

COURTESY OF THE ALTERNATIVE-DOCTOR

MMR and Acquired Autism (Autistic Enterocolitis)

- A Briefing Note
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Contents

[Executive Summary](#)

[Part A: A Novel Syndrome](#)

- [1. What Is Acquired Autism/Autistic Enterocolitis](#)
- [2. The New Syndrome](#)
- [3. Recognised Adverse Reactions to MMR](#)
- [4. Contraindications To Receiving MMR](#)
- [5. UK Families Taking Legal Action](#)
- [6. UK Vaccine Damage Payment Scheme](#)
- [7. Families Taking Legal Action in the US over Thiomersal and Autism](#)
- [8. MMR Litigation in Japan](#)
- [9. The UK Department of Health's Position over MMR](#)
- [10. Position of the US Center For Disease Control on MMR/Autism](#)
- [11. The Parents Have Seen What They've Seen.....](#)

[Part B: The Costs of Autism](#)

- [12. The Financial Costs - Autism Is Costing Billions](#)
- [13. Estimates](#)
- [14. Failure to Monitor Increases In UK Autism Numbers](#)
- [15. "Now Almost Everyone Knows Someone Who's Autistic"](#)
- [16. University of Cambridge Research](#)
- [17. University of Sunderland Research](#)
- [18. UK National Autistic Society Estimates](#)
- [19. Report by Fiona Loynes for UK All Party Parliamentary Group, Dec. 2001](#)
- [20. Report for the National Autistic Society, Autism In Schools, May 2002](#)
- [21. Is Autism Increasing? - Some Recent Official UK Pronouncements](#)
- [22. Autism In The USA](#)
- [23. Autism Elsewhere](#)

[Part C: Evidence That Increases Are Real](#)

- [24. California](#)
- [25. The MIND Study, California](#)
- [26. New Jersey](#)
- [27. Atlanta Study](#)

[Part D: Reviews Questioning the Autism Epidemic](#)

- [28. Paper by Fombonne, UK Medical Research Council, Pediatrics, January 2001](#)
- [29. Paper by Wing, Centre for Social & Communication Disorders, London 2002](#)
- [30. Position of Dr. B. S. Siegal, University of California, 2002](#)
- [31. Study by Croen et al, July 2002](#)
- [32. Editorial by Fombonne, Journal of the American Medical Asscn., January 2003](#)

Part E. Studies That Have Been Used To Disprove An MMR/Autism Link

33. Stokes et al paper, Journal of American Medical Association (JAMA), Oct. 1971
34. Study by Peltola and Heinonen, Lancet, April 1986
35. Paper by Miller, Miller et al, The Practitioner, January 1989
36. Gillberg Study, Sweden, British Journal of Psychiatry, 1991
37. Commentary by Gillberg and Heijbel, Autism, 1998
38. Letter by Fombonne, Pediatrics, March 1998
39. UK Committee on Safety of Medicines Study, June 1999
40. Paper By Taylor, Miller and Farrington, Lancet, June 1999
41. Paper by Miller & Farrington to US Government Reform Committee, April 2000
42. Patja, Peltola et al Study, Finland, Pediatric Infectious Disease Journal Dec. 2000
43. Kaye, Melero-Montez and Jick Study, British Medical Journal, 2000
44. Dales, Hammer and Smith Study, JAMA, March 2001
45. De Wilde, Carey & Richards Study, Br. Journal of General Practice, March 2001
46. Davis et al study, Archive Pediatrics Adolescent Medicine, 2001
47. Further Paper by Farrington, Miller and Taylor, Vaccine Journal, 2001
48. Fombonne & Chakrabarti Study, Pediatrics, October 2001
49. Further Paper by Taylor, Miller et al, BMJ.com, February 2002
50. Review by Donald and Muthu, Bazian Limited, pub British Medical Jnl June 2002
51. Study into Childhood Gastrointestinal Disorders and Autism, August 2002
52. Study, Madsen et al, Population-Based study, MMR/Autism, Denmark, Nov 2002
53. Paper, Neurologic Disorders after MMR Vaccination, Makela et al, Dec 2002

Part F: Reviews Concluding There Is No Evidence Of A Link

54. Medical Research Council Ad-Hoc Review, March 1998
55. Presentation by Miller to UK All Party Parl. Group on Primary Health Care, 2000
56. Medical Research Council Sub-Committee Report, March 2000
57. Review by US Institute of Medicine, 2001
58. Review by Strauss and Bigham, Health Canada/Un. Of British Columbia, 2001
59. Elliman, Bedford and Miller Review, Arch. of Diseases in Childhood, Oct. 2001
60. Medical Research Council Review, July-December 2001
61. Further Review by US Institute of Medicine, February 2002
62. Review of the Scottish Executive MMR Expert Group, April 2002

Part G: The MMR Original Safety Trials Debate

63. Wakefield & Montgomery "Through A Glass Darkly" MMR safety-studies paper
64. Dr. Peter Fletcher Commentary, Journal of Adverse Drug Reactions, 2001
65. Dr. Stephen Dealler Commentary, Journal of Adverse Drug Reactions, 2001
66. Dr. F. Edward Yazbak Commentary, Journal of Adverse Drug Reaction, 2001
67. The Wakefield/Watson/Shattock Rebuttals
68. The UK Department of Health's Repudiation of "Through A Glass Darkly".

Part H: Studies That Point Towards The Plausibility Of An MMR/Gut/Autism Link

69. Paper by Eggers, Klinical Paediatrics, March 1976

- [70. Weizman, Weizmann, Szekely et al Study, Am. Journal of Psychiatry, Nov. 1982](#)
- [71. Delgiudice-Asch and Hollander Study](#)
- [72. Paper by Dr. H. Fudenberg](#)
- [73. Paper by Dr. Reed Warren](#)
- [74. Warren and Singh Study, Immunogenetics, 1992](#)
- [75. Singh, Warren, Odell, Warren and Cole Paper, March 1993](#)
- [76. Singh, Warren, Odell et al Study, Brain Behaviour, March 1993](#)
- [77. Oleske and Zecca paper](#)
- [78. Binstock paper](#)
- [79. Anne-Marie Plesner Letter, Lancet, February 1995](#)
- [80. Paper by Thompson, Montgomery, Pounder & Wakefield, Lancet, April 1995](#)
- [81. Gupta, Aggarwal and Heads Study, Journal of Autism and Dev. Disorders, 1996](#)
- [82. Montinari, Favoino and Roberto paper, Naples conference May 1996](#)
- [83. Auwaerter and Griffin paper, Clinical Immunology and Immunopath., May 1996](#)
- [84. Cook, Courchesne et al Paper, Molecular Psychiatry, May 1996](#)
- [85. Griffin and Hussy Study, Journal of Infectious Diseases, June 1996](#)
- [86. Martinez et al Study, Proceedings of National Academy of Sciences, 1997](#)
- [87. Paper by Zecca, Graffino et al, Meeting of National Inst. of Health, Sept. 1997](#)
- [88. Weibel, Caserta and Evans Study, March 1998](#)
- [89. Wakefield et al "Early Report", Lancet, February 1998](#)
- [90. Paper by Montgomery, Morris et al \(publication date/details not yet known\)](#)
- [91. Sabra, Bellanti and Colon letter, Lancet, July 1998](#)
- [92. Further Paper by Singh and Yang, Pharmaceutical Journal, October 1998](#)
- [93. Uhlmann, Sheils et al Paper](#)
- [94. Bitnun et al Study, Clinical Infectious Diseases Journal, October 1999](#)
- [95. Paper by Dr. Singh to the US Committee on Government Reform, April 2000](#)
- [96. O'Leary Paper Presented to US Congressional Oversight Committee, April 2000](#)
- [97. Kawashima, Takayuki et al Study, Digestive Diseases and Sciences, April 2000](#)
- [98. Hagenbuch, Kullak-Ublick et al Study, Journal of Pharm. Exp. Ther., July 2000](#)
- [99. Wakefield et al Paper, American Journal of Gastroenterology, September 2000](#)
- [100. Statement by Professor Walter O. Spitzer, December 2000](#)
- [101. Furlano, Anthony et al Study, Journal of Pediatrics, 2001](#)
- [102. Study by Jyonouchi, Sun and Le, J. Allergy & Clinical Immunology, Feb. 2001](#)
- [103. Study by Jyonouchi, Sun and Le, J of Neuroimmunology, 2001](#)
- [104. Paper by Spitzer, Aitken et al, Journal of Adverse Drug Reactions & Tox., 2001](#)
- [105. Paper by Dr. Ken Aitken to the Scottish Society for Autism, 2001](#)
- [106. Paper by Imani and Kehoe, Clinical Immunology, September 2001](#)
- [107. Paper by Dr. Timothy Buie, Oasis 2001 Conference for Autism, Portland, US](#)
- [108. Paper by Uhlmann, Wakefield, O'Leary et al, J. of Clinical Pathology, Feb. 2002](#)
- [109. Paper by Singh and Nelson, February 2002](#)
- [110. Review by Wakefield, Puleston, Montgomery et al, Aliment Pharm. Ther. 2002](#)
- [111. Report of Study by Comi et al, Johns Hopkins Hospital, Baltimore, April 2002](#)
- [112. Paper by Torrente, Ashwood, Day et al, Lancet, May 2002.](#)
- [113. Paper to 102nd GM of American Soc for Microbiology by Singh et al, May 2002](#)

- [114. Study by O'Leary et al, to be presented to Path Soc of GB and Ireland July 2002](#)
- [115. Wakefield Paper Presented to US Government Reform Committee, June 2002](#)
- [116. Paper to US Government Reform Committee by Dr Kringsman, June 2002](#)
- [117. Unpublished Research by Dr Paul Shattock, University of Sunderland, June 2002](#)
- [118. Paper by Sheils, Smyth, Martin & O'Leary, Trinity College Dublin, 2002](#)
- [119. Paper by Dr. Vijendra Singh, Utah State University, August 2002](#)
- [120. Paper by Finegold, Molitoris, Song, J. Of Clinical Infectious Diseases, Sept 2002](#)
- [121. Further paper by Jyonouchi, Sun & Itokazu, University of Minnesota, Oct 2002](#)
- [122. Paper, Treatment of Late Onset Autism, Matarazzo, Univ. of Sao Paulo, Nov 2002](#)
- [123. Unpublished letter by Dr. Wakefield to the New Eng. J. of Medicine, Nov 2002](#)
- [124. Study by Croonenberghs et al, University of Antwerp, December 2002](#)

Part J: Other Relevant Papers

- [125 US Developmental Delay Registry Report, 1994](#)
- [126 Stratton et al Study, National Academy Press, 1994](#)
- [127. Paper by Carbone.](#)
- [128. Iizuka, Saito et al Study, Gut, May 2001 \(Mumps Study\)](#)
- [129. Statement by Spitzer, US House of Repres. Govt Reform Committee, April 2001](#)
- [130. Statement by Dr. Jefferson, Cochrane Collaboration, Oxford, October 2002](#)

Part K: Future Papers Investigating A Link/Prevalence

- [131. Fombonne et al Study, London](#)
- [132. Charman et al Study, London](#)
- [133. Study by Professor Andrew Hall, London](#)
- [134. Study by Takahashi et al, Tokyo](#)
- [135. Study by Rall, Fox Chase Cancer Center, US](#)
- [136. Studies Commissioned by the US Center for Disease Control](#)
- [137 UK National Institute for Biological Standards and Control Study](#)
- [138. Study by University of California at Davis into Environmental Factors](#)
- [139 Other UK Studies funded by the Medical Research Council](#)
- [140 Study by Autism Center, University of Medicine & Dentistry, New Jersey, US](#)
- [141. Study by Center for Disease Control, New Jersey, US](#)
- [142. Study by Robert Wood Johnson Medical School, New Brunswick, US](#)
- [143. Survey by New Jersey Answers for Autism](#)

Part L: The Thiomersal Issue

- [144. Thiomersal's Possible Role](#)
- [145. Thiomersal In Vaccines: Statement of US AAP/Public Health Service, July 1999](#)
- [146. UK Vaccines With Thiomersal](#)
- [147. Scientific Review by US Center for Disease Control, Simpsonwood, June 2000](#)
- [148. Press Release by Waters and Kraus, March 2002](#)
- [149. UK Medicines Control Agency Position](#)
- [150. US CDC Thiomersal Studies](#)
- [151. Pichichero et al Study into Mercury Concentrations, Lancet, November 2002.](#)

[Part M: Flawed UK Regulatory and Monitoring Systems](#)

- [152. Fighting Measles, Missing Autism, Overlooking Damage?](#)
- [153. Has the Medicines Control Agency Missed the Syndrome?](#)
- [154. UK Department of Health Re-Launch of MMR, January 2001](#)

[Part N: UK and US Political Initiatives](#)

- [155. UK House of Commons Health Committee, Westminster](#)
- [156 UK All Party Parliamentary Group on Autism, Westminster](#)
- [157. Scottish Parliament, Edinburgh](#)
- [158. UK Liberal Democrats](#)
- [159. UK Conservatives](#)
- [160. US House of Representatives Government Reform Committee](#)

[Part P: Some Conclusions and Some Unanswered Questions](#)

- [161. Some Broad Conclusions](#)
- [162. Some Unanswered Questions](#)

EXECUTIVE SUMMARY

- This note - which has been put together by the parent of a child who became autistic after immunisation - sets out the concerns of parents whose children have degenerated into an acquired-autistic state after MMR or measles vaccines.
- It does not attempt to cover every single piece of the available scientific literature for or against an MMR/autism link, but it reviews about 70 of the most recent, most pivotal, or most frequently-quoted studies and papers.
- Its key finding is that there has not been a single credible study that can robustly refute the claims of the parents that their children's acquired autism has been caused by MMR or related vaccines. Each of the studies that seeks to "disprove" an MMR/autism link can be argued to be flawed in design or ambiguous in results. These flaws are discussed in detail in the text.
- It also notes that all but one of the studies that seek to disprove an MMR/autism link did not look at the actual children themselves, but rather were based upon statistical analyses of the medical records of the wider population. Such epidemiological studies are not appropriate to the identification of relatively-rare adverse outcomes.
- Such studies also fail to address the problem - what was it that damaged the specific children whose parents are now taking action through the UK High Court?
- The one study that has both claimed there is no MMR/autism link and also actually looked at a sub-set of the damaged children was unable to prove or refute the suggested association with MMR on the basis of the information available - although it went on, despite this, to insist that MMR was safe. And - note - this was not a clinical study. No children were actually examined.
- Parents who have scrutinised the studies quoted by the Department of Health as "proof" of there being no link have found that such studies crumble easily when pressed. To give just one example, the Finnish study by Patja, Peltola et al was very loudly heralded at the start of 2001 by the Department of Health as convincing and conclusive proof that MMR was safe. After intense critical scrutiny by parents and media, by the end of 2001 the Medical Research Council was forced to admit that Patja, Peltola et al's original 1998 paper "*did not examine the relationship of MMR and autistic spectrum disorders.....and does not therefore provide useful evidence on this point.*" Of the later 2000 paper by Patja, Peltola et al, the MRC admitted: "*The findings need to be interpreted with some caution, as cases of autistic spectrum disorder or bowel disorders not considered at the time attributable to MMR would not necessarily have been reported*". Quite a retreat.

- In contrast, the parents find that there are a number of studies that suggest that MMR could be causing acquired autism (or "autistic enterocolitis") in significant numbers of children.
- Not all of these studies originate from only one group of researchers, as has sometimes been asserted by those who defend MMR. The studies that point to a link have involved a growing number of research teams, in several countries. Other studies, whilst not specifically targeting MMR, offer further clues as to what may be happening, and are consistent with an MMR involvement.
- Furthermore, many of the studies that suggest that there is an MMR/autism link are based upon the scientific analysis of data gathered from detailed individual medical examination, and upon medical samples taken from the children concerned. These are the studies that actually seek to address the two key questions, "what is the damage sustained by this specific child, and what exactly precipitated the damage to this specific child?".
- A "house of cards" has thus been constructed by the UK Department of Health over the past five years, with repeated assurances being given to the public, but with these being based upon a lop-sided, partisan and selective gathering and interpretation of the available evidence.
- This briefing note also finds that there are other related concerns - from the regulatory bodies themselves - about the risk of permanent developmental damage from thiomersal-containing vaccines, though it is not yet clear whether these problems are directly interlinked biologically to the MMR/autism problems (we are told that MMR in itself does not contain thiomersal). Class-action lawsuits are now under way in the US (see later sections) over thiomersal and autism, just as they are in the UK over MMR and autism.
- Although complete and precise scientific proof of how the children have been damaged by vaccines and become autistic is still emerging, there have been numerous vital clues over the past five years or more - clues that all too often have been ignored, or, worse still, rejected out of hand, by the authorities.
- The medical establishment has repeatedly asked itself the wrong question. It has asked itself "Is MMR safe?", hoping for an affirmative answer. In contrast, researchers and parents have asked two very different questions: "What is wrong with this child?", and "Why did this child change from being healthy to being autistic?". It is answering these latter two questions that should be the key issue.
- The children that have been damaged have had their lives ruined. They were previously healthy. They now have seventy or eighty years of mental handicap ahead. Whether their sacrifice is justified in the interests of wider public health is not the point at issue.

- Finally, this briefing note poses a number of unanswered questions about MMR, and about the UK children that are believed to have been severely damaged by its administration

PART A - A NOVEL SYNDROME

1: What Is Acquired Autism/Autistic Enterocolitis?

- Autism is not an illness in itself, so much as a manifestation of a dysfunction in certain parts of the central nervous system, particularly affecting language, cognitive and intellectual development and the ability to relate to others.
- The "classic" form of autism was first described by Dr. Leo Kanner. These children were different from normally-developing children from birth.
- However, a very different form of autism has now begun to predominate. In this, children develop normally, passing all their developmental milestones, and then later acquire an autistic-like condition. They lose their previously-demonstrated speech, learned behaviour and social skills. In effect, they dissolve into a state of mental impairment, of varying severity. Often the damage is severe or very severe, and usually the damage is permanent.
- This late onset of autism typically follows the receipt of MMR vaccination. It does not necessarily occur immediately afterwards - onset of autism is not in any case an "acute" reaction - and there are now grounds for believing that onset following vaccination may be very gradual indeed, spread over at least many weeks, more probably several or many months, or even in some cases several years.
- Crucially, the onset of this acquired form of autism is accompanied by other visible manifestations of problems. These include bright red ears and dark rings under the eyes after certain foods, gluten and casein intolerances, hyperactivity, night sweating and loss of temperature control, and chronically poor sleep patterns.
- The arrival of these problems and the degeneration of the child into autism as a "package" strongly suggests that they are interconnected
- The timing of onset following vaccination is described by the UK Department of Health as a coincidence. Their argument is that it is "noticed" around this time, because this is a time when child development is most rapid, and any failure most noticeable.
- However, very significantly, much older children have also degenerated into autism after MMR. If degeneration in affected children always follows immunisation with MMR or measles-containing vaccine, regardless of the age of the child, then it implies that the link is not coincidental.
- Also, no cases are known, at least to campaigning parents, of any children who have become autistic just before MMR.

- Also, it is not simply a failure to develop. The children have developed normally, then inexplicably acquired their autistic state. This protracted event has been directly observed by parents and relatives, and in many cases recorded on photographs and video footage.
- No credible alternative explanation for why a previously-healthy child should become severely autistic has been put forward. The unheralded acquisition of a state of severe disability, in a substantial number of hitherto-healthy children, has to have a significant causal trigger.
- Undoubtedly there are other factors involved, pointing to a predisposition of certain children to be vulnerable to damage, of varying severity. Research should be trying to pinpoint those factors, but is not. It is being held up by the refusal of the medical establishment in the UK to recognise the problem, or even to recognise the increase in autism.
- Also coinciding with the late onset of autism in many of the children (or other damage - autism is not the only manifestation of there being a problem), has come gastrointestinal problems such as alternating bouts of diarrhoea and constipation, chronic abdominal pains and bloating.
- Examination of children has identified a novel form of inflammatory bowel disease, ileal-lymphoid nodular hyperplasia. This has emerged after ileocolonoscopy of affected children and analysis of samples. This research has not only come from the Royal Free Hospital, London, but also from other centres in the US.
- The simultaneous onset of these problems after a normal early development suggests that it is highly likely that these other elements are linked into the biological explanatory sequence of autism, notably through the pathway of gut damage and either the penetration of the blood-brain barrier or the triggering of some other process, such as serious myelin damage (in basic terms, the myelin sheath is the "insulation" around the neurons or "wires" of the brain).

2: The New Syndrome

This is a very brief summary of the new syndrome of autistic enterocolitis:

- In a 200-strong cohort of children examined through ileocolonoscopy at the Royal Free Hospital, London, an almost 100% incidence of ileal-lymphoid nodular hyperplasia has been found. This condition manifests itself as swollen lumps throughout the intestinal tissue of autistic children. The condition is very rare in non-autistic children.
- The condition is believed to have developed in each case in the period following MMR immunisation

- Because of its swollen and hyperplastic condition, undigested toxins, having not been stopped by either the intestine or the liver (which can also be damaged) may then be able to attack the central nervous system. The evidence for the complete pathway of damage is uncertain at present, due to lack of research.
- An alternative pathway of damage may be that the virus(es) in the vaccine, or other constituents of the vaccine, may be inflicting the actual damage, or interfering with the brain's further development by damaging myelination. Comprehensive studies to determine this have also yet to be undertaken.
- It is also possible that thiomersal, a mercury-based preservative that has been routinely used in a number of vaccines, may have played a role. Again, adequate research has not yet been done.
- Damage may in the event be via a combination of these pathways.

