immunology 2002 Jan.;109(1):S232.

[24] Bitnun A, Shannon P, Durward A, Rota PA, Bellini WJ, Graham C *et al.* Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. Clin Infect Dis 1999 Oct.;29(4): 855–61.

[25] Bradstreet JJ, El Dahr J, Anthony A, Kartzinel JJ, Wakefield AJ. Detection of measles virus genomic RNA in cerebrospinal fluid in children with regressive autism: a report of three cases. Journal of American Physicians and Surgeons 2004 Summer;9(2):38–45.

[26] Wakefield AJ, Stott C, Limb K. Gastrointestinal comorbidity, autistic regression and measles-containing vaccines: positive re-challenge and biological gradient. Medical Veritas 2006 Apr.;3(1):796–802.

[27] Jefferson T, Price D, Demicheli V, Bianco E, European Research Program for Improved Vaccine Safety Surveillance (EUSAFEVAC) Project. Unintended events following immunisation with MMR: a systematic review. Vaccine 2003 Sep. 8;21(25-26):3954–60.

[28] Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children Cochrane Database Syst Rev. 2005 Oct. 19;(4):CD004407 (Review).

[29] Commentary by Dr. Peter Fletcher, Journal of Adverse Drug Reactions & Toxicology 2001;20(1):47– 63.

[30] Wakefield AJ, Montgomery SM. Through a glass darkly (A look back at MMR's safety trials). Journal of Adverse Drug Reactions 2000; 19(4):265–83.

doi: 10.1588/medver.2007.04.00156