3. Recognised Adverse Reactions to MMR

As a background to the controversy about MMR's safety, it is important to make clear that there is already a range of adverse reactions to the vaccine that are recognised by the manufacturers themselves, if not by the UK Department of Health. The latter insists that the vaccine is safe and has a good safety record worldwide. However, the February 2000 edition of the manufacturer's notes, issued by Merck & Co., lists the following possible adverse reactions reported during clinical trials:

- (body as a whole) panniculitis, atypical measles, fever, syncope, headache, dizziness, malaise, irritability
- (cardiovascular system) vasculitis
- (digestive system) pancreatitis, diarrhoea, vomiting, parotitis, nausea
- (endocrine system) diabetes mellitus
- (hemic and lymphatic system) thrombocytopenia, purpura, regional lymphadenopathy, leukocytosis
- (immune system) anaphylaxis and anaphylactoid reactions, angioneurotic edema, bronchial spasm
- (musculoskeletal system) arthritis, arthralgia, myalgia
- (nervous system) encephalitis, encephalopathy, measles inclusion body encephalitis (MIBE), subacute sclerosing panencephalitis (SSPE), Guillain-Barre Syndrome, febrile

convulsions, afebrile convulsions or seizures, ataxia, polyneuritis, polyneuropathy, ocular palsies, paresthesia. On encephalitis, the Merck notes state that "*the data suggest the possibility that some of these (reported) cases may have been caused by measles vaccines.*"

- (respiratory system) pneumonitis, sore throat, cough, rhinitis
- (skin) Stevens-Johnson syndrome, erythema multiforme, urticaria, rash, burning/stinging at injection site, wheal and flare, redness, swelling, induration, tenderness, vesiculation at injection site
- (special senses - ear) nerve deafness, otitis media
- (special senses - eye) retinitis, optic neuritis, papillitis, retrobulbar neuritis, conjunctivitis
- (urogenital system) orchitis
- (other) "death from various and in some cases unknown causes has been reported rarely following vaccination with MMR; however, a causal relationship has not been established"

The above, although qualified in Merck's preamble as being "without regard to causality", does suggest that rare or relatively rare serious adverse events are not unknown and are already recognised by the manufacturers of MMR. In this context, the possibility of an unrecognised adverse event such as autism - particularly if its onset is insidious - becomes rather more credible.

It is also interesting to see that numerous adverse reactions to MMR have actually been reported in the past, as well as adverse reactions to single vaccines. Although links between adverse events and vaccines are invariably routinely denied by medical and health bodies, it is stretching credibility to suggest that all of these reported adverse events are unconnected with prior vaccination.

The following statistics are taken from the US VAERS (vaccine adverse events reporting system) database, covering the period from 1st January 1990 to 6th March 2001.

The table below also includes some other vaccines, for comparison. It should also be noted that a very small percentage indeed - perhaps as low as 1% - of adverse events are actually reported to VAERS in practice, and the real numbers will therefore be very much higher. Many of these reactions are extremely minor and transitory, but a considerable number are also very serious, and some reactions are fatalities.

(vaccine)	Reported adverse events	Reported serious adverse events	Reported deaths	% of total events reported as serious**	% of adverse events reported as deaths**
Dipther Tet	1,492	189	15		
DTAP	10,348	1,422	283		
DipTetPert	21,163	3,286	794		
DTPH	6,212	928	254		
Flu	15,351	2,082	324		
Hepatitis B	32,209	4,676	662		
HibV	21,726	3,905	932		
Measles	414	61	7	15%	2%
Measles M	34	25	2	74%	6%
MMR	20,974	2,586	132	12%	1%
Measles R	117	23	0	20%	0%
Mumps	54	19	3	35%	6%
Polio live or	24,702	3,541	970		
Pneumococ	5,841	712	95		
Rubella	685	100	1	15%	0%
Tetanus Dip	9,566	520	12		
Varicella	12,635	590	31		
TOTALS*	201,815	27,768	4,965	14%	2%

Notes: * totals include a number of other vaccines, not included in the table,

** percentages only calculated selectively for components of MMR. Full titles of those vaccines itemised in the table are (1) diptheria tetanus, (2) diptheria tetanus acellular pertussis, (3) diptheria pertussis tetanus, (4) diptheria pertussis tetanus haemophilus B, (5) influenza, (6) hepatitis B, (7) haemophilus B, (8) measles virus live, (9) measles mumps virus live, (10) measles

mumps rubella virus live, (11) measles rubella virus live, (12) mumps, (13) poliovirus live oral, (14) pneumococcal, (15) rubella virus live, (16) tetanus diphtheria adult, (17) varicella.

It is noteworthy that MMR and the various other components of vaccines for measles, mumps and rubella appear to account for 2,814 reported serious adverse events and 145 deaths. This has to be set against the many millions of doses administered, but also against the likely levels of under-reporting. For the autism issue, under-reporting is likely to be very high indeed, perhaps even almost total, due to lack of knowledge on the part of both parents and health professionals.

4. Contraindications to Receiving MMR

This list of potential contraindications to receiving MMR, contained in the Merck manufacturer's information sheets, is also lengthy. It is very questionable as to whether all parents of UK recipients of MMR during the late 1980s and the 1990s were questioned in detail on these aspects before their child received MMR: Contraindications include:

- Hypersensitivity to any component of MMR, including gelatine
- Anaphylactic or anaphylactoid reactions to neomycin
- Febrile respiratory illness or other active febrile infection
- Patients receiving immunosuppressive therapy
- Individuals with blood dyscrasias, leukemia, lymphomas of any type or other malignant neoplasms affecting the bone marrow or lymphatic system
- Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses
- Patients with cellular immune deficiencies or hypogammaglobulinemic and dysgammaglobulinemic states. The Merck information sheets note that "Measles inclusion body encephalitis (MIBE), pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection has been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine"
- Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated

Some of the above contraindications could be partly relevant to the MMR/autism issue. And clearly, if a hitherto-unrecognised syndrome such as the insidious onset of autism, should exist

but go unreported, then the list of contraindications would remain too narrowly defined until the syndrome became recognised. Much therefore depends on the effectiveness of reporting systems and length of follow-up. These issues will be covered later.

5. UK Families Taking Legal Action

- Between 2,000 and 3,000 families whose children became autistic or had other serious adverse events after MMR are believed to be now taking legal action, or actively seeking to take legal action, in the UK, against MMR manufacturers Aventis Pasteur MSD Ltd, Merck and Company Inc, SmithKline Beecham & French Laboratories Ltd and SmithKline Beecham Plc. The trial date is currently fixed for October 2003 in the High Court of Justice in London.
- Leading UK legal firms involved are Alexander Harris, Freeth Cartwright Hunt, and Hodge Jones & Allen. The action is being brought under the European Union's Product Liability Directive, the Consumer Protection Act.
- Cases include children who received Aventis Pasteur MSD's Immravax and Glaxo SmithKline's Pluserix brands of MMR vaccine. These brands were withdrawn by the UK Department of Health in 1992, two years after a similar vaccine containing the Urabe strain of mumps virus was withdrawn in Canada, following reports of meningitis.
- The UK lawyers Alexander Harris have stated that a clear pattern of events began to emerge when they were contacted by families, with children who had been developing well, both physically and intellectually, before the MMR vaccine, then acquired their autistic state after the vaccine. This condition was often accompanied by other symptoms, with sometimes only a gradual decline into autism. Many of these children are now chronically ill and mentally or physically disabled.
- By 2002, the number of UK cases of alleged damage by MMR was growing rapidly, with an increase of well over a hundred cases in the space of a few weeks.

6. UK Vaccine Damage Payment Scheme

It is sometimes alleged that parents are all too ready to turn to litigation to seek damages for autism, as part of the "compensation culture". However, caring for a child with autism is expensive over a lifetime. It destroys or very severely damages the child's quality of life, and their opportunities for earnings. It also severely damages family quality of life, and frequently reduces family income dramatically.

The only recourse other than to litigation has been the UK Vaccine Damage Payments Scheme (VDPS). However, no cases of autism have succeeded in the VDPS to date, and indeed, the scheme has a history of rebutting claims of all kinds.

The VDPS was introduced in 1979 by the Callaghan Government as a response to the 19878 Pearson Report. One of the latter's conclusions had been that "the Government.....should be liable in tort for severe damage suffered by anyone (adult or child) as a result of vaccination which has been recommended in the interests of the community".

The VDPS is administered by the Vaccine Damage Payments Unit, which gives effect to the decisions of the "SEMA Group", a medical agency sub-contracted to the Government's Department of Work and Pensions. Any subsequent appeals on both fact and law are made to Vaccine Damage Appeal Tribunals, and there is no further appeal avenue, although the Secretary of State may reverse a Tribunal decision.

The VDPS does not provide compensation per se, but a "contribution" towards the expenses of bringing up a disabled child. VDPS payments are not admissions of negligence, nor are they the result of strict liability (I am grateful to researcher Dr. Stephanie Pywell, University of Hertford, UK, for this and subsequent information).

In June 2000, substantial changes to the VDPS were announced, in response to heavy public criticism and press campaigns. Three changes were proposed:

- Increasing the £40,000 (formerly £30,000) statutory payment to £100,000. This was effected from July 2000
- Increasing the absolute six-year time limit for claims to any time up until a claimant's 21st birthday
- Lowering the disability threshold (level of damage) from 80% to 60%

However, the scheme remains deeply adversarial, and very few payments are made, not surprisingly as the process involves ordinary members of the public taking on the medical establishment, without funding for studies or access to advocacy resources. The award rate data for the VDPS is as follows (1978-2000):

- Over the 21 years, 4,111 claims were submitted
- Of these, just 415 were given initial awards. Of these 415, almost all were in the first seven years of the scheme. In the first seven years, between 1978-79 and 1984-85, 3,085 claims were submitted and 390 awards were made, an initial-award rate of about 13%
- In the second seven years of the scheme, 1985-86 to 1991-92 inclusive, 370 claims were submitted but only 15 awards were made, an initial-award rate of just 4%
- In the most recent seven years for which data is to hand, 1992-93 to 1998-99 inclusive, 656 claims were submitted (note the increase) but only 10 awards were made, an initial-award rate of about one and a half per cent. This represents a quite extraordinary rate of rejection.
- Even with Section 4 awards (subsequent to a review of the medical reasons by an independent tribunal) and Section 5 awards (subsequent to an appeal to the Secretary

of State), the award rates remain very low. Although 479 Section 4 awards were made - a greater number than the 415 initial awards over the 21 years - after appeal, the number of awards in recent years remains very low, only a handful of Section 4 awards succeeding. Only one Section 5 award to the Secretary of State has succeeded in 21 years.

A survey of the scheme was undertaken by the UK parents' group JABS. It found that rejection rates were especially high in MMR cases. Just six out of 93 claims succeeded. Three of these related to the early Urabe strain of MMR vaccine, which was very hurriedly withdrawn by the UK Department of Health in 1992.

7. Families Taking Legal Action in the US over Thiomersal and Autism

- A class action over autism is now also under way in the US, led by a large consortium of specialist lawyers. This action is based upon autism and other damage being caused by thiomersal, a mercury-based preservative. This is used in some vaccines, but reportedly not MMR. However, as noted, it is possible that damage caused by MMR and damage caused by thiomersal may be interlinked biologically. (The thiomersal issue is considered in detail in a later section of this Briefing Note).
- The initial US lawsuit was filed by Walters & Kraus (Dallas, Texas, contact C. Andrew Waters). Other law firms taking action are Anderson & Krieger (Temecula, California), Dogan & Wilson ((Pascagoula, Mississippi), Doran & Murphy (Buffalo, New York), Evert & Weathersby (Atlanta, Georgia), Gallagher, Lewis, Downey & Kim (Houston, Texas, contact Michael Gallagher), Hendrickson & Long (Charleston, West Virginia), Jones, Martin, Parris & Tessener (Raleigh, North Carolina), Leach, Schwarz & Strassberg (Bala Cynwyd, Pennsylvania), Martzell & Bickford (New Orleans, Louisiana), Miller and Associates (Alexandria Virginia, lead partner Michael J. Miller), Williams Dailey (Portland Oregon, contact Michael Williams) and Wise & Julian (Alton, Illinois). The above list is not exhaustive, and more firms are also expected to become involved.
- A large number of parents have contacted US lawyers. Lewis, Downey & Kim reports that it has been contacted by several thousand families and (as at March 2002) was considering nearly one thousand cases, with about 50 filed at that time. The claims include product liability, conspiracy and fraud. Waters & Kraus have indicated that the potential scale of the claims is immense. An individual claim could run to \$10m-30m for a life-care plan alone, plus damages reflecting emotional distress and pain.
- The US defendants are Aventis Pasteur Inc., Pfizer Inc., Glaxo SmithKline, Merck and Co., Abbott Laboratories, American Home Products, Baxter International Inc., Eli Lilly & Co., Johnson & Johnson, Sigma Chemical Co., Lederle Inc., Wyeth Pharmaceuticals Inc., Parke-Davis & Company, American International & Chemical Spectrum and Aldrich Chemical Co. The lawyers employed by Eli Lilly are Shook, Hardy & Bacon (Kansas City).

- In June 2002, notice was given by the PR Newswire service that all defendants had now been served in a lawsuit filed on 3rd April 2002 in the United States District Court for the Eastern District of New York on behalf of three groups, against the manufacturers of thiomersal, and against the vaccine manufacturers that use or used thiomersal in manufacturing or distributing childhood vaccines
- Plaintiffs and the plaintiff class defined as Sub Class One have been diagnosed with autism or neurodevelopmental disorders, as well as other severe and permanent health consequences claimed to be the result of exposure to high levels of mercury contained in thiomersal.
- Plaintiffs and the plaintiff class defined as Sub Class Two claim an increased risk of developing autism, other serious neurological disorders, or other severe and permanent health consequences as a result of exposure to high levels of mercury contained in thiomersal
- Plaintiffs and the plaintiff class defined as Sub Class Three have claims based upon the injuries to their children as well as claims for medical monitoring of their children who have not yet manifested an injury, but who must be continuously monitored due to their exposure to the high levels of mercury contained in childhood vaccines.
- By July 2002 it was reported in the Indianapolis Star that Eli Lilly was facing at least 45 lawsuits over its role in developing and selling (for more than 40 years) the thiomersal vaccine preservative. By this time, nationally, the manufacturers in the US faced over 60 lawsuits.
- In May 2002 it was also reported that a class action had commenced in the Canadian courts. A lawsuit was filed on 8th May 2002 in Ontario Superior Court on behalf of children who became autistic after receiving vaccines containing thiomersal. The action is being brought by lawyers Klein Lyons against Aventis Pasteur.

It is also noteworthy that there is a legal precedent in the US courts for autism being triggered by multiple vaccination, even if not by measles-containing vaccine. In the United States Court of Federal Claims, in the case of Eric Lassiter v. Secretary of the Department of Health and Human Services, in a judgment filed on December 17th 1996, a case of autism was successfully brought by the parents of Eric Lassiter. The decision of entitlement was as follows:

"This case arises under the National Vaccine Injury Compensation Program. Petitioner's mother, Mrs. Mary Lassiter, filed this claim on behalf of her son on September 26th 1990, alleging that as a result of the administration of a diphtheria-pertussis-tetanus (DPT) shot on April 19th 1972, the petitioner sustained an injury set forth on the Vaccine Injury Table (s14 of the Act), namely an encephalopathy, with permanent neurological damage. Respondent defends by arguing that because no contemporaneous medical records exist that document conclusively that the onset of the injury occurred within the requisite time frame, petitioner has not established a Table injury. Respondent argues further that

petitioner's condition, more likely than not, is due to autism and is unrelated to the DPT vaccine. Following a careful review of the record in its entirety, the Court concludes that Eric Lassiter is entitled to compensation."

The judgment also included the following paragraph:

"A careful interpretation of the literature indicates that autism can be mirrored by a condition that includes "autistic-like" signs or symptoms. Eric's condition has never been diagnosed conclusively as autism according to the medical records. The predominating diagnosis refers instead to "static encephalopathy with autistic tendencies in addition to delayed development"".

The judgment concluded:

"In summary, respondent's (Department of Health & Human Services) evidence and proffered explanations are weak, unconvincing and insufficient to support a finding of an underlying metabolic or genetic disorder as the cause of Eric's affliction. Petitioner (Lassiter) has presented a better case in support of a Table injury. The Court concludes that a preponderance of the evidence requires a finding for the petitioner."

However, the progression of the US litigation over vaccines and autism has been made very much more uncertain by the insertion of four clauses in the US Homeland Security bill in December 2002, debarring families from filing lawsuits against Eli Lilly & company over thiomersal. The inclusion of these clauses has been strongly criticised by a range of US politicians, including Rep. Dan Burton (R-Indiana), Sen. Debbie Stabenow (D-Michigan), and Sen. Patrick Leahy (D-Vermont).

A move to seal all documents was also made, then withdrawn in December 2002, by the US Department of Justice.

In January 2003, a Bill was to be introduced in Congress which would focus solely upon the reversal of clauses 1714/15/16/17 of the December 2002 Homeland Security Bill, which were the clauses that protected Eli Lilly from lawsuits. This bill was introduced by Sen. Debbie Stabenow, and co-sponsored by Sen. Barbara Boxer (D-California), Sen. Tom Daschle (D-South Dakota), Sen. Mark Dayton (D-Minnesota), Sen. Christopher Dodd (D-Connecticut), Sen. Byron Dorgan (D-North Dakota), Sen. Richard Durbin (D-Illinois), Sen. Dianne Feinstein (D-California), Sen. Mary Landrieu (D-Los Angeles), Sen. Frank Lautenberg, Sen. Patrick Leahy (D-Vermont), Sen. Carl Levin (D-Michigan) and Sen. Paul Sarbanes (D-Maryland).

Documents relating to thiomersal's original testing by Eli Lilly have been subpoenaed by the House of Representatives Committee on Government Reform (see also later sections on thiomersal and on the US Congress and Government Reform Committee). Thiomersal is believed to have only ever been tested on 27 people (who were dying from meningitis) in 1929. Eli Lilly maintain that, although all 27 died, it was not due to the thiomersal. Further details are in the later sections.

8. MMR Litigation in Japan

Only limited information has been obtained on litigation under way in Japan. This information is based upon a press report in the Yomiuri Shimbun (Daily Yomiuri).

- The Japanese Government was forced in April 2002 to release documents on MMR after a group of plaintiffs invoked a new public information disclosure law.
- The group intends to use these documents as evidence in a lawsuit that claims that MMR caused the deaths of their children. It has been alleged that there has also been a cover-up over the earlier delay in banning the vaccine in Japan. MMR was introduced into Japan in 1989 (one year after the UK), but was discontinued in 1993 after it had caused numerous cases of aseptic meningitis, a side-effect of mumps
- The documents disclosed include records of Japanese Health Ministry research carried out on the frequency of side-effects, during the six months following MMR's introduction. According to the documents, the October 1989 interim report of the research includes data indicating that 1 in every 637 children in Gunma Prefecture and one in every 706 children in Miyazaki Prefecture suffered side-effects. The vaccination committee, however, did not discuss these figures at a meeting held on October 25th 1989, but instead focussed on the lowest figure obtained from Aichi Prefecture, in which 1 in every 28,477 children suffered side-effects. The committee then announced that the frequency of side-effects was "1 in every several thousand to 30,000".
- The final calculation revealed that 311 of 630,157 children who took the vaccine suffered side-effects, and the committee on December 25th that year revised the figures in the data to "1 in several thousand", whereas it was in fact one in several hundred.
- The adverse event data also included data on the number of inpatients, which was 39 as at December 1989. The committee, however, reported publicly that symptoms of aseptic meningitis were only slight, and that all of the victims had recovered. The children's lawyer, Tatsuro Shigemura, commented that the released documents clearly revealed that the Health Department had hidden uncomfortable data and had then delayed the discontinuation of MMR.
- Litigation is also known to be under way in Canada and in Sweden

9. The UK Department of Health's Position On MMR

- Despite research pointing to an original failure to properly conduct safety tests with adequate follow-up of MMR (see later), and emerging research linking MMR with autism (autistic enterocolitis syndrome) and/or inflammatory bowel disease, the UK Department of Health and other medical institutions continue to insist that MMR is safe
- This claim is based upon advice of the UK Committee on Safety of Medicines and Joint Committee on Vaccination and Immunisation - both of which would suffer a catastrophic loss of public confidence, should such a link emerge - and a number of

studies, all of which arguably have severe methodological weaknesses or inconclusive outcomes. Details follow later in the text.

- Much of the support for MMR, and denial of a link with autism, is based around a very small number of these studies, which the various sectors of the medical establishment have then endorsed.
- There have also been general reviews of the MMR/autism issue by the Medical Research Council, most recently in late 2001, and by other bodies. These reviews have failed to find a link between MMR & autism. The parents believe this failure was inevitable, given the past lack of funded research into causes, and the superficial nature of these reviews, which have accepted "absence of evidence" as "evidence of absence" of a link.
- The outcome of these reviews, and other published papers, has then been misrepresented or misinterpreted by the Department of Health as hard evidence that there is not a link.
- The DoH-sponsored impression of "a growing body of evidence" that there is no MMR/autism link is therefore illusory - the "house of cards".
- The Department of Health's position on MMR has been endorsed by many of the major medical institutions, though it is questionable whether these institutions have themselves fully considered, in adequate detail, all the evidence on both sides of the argument.
- It is also unlikely that any of these bodies has met with parents or listened sufficiently attentively to their accounts of how their children degenerated. It is likely that some of the bodies, and spokespersons, backing MMR and refuting a link with autism are entirely basing their confidence upon a few selected studies, and that their knowledge of the actual children believed to have been damaged is very poor. Their detailed knowledge of the studies that point towards there being a problem may be weak and incomplete.
- The starting point should be to listen to the patient. Most of those giving reassurance have never even met the patient, nor the patient's parents, nor examined the affected child, nor reviewed their medical case-notes.
- Despite the DoH's position of "MMR or nothing" (and increasing numbers of parents seem to be choosing the latter), when MMR was introduced in 1988, the UK National Health Service advice to doctors was that single vaccines should be made available for any parents not wishing their child to have MMR.

- In the pamphlet, *Immunisation Against Infectious Disease*", which accompanied the introduction of MMR to the UK, it stated: "For children whose parents refuse MMR vaccine, single antigen measles vaccine will be available" (source: Joint Committee on Vaccination and Immunisation, 1988). It is unclear when, or why, this advice was withdrawn by the DoH, but it may have followed discontinuation of the single vaccines as an economy measure.
- During the years 1998-2002, a one-sided view of the MMR/autism issue has thus been adopted by the Department of Health and its satellite organisations, much of it aimed at restoring public confidence in immunisation, to fight communicable diseases, rather than rigorously searching-out the cause of the damage to the actual children. Fresh publicity issued during early 2002 took a one-sided view of the debate, and ignored some key scientific evidence such as the January 2002 research by Dr. Vijendra Singh (see later), despite the latter being widely available in advance of the date of the Department's publicity.
- A similar denial process has occurred in the US, but its main roots lie in the UK, and based on (mainly statistical) advice stemming from only a very small number of sources.
- At the end of 2001, the UK Department of Health released a "Top 10 Truths/Top 10 Myths" leaflet about MMR, and this is summarised below, with a critique alongside:

(UK Department of Health's "Top 10 Truths")

<i>(Department of Health "Truth")</i>	<i>(Critical Response of Parents)</i>
MMR is safest way to protect children	Does not address the alleged damage
Over 500m doses of MMR have been used in over 90 countries	Almost all those countries have no autism database. Only US has good data - and this shows a steep rise in autism
No country in the world recommends single vaccines	No country in the world has yet acknowledged that there may be an MMR/autism link, either, but that may yet follow in time. Some countries permit single vaccines as a choice.
Children who are not immunised with MMR increase the chance of infection in others.	True. But those children could still receive single vaccines. And there may yet be a massive loss of confidence in all vaccination, if the children win in the High Court. It would therefore be prudent to think of this possibility, and permit choice now.
The evidence is that MMR does	There is evidence that suggests that it may do. Every

not cause autism or IBD (a number of studies are quoted, but only those which suit the Department's stance)	one of the quoted studies that "disproves" an MMR/autism link can be flawed (see elsewhere in this document).
Wakefield et al in 1998 said "We did not prove an association".	True. The research is still unfolding. Time did not stop in 1998.
Single vaccines put children at risk	The Department's argument is based upon a supposition that some children would not complete the full course of vaccines. But if the children win in the High Court, and the Department is shown to have misled the public (either unknowingly or knowingly), the damage will be far greater. And already, some children are avoiding any measles vaccine. The Department's argument is already having a perverse consequence, and may eventually massively backfire..
MMR was thoroughly tested before introduction into the UK in 1988.	In the context of adverse outcomes with an insidious long-term onset, MMR was not properly tested. Advice at the time to explore possible adverse effects was not followed up. By disputing historical facts, the Department reveals its bias.
Two doses of MMR are needed to protect children.	The efficacy of MMR in terms of preventing measles is not the point at issue.
There are very few children with genuine contraindications.	This does not address the MMR/autism link. It also does not square with the manufacturer's own information sheets, which imply a substantial number of possible adverse effects.

The Department of Health's "Top 10 Truths" leaflet ends with the reassuring statement, "*All of the above are correct*"! The above critique suggests that the "truth" is nowhere near clear-cut, and the Department's position is thus exposed as artificial and one-sided.

(UK Department of Health's "Top 10 Myths")

<i>(Department of Health "Myth")</i>	<i>(Critical Response of Parents)</i>
Getting protection by catching the disease is better.	This is not the issue in dispute.
Three viruses given at the same time is too much for children.	It may yet prove to be. The Department has no evidence (in the context of the MMR/autism debate) to

	the contrary, in relation to live viruses.
Other countries recommend that MMR is given as separate vaccines.	Of course they don't. Perhaps this is because no country has yet woken up to the problem. As yet, there is insufficient evidence to alter this position.
Measles, mumps and rubella are rare in the UK so there is no need to immunise.	This is not the issue in dispute.
MMR causes autism and bowel disease.	There is evidence pointing towards an MMR/autism/IBD connection. Until this area is thoroughly researched, it is scientifically untenable to rule it out.
There was a scientific paper that linked MMR and autism/IBD	There have now been a number of such papers. They form part of an unfolding story.
Giving MMR as separate vaccines reduces the risk of side effects.	It is not possible to prove/disprove this until proper clinical research has been funded and conducted.
The vaccine was not properly tested.	In the context of the MMR/autism debate, and the alleged link, this is factually true, and it is extraordinary for the Department to claim otherwise. Even the Department cannot re-write history.
My child has already received one dose, so does not need a second dose.	This is not the issue in dispute.
My son does not need protection against rubella, my daughter does not need protection against mumps.	This is not the issue in dispute.

The Department of Health's leaflet ends, "*All of the above are wrong*". In the view of the parents, of the "Top 10 Myths", four are irrelevant to the debate about an MMR/autism link, one statement about a "Myth" is factually incorrect, and the remainder can readily be disputed because the research has not been completed, or in some cases even commissioned, to decide the issue either way.

The position in the US is no different. In summer 2002, the US Center for Disease Control (CDC) updated its "Frequently Asked Questions" (FAQs) on the MMR/autism issue. It asked the question: "What have studies found regarding MMR vaccine and autism?"

Its answer was "Epidemiologic studies have shown no relationship between MMR vaccination in children and development of autism". However, what it did not acknowledge, or discuss, was that "studies" in the original question should have included both clinical and epidemiological studies, with greatest weight being attached to clinical findings. Its answer ducked the issue of clinical studies, focussing solely on epidemiological studies (see later for a critical review of these).

10. Position of US Center for Disease Control on MMR/Autism

The position of the US Center for Disease Control is summarised as follows (taken from their website in February 2002, but believed to be unchanged as at February 2003):

- Is there any scientific evidence that provides a link between autism and vaccination? - To date there is no convincing evidence that any vaccine can cause autism or any kind of behavioural disorder. A suspected link between MMR vaccine and autism has been suggested (but this).....may simply be an.....unrelated chance occurrence.
- Is there a theoretical possibility that there is a connection between autism and MMR vaccine, or any other vaccine? - If measles vaccine or any other vaccine causes autism, then it would have to be a very rare occurrence, since millions of children have received vaccines without ill effects.
- What are the known side-effects associated with MMR? - About 5-15% of vaccinees may develop a fever 5-12 days after MMR, and 5% may develop a rash (comment - not clear if this means 5% within the 15% or 5% plus the 15%). Central nervous system conditions, including encephalitis and encephalopathy, have been reported with a frequency of less than one per million doses administered
- What is the federal government doing to protect the health of persons who receive MMR? - There are no proven data to suggest that measles vaccine will increase the risk of developing autism or other behavioural disorders.

Comment: the above is neither comprehensive nor balanced, and its one-sided reassurance is therefore unhelpful. The details of the above could even be challenged on the grounds of factual accuracy. Point one is particularly threadbare.

11: The Parents Have Seen What They've Seen.....

It is not in dispute that vaccines have saved millions of lives. The MMR/autism parents are not anti-vaccination in principle. These parents all took children to be vaccinated. We all recognise the need to protect children from diseases.

But saving lives from diseases doesn't justify ruining significant numbers of lives from unrecognised and unmonitored vaccine damage.

It is also felt by many parents that the mantra "the benefits of vaccination outweigh the risks" has become increasingly skewed by

- (a) occasionally overstating the dangers of diseases, citing experience of diseases from poor and underdeveloped countries, or UK experiences from half a century ago, or pointing to recent deaths (e.g. Ireland) where other factors played a major part, or
- (b) grossly underplaying or dismissing outright any risks from vaccination. This latter has been aided by the extremely poor monitoring of adverse outcomes, and by the authorities strenuously refusing to accept that an adverse outcome was the result of a vaccine.

All affected parents are in the privileged position of having watched their child degenerate. It is a powerful first-hand experience. Comparing notes results in finding that other parents have undergone extremely similar experiences. Unfortunately, such experiences are not part of a scientifically-controlled study, so are routinely dismissed by the Department of Health as anecdotal.

- Usually there appears to be a very gradual degeneration over many weeks and months, not an acute event, more akin to (eg) the onset of cancer than the rare acute reactions to vaccines seen in the past.
- But all the attention of the past upon possible adverse reactions to vaccines has focussed upon acute near-immediate events.
- The onset of gut/bowel problems and hyperactivity have accompanied the onset of autism. Some link between them is therefore likely, even without detailed research.
- An anecdote is an anecdote. A consistent pattern of anecdotes is much more powerful. What we have is a consistent detailed pattern of reports from parents. The importance of this pattern has been ignored by the Department of Health.

PART B - THE COSTS OF AUTISM

12: The Financial Costs - Autism Is Costing £\$Billions

Quite apart from the immense social costs of autism, there are the huge financial costs. Autism affects every UK and US taxpayer. In the UK, the costs comprise:

- Health costs - specialist hospital visits, GP visits, prescriptions, exclusion diet costs
- Education costs - special schools, extra teachers, extra teaching assistants, extra training
- Transport costs - taxis plus drivers and escorts, plus local authority management costs, plus environmental/congestion costs of extra traffic
- Social Services costs - respite care costs, transport, management, inspection, reviews
- Loss of earnings of parents acting as carers
- Social Security costs - carers allowances, disability living allowances
- Inland Revenue costs - loss of earnings of parent, loss of revenues from child when he/she reaches earning age
- Wider economic costs - loss of gross domestic product to the national economy

It would be interesting to know if the UK Treasury had a view on these costs, and whether sufficient resources were being devoted to investigating acquired autism and other forms of autism, as they represent a significant loss to the wider national economy. Is autism too important to be left to the Department of Health?

13: Estimates

In June 2000 a study for the Mental Health Foundation found that

- the annual costs of autistic disorder in the UK were at least £1 billion
- individual lifetime costs per child affected could run to £2.94 million each.

The full costs, taking into account wider economic costs, are probably considerably higher still.

14. Failure To Monitor Increases In UK Autism Numbers

- There has been a consistent argument on the part of the authorities, and those seeking to defend MMR, that the apparent rise in autism may be largely a matter of better recognition. This has received some backing from autism researchers. But where hard UK or US data is available, increases are far too steep, and in far too short a timescale, to be credibly ascribed to better recognition alone..
- For this to be "better recognition" or "improved diagnosis", this would have required these children to have been missed, simultaneously, by their parents, their relatives, their doctors and their teachers in the past This is simply not credible. For example, the increase in autism 1992-99 in Wakefield, West Yorkshire, local education authority was from 5 cases to 111 cases. If increased autism is down to better recognition, it would mean that, back in 1992, there really were 111 cases, but only 5 were recognised, and the remaining 106 were missed, and by all the parties - parents, doctors, health visitors, teachers - concerned. This is completely implausible.
- Undoubtedly there has been some degree of better recognition and reclassification, following introduction of ICD-10 (international classification of diseases/disorders) criteria in 1992, and DSM-IV (diagnostic statistics manual) criteria in 1995. But this will account for only a minority of the growth.
- The UK DoH has failed to monitor autism, and is still failing to (despite a specific 1997 recommendation of the House of Commons Health Committee to do so). Is it now afraid of what it might find? If it does decide to monitor autism, will it find that numbers are high and then claim it has always been so?
- UK Health Boards/Authorities are also failing to monitor autism locally. Health Boards/Authorities have little data and no consistent approach. At the health authority level, official figures vary wildly, by factor of 300-fold, i.e. 300-times (not 300%). The data is an extraordinary mess.
- In the year 2000, only 1 in 6 UK Boards/Authorities had any credible figures at all. Most used estimates from textbooks.
- The Scottish schools census now includes autism. The census commenced in 1998. The 1999 census showed 18% increase over the 1998 census. The 2000 census showed a 31% increase over the 1999 census. The 2001 census will report during mid-2002.
- There are other indications of the level of increases: Kaye et al paper (see later) found a sevenfold increase 1988-99 in UK. An unpublished 1999 paper by Dr. Fiona Scott, Autism Research Unit, Cambridge, indicated autism at eleven times the expected level (1 in 174) - see later.
- The 2001 Medical Research Council review found autism to be at 1 in 166, many times higher than hitherto thought. Sixteen studies published between 1966 and 1991 found

rates of between 1 in 3030 and 1 in 625. A rate of 1 in 166 is nearly four times higher than 1 in 625, itself the highest of these sixteen, and from a relatively-recent study in 1983.

The repeated official line that the apparent increase is down to better recognition may therefore be little more than a counsel of complacency.

In December 2002, a Parliamentary Written Question (84502) confirmed that there is now in place a "Good Practice Guidance on Autistic Spectrum Disorders", in the UK, published by the Government's Departments of Education & Skills and of Health. This is intended to raise awareness amongst schools and local education authorities. However, it is probably just one of many thousands of such well-intentioned documents, is non-statutory, and is probably lost in the stream of paper raining down on local government from central government.

UK schools and local education authorities have a duty to identify, assess and make suitable provision for children with special educational needs. However, there seems to be no duty upon either the health authorities at the local level or the Department of Health at Government level to improve the data position over autism - doubtless to the latter's relief. Perhaps centrally-collated figures showing steep increases would beg uncomfortable questions as to the causes. The UK Department of Health seems to regard autism as a problem for local education authorities - not for the Department.

15. "Now Almost Everyone Knows Someone Who's Autistic"

Autism was a very rare condition, but is now almost regarded as commonplace. Very many cases are now of late-onset autism, whereas almost all used to be cases from birth. We have to ask why this is.

Some UK research noted the sharp increases in autism in the 1990s. A paper by Powell et al, Department of Public Health and Epidemiology, University of Birmingham, UK, *Changes in the Incidence of Childhood Autism and Other Autistic Spectrum Disorders in Pre-School Children from Two Areas of the West Midlands, UK*, was published in *Developments in Medicine and Child Neurology*, September 2000. This looked at the incidence of childhood autism and ASD in pre-school children between 1991 and 1996.

The study found that there were year-on-year increases in classical autism during this period of 18%, but for "other ASDs" the annual increase was no less than 55%. But the study then concluded that this was due to clinicians being increasingly able or willing to make a diagnosis. The possibility of an underlying genuine increase, and any follow-on question as to causes, does not appear to have occurred to the study team.

But parents of children believe to have been damaged by MMR strongly believe that part of the increase is down to a new phenomena, autistic enterocolitis.

It is not the autism of the past. Such a severe acquired regressive syndrome after a normal early childhood would have been noticed in the past by parents, and recognised medically, and also reflected in much higher historic rates of prevalence/incidence.

In the parents' view, there is clear evidence of recent dramatic rates/increases:

- examples - an East Surrey 1/69 rate amongst three year old boys, 1/139 rate amongst three year old boys+girls combined (source: personal communication of 10/6/99 from Caroline Clark, Commissioning Manager, Learning Disability Services, East Surrey Health Authority). The letter from East Surrey stated: *"In the remaining half of the District, it is estimated that there are at least 50 children on the autistic spectrum under the age of five. A special needs audit has been undertaken of children aged three by the community paediatrician. This is the age where the paediatrician expects to identify children at the more severe end of the autistic spectrum. Thirty-six children have been identified during the last two years as presenting with autism, of which twenty-nine were between the ages of two and three, with seven children slightly older. The general population is around 2,500 children (born) per year in this part of the District. The prevalence of autism indicated by the audit is 0.72% (1 in 139) but with 1.44% (1 in 69) for young boys."*
- Bromley Autistic Trust figures show a 1990-94 increase of 280% over 1980-84 figures (source: personal communication of 16/9/99 from Miss C. M. Povey, Services Director, Bromley Autistic Trust)
- Wakefield LEA autism pupils up from 5 to 111 in seven years (source: survey by David Brown, a specially-seconded headmaster from the Park School, Wakefield, on behalf of Wakefield Local Education Authority, 1999)
- Telford health data up from 4 new cases per year in 1990 to 17 per year 1998 and again 1999 (source: personal communication of 20/11/00 by Dr F. R. J. Hinde, Consultant Paediatrician, Princess Royal Hospital, Telford)
- As noted, Scottish schools census up 18% in one year (1999 vs. 1998), and then a further 31% in the next year (2000 vs. 1999); (source: Scottish Annual School Censuses, available from Scottish Education Office, tel 0131 556 8400)

On December 22nd 2002, the UK Observer newspaper carried a report on the apparent epidemic of behavioural problems amongst UK schoolchildren. Whilst not confined to autism (the report cited hyperactivity and attention-deficit disorder), the Observer's report suggested a steep rise in the incidence of problems. Figures obtained by the newspaper suggested that numbers of schoolchildren with attention-deficit disorder (ADD) or attention-deficit hyperactivity disorder (ADHD) had reached 345,000, and that one child in twenty between the ages of 6 and 16 years had one or other condition. The Observer also found out that

prescriptions for Ritalin, to counter these disorders, had increased markedly, from 91,100 in 1997 to 208,500 in 2001.

In the US, the Brown University Child & Adolescent Behavioural Letter (18(3): 1: 304, 2002) carried the following details:

- A study into attention deficit hyperactivity disorder (ADHD) was undertaken, based on parent and teacher reports concerning 6,099 children in 17 public elementary schools. The study was undertaken by researchers working for the National Institute of Environmental Health Sciences in North Carolina
- When the researchers surveyed parents in a typical county of rural and suburban communities - Johnston County, North Carolina - the parents reported that more than 15% of boys in grades 1st through 5th had a diagnosis of ADHD, with about 10% (i.e. two-thirds of those diagnosed) receiving medication.

Although ADHD is not autism, it may share some common causal pathways, particularly multiple food allergies and gut permeability. The finding is thus of interest to the MMR/autism debate.

16. University of Cambridge Research

On 18/2/01, the UK *Sunday Telegraph* reported on research undertaken by Dr. Fiona Scott at the Autism Research Centre at the UK University of Cambridge. The research, *Prevalence of Autism Spectrum Conditions in Children Aged 5-11 Years in Cambridgeshire UK*, by Scott, Baron-Cohen et al, which is due to be published shortly, was undertaken across schools in Cambridgeshire.

The study aimed to establish prevalence of the broader autistic spectrum, including Asperger syndrome in 5-11 year olds in Cambridgeshire, UK. Cases of diagnosed autism spectrum condition in children who were in Cambridgeshire schools and aged 5-11 on 31st December 1999 were sought out using public records, screening instruments, educational psychology and special educational needs coordinator records.

It found that:

- One in 175 (58/10,000) children was autistic, whereas previous studies had pointed to a rate of 1 in 2000 (5/10,000)
- This was 11 times higher than the rate of classic autism, but in line with other recent national and international rates for the broader spectrum.
- In responding mainstream schools, the prevalence was 1 in 300. In the responding special schools, the prevalence was 1 in 8.
- Extrapolated across the UK, that would imply 30,000 primary school (age 5-11) children with autism

- The overall sex ratio of the children was 4 to 1 male to female, but in mainstream schools it as 8 to 1.
- Linking these rates to estimated costs of education and care for sufferers would give a figure of as high as £5 billion per year, year after year. The Cambridge autism figures were described as "*if anything an under-estimate*". They included only children with a definite clinical diagnosis. Any child who had only been "statemented" (= educational needs-assessed) as autistic, but not yet clinically diagnosed, was not counted
- One in eight children with special educational needs was suffering from some form of autistic spectrum disorder. The increase of actual numbers over previously-assumed numbers would have enormous cost implications for central and local Government
- A year-2000 report for the UK Mental Health Foundation by Professor Martin Knapp for the UK Institute of Psychiatry used the earlier "textbook" rate of autism of 5/10,000 to put the total UK economic cost of autism at £1bn. The Knapp report estimated the lifetime cost of a severely-affected child at £3m, for a high-functioning autism child at £0.8m, and for an Asperger's syndrome child at £0.5m. The revised £5bn per year estimate is based upon these costs.

17. University of Sunderland Research

An unpublished study by the UK University of Sunderland found a tenfold increase in diagnosis of autism, during the years 1989-93.

18. UK National Autistic Society Estimates

The NAS issued a factsheet in early 1997 which gave the following prevalence rates:

- People with Kanner syndrome (IQ less than 70) 5/10,000, or 1 in 2,000
- Other spectrum disorders (IQ less than 70) 15/10,000, or 1 in 666
- Asperger's (IQ 70 or above) 36/10,000, or 1 in 278
- Other spectrum disorders (IQ 70 or above) 35/10,000, or 1 in 286

Combined total of above four groups 91/10,000, or 1 in 110

The above implies a very high level of autism in the UK, and the previously-described studies seem to bear this out.

The NAS reach its 91 in 10,000 or 1 in 110 rate by taking the Wing & Gould study (Camberwell, London) of 1979, which looked at children with an IQ of under 70 and found a rate of 20 per 10,000, and adding this to the study by Ehlers & Gillberg (Sweden) of 1993 which looked at autistic children with an IQ of over 70 and found a rate of 71 per 10,000 (1 in 141).

The 91/10,000 rate is thus "merged data", collected in two different countries and some years apart, and thus needs to be treated with caution, particularly if rates have since been rising further. The Wing & Gould study is now over two decades out of date, and also pre-dates MMR introduction into the UK.

19. Report by Fiona Loynes, UK All-Party Parliamentary Group on Autism, Dec. 2001

The purposes of this report included:

- To establish numbers of children with autistic spectrum disorders
- To learn whether UK local education authorities believed there had been a recent increase in the last five years
- To ascertain whether LEAs routinely collected data

The findings included the following:

- 100 out of 115 LEAs reported an increase in autism in the past five years. Some reported small increases, others reported far higher increases, in one case by 77%.
- The study compared the expected prevalence rate of all autistic spectrum disorders in each LEA (91 in 10,000 or 1 in 110) with the actual recorded number of children with ASD and a Statement of Educational Needs (21 in 10,000 or 1 in 476). If the estimated numbers are correct, then the implication is that 75% of children with autism do not become included in the Statement data, because they have no Statement.
- Only 44 out of the 100 LEAs reporting an increase had actual data. Some of these reported dramatic increases, up to 400% in four years.

20. Report, "Autism In Schools - Crisis or Challenge", National Autistic Society UK, May 2002

- This report was compiled from the findings of a survey carried out in seven local education authorities across England, Wales and Scotland, although the Scottish findings were reported separately. The England and Wales survey involved 373 individual surveys, with a response rate of over 30%, covering a pupil population of 133,000. The study found that:
- 1 in 86 children in mainstream schools had special educational needs that were related to ASD.
- The rate of ASD is three times higher in primary than in secondary schools. In primary it is 1 in 80, in secondary it is 1 in 268.
- This is in addition to children with ASD in special schools. In special schools, 1 in 3 children has ASD-related needs.

21. Is Autism Increasing? - Some Recent Official UK Pronouncements

These are some recent, and sometimes self-contradicting, statements:

- *"There is no good evidence that the frequency of autism has increased since the introduction of MMR"* - Tessa Jowell, then Minister for Public Health, October 1997 (personal communication to David Thrower)
- *"The true incidence of autism is uncertain"* - Sir Kenneth Calman, then Chief Medical Officer, March 1998
- *The apparent rise in autism in the UK began more than ten years before the introduction of MMR"* - Tessa Jowell, in June 1998
- *"Rates of autism are rising, but not because of MMR"* (Committee on Safety of Medicines, June 1999)
- *"There is no robust data on the prevalence of autism before and after MMR's introduction"* - Brent Taylor, in a June 1999 study heavily quoted by the Department of Health
- *"Numbers of cases of autism are rising, but the reason for this is unclear"* - John Hutton, Minister for Public Health, December 2000
- *"Methodological differences between studies, changes in diagnostic practice and public and professional awareness are likely causes of increases in prevalence. Whether these factors are sufficient to account for increased numbers of identified individuals, or whether there has been a rise in actual numbers, is as yet unclear"* - Medical Research Council 2001 review, quoted by the Scottish Parliament Expert Group May 2002.
- *"Two thirds of (surveyed) teachers felt that there were more children with ASD now than five years ago. This (is) consistent across age groups and in all types of education provision, special and mainstream"* (Report of the National Autistic Society, May 2002)

22. Autism In The USA

- The UK Department of Health is fond of saying how MMR is safely used in 32 countries, including the USA, as though its use elsewhere is proof in itself that it is safe. Recent claims have even referred to 100 countries. But the USA, at least, has clear evidence of an autism epidemic. Other countries may also be becoming aware of increases, for example Finland, where a 400% increase in cases has been alleged since was MMR introduced.
- The US has IDEA (Individuals with Disabilities Education Act). This picks up numbers of schoolchildren with developmental problems. Autistic pupils are up from 12,222 to 78,717 between 1992-1993 and 2000-2001 (Source: US IDEA State data).

- To the above total also has to be added a further 15,581 cases of autism amongst children aged 3-5 years, as at year 2000 (this number will have since increased further).
- There have been huge increases in some States between 1992-1993 and 1999-2000 - up 885% in Alabama, 529% in Connecticut, 435% in Florida, 513% in Idaho, 636% in Kansas, 561% in Minnesota, all in just seven years (Source: US State data, Individuals with Disabilities Education Act)
- It is also interesting that individual towns such as Round Rock, Texas, are reported to be up from 6 cases to 115 cases in eight years - very much like Wakefield Local Education Authority in the UK (up from 5 to 111 in seven years). On the face of it, this suggests that UK increases may very closely match those in the USA.
- It has been alleged that Brick Township (New Jersey) has manifested an "autism cluster". Some 40 of Brick Township's 6,000 3-10 year olds have autistic spectrum disorder. It has made Brick Township the "autism capital of the USA" (but note, East Surrey rates in the UK are higher still). In Brick Township, Federal investigators collected data on surface and ground water, sites of industrial spillages and waste dumping, and also ensured that there had been correct diagnosis of the actual children. They have found nothing untoward. Their findings were reported in April 2000.
- The following is taken from the statistics produced by the Department of Education in the United States, for numbers of children aged 6-21 served by IDEA (Individuals With Disabilities Discrimination Act) who have autism. It compares the increase over the eight years between 1992-93 and 2000-01:

<i>State</i>	<i>1992-1993</i>	<i>2000-2001</i>	<i>Percentage Increase</i>
Alabama	68	765	1,025
Alaska	8	195	(almost infinite)
Arizona	199	1,119	462
Arkansas	30	671	2,137
California	1,605	10,557	558
Colorado	14	453	(almost infinite)
Connecticut	164	1,225	647
Delaware	15	263	1,653
District of Columbia	0	103	(infinite)
Florida	582	3,926	575

Georgia	262	1,916	631
Hawaii	52	276	431
Idaho	39	291	646
Illinois	5	3,103	(almost infinite)
Indiana	273	2,621	860
Iowa	67	537	701
Kansas	74	619	736
Kentucky	38	864	2,174
Louisiana	409	1,145	180
Maine	37	444	1,100
Maryland	28	1,933	(almost infinite)
Massachusetts	493	575	17
Michigan	288	4,075	1,315
Minnesota	296	2,448	727
Mississippi	0	385	(infinite)
Missouri	336	1,589	373
Montana	20	163	715
Nebraska	4	337	(almost infinite)
Nevada	5	394	(almost infinite)
New Hampshire	0	342	(infinite)
New Jersey	446	2,925	559
New Mexico	16	225	1,306
New York	1,648	5,943	260
North Carolina	786	2,374	202
North Dakota	9	118	(almost infinite)
Ohio	22	2,217	(almost infinite)
Oklahoma	31	666	2,048

Oregon	37	2,516	2,516
Pennsylvania	346	3,304	855
Puerto Rico	266	473	78
Rhode Island	19	309	1,526
South Carolina	141	852	504
South Dakota	36	227	531
Tennessee	304	935	208
Texas	1,444	6,023	317
Utah	105	584	456
Vermont	6	160	(almost infinite)
Virginia	539	1,983	268
Washington	476	1,620	240
West Virginia	101	312	209
Wisconsin	18	1,823	(almost infinite)
Wyoming	15	94	527
Total	12,222	78,717	overall increase 644

(Source: Individuals With Disabilities Education Act data, US Department of Education. Note: Where increases are from a very low base figure, these have been expressed as "almost infinite".)

- For every two cases there were in 1993, there are now thirteen. And the latest 2000-2001 figures represent a single-year increase of 20% over 1999-2000
- The current estimate for the year-end of 2002 is 94,000-95,000.
- It seems obvious that the US has an autism epidemic. The UK is a similar health environment to the US, so it also seems reasonable to conclude that the UK probably has an autism epidemic, too, but just hasn't yet realised it.
- Dr Bernard Rimland of the US Autism Research Institute, San Diego: "*Some supposed experts will tell you that the (US) increase reflects only greater awareness. That is nonsense. Any paediatrician, teacher or school official with 20 years experience will confirm there is a real increase, and the numbers are huge and growing*".

As in the UK, health officials in the US have tried to explain away these increases as being the result of greater awareness, better recognition and broader diagnostic definition. Doubtless these play a part, but the authorities seem to want to use these factors to explain all the increase, without having any hard evidence to support their stance.

In April 2000, giving evidence to the Government Reform Committee hearings into autism's increase, Dr. Coleen Boyle, Associate Director for Science and Public Health at the Center for Disease Control, stated that UK rates in 1966 had been 4 to 5 per 10,000 (1 in 2,500-2,000). Studies from outside the US since 1985 had indicated 12 per 10,000 (1 in 833). Recent studies had been higher still. There had been only two population-based studies in the US, both in the 1980s, indicating prevalence of 1.2 to 3.3 per 10,000 (1 in 8333 to 1 in 3030).

Two years on, giving evidence to the same Congressional committee, Dr. Coleen Boyle acknowledged the case of Brick Township New Jersey, where the CDC had found a rate of ASD of 6.7 per 1,000 (note: per ONE thousand), or 1 in 149. She stated that the previously-accepted background rate was 1-2 per 1,000 (comment - but this does not square with her evidence in the year-2000 Washington hearings?). She stated "*We cannot determine whether rates are increasing or not, because we do not have comparable data from earlier years*".

But the thrust of her earlier comments implied that, even if increases were demonstrated, this was down to better awareness etc., and at no point did she appear to confront the possibility that increases were real, and then confront the (very difficult) question, "What was causing the increase?". The CDC strategy seems to be to cast doubt upon the increase, rather than seek the cause. The CDC strategy might be summed up as follows:

- Cast doubt upon the accuracy of the data, and thus draw attention, and the focus of debate, away from the cause of the increase and towards the data issue
- Stress the need for better data (which no one would argue against)
- Announce new comprehensive data-gathering exercises, which will take time.

By early 2003, evidence that increases were real was beginning to accumulate - see next main section.

23. Autism Elsewhere

Information on autism in Canada does not appear to be anything like as comprehensive as that in the US, but press reports are indicating a recent increase. In May 2002, a study by the Ontario government health ministry indicated that numbers were increasing sharply, with 800 children younger than six years of age being newly diagnosed during 1998. This represented a 53% increase over numbers diagnosed two years earlier.

The Ontario government study also found that 2,863 children younger than seven were diagnosed with autism between 1991 and 1998. The study was not released until the efforts of a parent, Professor Marianna Ofner-Agostini of the University of Toronto, forced the issue.

The issue is now being debated in other developed countries elsewhere in the world. A New Zealand doctor, Dr. Mike Godfrey, wrote to the UK *Scotsman* newspaper in early 2002 as follows: *"I have so far analysed 866 children's histories, with 260 being unvaccinated. There are no cases of autism, epilepsy or Crohns Disease and only a handful of other diseases in this latter (unvaccinated) group. There are 16 autistics, 12 epileptics, 8 cases of Crohns, plus cases of other illnesses, in the vaccinated 606 children."*

PART C: EVIDENCE THAT INCREASES ARE REAL

24: California

California has probably the most useful and detailed autism data in the world, going back to 1970. Trends monitored there have a potential worldwide significance.

- The rise in autism was first highlighted by a report *Changes in the Population of Persons With Autism and Pervasive Developmental Disorders in California's Developmental Services System, 1987 through 1998 - A Report to the Legislature*, tabled on March 1st 1998 by the Department of Developmental Services, Sacramento, California Health and Human Services Agency.
- Department of Developmental Services data, released at the start of 2002, shows that a record number of professionally-diagnosed DSM-IV criteria autism cases, 2,725 cases, entered the State system during 2001.
- This year-2001 number represents a 20% increase over the year 2000, itself a record.
- In 2001, there were more cases of level-one autism in California than in 1994, 1995 and 1996 combined.
- Historically, autism made up 3% of childhood disability in the State Developmental Services system. It now comprises 35% of the total.
- Two out of three persons with autism in California's child-developmental system are now young children between the ages of 3 and 13. Eight out of ten persons with autism have been born since 1980 (1980 was the year that California mandated the full complement of childhood vaccines as a condition of school entry. MMR was also introduced in California 1979-80).
- California now has 16,802 persons with level-one autism in its Developmental Services system.
- The total intake for the three years 1999-2001 was 6,596. This compares with a total intake for the twenty-five years 1970-1995 of 6,527 cases.

This does not include children with persistent developmental disorder, non-specific (NOS) developmental delays, Asperger's or and other autistic spectrum disorder - it is therefore the tightest definition of the severe-case numbers.

Statistics on autism in the individual regional centres in California, run by the state Department of Developmental Services, also show a sharp rise in the period 1998-2002:

(regional centre)	At 7th Jan 1998	At 3rd Jan 2002	Increase %
Alta	400	683	71%
Central Valley	150	361	141%
East Bay	606	1,087	79%
E. Los Angeles	443	976	120%
Far Northern	125	217	74%
Golden Gate	371	499	35%
Harbor	639	1,113	74%
Inland	568	1,195	110%
Kern	141	262	86%
Lanterman	418	842	101%
North Bay	215	350	63%
N. Los Angeles	742	1,746	135%
Orange	670	1,621	142%
Redwood Coast	76	103	36%
San Andreas	360	666	85%
San Diego	609	1,186	95%
San Gab/Pomona	581	937	61%
S. Central LA	549	874	59%
Tri-Counties	352	725	106%
Valley Mountain	153	373	144%
Westside	613	986	61%
(Statewide Total)	8,781	16,802	91%

Since this data was released, further rises have been recorded:

- The quarterly data reported from the California Department of Developmental Services for the period April-July 2002 added a further 846 new children with level-one DSM-IV autism to the Department's caseload. These 846 cases represented a new record high in the 31-year history of the system.
- The increase was 18% higher than for the comparable quarter in the previous year. Autism now constitutes 40% of all developmental-disability intake for the California system.
- On average, nine new cases are being added to the system, every day, seven days a week.
- To set the 2002 figures in context, over the 28 years from 1971, to 1999, California produced 10,206 cases. In the subsequent three and a half years, 1999 to mid-2002, a further 8,554 new cases were added.

Comment: the above suggests a major rise in autism incidence in California.

25. The MIND Study, California

Following mounting concern at the apparent steep increase in autism in California, an urgent study was launched by the MIND Institute. Its findings were released on 17th October 2002, and appear to finally confirm (but see other contradicting studies in the following section) that autism has risen steeply.

The study was led by Dr. Robert Byrd, whose team had previously enrolled 684 Californian children who were receiving services from one of the Department of Developmental Services regional centers. Byrd's team systematically gathered information for children in two age groups, 7-9 year olds, and 17-19 year olds. These were drawn from families of 375 children with a diagnosis of full-syndrome autism, and families of 309 children with a diagnosis of mental retardation without full-syndrome autism.

The study findings were that:

- The unprecedented increase in autism in California is real and cannot be explained away by artificial factors such as misclassification and criteria changes. Autism is on the rise in California and the study team does not know why
- The observed increase cannot be explained by a loosening in the criteria
- Some children reported with mental retardation and not autism did meet criteria for autism, but this misclassification does not appear to have changed over time
- Because more than 90% of the children in the survey are native to California, major migration of children into California does not contribute significantly to the increase in autism
- A diagnosis of mental retardation associated with autism had declined significantly between the two age groups studied.
- The percentage of parent-reported regression (loss of milestones) does not differ between the two age groups studied
- Gastrointestinal symptoms, including constipation and vomiting, in the first fifteen months are more commonly reported by parents in the younger group

Comment: the above study appears to offer firm evidence of a major rise in prevalence.

26. New Jersey

Data on autism in New Jersey, recorded by the IDEA system for individuals with disabilities who require special education, suggest that there is a vast preponderance of cases amongst children/young people ages 6-21 amongst the youngest ages. The following figures relate to the position as at 1st January 2002:

age	6	7	8	9	10	11	12	13
nos	514	505	465	439	360	257	208	165
Age	14	15	16	17	18	19	20	21
nos	145	124	81	73	58	63	30	14

The total number of cases is 3,501. This equates to an average of 219 for each age-year. For ages 11 and under, the number exceeds this average, and for ages 12 and over, it is less than this average.

The youngest three years average out at 495 cases. The oldest three years average out at 36 cases. The average of the youngest years is about 14 times that of the oldest three years.

In an article published by the US Autism Autoimmunity Project at the end of December 2002, Dr. Ed Yazbak set out the evidence for there having been a huge rise in autism in Rhode Island, New Jersey:

- The Special Education Census published yearly by the Rhode Island Department of Education listed 14 categories of primary disability, by school district. Two categories, autism, and behavioural disorders, had risen sharply.
- Autism had increased by 1,115% (one thousand, one hundred and fifteen per cent) between 1994 and 2002 in Rhode Island schools. On 30th June 1994, there had been 41 students at the schools with a diagnosis of autism. By June 30th 2002, that number stood at 498.
- The more restrictive diagnostic criteria of DSM IV had been used, exclusively, since 1994, and had remained unchanged. Rhode Island has one main diagnostic center, one paediatric psychiatric hospital and very few paediatric neurologists, so consistency in application of diagnostic criteria would be high.

Comment: the above seems to confirm that the recent very steep rises in California are also being witnessed elsewhere in the US.

27. Atlanta Study, Prevalence of Autism in a US Metropolitan Area, by Yeargin-Allsopp, Rice et al, published in the Journal of the American Medical Association, 2003, Jan 1st, 289: (1): 49-55

This study was at last an acknowledgment at the US Center for Disease Control & Prevention that autism was at a higher real level than two decades ago. Its conclusions directly undermined the evidence of one of its participants, Dr. Coleen Boyle, to the US House of Representatives Government Reform Committee, only a short time earlier, that autism was a very rare condition.

- The objective of the study was to determine the prevalence of autism among children in a major US metropolitan area, and to describe the characteristics of the study population.
- The study looked at children aged 3 to 10 years in the counties of metropolitan Atlanta, in 1996. Cases were identified through screening and abstracting records at multiple medical and educational sources, with case status determined by expert review.
- The results were that 987 children were identified, displaying behaviour consistent with DSM-IV criteria for autistic disorder, PDD-NOS or Asperger disorder.
- The prevalence for autism was found to be 34 cases per 10,000
- The conclusion was that the rate of autism found was higher than the rates from studies conducted in the US during the 1980s and 1990s, but was consistent with those of more recent studies.

Comment: this study, too, supports the view that autism has greatly increased. The study is notable for being a CDC-sponsored study, using CDC personnel.

PART D - REVIEWS QUESTIONING THE AUTISM EPIDEMIC

Despite the evidence that autism has increased very greatly since the 1970s and early 1980s, several researchers maintain that this is not the case.

28. Paper by Fombonne, Medical Research Council Child Psychiatry Unit and Institute of Psychiatry, *Is There An Epidemic of Autism?*, Pediatrics, January 2001

At the end of January 2001, a paper, "*Is There An Epidemic of Autism?*" was published by Dr. Eric Fombonne. The paper sought to deny that autism had really increased, and criticised the "*poor research methodology*" of Dr. Andrew Wakefield, and said "*There is no need to raise false alarms on putative epidemics nor to practice poor science.....*"

- Fombonne criticises the California increase on the basis of in-migration, possible changes within the population make-up, the change from DSM-III to DSM-III-R in 1987, the introduction of diagnostic categories for Asperger, Rett and childhood disintegrative disorder in DSM-IV in 1994, the effects of earlier diagnosis adding to the totals, and other factors.
- His most useful conclusion is that "*we simply lack good data*". He raises doubts about the apparent epidemic, but is then unable to refute it either.

In an excellent FEAT (parents' group) critique (8th Feb 2001), Mark Blaxill goes carefully through Fombonne's previous work and argues that Fombonne has become inconsistent. He points out key flaws in Fombonne's previous work, and criticises his criticisms of the California data and his scientifically-unsupported assertions

29. Paper by Lorna Wing, Centre for Social & Communication Disorders, Elliot House, Bromley, Kent, UK and David Potter, UK National Autistic Society, *The Epidemiology of Autistic Spectrum Disorders: Is The Prevalence Rising?*, 2002

This paper noted that:

- For decades after Kanner's original paper in 1943, autism was generally considered to be a rare condition with a prevalence of around 2 to 4 cases per 10,000 children. Then in the late 1990s, prevalence rates of up to 60 cases per 10,000 for autism, and even more for the whole ASD spectrum, were reported.
- Reasons for this included changes in diagnostic criteria, development of the concept of the wide autistic spectrum, different methods used in studies, growing awareness and knowledge amongst parents and professionals, the development of specialist services, and the possibility of a true increase in numbers.

The paper argued that not one of the possible environmental causes, including MMR, had been confirmed by independent scientific investigation

The paper maintained that there was "strong" evidence that complex genetic factors played a major role in aetiology (Comment: this point and the one above seemed to be treated as "either/or" explanations rather than in combination)

In direct contrast with the 2002 California paper, this paper concluded that "the evidence suggests that the majority, if not all, of the reported rise in incidence and prevalence is due to changes in diagnostic criteria and increased awareness and recognition of autistic spectrum disorders. Whether there is also a genuine rise in incidence remains an open question".

30. Position of Dr. Bryna S. Siegal, Director, Pervasive Developmental Disorders Center, University of California at San Francisco, 2002

The August 2002 issue of Paediatric News carried a report by Sherry Boschert, about the position of Dr. Bryna S. Siegal of California, expressed at a meeting on developmental disabilities sponsored by the University of California at San Francisco. Dr. Siegal's view is that:

- Prevalence in autism in California increased from 5 per 10,000 in 1987 to 15 per 10,000 in 1994, yet during the same time, diagnosis of mental retardation declined by a similar amount, dropping the State prevalence of mental retardation from about 27 per 10,000 to around 18 per 10,000.
- Changing social attitudes have shifted stigma away from autism and onto mental retardation
- Autism is partly now preferred because it is associated with a higher level of State services. Dr. Siegal claims that many letters from parents actively seek a diagnosis of autism
- These are not the only factors fuelling what she describes as an "illusory" epidemic of autism. The inclusion of the diagnosis of pervasive developmental disability into the former DSM-III classification in 1980, creating DSM-III-R (or III-revised) resulted in autism rising by one-third. In 1994, the creation of DSM-IV, which included Aspergers cases, further increased the numbers.

Comment: these views have been strongly contradicted by:

- The views of parents, professionals and others, who testify that autism is now being seen in unprecedented numbers
- The point that the autism of the past largely comprised children who were autistic from birth or from a very young age, and that the "new variant" regressive autism was apparently largely unseen and unreported until the late 1980s, and that it is extremely

unlikely that dramatic regression and loss of milestones would have been missed in the past

- Detailed research carried out by Dr. Robert S. Byrd in late 2002 (reported elsewhere in this note), in California, finds that the apparent increase in autism is real, and not ascribable to reassignment from other categories

31. Study by Croen, Grether, Hoogstrate and Selvin for the California Department of Health Services, July 2002

The authors conducted a population-based study of eight successive birth cohorts to examine the degree to which improvements in detection and changes in diagnosis have contributed to the observed increase in autism prevalence. Children born in 1987-1994 who had autism were identified from State registries. To evaluate the role of diagnostic substitution (re-assignment from other categories), trends in prevalence of mental retardation without autism were also investigated.

- A total of 5,038 children with full-syndrome autism were identified from 4,590,333 births, giving a prevalence of 11 per 10,000
- During the study period, prevalence of autism increased from 5.8 per 10,000 to 14.9 per 10,000
- During the same period, the prevalence of mental retardation without autism decreased from 28.8 per 10,000 to 19.5 per 10,000.
- The data, in the view of the researchers, suggests that improvements in detection and changes in diagnosis accounts for the observed increase in autism. However, they also conclude: "Whether there has also been a true increase in incidence is not known".

Comment: this report backs the views of Dr. Siegal (see above) and Dr. Fombonne (see below), but contradicts the study by Dr. Byrd (see elsewhere). The authors also acknowledge that their study cannot rule out that there has been a real increase. The criticisms applied to Dr. Siegal's work also apply here.

32. Fombonne, editorial, Journal of the American Medical Association, January 1st 2003 Vol 289, No.1 49

At the start of 2003, Dr. Eric Fombonne wrote an editorial in the Journal of the American Medical Association that appeared to acknowledge that there had been some real increase in autism, but which also attempted to explain this away to as great a degree as possible through the usual recourse to references to better awareness, less restrictive criteria and a greater willingness to diagnose.

Fombonne's key points were that:

- That the prevalence rate of 34 per 10,000 (1 in 294) was likely to actually be an underestimate, because high-functioning autism cases were likely to have been missed.
- The lower reported prevalence in 3- and 4-year olds might reflect lower sensitivity of case identification for disorders, which were often diagnosed later
- There was an unexpected decrease in prevalence amongst 9- and 10-year olds. Fombonne dismisses the idea that this might imply that the younger the birth cohort, the greater the level of autism as being "biologically implausible". Yet this is open to obvious question - what if an external factor had altered during this time? Fombonne does not address this possibility.

Fombonne concluded that a rate of 41-45 per 10,000 (1 in 222) might be a more accurate rate of prevalence. He noted in his editorial that other studies suggested rates of 60 per 10,000 when pervasive developmental disorder-not otherwise specified (PDD-NOS) and Aspergers syndrome were taken account of.

He then addressed the issue as to whether the prevalence of autistic spectrum disorder (ASD) had increased over time. His benchmark was the 1970s Wing and Gould study in Camberwell, London, which pointed to a rate of 20 per 10,000 for severe-impairment cases. Other earlier studies had point to rates of 4 or 5 per 10,000, and more recent studies cited by Fombonne pointed to rates of more than 10 per 10,000. Fombonne's conclusion was that the most recent rates of prevalence were three or four times higher than 30 years ago.

Fombonne, seemingly searching for an uncontroversial explanation for any increase, then examined whether this increase implied a broadening of criteria and improved methods of case-finding during studies. He pointed to what he described as the "major" changes in criteria:

- Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), 1980
- DSM Revised Third Edition (DSM IIIR), 1987
- DSM Fourth Edition (DSM IV), 1994.

He argued that there was strong evidence that differences in methods for case finding could account for a "huge" proportion of the variability of prevalence estimates between surveys. Referral rates were also unreliable, due to confounding factors. This, and other factors, he concluded, combined to offer "good" evidence to support the contention that higher rates of prevalence reflected changes in diagnostic practice, improved identification and availability of services. The hypothesis of an increasing trend in the incidence of autism could not, in his view, be fully tested because of the inadequacy of studies to date. Fombonne dismissed any association with MMR (citing his own study work and studies by Madsen and by Taylor and Miller as proof), and dismissed evidence of any connection with thiomersal as being "weak".

Fombonne was also quoted in the New York Times of 31st December 2002 as stating: "No strong candidate environmental exposures have been identified.....Claims of an association with

MMR have not been borne out by recent studies, and evidence for causal association with other exposures such as mercury-containing vaccines is weak".

The study being commented on by Fombonne was that by Dr. Marshalyn Yeargin-Allsop et al, detailed earlier.

Comment: the editorial by Fombonne offers no hard evidence against a vaccine/autism link, and, whilst offering some arguments in favour of questioning the precise scale of the apparent major rise in autism prevalence, fails to demolish the central assertion of many parents, that autism has grown immensely in a couple of decades. No alternative explanations for the rise are offered by the Fombonne editorial.

PART E - STUDIES THAT HAVE BEEN USED TO DENY AN MMR/AUTISM LINK

This section deals with the numerous recent official studies and reviews, many in the UK but some in the US or elsewhere, that "prove" there is no connection between autism and vaccination.

As will be seen, all when scrutinised critically are actually either irrelevant, inconclusive, or are seriously methodologically questionable.

- The UK Government's advice on MMR and autism comes from the DoH, the Medicines Control Agency (MCA), the Committee on Safety of Medicines (CSM) and the Joint Committee on Vaccination and Immunisation (JCVI). These bodies are closely intertwined, and have based their position on a barely more than a handful of studies. Further advice has come from the Medical Research Council.
- Much of the focus has been upon the need maintain public confidence in MMR to prevent communicable diseases, rather than the need to investigate specific cases of alleged damage.
- The studies are also of random groups of children, but not of the actual children reported by parents as damaged by MMR.
- Finally, the Department of Health has implied in the past that the evidence for a link between MMR and regressive autism has come from only one team of researchers, which is not factually correct. However, the very same criticism can be levelled at the "anti-link" camp. A significant proportion of the studies below only comes from a very small number of sources, some very close to the Department of Health itself.

33. Stokes et al Paper, Trivalent Combined Measles Mumps Rubella Vaccine, Journal of the American Medical Association, 4th October 1971

This paper, by Stokes, Weibel, Villarejos, Jorge, Arguedas, Buynak and Hilleman, has assumed more importance recently (see later Wakefield/Watson/Shattock debate section).

- The paper stated that triple vaccines were desirable to simplify administration, reduce costs and minimise visits (my emphasis). There was no mention of greater effectiveness, or inherent drawbacks with single vaccines.
- There were three trials, firstly of 30 children in Philadelphia, then of 214 children in Philadelphia, then of 440 children in rural Costa Rica and San Salvador, total 684 but (note) of very different economic and geographical backgrounds.

- The mean ages of children in the three trials was 1.1, 1.5 and 3.0 years. Note that the present age of receiving MMR is about 14 months, and therefore the vast majority of the trial children were significantly older than today's UK MMR recipients. Some 64% were also not from Western social/health backgrounds.
- The 30 children's parents were given report cards for recording temperatures for 28 days, and queried at six to nine weeks. For the 214 child-cohort and the 440 child-cohort trials, follow-up was 28 days. The parents were instructed to notify any significant illnesses during the 28-day period, and were queried at the second bleeding, six to nine weeks after vaccination - but the implication is that this query may have covered the 28-day interval, not longer.
- The study noted that "*the fifth to twelfth day after vaccination is the critical time period for occurrence of the expected low incidence of febrile reaction*", also that the significance of the difference between vaccinees and controls in terms of miscellaneous subsequent complaints (gastroenteritis included) was "doubtful" (though it was actually very marked in the study tables, up to 18/228 of vaccinees with gastroenteritis, compared with at most 3/106 of controls)
- At no point in the study was autism mentioned as a risk-factor or an actual outcome. Clearly, the possibility was not even considered. The study noted the lack of arthritis and arthralgia.

Overall verdict: this study is not relevant to disproving an MMR/autism link

34: Study of Twins By Peltola and Heinonen, *Frequency of True Adverse Reactions to MMR Vaccine; A Double-Blind Placebo-Controlled Trial in Twins*, National Public Health Institute and Children's Hospital, University of Helsinki, Finland, published Lancet, April 26th 1986

This study sought to check levels of adverse reactions following MMR. MMR was introduced into Finland in 1982, being administered at 14-18 months and at 6 years, using Merck Sharp Dohme Viravac.

- The study was a double-blind crossover study involving 581 twins. The vaccines were administered blind, but one twin of each pair first received active MMR, then three weeks later, received a placebo. The other twin was given the placebo first, then three weeks later received MMR.
- Each twin was given a colour coded questionnaire to be completed daily by parents, for 21 days after the injections.

In theory, this should have provided a foolproof test of how reactive MMR was. However, the study completely founders on:

- the issue of the potential time-delay between receipt of MMR and any possible gradual degeneration into autism. If such a delay could exceed 21 days, then the study would have missed it as an adverse reaction
- Secondly, the linking of autism/developmental delays with MMR, or indeed any other vaccine. Parents in 1982, or indeed until about mid-1997, were not linking MMR with autism. It is extremely unlikely that regressive autism would have been connected, in the minds of either parents or the study authors, with MMR back in 1982. Virtually no literature or press reports had appeared on the issue.
- As with the original safety trials of MMR (see later papers), this study was not designed to verify whether rare and complex adverse events might follow months or years after MMR.
- The study only looked at one brand of MMR. As subsequently transpired, some brands of MMR used in the UK and elsewhere had a less satisfactory safety record than others, and (in the UK) were withdrawn at very short notice in 1992. A study with Viravac cannot be used to give safety clearance to other brands if the brands are found to have been variable.
- A further criticism is that the study is still quite small in relation to rare events. It involved 581 twins. All other things being equal, if a rare adverse outcome occurred at a rate of 1 in 2 x 582, or less frequently, this study would not have found it.

The authors did actually acknowledge this, stating:

- *"The study was designed to explore relatively common symptoms and signs occurring after the vaccination" (they mean, "within 21 days of"), and*
- *"Rare reactions due to the MMR vaccine cannot be studied with this small sample".*

It is therefore suggested that this study, regarded as the "gold standard" by the exponents of MMR, offers no evidence for or against an MMR/autism link; it is clearly irrelevant. Overall verdict: this study is not relevant to disproving an MMR/autism link

35: Study by Miller, Miller, Rowe et al, *Surveillance of Symptoms Following MMR Vaccine in Children*, The Practitioner, Vol 233, 8th January 1989

This paper was to report the incidence and severity of clinical reactions before the start of the UK national MMR programme. MMR was offered to 10,000 children in three districts in the UK, with a post-vaccination follow-up of every child.

Two types of MMR were introduced, Immravax in Somerset, England, and Pluserix in Fife, Scotland, and North Hertfordshire, near London. Both vaccines contained Schwarz measles and

Urabe 9 mumps vaccine, and both later had to be withdrawn in 1992 for safety reasons, in connection with risks of aseptic meningitis. These risks were not detected by this study.

The study found that:

- Of the 7,247 children aged 1-2 years, 38% had either no symptoms or symptoms for only one day
- 18 had convulsions. Fifteen were admitted to hospital.
- Of the children aged 4-5 years, 61% had either no symptoms or symptoms for one day. There were no convulsions and no hospital admissions.
- Follow up was for 21 days. However, 114 children were followed up through diary records for a further 21 days, total 42 days.
- Comparison of symptoms of children after MMR was made against symptoms of children after measles vaccination - not unvaccinated children.
- The study concluded that symptoms reported after MMR appeared to be similar in nature, frequency, time of onset, and duration, to those recorded in earlier studies after monovalent measles vaccine

Comment: as with the original safety trials of MMR, follow-up was extremely short and only immediate/near-immediate reactions noted. The study did not look at autism, but effectively cleared the way for MMR's general introduction into the UK. It is noteworthy that the study was co-authored by Dr. Elizabeth Miller, who subsequently authored or co-authored several of the studies that have been used as "proof" that there is no MMR/autism link. It is also noteworthy that, as noted, this study missed the aseptic meningitis problem of MMR, and that the brands of MMR with Urabe strain mumps virus subsequently had to be withdrawn, in 1992, at extremely short notice.

Overall verdict: this study fails to disprove an MMR/autism link

36. Gillberg Study, Sweden, *Is Autism More Common Than Ten Years Ago?*, British Journal of Psychiatry, 1991, 158; 403-409

The paper reported a study in Sweden by Gillberg et al, 1991. It has been partially updated since (see below).

- Gillberg looked at tiny sample of autistic children (55 of typical autism, just 19 of atypical autism), in Goteburg and Bohuslan. The study, actually a mish-mash of three studies with differing criteria, does not mention vaccination, does not state the coverage of

MMR, does not include data on uptake or demographic factors, and is therefore irrelevant to the MMR/autism debate.

- It had tracked down cases of autism unscientifically, by word of mouth, doctors etc., then allocated them by d.o.b. to "pre-MMR" and "post-MMR" eras
- The study's case-selection being a few cases out either way would neutralise or completely reverse the findings of the study.
- The paper does acknowledge that the rate of autism has increased but "explains" this through changes in population structure and "better diagnosis".

Overall verdict: this study offers little evidence that MMR does not cause autism, particularly as it is so small.

[Feb 2003] [Professor Christopher Gillberg](#)

37. Paper by Gillberg and Heijbel, Commentaries, Autism, Vol 2 (4) 423-430, 1998

This further paper by Gillberg was published following the appearance of the Wakefield et al "Early Report" paper in The Lancet in early 1998.

Gillberg and Heijbel stated that they had re-analysed the data from their population study of autism performed in the late 1980s and published in 1991 (as above). The children in that study (n = 55) had been born in the ten-year period 1975-84. The authors claimed that as MMR was introduced in Sweden for 18-month-old children in 1982, with coverage increasing rapidly to 90%. The authors then argued that if there was an MMR/autism link, then children born from July 1980 onwards (i.e. The post-MMR generation) would be expected to be at increased risk. The 55 children were therefore divided into 34 (62%) pre-MMR and 21 (38%) post-MMR.

The authors then argued that had there been a strong effect of MMR, they could have expected more than 45% of the 55 cases of autistic children to have fallen into the post-MMR group. As this was not the case, then their study did not support the hypothesis of an association between MMR and autism

The authors also again claimed that in their parallel study of 19 atypical autism cases, there would have been a similar effect, and therefore that again there was no support for an association.

Overall verdict: as with the original study, these numbers were so small as to render this study, and its conclusions, as virtually without value in the context of proving/disproving an MMR/autism link. Statistical/epidemiological studies based upon cohorts numbering 55 and 19 cases are far too small. It is extraordinary that the UK Department of Health was using this study in the late 1990s to "disprove" the suggested association.

38. Letter by Dr. Eric Fombonne, *Inflammatory Bowel Disease and Autism, Pediatrics, March 28th 1998*

This letter set out two studies that attempted to prove that there was no connection between inflammatory bowel disease/Crohn's disease and autism. The first study looked at UK clinical data collected by the Child & Adolescent Psychiatric Services of the Maudsley Hospital, London.

- For ASD, three diagnostic groups were examined, autism, atypical autism including disintegrative disorder, and pervasive developmental disorder
- Medical disorders were coded for a 25-year period, including Crohn's and ulcerative colitis, for 8889 patients.
- Of the 8889 patients, 987 were born in 1987 or later, and were therefore most likely to have been exposed to MMR. Of these, 201 had ASD.
- Of the 8889 children, only two had Crohn's, and both were non-autistic. None had ulcerative colitis.

For the second study, a similar approach was undertaken. Fombonne surveyed medical, behavioural and intellectual disabilities amongst 6100 French children.

- He found 174 cases with autism.
- One child of the 6100 had Crohn's, and one had ulcerative colitis. Neither were autistic
- The conclusion that Fombonne drew was that these data provide no support for the hypothesis of an association between IBD and autism.

Overall verdict: neither of these studies offer any evidence to disprove an MMR/autism link.

39. UK Committee On Safety of Medicines Study, *Report of the Working Party on MMR Vaccine, Committee on Safety of Medicines, June 1999*

This study looked at the medical records of some of the children who are now taking High Court action. Their details were provided by their lawyers.

The study admitted:

- Information on the children was extremely variable in quality and completeness
- It was "difficult" to draw conclusions about any causal association (verbatim quote: "*the information evaluated has important intrinsic limitations as regards assessing whether the vaccines are or are not causally associated with the adverse effects*")

- It was not feasible to review the less common adverse side effects

The study was effectively run as knockout competition. Each case had to pass four hurdles (all four) to be counted as being caused by MMR. The four hurdles were: (1) have either the diagnosis or clinically relevant signs/symptoms been confirmed medically? (2) was the onset of the possible adverse effect within six weeks of immunisation with MMR? (3) was there history prior to immunisation relevant to the possible adverse effect? (4) was there evidence of other causes for the possible adverse effect?

- Six weeks after immunisation was chosen as a cut-off point for a close temporal association because (quote) "*this is the maximum period in which viral replication can be detected after immunisation*". But this probably missed many cases, and is arbitrary. The Spitzer, Aitken et al study (see later) renders this six-week limit as irrelevant.
- At every stage, the study looked for other "causes" to explain-away the cases, and took every opportunity to ascribe cases to these "causes". In most cases, it was assumed at every stage without scientific justification that autism was "caused" by other factor rather than MMR. But it is not known what causes autism. Therefore there is a gross study bias, and the study rests upon unscientific assumptions.
- The other assumed "causes" were the child's previous medical history, comprising having a parent/sibling with speech or behavioural problems, an obstetric history of pregnancy complications (these, alone, were not considered as "causes"), signs/symptoms of encephalopathy, a head circumferences larger than the 97th percentile, or history of unspecified viral illnesses, bronchiolitis, rubella, measles, or a minor head injury.
- The study eventually only looked at 92 cases of autism in detail (plus 15 Crohn's), and was left with a residue of 8 autism cases and four of the Crohn's it could not "explain" away. These were then just set aside, without explanation.
- What the study did was to introduce so many extraneous considerations, and accord these such an importance, that hardly any case with sufficiently-clear documentation remained to survive the appraisal process. This eliminated almost all cases. The study then appears to have then simply set aside the residue.
- The study text commented that (quote) "*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*". This would seem to inevitably render the study as inconclusive. But the study's conclusions did not reflect this sentence.
- The wording of the final conclusion left a small exit-route for any possible future U-turn: ""*On the basis of all the available evidence, the demonstrated benefits of MMR or MR vaccines far outweigh any possible risks*" (my emphasis).

- The DoH's press release 0342 of 1999 spun the study's conclusions further - "*Two New Independent Studies Have Not Found A Link Between MMR Vaccination And Autism*"

Note: this is the only study to date to have both looked at the actual children reported to have been damaged and to have "cleared" MMR. But as the above criticisms show, the study was actually self-admittedly inconclusive. It also failed to medically examine the actual children.

Overall verdict: this study does not disprove an MMR/autism link.

40. Paper by Taylor, Miller, Farrington et al, *Autism and Measles Mumps Rubella Vaccine: No Evidence for a Causal Association*, Lancet 1999, 353, 2026-9

The study, designed by Dr Elizabeth Miller of the Public Health Laboratory Service, was wholly inconclusive, but has been widely presented as conclusive proof of the absence of any link between MMR and autism.

- It only looked at 498 cases, far too small a sample for a robust statistical (case-series analysis) test. The study attempted to track-down children through special schools and local authority special needs registers - a method that is open to question, as it probably misses many cases. The study describes itself as "*a large regional sample*", but it was actually very small.
- Taylor, Miller found a steep increase in autism, ("*There was a steady increase in cases by year of birth*"), but did not explain it.
- Also, the study looked for a time-clustering of parental concern six months after MMR, found it, but then dismissed it unconvincingly by saying it was "*related to the difficulty of defining precisely the onset of symptoms*". But this method, of precisely identifying a date, was meant to be the very basis of their study.
- Also, the study did not include in its post-MMR numbers those children born 1986-87 who later received it, nor those 2/3/4 year olds who had MMR at this older age.
- It also missed children who had single vaccines, then MMR later. It not only misses these from "post-MMR" numbers, but added them to its pre-MMR numbers. The whole study is thereby compromised. The authors have since sought to clarify this in correspondence in The Lancet, but unconvincingly.
- Autism is sometimes not diagnosed for years after. It is very difficult to pin down an actual "date" of diagnosis, and many children don't receive any formal diagnosis anyway (contact National Autistic Society, which did a study on this, tel 0207 833 2299). The Taylor Miller study doesn't recognise this.

- The study seems to have been designed to clear MMR, not to test whether there is a link with autism. The study struggles, and fails, to disprove a link.
- Also, the study is described by the UK DoH as "independent". But Taylor was co-author of a 1988 paper clearing the safety of triple vaccines, Miller was described in Daily Express press reports of 1/01 as "*a colleague of Dr David Salisbury*" (head of the DoH Immunisation & Communicable Diseases Branch, which runs the MMR programme), and the study was funded by the UK Medicines Control Agency, a satellite of the DoH.
- The authors have been repeatedly challenged by other researchers to release their raw data but have refused. Yvette Cooper, the UK Minister for Public Health, has backed up their refusal.

Overall verdict: despite its claims, this study cannot be taken as proof of there being no MMR/autism link, due to its apparent serious methodological flaws.

(Note: this study has been claimed by the UK Medical Research Council to represent "strong positive evidence" of there being no MMR/autism link)

41. Paper by Miller and Farrington to US Government Reform Committee Hearings, *Written Testimony to the Congress of the United States Committee on Government Reform Hearing On The Challenges of Autism - Why The Increased Rates, April 2001*

In their submission to the US House of Representatives Committee on Government Reform Hearing, which was investigating increases in autism and possible links with vaccination, Miller and Taylor re-stated:

- *"Our conclusion, based on the findings of our study, is that there is no evidence of a causal association between MMR and autism".*
- *"The case series method has a proven track record with respect to identifying and measuring a risk of adverse events after various vaccines".*
- *"In our study, we showed that the increase in the prevalence of diagnosed autism in recent birth cohorts occurred during a time when the coverage of MMR vaccine in the same cohorts has been constant. The rise cannot therefore be related to the use of MMR vaccine."*
- *"There is no credible epidemiological evidence to support the view that measles vaccination is a risk factor for Crohn's disease or any other inflammatory bowel disorder".*

However, as explained in the section covering the original paper by Miller, Taylor and Farrington, there are major questions over the methodology of this paper; these, of course, can also be applied to Miller and Farrington's paper to the Government Reform Committee.

42. Patja, Peltola et al Study, *Serious Events Rarely Related to MMR Vaccine: Natural Diseases Outweigh Risks*, Pediatric Infectious Disease Journal, 2000;19; 1127-1134 (December)

This Finnish study, usually referred to as the Peltola study, concluded that serious events rarely were related to MMR. The study was initiated in 1982, when MMR was introduced. A nationwide surveillance system was set up to detect serious adverse events, reviewing patients' clinical records and where taken, serum samples. However, the study relied on passive surveillance - a fatal flaw - and only followed up acute adverse events - a further fatal flaw.

According to the report,

- 173 potentially serious adverse reactions were claimed to have been caused by MMR, out of almost 3 million doses.
- There were 77 neurologic reactions, 77 allergic reactions, 22 miscellaneous reactions and one death.
- Some 45% of these reactions were dismissed by the study as probably caused or contributed by other factors.
- Peltola admitted on BBC Radio 4 on 13/1/01 that the Finnish study was not designed to look at either autism or inflammatory bowel disease. He confirmed that the study was not specifically designed to look for autism, as no-one had ever raised this issue at the time.
- The Peltola study simply identified the 173 children (out of 1.8m persons, including troops), who had acute reactions to MMR, then followed only these children up. The study followed up the wrong children. No-one has ever suggested that autism follows an acute reaction.
- There would almost certainly have been potential autism cases amongst the remainder of the 1.8m, but these were missed, because they were excluded from the study, as it had a 3-week cut-off for reporting reactions. After that point, the remaining (theoretically, 1,799,827) children/other persons were ignored.
- Peltola relied on referrals from health workers out in the field, who would never have connected degeneration into autism, several months/years after MMR, as being a potential adverse reaction to a vaccine. The alleged syndrome was not known of by scientists, let alone by health-workers in the field, at that time.

- The UK DoH interpretation of this study, widely trumpeted during 1/2001, is that Peltola "clears" MMR of a link with autism/IBD. It is difficult to accept that this "conclusion" has any degree of scientific justification. It appears that the DoH's "conclusions" have been retrospectively bolted-onto an old and irrelevant study.

There are other awkward facts regarding the Peltola study:

- The study was part-funded by Merck Sharp Dohme (MMR manufacturers).
- The study barely refers to autism or IBD.
- Reviews of the study (eg December 2000 Medscape) do not even mention autism/IBD, which are obviously not seen by the reviewers as a relevant aspect of this study.

Despite this, the Peltola study continues to be cited by the UK medical establishment as conclusive proof that there is no link between MMR and autism. As late as 12/2001, Dr. Simon Fradd of the General Medical Council's Doctor-Patient Partnership quoted this study by Peltola on BBC Radio 4 as conclusive proof of the absence of any link.

The UK DoH also said in a personal communication, referring to all the various studies: "*the follow-up time (three weeks) was based on knowledge of the replication rates of the vaccine viral components.....it is recognised that such a study could not establish a causal relationship with extremely rare events..... millions of children have received MMR in other countries such as Finland and the USA; no serious long-term complications have been identified....*" (my emphasis).

Overall verdict: this study is wholly irrelevant to the issue of whether MMR can cause autism.

43. The Kaye, Melero-Montes and Jick Paper, MMR Vaccine and the Incidence of Autism Recorded by General Practitioners: A Time Trend Analysis, British Medical Journal, February 2001

This paper attempted to prove that there was no link between MMR and autism because, although autism increased when MMR was introduced, it has carried on increasing since, even though MMR's coverage reached near-saturation almost immediately after its introduction into the UK in late 1988.

- The study looked at 305 children (254 boys) aged 12 or under with autism diagnosed in the years 1988-99. It also looked at 114 boys aged 2 to 5 years born in 1988-93. It used the UK General Practice Research Database.
- The study found that autism had increased sevenfold from 0.3 per 10,000 in 1988 to 2.1 per 10,000 in 1999 (note how low this figure is compared with other studies)

- In the 114 boys born 1988-93, it found autism had increased fourfold, from 8 per 10,000 (1 in 1250) for boys born in 1988, to 29 per 10,000 (1 in 345) for boys born in 1993, during a period when MMR take-up was claimed to be constant at around 97%.
- The study concluded that no correlation existed between MMR and autism, and that the explanation for increased autism remained uncertain
- However, the authors acknowledge that their methods were a "second-best", because what they really wanted to do was compare vaccinated and unvaccinated cohorts of children. They said that this was impossible because only 3% of cases and controls did not receive MMR. Given the very small numbers of autism cases they in the event actually looked at, this seems an unconvincing argument for abandoning their preferred approach
- The authors then argue that if MMR was a major cause, then the risk of autism should have stopped rising within a few years.
- However, they also admit that the diagnosis of autism was not confirmed from original records, but conclude that "*differential misclassification of the diagnosis in vaccinated and unvaccinated children is unlikely to vary over the period of the study*", though no evidence is offered to back this claim.
- They also acknowledge that time trend analysis is a "*relatively crude method*".
- The study authors go on to speculate that the increase in autism that they found "*could be due to increased awareness of the condition among parents and GPs, changing diagnostic criteria or environmental factors*", without subjecting these "explanations" to any detailed scrutiny.
- The authors also acknowledge the further limitation that they have not yet obtained and evaluated full clinical record information from GPs to describe more fully the characteristics of children diagnosed with autism and to explore other possible explanations. Yet they still dismiss MMR, despite this shortcoming.
- It might be the case that the increase in autism that the authors find, over the period 1988 to 1997 (note - not 1999 - the study figures actually fall away after 1997) could be due to a hybrid explanation, with increases in the early years due to MMR and then continuing further increases in the later years due to better awareness. There is nothing in the study to refute this criticism
- It is also unclear how the issue of re-vaccination has been dealt with. What of the seven million children vaccinated or re-vaccinated in 1994 in the UK "Operation Catch-Up" programme? Couldn't the continuing rise in diagnosed cases in 1995-97 be due to Operation Catch-Up? The study does not mention it.

- It is interesting that the Finland study team (Patja et al) said "*Causality between immunisation and a subsequent untoward event cannot be estimated solely on the basis of a temporal relation.*" Yet the Kaye et al study uses a basically similar approach to "prove" there is no link, comparing temporally-linked trends in MMR take-up and autism increases.
- There is also a question over the use of mercury-based preservative (thiomersal, or thimerosal) in vaccines. This was used in the late 1980s and early 1990s, but has reported to have been largely phased-out in the US, with a free exchange system being operated by the manufacturers. No such exchange has operated in the UK, with existing thiomersal-based stocks being used up on the children. Autistic enterocolitis may involve thimerosal as part of the damage sequence.
- If it did, and following a change in formulation, then this might well explain continued rises in autism through the 1990s, then a fall-away in increases at the end of the decade, as was actually found by Kaye et al. Did the industry change the preservative formulation as public concern grew? And has this affected the statistics of autism?

Overall verdict: this study offers no convincing evidence against an MMR/autism link.

44. Paper by Dales, Hammer and Smith, *Time Trends In Autism and in MMR Immunisation Coverage in California*, Journal of the American Medical Association, March 7th 2001 Vol. 285, No. 9, 1183-1185

This paper, entitled "Time Trends in Autism and in MMR Immunisation Coverage in California" is one of the least conclusive and least robust of all the research of recent years. It appeared in JAMA, March 7th 2001, but it is surprising that it achieved such a high profile within the UK, so weak was its hypothesis and so inconclusive its contents.

The paper attempted to determine if a correlation existed in trends of MMR immunisation coverage and autism occurrence. It did this by examining data from 21 regional centres covering the whole of the State of California.

During the years examined, 1980-94, MMR take-up was about 72% prior to 1988 and about 82% after 1988. Autism increased from about 200 in 1980 to about 1200 in 1994. The trend of increasing autism continued after the introduction of MMR and was claimed to be unaffected by the increase in take-up.

This hypothesis, of a correlation, could be criticised as not being useful to the detection of any MMR/autism link. Although immunisation coverage can be determined, with a specific "date of immunisation", autistic spectrum disorder ranges from the mild to the severe, its onset ranges from the rapid to the gradual, and its diagnosis varies from a timely and accurate diagnosis to no diagnosis whatever. This apparently was not taken adequate account of by Dales et al.

The study did acknowledge some weaknesses itself:

- *"Diagnosis is not always straightforward"*. This is an extreme understatement.
- *"California Department of Developmental Services' report stresses that its patient caseload data cannot be used as a true measure of changes over time in autism incidence because other factors can affect trends in system case numbers"*
- *"Observation of parallel trends over time.....generally do not constitute strong evidence for a causal association between the two events"*
- *"As the system expanded and matured over time, the proportions of California children enrolling and the distribution of ages at enrolment likely (my emphasis) changed over time as a result"*. Clearly, the authors do not know, one way or the other, not do they attempt to quantify this to enable their reliance on the data to be validated, or appropriate potential distortions in the data eliminated.
- *"Also, the proportions of children enrolling in the system who were born outside California may (again, my emphasis) have changed over this time period"*. Again, they do not know, have not attempted to quantify this factor, and cannot correct for it.
- *"The data presented herein have some limitations. It would have been useful to examine individual immunisation and autism records on the same children; however, these could not be linked"*. What the authors are saying here is, they would like to have done a rigorous study, but they couldn't obtain the data.
- *"Further, the childhood immunisation coverage data used in this study do not provide precise quantification of the percentage of children who received the combined MMR vaccine product vs. separate injections"*. This is an admission that one element of the two elements that provide the statistical comparison that is central to their hypothesis, is inaccurate. They go on to say that historical data from elsewhere in the US *"strongly suggests"* that the use of separate vaccines was *"rare"* for the 1984-94 birth cohort. How strong? How rare?
- Despite this catalogue of drawbacks and "softness" - or complete absence - of data, the authors then go on to claim that they have been *"unable to demonstrate a correlation between secular trends in early childhood MMR immunisation coverage and autism caseload"*. A dispassionate and objective observer would find this wholly unsurprising.
- The assumption that there would be a plateau in the increase in MMR (to match a plateau in take-up of MMR) would only be valid if the background susceptibility of the infant population has remained constant. If successive generations of children became increasingly susceptible to an adverse event such as autism, caused by MMR, then this might well be reflected in a continuing rise in autism. This obvious possibility is not

addressed. It does not have to be the case that the relationship between MMR and autism is a simple linear one, without other factors being involved.

Overall verdict: this study is not relevant to disproving an MMR/autism link. If the study does have a value, it is to demonstrate that extremely weak studies are not only capable of achieving publication - apparently without attracting peer-review criticism - but also that they are then uncritically welcomed, and publicised, by one side of the argument. This in itself is illuminating.

45. Paper by DeWilde, Carey, Richards et al, *Do Children Who Become Autistic Consult More Often After MMR Vaccination*, British Journal of General Practice, March 2001

This paper appeared in the *British Journal of General Practice*, March 2001. It attempted to test the hypothesis that a degeneration into autism, with subsequent diagnosis, would be reflected in increased consultations with the child's general practitioner.

This would appear to be an extremely weak hypothesis to test. For example:

- It may be difficult to place a definite date upon degeneration
- Parents may not seek assistance from their GP immediately, or even at all in some cases
- Parents may seek advice from health visitors or other health professionals
- Parents may see a GP only once, to obtain a referral to a specialist paediatrician
- Parents may see their GP for reasons unconnected with autism, confusing the data in some cases
- Parent may be extremely reluctant to see their GP, because of the sometimes extreme practical difficulties of taking an autistic child to a public surgery, with waits etc.

The study authors do not acknowledge any of these serious potential methodological flaws, nor do they attempt to quantify them in an attempt to validate the effectiveness of their methodology.

The authors looked at only 71 cases of autism, a small sample by any standard for testing a statistical hypothesis, and identified numbers of consultations from a primary health care database. It found that there was no significant difference between cases and controls for numbers of consultations in either the six months before/after immunisation, or the two months before/after immunisation.

The study also noted

- that there was a significant fall-off in consultations in the six months after immunisation, in both cases and controls. However, it did not address the possibility that this might have been for two entirely different reasons, with healthy children not needing to be taken to their GP, and autistic children not being seen by their GP for other reasons such as those set out earlier. The study simply assumed that the fall-off in the cases and the control group was for the same reason, without evidence to underpin this assumption.
- It acknowledged that it could be criticised because the study authors "*cannot confirm that our cases truly suffer from autism*"
- The study, like almost all other studies that "prove" no MMR/autism link, did not specifically address the cohort of children alleged to have degenerated as a consequence of MMR, and who are now proceeding through the legal processes
- It acknowledged that "*some diagnoses will have been missed*"
- It admitted that "*it seems unlikely (my emphasis) that these will be specifically those associated with MMR*", although it offers no evidence to support this assumption.
- The study notes that "*the clear difference in consultations in the six months before the diagnosis of autism*" (between cases and controls) "*emphasises that consultations were being recorded and that differences in consultation rates between cases and controls were detectable*". But the study does not address the possibility that the higher frequency of consultations by cases is linked to a potentially-associated condition, such as otitis media (and consequent antibiotic use), and that cases moved from more frequent consultations than controls for such a condition, to more frequent consultations than controls for a wholly different and more serious condition.

Overall verdict: this study is not relevant to disproving an MMR/autism link. In short, there are so many caveats, acknowledged and unacknowledged shortcomings and other methodological limitations to this study that its conclusions are virtually valueless. Again, it is illuminating that it has been so well received by one side of the debate (the UK Department of Health).

46. Study by Davis et al, *Measles-Mumps-Rubella and Other Measles-Containing Vaccines Do Not Increase the Risk of Inflammatory Bowel Disease, Archives of Pediatrics and Adolescent Medicine, 2001, 155: 354-359*

This study was conducted in the US on the populations of four health maintenance organisations as part of a vaccine safety programme co-ordinated by the Centres for Disease Control and Prevention.

The study focussed on the following questions:

- Was the age of first vaccination with MMR or other measles-containing vaccine, or receipt of vaccination itself, associated with an increased risk for Crohn's disease or ulcerative colitis later in life?
- Was receipt of MMR or other MCV associated with the acute onset of disease shortly following vaccination?

In each of the areas, trained staff reviewed medical records. Cases were of individuals enrolled since birth (some as early as 1958) to 1989. It was claimed that consistent criteria were used for definite and probable diagnosis of Crohn's disease, ulcerative colitis or unspecified irritable bowel disease. This involved diagnosis by a gastroenterologist, "with signs and symptoms and a diagnostic test for IBD". Five controls were selected for each case, matched by sex, health organisation and year of birth. Dates of vaccination, type of vaccine and date of diagnosis were also recorded.

There were 155 cases of IBD with 152 definite or probable cases. Seven had no discernible onset, two were of "unspecified disease" and one was vaccinated when older than 10 years. This left 142 cases and 432 controls for further analysis.

The study found that:

- the risk of inflammatory bowel disease was the same whether for vaccinated or unvaccinated people
- there was an average of 140 months between vaccination and diagnosis for cases.
- Only 1% of cases developed inflammatory bowel disease within a year of vaccination
- Only 1% of controls developed inflammatory bowel disease within a year of vaccination.
- Whether children were vaccinated before 12 months, between 12 and 18 months, or after 18 months, showed no difference in the risk of developing inflammatory bowel disease

However, the study team had to acknowledge several serious limitations to this study:

- Only patients with a physician diagnosis (usually a gastroenterologist) were included. This could have potentially missed many cases, particularly if those missed were of an insidious new variant
- The team acknowledged the inherent limitations of diagnostic accuracy in any retrospective study

- They had little information on children or adults with non-specific colitis that did not lead to an eventual diagnosis of IBD - surely a key failure, given the nature of the research by the Wakefield team at the Royal Free Hospital in London
- There was an acknowledged limitation over statistical power. The report admitted: "*We were able to effectively rule out associations larger than 2-fold between ever being vaccinated with MMR and developing IBD, and associations larger than 3-fold between vaccination with other measles-containing vaccines and IBD. However, we had a limited sample size from which to look at the independent associations between vaccination and either Crohn's disease or ulcerative colitis, or at the relationship between timing of vaccination early in life and subsequent risk for Crohn's disease or UC.*" This seems to be a serious self-criticism, yet oddly it does not seem to have had much effect on the study's assertive conclusions.

The study's reliance on patient records should also be questioned. The analysis of records can by definition be only as good as those records themselves. No study (as far as is known) has yet endeavoured to verify whether children suffering from acquired autism, ileal lymphoid nodular hyperplasia or non-specific colitis have medical records that accurately reflect these conditions. There are grounds for suspecting that the very reverse may be the case. The difficulties in obtaining a clear and timely diagnosis of autism are well known. The nature of the autism problem, with many patients without speech, means that the precise nature of the patient's complaints and symptoms may be poorly recognised, and even more poorly recorded.

Overall verdict: although this study at first sight appears more persuasive than some others, it too fails to provide convincing evidence against an MMR/autism link. The study may be seriously flawed due to its retrospective nature, when the condition in question (acquired autism after MMR/MCV) has only recently received publicity, and because of doubt over records.

47. Further Paper by Farrington, Miller and Taylor, *MMR and Autism: Further Evidence Against a Causal Association, Vaccine, 19 (2001) 3632-3635*

When it became apparent to Taylor, Miller and Farrington that the time-lapse for degeneration into autism might be a protracted one, they were obliged to re-analyse their earlier data.

- Farrington, Miller et al repeated their view of the original Wakefield study, that it was very small (12 children) and that the interval between receipt of MMR and first behavioural symptoms varied from 24 hours to two months. However, the Wakefield study cohort subsequently grew to about 200, and this has not been acknowledged by Farrington, Miller et al in this further paper.
- The Farrington, Miller et al study also has not taken account of the Spitzer, Aitken et al study and its implications (see later sections). They also maintain that they "*found no evidence to support a causal association*". But they themselves, in their first study,

unconvincingly dismissed a clustering of parental concerns at around six months. They maintain this unconvincing stance.

- Farrington et al concluded that the temporal association found by Wakefield et al was "*a combination of selection bias and chance*". This latter is a highly contentious conclusion, suggestive of wishful thinking, in the same way as the dismissal of the six-month clustering was.
- In this second paper, the authors seek to re-test their earlier conclusions by removing any preconceived fixed-time interval between vaccination and the onset of autism. Again, they use a statistical methodology, self-matched case-series analysis, but once again with a very small (for this method) data set of just 64 cases of what they describe as "unvaccinated" children with autism - presumably, they mean "unvaccinated with MMR" - plus 231 cases of children with autism who had received one dose of MMR, and a further 62 cases of children who had received two doses of MMR (total 357 children).

The study found that:

- for the 357 cases, the observation periods had a median of 89 months, a maximum of 191 months.
- The oldest age at diagnosis was 180 months.
- Some 64 did not receive MMR.
- Some 43 received MMR after age 2 years, at median age 57 months, maximum 165 months.
- Some 62 cases received a second dose of MMR, at median age 54 months, maximum 159 months.

The comparison of relative incidence for each group finds that there is little difference between those that had received MMR and those previously referred to as "unvaccinated", but which seems to have really meant "vaccinated with single-antigen measles vaccine" - the paper is not clear.

The major criticism of the earlier paper using this data (see above section) were that there was only a proxy for "onset of autism" (a questionable term in itself). The original study measured diagnosis, parental concern and regression (if applicable) from medical records. But these would be variably delayed from any actual "onset event". The very poor correlation between these proxies and the "event" means that the analysis loses all statistical power.

Major criticisms of this further re-worked paper's statistical methodology are that:

- Regarding the whole period following MMR as being "at risk" is questionable.
- Looking to see if those who have MMR earlier have a proxy variable earlier is erroneous, when one observes the very narrow timescale for the application of MMR in this paper. When the input signal (the age of receipt of MMR) has very little variability, one would be unlikely to find this reflected in the output signal (date of diagnosis)
- The above flaw means that the only statistical power left is coming from finding any difference between those who have MMR and those who have not. But most of those who do not have MMR are those older children who are of the pre-MMR generation. So Farrington et al's analysis is effectively asking whether those who are older had had an earlier or later onset of autism (as measured by the proxy variables).

Overall verdict: this study fails to provide any convincing evidence against an MMR/autism link.

(Note: this study has been claimed by the UK Medical Research Council to represent "strong positive evidence" of there being no MMR/autism link)

48. Paper by Fombonne & Chakrabarti, *No Evidence for a New Variant of Measles-Mumps-Rubella-Induced Autism*, Pediatrics, Vol. 108 No. 4 October 2001

This paper examined whether there is a new phenotype of autism involving regression and gastrointestinal symptoms.

It is suggested that where this paper is flawed is in the assumptions underpinning the hypotheses that are tested. All else stems from that. Fombonne & Chakrabarti assume that if autistic enterocolitis existed, then one or more of the following six predictions should be supported by empirical data:

- Prediction (1) - "*childhood disintegrative disorder has become more frequent*". (The study found the prevalence of childhood disintegrative disorder to be 0.6/10,000, or 1 in 16,666. But this seems far too low in comparison with other recent studies).

Comment - historic data is not available to prove this either way. The claim that the present rate of 1 in 16,666 represents no increase is further undermined by its non-credible low level. Other studies have found rates very many times higher. This strongly suggests that the study is flawed.

- Prediction (2) - "*the mean age of first parental concern for autistic children who are exposed to MMR is closer to the mean immunisation age than in children who are not exposed to MMR.*"

Comment - the study found that there was no difference in the mean age at first parental concern between the two samples exposed to MMR (19.3 months and 19.2 months) and the

pre-MMR sample (19.5 months). But no argument has been presented as to why there should be a difference. A difference might be expected, but its absence in itself does not prove anything. It is perfectly possible that childhood disintegrative disorder has several causes, and that the arresting of development could be noticed at around the same time. Pre-MMR children who became autistic may well have become so due to an adverse outcome from monovalent measles vaccine. This possibility does not seem to have occurred to Fombonne. There is also a simplistic focus upon MMR alone as a sole factor, working in isolation, rather than as part of a complex process.

- Prediction (3) - "*regression in the development of children with autism has become more common in MMR-vaccinated children.*" The study found that the rate of developmental regression reported in the post-MMR sample (15.6%) was not different from that in the pre-MMR sample (18.4%) and therefore there was no suggestion that regression in the development course of autism had increased in frequency since MMR was introduced. The study also found that in the epidemiologic sample, the subset of autistic children with regression had no other developmental or clinical characteristics, which would have argued for a specific etiologically distinct phenotype.

Comment - the samples were small. The study used three samples, a post-MMR sample of 96 children with PDD, a pre-MMR sample of 98 autistic patients, and a post-MMR sample of 68 autistic patients. These are very small numbers to use in a statistically-based study. Fombonne and Chakrabarti's results should thus be treated with caution, as a few cases either way would impact upon their conclusions.

- Prediction (4) - "*the age of onset for autistic children with regression clusters around the MMR immunisation date and is different from that of autistic children*". The study found that parents of autistic children with developmental regression detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months). The study also found that the mean intervals from MMR immunisation to parental recognition of autistic symptoms were comparable in autistic children with or without regression (248 days vs 272 days, not significant).

Comment - but regression might not necessarily be expected to "cluster round", but may follow MMR at a delay of weeks, months or years. There is no scientific justification for assuming that children with regression after MMR should have their condition recognised at a different time to those who did not regress after MMR. In any event, it is stated that the difference between 248 days and 272 days is not significant, but it is almost 10% different, and this difference has not been explained.

- Prediction (5) - "*children with regressive autism have distinct symptoms and severity profiles.*"

Comment - little scientific justification for testing this assumption is given in the study, which also refers to external features such as behaviour, when the real focus of interest should be on

gut biopsies and ileocolonoscopies of the actual children, which of course were not done in this study. Not enough is known about autistic enterocolitis to make such an assumption about external characteristics into a key test.

- Prediction (6) - "*regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder*".

Comment - but the children in this study did not undergo ileocolonoscopy. Their condition was medically unresearched.

Other comments:

- this is a statistical analysis of random groups of children, not of the children whose cases are going to the High Court. The numbers are extremely small, too small for a reliable interpretation to be made
- The assumption seems to have been made that children could not have been damaged by vaccines other than MMR. The Lassiter court case outcome (US) means that there is evidence, that has been accepted in a Court that other multiple vaccines also trigger autism.
- What this study set out to do was not to investigate the cause(s) of damage to specific children, but to clear MMR of any complicity. At first sight, it succeeds in the latter, but at closer analysis, it makes numerous unfounded assumptions that considerably weaken the strength of its conclusions. At worst, it demonstrates the central flaw of designing a study hoping to achieve a desired outcome, rather than to investigate a problem.

Overall verdict: this study fails to provide any convincing evidence against an MMR/autism link.

(Note: this study has been claimed by the UK Medical Research Council to represent "strong positive evidence" of there being no MMR/autism link)

49. Paper by Taylor, Miller et al, *Measles Mumps and Rubella Vaccination & Bowel Problems or Developmental Regression in Children with Autism: Population Study*, published BMJ.Com, 8th February 2002

The objective of this paper was to investigate whether MMR vaccination was associated with bowel problems and developmental regression in children with autism, and to look for a "new variant" form of autism.

Some 278 children with what the authors defined as "core autism", and a further 195 with "atypical autism" were studied. These were identified from disability registers. The children were born 1979-1998.

The outcome measures that were studied were:

- Recorded bowel problems lasting at least three months
- Age of reported regression (where it was a feature)
- Relation of these to MMR

Of the 473 children whose records were reviewed, 81 (17%) were reported to have associated bowel problems, comprising:

- 42 with constipation
- 7 with constipation and diarrhoea
- 19 with diarrhoea
- 7 with food allergy
- 2 with non-specific colitis with ileal-lymphoid nodular hyperplasia
- (4 noted as "others")

The study reported that:

- The proportion of children with developmental regression (25% of the overall) or bowel symptoms (17%) did not change significantly during the 20 years from 1979 (MMR being introduced in October 1988)
- No significant difference was found in rates of bowel problems or regression in children who received the MMR vaccine before their parents became concerned about their development, compared with those who received it only after such concern, and those who had not received MMR.
- A possible association between non-specific bowel problems and regression in children with autism was seen, but this was unrelated to MMR
- The study concluded that its findings provided no support for an MMR-associated "new variant" autism, and further evidence against involvement of MMR

The study admitted that it had the "strengths and weaknesses of data based on case notes. Data was not recorded systematically and there was variability in the level of detail."

Comment - there are several major criticisms that can be made of this study.

- Most importantly, it was an epidemiological study of case notes, not a clinical study (with examination and clinical analysis of samples) of the cohort of children believed to have been damaged.
- No clinical examination appears to have been undertaken by the study team, and it is highly questionable whether such examination or analysis was ever undertaken in the past by paediatricians or specialists in the field, either. This greatly reduces the value of this study.
- Equally importantly, the study relies heavily upon the accuracy of child health records. Experience suggests that the health records of autistic children do not accurately reflect their condition, with numerous specialists and agencies involved and with the records not necessarily accurately reflecting the information supplied by parents, due to poor reporting, poor recording and undervaluing of parental "anecdotal" evidence.
- For health records to be relevant to an assessment of a novel syndrome, which was first only widely reported in 1998 (and has been repeatedly denied by the Department of Health ever since), health professionals would have to connect what the parents were reporting, and the condition of the children, with the new syndrome. They would also then have to have commissioned appropriate clinical examination of the children, and ensured that this was accurately recorded.
- It is patently obvious that this would not have happened for the perhaps the first nineteen of the twenty years 1979-1999. The study is therefore trying to assess records made in an era before in-the-field awareness existed, and in all probability without any appropriate clinical examination or analysis ever having taken place in the past, as well as during the study.

These major criticisms would appear to leave the study seriously lacking relevance. Despite this, the study was described by the Department of Health as "elegant".

The independence of the study also must be questioned.

Dr. Elizabeth Miller, head of the Immunisation Division of the Government's Public Health Laboratory Service, was a direct participant at the Department of Health's re-launching of the MMR programme in January 2001, and thus cannot be regarded as a detached "outside" researcher.

And as long ago as December 1997, Professor Brent Taylor described Dr. Andrew Wakefield, in writing, as "*a zealot.....who thinks that MMR is the cause of all the problems of the Western world.*" This suggests that Taylor's stance towards the alleged MMR/autism issue was set several years ago. Researchers are entitled to their views, but, if these are expressed in such a highly charged manner, then it is only right that such prior remarks should be set alongside

their study findings, particularly when such findings are regarded, and publicised, by Government as an "independent" study.

There are other serious methodological criticisms of this latest Taylor, Miller study:

- The study looks at percentages of autistic children, giving the impression that background rates of autism aren't increasing. What the study findings should also include is a plot of the actual numbers of cases diagnosed per year, and of inflammatory bowel disease/other aspects. This is a crucial omission. It is impossible from the study report to tell whether these numbers (as opposed to percentages) have changed over time.
- The study does not reveal the sample sizes for each year. How many children fall in each year is not shown. It also therefore does not confirm whether the distribution is even, across the years. This makes the data impenetrable to outside scrutiny. (Note: on ITV's "Dimbleby" discussion programme on 10th February, Prof. Taylor was challenged by the National Autistic Society to release his raw data for independent analysis, and declined to do so).
- Following on from the above, any logistic regression on year of birth is going to be highly underpowered as a way of detecting any MMR effect.
- The study does not make clear exactly how many of the 473 had MMR how many times, and precisely when. This is a fundamental failure in methodology.
- Notably, the study does not take the most obvious route of all, of comparing a large group of MMR-vaccinated children (10,000+) with another large group (10,000+) of unvaccinated children. An epidemiological study could have been undertaken of such groups. A study of only 473 children is far too small to detect relatively-rare adverse outcomes. The study size is so small that in some years there may have been no more than a handful of children.

(Note: the study by Wakefield O'Leary et al looked at about 200 children, but this was a clinical study, not an epidemiological study. A cohort of 200 children in a clinical study is vastly more reliable than a cohort of 473 children in an epidemiological study).

- As only 17% of the sample had "not had" MMR, and only 18% had "reported bowel problems", this means that the study inevitably is not very powerful.
- According to Taylor Miller et al, their study identified just two children with ileal-lymphoid nodular hyperplasia, the novel syndrome being studied by Wakefield et al. This is either wholly inadequate because it is such a tiny sample, or it alternatively suggests that the case-notes missed many cases amongst the remaining 473 cases. It would be extremely surprising if the ILNH condition being studied by Wakefield only

occurred in 2/473 children. What this suggests is that very few children out of the 473 have been clinically investigated to ascertain whether or not they have ILNH.

- The cohort of children identified by the study as having "bowel problems lasting three months" is highly unspecific and vague. Records would be most unlikely to accurately reflect the extent, intensity, nature or length of time these "problems" consisted of.
- The percentage of "regressing" children is identified as being 25%, yet Simon Baron-Cohen's CHAT system uses a rigorous definition which gives a rate of 10%. This difference suggests that the Taylor Miller definition may have been unusually wide
- "Parental concern" is not defined. It is not clear whether this equates to a visit to the GP, or to personal parental doubt. It is unlikely that health records would accurately reflect this, particularly if onset was insidious.
- Perhaps the most interesting finding is that there is a reported highly significant association between developmental regression and bowel problems. But as 87% had MMR, and only 31 had bowel problems, one might expect 27/31 of those with bowel problems to have had MMR, and 4/31 to have not had MMR. This again has very little statistical power, because the numbers are so very small as to be capable of being influenced by pure chance, in addition to other methodological flaws described elsewhere such as poor or inaccurate records.
- It is also not clear which children that had "had MMR", also had the booster as well as the early immunisation, the booster but not the early immunisation, or the early immunisation but not the booster.

In subsequent British Medical Journal correspondence, the paper was also heavily criticised over its statistical methodology and the refusal to release raw data. These criticisms were by Aubrey Blumsohn, a Senior Lecturer at the University of Sheffield, UK. His main points were that the authors provided no statistical confidence limits in relation to several key findings

The most extraordinary feature of this inconclusive study was the way it was hailed as providing "conclusive" irrefutable evidence that there was no link, despite its many serious drawbacks. Its publication was met with a further claim by the Scottish chief medical officer, Dr. Mac Armstrong, that any calls to mount clinical studies into the MMR/gut/autism issue would be "resisted". This line of argument was repeated in a UK television interview by Dr. Elizabeth Miller on 13th February 2002.

Conclusion: this study offers no evidence against an MMR/autism link.

(Note: this study has been claimed by the UK Medical Research Council to represent "strong positive evidence" of there being no MMR/autism link)

50. Review by Donald and Muthu, Bazian Limited, London UK, published in the British Medical Journal, June 2002

This was not a new study, but a review of existing studies. It claimed that it followed the most in-depth analysis of the scientific literature to date, looking at 2,000 existing studies and papers, and offered clear reassurance for parents. However, only 36 studies were actually cited, the remainder having apparently been disregarded on the basis of self-imposed restrictive criteria for inclusion in the review.

The study found:

- no evidence of an MMR/autism link.
- strong evidence that both MMR and single measles vaccination virtually eliminated risk of measles and measles complication
- Consistent evidence that MMR and single measles vaccines are associated with small similar risks of self-limiting fever within three weeks of vaccination

Comment: there are a number of fundamental (and severe) criticisms that can be made of this review's methodology:

- The study was only a review. It offered no fresh evidence.
- It was not a clinical study. It did not examine any children.
- As the syndrome of autistic enterocolitis is a novel one, it is unsurprising that a review of past literature would not find evidence of an MMR/autism link. In the main, such studies have neither been undertaken nor reported. If you look into an box that is known to be empty, you should not be surprised at finding nothing.
- The review effectively asks the wrong question, "*Is MMR safe?*", whereas the fundamental questions should be "*What is wrong with these specific children, what are the features of their condition, and what damaged these specific children?*".
- Absence of evidence is not evidence of absence
- The study deduced that, because there had not been a "stepwise" increase in autism following MMR's introduction, there could not be an MMR/autism link. However, this does not take account of delays in diagnosis, differential risk in relation to different strains of MMR and the withdrawal of two brands in 1992 due to side-effects.

The study (inexplicably) took only the February 1998 paper by Wakefield et al as being the published evidence for any MMR/autism link, and appeared to disregard a considerable number of subsequent papers (all of which are reviewed later in this Briefing Note).

In effect, all the study could reasonably have concluded is that there is a lack of published research that is relevant to the question. However, the researchers claimed that their paper should signal the end of the MMR/autism debate. Dr. Donald appeared on BBC Radio 4's Today programme and stated that "It was time for the parents to stop chasing shadows" (re MMR).

Conclusion: this review offers no hard evidence whatever against the possibility of an MMR/autism link.

51. Study into Relationship Between Childhood Gastrointestinal Disorders and Autism: Nested Case-Control Study Using Data from the UK General Practice Research Database, British Medical Journal Volume 325, pp 419-421, Boston University (researchers' details not known), August 2002

This study identified 96 children with autism from the UK General Practice Research Database between 1988 and 1999 (MMR was introduced into the UK in October 1987). Each case was matched with up to five controls without autism. The study considered the time relation between MMR vaccination and the onset of gastrointestinal symptoms among the cases.

Findings were:

- No increase in a history of gastrointestinal disorders, coeliac disease, food intolerance or recurrent gastrointestinal symptoms among children with autism compared with normal controls
- No temporal association between MMR vaccination and the onset of gastrointestinal symptoms in children with autism

The authors acknowledged that they could not exclude the possibility that some children in the study had sub-clinical gastrointestinal symptoms before their presentation with autistic behaviour. However, they commented that the children described by Wakefield and colleagues had symptomatic gastrointestinal disease.

The authors also could not exclude the possibility that severe gastrointestinal disease might be associated with the development of autism in certain individuals. However, they thought that this was likely to be uncommon.

Comment: the authors themselves acknowledge the shortcomings of their methodology. Further criticisms are that child health records are unlikely to fully reflect a novel gastrointestinal condition that is subtly different to Crohn's Disease or ulcerative colitis. No children were examined. The study apparently failed to distinguish between late-onset regressive-type autism and autism from infancy or birth.

Conclusion: this study does not disprove a link between MMR and certain sub-types of autism.

52. Study by Madsen, Hviid, Vestergaard, Schendel, Wohlfahrt, Thorsen, Olsen and Melbye, A Population-Based Study of Measles-Mumps Rubella Vaccination and Autism, New England Journal of Medicine, November 2002, 347: 1478-1482.

This study paper attracted a great deal of attention, largely uncritical, when it was published towards the end of 2002, mainly because of its claimed size and, of course, its conclusion that there was no evidence of any MMR/autism link. The paper featured:

- A retrospective cohort study of all children born in Denmark from January 1991 through till December 1998
- MMR vaccination data obtained from the Danish National Board of Health. Information on the children's autism status was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals and outpatient clinics in Denmark
- Of the 537,000 children in the cohort, 441,000 had received MMR. The study identified 316 children with a diagnosis of autistic disorder and a further 442 with a diagnosis of other autistic-spectrum disorder (total 758). (Note: 758 cases amongst 537,000 children represents a rate of 1 in 709, or 14 per 10,000).
- After comparing autism amongst vaccinated and unvaccinated children, the study concluded that there was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autistic disorder.

After initial uncritical review by the press, this study received a very thorough analysis by the parents, notably Dawn Richardson of the US parents' group PROVE and Sally Bernard of the group Safe Minds. Richardson's and Bernard's key criticisms were:

- One of the omissions of the study was its failure to consider the thiomersal issue. The parents' view as at the end of 2002 was that the thiomersal aspect and the MMR aspect were interlinked in the pathogenesis of autism. Press reports confirmed that thiomersal was removed from Denmark's vaccines prior to the birth-dates of the children in the study cohorts. It therefore remains unstudied as to whether a child's immune response, inhibited by elevated mercury levels from thiomersal, has a lessened ability to respond to the measles virus in MMR. The Madsen study does nothing to address this.
- The Madsen study only focussed on MMR and not other vaccines implicated in autism
- The study (as noted elsewhere) failed to distinguish between different types of autism
- An epidemiological study of this scale would be unable to detect a potential connection between the persistence of measles virus in susceptible children and autism. The number of regressive-autism cases (out of 758) would be too small to give statistical power to any conclusions (note: in an epidemiological study, large numbers are needed. This criticism would not apply to a clinical study, such as conducted by Wakefield when at the Royal Free Hospital).
- The Madsen study paradoxically appears to imply support for a thiomersal role, since it suggests that autism in Denmark is at a much lower rate of incidence than in the US or UK
- Only psychiatric records were assessed - not medical records. There was no data on gastrointestinal symptoms. No cerebral spinal fluid or gastrointestinal samples were taken or analysed.
- The study covered eight birth cohorts, but two of these, born in 1997 and 1998, were only one or two years old when the data records were obtained by the study at the end of 1999. These age groups are too young in most cases to either have a diagnosis of

autism or (probably) to have received MMR. Therefore, in these two cohorts, true autism rates will be underestimated, and vaccination rates over-estimated.

- Children who were in fact vaccinated were assigned to the unvaccinated group if they were diagnosed with autism before they had received MMR. This blurs the distinction between vaccinated and unvaccinated groups. It is not clear what effect this would have on the results.
- A number of the measures used to arrive at the conclusion that autism/ASD disorders were not associated with MMR are irrelevant, including age at vaccination with MMR, time interval between receipt of MMR and diagnosis of autism, and year of MMR vaccination.
- As the authors themselves acknowledge (page 1481), they had no information on the presence or absence of any family history of autism. There was considerable publicity in Denmark in 1993 on MMR/autism linkages. It is quite possible that those families with a history of autism went on to avoid MMR, undermining the study findings.
- The decision by the study team to register as autistic cases only those children who only met two strict diagnostic criteria could have meant that many affected children would have been excluded
- The study does show that MMR is not the cause of all autism - but no-one has ever suggested that it was

Comment: there are many shortcomings to this study. No child was evaluated for immune system dysfunction, inflammatory bowel disease or the presence of measles RNA in their blood, intestines or cerebral spinal fluid.

53. Paper, *Neurologic Disorders after Measles-Mumps-Rubella Vaccination*, Makela, Nuorti and Peltola, Hospital for Children and Adolescents, Helsinki University Central Hospital, and Department of Infectious Disease Epidemiology, National Public Health Institute, Helsinki, Finland, published in *Pediatrics*, Vol 110 No. 5, November 2002, pp 957-963.

This was yet another retrospective study. The objective of the study was to assess whether an association prevails between MMR vaccination and encephalitis, aseptic meningitis and autism.

The study was based on the linkage of individual MMR vaccination data with a hospital discharge register. It was conducted amongst 535,544 one to seven year olds, who were vaccinated between November 1982 and June 1986 in Finland.

For encephalitis and aseptic meningitis, the numbers of events observed within a three-month risk interval after vaccination were compared with the expected numbers estimated on the basis of occurrence of encephalitis and aseptic meningitis during the subsequent three-month intervals.

Changes in the overall number of hospitalizations for autism after vaccination throughout the study period were searched for.

In addition, hospitalizations because of inflammatory bowel disease were checked for the children with autism.

The results were:

- Of the 535,544 children who were vaccinated, 199 were hospitalized for encephalitis, 161 for aseptic meningitis and 352 for autistic disorders.
- In 9 children with encephalitis and in 10 with meningitis, the disease developed within three months of vaccination, revealing no increased occurrence within this designated risk period
- The study detected no clustering of hospitalizations for autism after vaccination
- None of the autistic children made hospital visits for inflammatory bowel disease.

The following criticisms of this study were offered by Dr. Ed Yazbak of New Jersey:

- The original Peltola study (from which this study has germinated) was completed by 1996, a full two years before the first autism/MMR paper was published by Wakefield et al in The Lancet, February 1998.
- Peltola stated unequivocally in a BBC interview that his 1996-completed study did not address autism as a possible outcome from MMR vaccination
- Subsequent authors have criticised the 1996-completed study as being irrelevant to proving an MMR/autism link, one way or the other. The Medical research Council review of 2001 admitted that the Finnish study by Peltola was not robust enough to be taken as conclusive evidence.
- The Makela study does not account for why 352 cases of autism were hospitalised at all. Autism is not usually a condition that in itself leads to hospitalisation.

Conclusion: despite the supposedly large scale of this study, its fundamental methodological flaws mean that it cannot be deduced from its findings that there is no link between MMR and autism.

PART F - REVIEWS CONCLUDING THERE IS NO EVIDENCE OF A LINK

54. Medical Research Council Review By "Committee of 37 Independent Experts"

This was held as a one-off in March 1998 to examine the Wakefield team's "Early Report" published in 2/98 in The Lancet. It concluded

- that there was no current evidence linking bowel disease or autism with MMR
- there was thus no reason, arising from the work considered, for a change in the current MMR vaccination policy" (my emphasis - note the careful wording)

This review has now been overtaken by subsequent events, yet it continues to be quoted by the UK Department of Health, as though time had stood still.

55. Paper, *Conclusions on MMR Vaccine Safety by the All Party Parliamentary Group on Primary Care and Public Health*, House of Commons, UK (based on a presentation by Dr. Elizabeth Miller, Head of the Immunisation Division, Public Health Laboratory Service)

This paper reported on its review of MMR's safety, based upon a presentation by Dr. Elizabeth Miller of the Public Health Laboratory Service on 24th July 2000.

There are a number of serious concerns about this paper:

- The conclusion of the APPG and its invitees was that MMR was safe, and that concerns about the alleged links with autism/inflammatory bowel disease were unfounded. However, this is a very strong claim, in the absence of appropriate comprehensive studies. If a link is "unproven", that does not necessarily mean that a concern is therefore categorically "unfounded".
- Dr. Miller had demonstrated that MMR has enabled "excellent" control of measles, but that is not the point at issue.
- There was concern at the fall in MMR take-up. This, too, is not what is under scrutiny. It is MMR's safety that is in question. Concern over measles outbreaks and falling take-up may be legitimate, but are arguably being used here as a form of moral pressure.
- The APPG expressed concern about measles outbreaks elsewhere, e.g. Holland. The same comment applies. It is MMR's safety in the UK that is under scrutiny.
- The statement that "*all (hypotheses about a link) have originated from a single group of workers in the UK*" (at the Royal Free), and "none has been endorsed by independent

recognised medical experts anywhere in the world" is highly misleading. The Royal Free team have been at the forefront of research, but their work has been given backing by other researchers (to give just one example, the letter in the Lancet by Sabra, Bellanti and Colon, 1998), and the possibility of a link has been endorsed, or has been unable to have been ruled out, by other researchers. Other studies and reviews have been inconclusive either way. The position is still one of scientific uncertainty.

- Claims that the Joint Committee on Vaccination and Immunisation "*is composed of independent clinical and scientific experts*" are open to question. The JCVI does not include gastroenterologists - which is the key area of science under scrutiny in this issue. Its independence can also be questioned on two counts. Firstly, a number of its members have declared financial links with the pharmaceuticals industry. This could be argued to part-compromise their independence. Secondly, there is a collective professional interest in eliminating infectious diseases through immunisation. Such a body is therefore not wholly "independent" when it comes to assessing evidence for adverse side effects from vaccines, particularly if it involves a syndrome which, if acknowledged, could damage confidence in vaccines and lead to a resurgence in communicable diseases.
- The Committee on Safety of Medicines is also questionably "independent". It is a matter of record that 37 members of the CSM had between them, at the end of the 1990s, nearly 190 separate declared financial links with the pharmaceuticals industry, about one-half of which were personal financial links. Some of these links involve the manufacturers of MMR. The 190 links include shareholdings, consultancies, research funding and non-executive directorships. An impartial observer would find that these links could arguably weaken any claims of "independence".
- The claim that "*there is no evidence*" (for a link) is factually incorrect (see elsewhere).
- Claims of "*overwhelming evidence*" (against any link) do not address the inconclusive nature of many of the studies involved. There is still no hard evidence against a link. These studies also conflict with the direct first-hand accounts of the parents of the children believed to have been damaged.

It is disappointing, if understandable, that the All Party Group should produce such a report. The Group appears to have been given a presentation of only one side of the argument.

This review too has been overtaken by subsequent events.

56. The Medical Research Council's Report, Report of the Strategy Development Group Sub-Group on Research into Inflammatory Bowel Disorders and Autism, March 2000

This was yet another review group which, upon failing to prove that there was a link, then drew the unproven conclusion that, because they could not find one, it automatically followed that

there was no link. Membership of the group was messrs. McGregor (chairman), Driscoll, Frith, Jewell, Meade, Sewell, Smith, Tedder, Ward, Wing, Wright. The sub-group met four times, 1998-99.

- The group was to develop a strategy for further research, monitor and steer future MRC support, and report at least annually.
- The subgroup recognised that the level of MRC support, particularly for IBD (but why not autism?) was "*relatively weak*".
- The subgroup found that the case for autistic enterocolitis was unproven, and that the California autism increase "*may be due to wider definitions and increasing awareness*", though it offered no scientific evidence to support this comforting claim.
- It concluded that much remained unknown about autism and IBD, that MRC support for research was weak, and that "*between March 1998 and September 1999 there had been no new evidence to suggest a causal link*" (again, note the careful wording).

For autism, its recommendations included:

- Investigation of risk factors, large-scale epidemiological studies concentrating on late-onset cases (this led directly to the Professor Andrew Hall three-year study at London School of Hygiene & Tropical Medicine, but seemingly, to little else)
- Development of tests to investigate gastrointestinal involvement in autism (no progress on this has since been reported)
- Maintaining a watching brief for further evidence of any link

Despite the above, which implied continued vigilance, the chairman was openly dismissive of even the possibility of a link emerging, Professor Alan McGregor telling Reuters "*We see this as the end of the story*" (Reuters, 3/4/00).

57. Review By US Institute of Medicine, 2001

The Institute of Medicine undertook a review of the link between MMR and autism during 2001.

The Immunisation Safety Review Committee was asked to assess not only the scientific plausibility of the hypothesised association between MMR and autism but also the significance of the issue in a broader context. In the IoM's view, the plausibility assessment involved two components:

- An examination of the causal relationship between the vaccine and the adverse event

- An examination of any pathogenic mechanisms that support the hypothesis

The IoM set out a number of important reservations regarding the heavy reliance on epidemiological studies to prove/disprove any MMR/autism link:

- Studies may not have sufficient precision to detect very rare occurrences at a population level
- A poor understanding of the risk factors and a failure to use a standard case definition may also hamper the ability of epidemiological studies to detect rare adverse events
- Since MMR is virtually universal in developed countries, elucidating any association with adverse outcomes requires the creative use of administrative and other data sets and complex research designs
- The rarity of the individual autistic spectrum disorders, and the difficulty in determining their exact onset, and therefore the temporal relationship between onset and vaccination, makes certain epidemiological study designs (e.g. cohort studies) impractical.

The IoM Committee concluded that the evidence favours rejection of a causal relationship. However, the Committee also noted:

- Its conclusion did not exclude the possibility that MMR vaccine could contribute to autism in a small number of children
- The epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR leading to autism
- The proposed biological models linking MMR vaccine to autism, although far from established, are nevertheless not disproved

In a critique of the IoM Review in Autism Research Review International Newsletter, Vol. 15, No. 2, 2001, Dr. Bernard Rimland of the Autism Research Institute stated:

- The IoM did in fact NOT reject the hypothesis that MMR is a possible cause of autism (the IoM review is regularly quoted by the UK Department of Health as having "cleared" MMR of any link with autism)
- the IoM report actually supports, not refutes, what the parents contend.
- It should be the medical establishment's burden to have proved that the vaccines are safe, not the critics' burden to prove them unsafe - a key point.

- Two of those who issued the IoM press release had links with the manufacturers of MMR

(see also later for IoM review of the thiomersal preservative issue)

58. Review by Strauss, Field Epidemiology Training Program, Health Canada, Vancouver, British Columbia, and Bigham, Communicable Disease Epidemiology, University of British Columbia, Centre for Disease Control, Vancouver, BC, published in the Canada Communicable Disease Report journal, Minister of Health, Canada 2001

This was simply a review of published literature, and of course has become outdated by subsequent events. However, just as with other similar reviews, it did not appear to be particularly comprehensive in its scope even at the time of publication.

Between November 2000 and February 2001, the researchers conducted an internet search of Medline for publications from 1980 to December 2000, related to MMR vaccination or MMR infection and autism. Concurrently, they conducted a similar literature search for published articles from 1996 to December 2000 that examined the association between MMR vaccination or MMR infection and inflammatory bowel disease.

The authors noted that several population based studies "provided evidence that MMR vaccination is not associated with autism". The purview of their study in this respect included the studies (referred to elsewhere in this Briefing Note) by Gillberg, Taylor/Miller, Kaye et al, Patja et al and Fombonne.

In their discussion, they concluded that:

- A review of the literature since the publication of the Wakefield et al February 1998 paper revealed little evidence to support the hypothesis
- They noted that the review by the UK Medical Research Council also found insufficient evidence to support a link
- No new evidence was presented in scientific testimony at the hearings of the US Committee on Government Reform in 2000
- The study at the Royal free had important epidemiological weaknesses (Comment - the study was not an epidemiological study, but a review of a pattern of findings based upon clinical examinations)
- Studies that have looked specifically at the association between MMR and autism have generally found either no evidence of an association or evidence of a non-association
- Similarly, there is insufficient evidence to support a link between MMR and inflammatory bowel disease

The authors concluded that the evidence does not support a causal association between MMR and autism, and although there may be biologic plausibility for an association, there is lack of

evidence in five of the classic attributes of causality, (a) consistency, (b) strength of the association, (c) specificity, (d) dose response, and (e) experimental evidence.

Comment: this review has a number of weaknesses:

- It was not comprehensive enough at the time of publication, particularly in respect of published and unpublished evidence supporting a link
- It is of course now outdated, and fails to take account of fresh evidence (both for/against a link, but particularly for a link, when this is a novel and emerging syndrome)
- There is little merit in basing a review upon published research when virtually all relevant clinical (as opposed to epidemiological) research into investigating a link remains undone and unfunded
- The review relies almost entirely upon epidemiology and epidemiological sources. No children were clinically examined
- There does not appear to be any input from the parents of affected children, nor any examination of actual health records (which only have limited value in any case)
- As ever, absence of evidence is not evidence of absence

This review, like several others, turns the precautionary principle on its head. It takes the stance that, until there is comprehensive evidence of any MMR/autism/IBD link, then MMR is safe. The burden of proof is then thrown upon the parents (and a few researchers, who have obvious difficulty in attracting funding) to prove that there is a problem, rather than for the manufacturers of the vaccine and the administrators of public health medicine to prove that it is safe. This might seem reasonable when there are no emergent problems, but is profoundly questionable in the context of a novel syndrome and a clinical-research (as opposed to epidemiological-research) "black hole".

Conclusion: this review fails, despite its conclusions, to disprove an MMR/autism/IBD link, and has been overtaken by events.

59. Paper by Elliman, Bedford & Miller, *MMR Vaccine - Worries Are Not Justified*, *Archive of Disease in Childhood*, 2001: 85: 271-274 (October)

This review paper (by Elliman and Bedford) offered no new evidence, as was the case with the supporting commentary (by Dr. Elizabeth Miller), but simply re-presented previous work. The main conclusions were:

- Children are more at risk from separate measles, mumps and rubella injections than from the combined MMR
- There has been no research into the long-term effectiveness of single injections (Comment - but, again, the point at issue is the safety or otherwise of MMR, and damage to specific children - not the effectiveness of single vaccines)

The study authors acknowledged the receipt of funding from vaccine manufacturers to attend meetings and conduct research.

Dr. Elizabeth Miller's commentary included an attack on The Lancet for publishing the 1998 Wakefield "Early Report": "*Publication in respectable medical journals of (these) papers.....is a disservice to patients and health professionals alike*". Dr. Miller's commentary included the quote that MMR's "*safety evidence is so overwhelming*".

The Department of Health welcomed this latest "research" (which it was not), stating that "*single vaccines would put children at unnecessary risk and would have no scientific support whatsoever*".

The Elliman and Bedford paper did not review the work of Singh, amongst others.

60. Review By UK Medical Research Council, Review of Autism Research - Epidemiology and Causes, July-December 2001

The UK Department of Health and Medical Research Council jointly announced on 5th March 2001 that the DoH has asked the MRC to conduct a detailed review of the current state of knowledge about autism.

The review was chaired by Professor Eve Johnstone of the University of Edinburgh and Royal Edinburgh Hospital. The review was to suggest possible areas for further research development, including obtaining a clear and comprehensive picture of what is currently known about the incidence, prevalence and causes of autism, and how strong the evidence is which underpins that knowledge.

The main findings of the review, reported in December 2001, were:

- It found no association between autism and MMR (this was later misrepresented by the UK Department of Health as equating to "clearing" MMR and "proving" that there was no link - which the review did not)
- The prevalence of autism is higher than had been thought (a rate of 1/166 was quoted)
- The review claimed to have had "extensive" input from lay people. However, several refused on the grounds that at least four of the expert-group participants were already signed-up to the MMR manufacturers as paid witnesses in the forthcoming UK High Court cases. There was also strong concern from the outset from parents about balance in the review and its outcome.
- Most of the increase in autism was "explained" away by changes in definition and increased awareness. The report thus heavily played down any uncomfortable conclusion that the increase might be real

- Autism was found to result from several causes, with a genetic component. The interplay between genetic and environmental factors "was not yet known".
- The review accepted that a number of studies (reviewed elsewhere in this briefing note) offered "evidence" that there was no MMR/autism link, or alternatively, did not offer evidence to the contrary.
- Various priorities for further study were identified,.

What was most notable in the review's report was how few studies for/against an MMR/autism link were covered at all, seven at most against a link and only one (plus Wakefield) for.

- For "evidence" against a link, the review reported on just a handful of scientific studies - Taylor, Miller et al, Kaye et al, Smeeth et al (which had yet to report), De Wilde et al, Fombonne & Chakrabarti, Dales et al, and Patja, Peltola et al. Each of these studies is covered elsewhere in this briefing note, and each is shown to be flawed or inconclusive in its outcome. Yet the MRC review accepted all of these as "evidence" of no MMR/autism link.
- For evidence for a link, even less satisfactorily, the MRC rejected the hypothesis of Wakefield et al, and reviewed only one scientific study to support an MMR/autism link, this being Spitzer, Aitken et al (also reviewed elsewhere in this briefing note). The only conclusion the MRC drew from this study, which would of course have been in conflict with the MRC's no-link conclusions, was that the average age at diagnosis of UK children with autism was 4 years.

By disparaging the possibility of any link between MMR and autism, the review was able to sidestep having to suggest any research in this area. So "no evidence" meant "no future studies" in this controversial area - and "no future studies" will thus ensure "no evidence". It was clearly desirable for the MRC to avoid raising further concern about MMR in its conclusions.

61. Further Review By the US National Academy of Sciences Institute of Medicine on Child Vaccinations and Autoimmune Dysfunction, February 2002

This found that:

- Scientific evidence from epidemiological studies on whether asthma and allergy can be caused by multiple vaccinations was conflicting, and that the evidence "was inadequate to accept or reject a causal relationship"
- Epidemiological studies to date favoured rejection of a causal relationship between multiple immunisations and increased risk for infections and for type 1 diabetes

- There was some biological mechanism evidence that vaccines could increase the risk of immune dysfunction in some children, that could lead to increased infections and allergy, including asthma. The IoM stated that "the biological mechanisms evidence regarding increased risk for infections is strong".

On vaccine-induced neuroimmune dysfunction, the IoM Committee stated:

- *"The Committee was unable to address the concern that repeated exposure of a susceptible child to multiple immunizations over the developmental period may also produce atypical or non-specific immune or nervous system injury that could lead to severe disability or death. There are no epidemiological studies that address this. Thus the Committee recognises with some discomfort that this report addresses only part of the overall set of concerns of some of those most wary about the safety of childhood immunizations"*
- The Committee also expressed a new note of caution: *"As the array of available vaccines and disease-targets expands, the current emphasis on universal recommendations and on State mandates for vaccine use should be re-assessed"*.

A critique of the IoM report by the US parents' group PROVE pointed out that the report was drawn up only after a review of past literature, and did not involve new research, and that many of the authors of these past studies had conflicts of interest. Conflicts of interest were also held by some of those that contributed "constructive criticism" to the report, and some researchers who had identified links between autoimmune conditions and vaccines had not been permitted to make presentations to the IoM Committee.

62. Review of the Scottish Executive MMR Expert Group, Edinburgh, April 2002

This Expert Group was set up by the Scottish Executive (Parliament) in 2001 to:

- (a) describe the consequences of an alternative vaccination policy to MMR
 - (b) review evidence on the apparent rise in autism
 - (c) describe the process of vaccine testing and monitoring of adverse effects
 - (d) have regard to the role and remit of the Joint Committee on Vaccination and Immunisation, the Committee on Safety of Medicines and the Medicines Control Agency (all in London)
- The Expert Group took the view that the current scientific evidence does not support the hypothesised link between MMR and autism.
 - On adverse event reporting, the Group was only descriptive rather than critical.

- On the submissions presented to it, the Group concluded that these "supported the conclusion that MMR was appropriately and rigorously tested before introduction, consistent with standards and science relevant at the time". (Comment: this is a very guarded and carefully-worded endorsement. It also implies that subsequently-identified problems can be legitimately discounted if set in the context of past historical scientific understanding - clearly, an illogical stance, as knowledge must always necessarily be constantly updated as science advances, not measured against the state of science at some arbitrary point in the past. An absence of recognition of a problem in the past does not justify a lack of action in the present.).
- On the issue of single vaccines, the Expert Group's report stated that "*.....None of the submissions presented.....supported.....the options of single vaccines replacing MMR*". (Comment: this is inexplicable, as several of the oral and written contributions - including my own oral presentation to the Expert Group - very clearly questioned MMR's safety, and carried the clear implication that the option of single vaccines was preferable).

The Expert Group's report made a number of useful suggestions:

- Improve the monitoring of vaccine safety issues
- Vaccination records of patients should include details of the name and batch number of the vaccine administered
- The Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation (JCVI) should keep vaccine contraindications under review
- Health Ministers should appoint lay members and/or members of the public to the JCVI

A number of members of the Scottish Expert Group declared financial interests in relation to the manufacturers of MMR. These included Prof. Johnstone (major shareholder of Glaxo SmithKline), Dr. Bramley (non-personal research funding), the Very Rev Graham Forbes, Chairman (non-personal shareholding), Dr Goldblatt (is appearing as an expert witness on behalf of the manufacturers of MMR in the forthcoming High Court action, plus consultancy and other work, including for GlaxoSmithKline), Prof. Ritchie (lectures, seminars and trials sponsored by pharmaceuticals industry), Prof. Weaver (shares in GlaxoSmithKline) and Dr. Riley (shares in GlaxoSmithKline). The number of members with declared interests appears very high, and their nature surprising, given the sensitivity of the issues involved.

PART G - THE MMR ORIGINAL SAFETY TRIALS DEBATE

This section looks at a review of the original evidence for MMR's safety, published by Wakefield and Montgomery, subsequent comments from other researchers, and the response of the manufacturing industry and the UK Department of Health.

(Note: it is worth stating the obvious, that it should be for the manufacturers to prove that their product is safe, not for the parents of damaged children to prove otherwise - though this latter is what is now in effect occurring.)

63. Wakefield & Montgomery Through A Glass Darkly Paper (A Look Back At MMR's Safety Trials), Journal of Adverse Drug Reactions, 2000 19(4), 265-283)

Wakefield & Montgomery reviewed the following safety studies: Buynak et al 1969, Stokes et al 1971, Minekawa et al 1974, Schwartz et al 1975, Crawford and Gremillion 1981, Miller et al 1987. The following is an abbreviated summary of their findings:

- The Buynak study identified viral "interference". The follow-up period was only 12 days
- The Stokes study revealed persistent gastrointestinal problems in the US trial children. 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 serious 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 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. 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. 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 not additive but synergistic - a key point.
- The Eddes study (a small UK study) 1991 compared reactions to MMR with monovalent measles vaccine. High rates of gastrointestinal disorders (41.9% and 37.8%) were found. The authors dismissed these as normal background illness.
- The Miller study noted that diarrhoea was common (26% of vaccinees). The follow-up was only 21 days. This was a major missed opportunity to follow up a large cohort. (NB this was Dr. Elizabeth Miller, who has been so vociferous in criticising the Wakefield findings and in defending MMR, and who was co-author, and designed, the heavily-criticised 1999 Taylor, Miller North London study)
- 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.

It is also worth noting that the Wakefield and Montgomery paper is actually an argument for vaccination - but not using triple measles-containing vaccines. Wakefield and Montgomery are not anti vaccination per se. They argue that their duty is to the patient. Dr. Wakefield has been investigating the children brought to him, not campaigning against the UK DoH for its own sake. He is simply relating what he is finding.

64. Dr. Peter Fletcher Commentary, Journal of Adverse Drug Reactions & Toxicology, 2001, 20(1), 47-63 Oxford University Press

The peer review comments on Wakefield & Montgomery paper were very powerful. Peer reviewers included Dr Peter Fletcher, former Principal Medical Officer in the Medicines Division (now MCA), who was medical assessor to the Committee on Safety of Medicines. These are some summaries of his comments:

- *"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", and "There should have been strong encouragement to conduct a 12-month observational study on 10,000-15,000 children" (this was not done)*
- *"The granting of a product licence was premature"*

65. Dr. Stephen Dealler Commentary, Journal of Adverse Drug Reactions & Toxicology, 2001 20(1), 47 63 Oxford University Press

A subsequent letter was published in the Journal of Adverse Drug Reactions & Toxicology, 2001 20(1) from Dr. Stephen Dealler, Consultant Microbiologist at Burnley General Hospital, Lancashire UK. Dr. Dealler stated:

- The finding that measles virus ribose nucleic acid (RNA) in the gut wall of almost all the autistic children that had not suffered measles but had received MMR, when compared to non-autistic controls (O'Leary, Dublin) must be investigated further
- Research in the US showing that inflammation can be found not just in the large bowel and terminal ileum but in the duodenum and jejunum as well should not be ignored
- Data must be found to determine whether the measles virus is actually causative, or merely retained because of inflammation as a result of some other factor
- Autism that might be produced will not necessarily appear at a specific point after vaccination
- Complex long term control trials may be required to show MMR to not be involved in the pathogenesis of autism
- Research into the background pathogenesis of autism is currently shockingly inadequate

66. Dr. Edward Yazbak Commentary, Journal of Adverse Drug Reactions & Toxicology, 2001, 20(1), 47 63 Oxford University Press

In a further letter to the Journal of Adverse Drug Reactions & Toxicology, Dr. F. Edward Yazbak MD FAAP and Kathy Lang-Radosh MS of TL Autism Research, Falmouth Massachusetts, stated that:

- Many children with the new or acquired autism syndrome are normal until past their first birthday, and then develop symptoms in the second or third year of life, or even later
- These children actually lose previously-acquired skills

- Children with the new autism have gastrointestinal, neurological, sensory and endocrine difficulties
- They also have an inordinate number of infections, for which frequent and repeated courses of antibiotics have been used, often leading to candida overgrowth, with further consequent damage to the gastrointestinal tract and increased ileal permeability
- Additionally, sulphur transferase deficiency in certain children with autism causes decreased sulphating, which results in inadequate detoxification and reduced mucin formation, which further compromises mucosal integrity. The result is excessive absorption of noxious polypeptides
- While recent research has pointed to a genetic contribution of autism, a more likely aetiology of the apparent familial aspects of autism may simply be a family predisposition to immune disorders.

67. The Wakefield/Watson/Shattock Rebuttals - "Anything You Can Rebut, I Can Rebut Better"

The *Through A Glass Darkly* safety paper by Wakefield and Montgomery was strenuously criticised by Mike Watson, Medical Director of Aventis Pasteur MSD, the manufacturers of MMR.

But Watson's criticisms do not themselves stand up to scrutiny, as demonstrated below by Paul Shattock of the University of Sunderland Autism Research Unit. The only aspects that cannot be bottomed-out by Shattock are where the studies referred to by Watson have not been published.

- Watson maintains that observation period in trials (as reported in paper by Stokes et al, 1971) was up to 63 days, not up to 28 as reported by Wakefield. However, Shattock quotes Stokes study as saying "*Joint involvement was noticeably absent during six to nine week follow-up....Present studies with queries at six to nine weeks following vaccination did not reveal any occurrence of arthritis or arthralgia beyond the 28-day period for close observation*". The trial was therefore 28 days, with only queries for arthritis etc beyond this. The Wakefield version is therefore correct.
- Watson maintains that "MMR I" safety was investigated in four studies prior to licensing in US 1971 and UK 1972. Also, "MMR II" investigated by seven studies, two of which published. Immuvax also tested in seven studies. But Shattock questions whether studies are published or secret. Wakefield & Montgomery can only comment on what is published.
- Watson states that virologists generally accept wild measles virus only causes persistent disease in central nervous system, as subacute sclerosing panencephalitis (SSPE) or

measles inclusion body encephalitis (MIBE). Wakefield maintains potential for delayed intestinal pathology has been borne out by Fournier et al, 1968. Shattock response: the technology has failed to isolate measles virus RNA in affected children, but further progress is expected.

- Watson states that mutant measles virus genetic material can persist in tissues of apparently healthy people without causing disease (Katayama et al, 1998). Shattock response: so mutant measles can persist but vaccine strains cannot? - challenge for evidence to substantiate this claim.
- Shattock also makes the important points that (a) MMR test group in Stokes 1971 paper had way more GI problems than controls, (b) that in Schwartz et al paper 1975 the results of 282 children from Daytona Ohio and the 1192 from Santo Domingo and Panama were pooled (unscientific), and (c) why was gastroenteritis completely omitted from list of side effects when difference of incidence between groups were so blatant?
- Watson: "gold standard" in safety studies was placebo-controlled crossover study of 1162 twins in Finland 1982. More detail published by Virtanen, Peltola et al 2000. Shattock response: was the 1982 study published?/where? Also, the 2000 Peltola paper was actually only published after Wakefield & Montgomery paper submitted.
- Wakefield: follow-up interval reduced from 4 weeks in initial controlled trial to 3 weeks in subsequent trials. Watson: insists follow-up was up to 63 days. Shattock response: observations were for 28 days. At up to 63 days, parents asked about any significant illness - side effects listed in paper apparently excluded. No doubt Wakefield's 28 days is right.
- Watson: later MMR II studies had observation period of 42 days. Priorix studies had periods of 42-60 days. Shattock response: where are publication details?
- Watson: numerous post-marketing studies of MMR have been conducted and published. Shattock response: references please? Why haven't they been quoted by DoH, why can't anyone find them?

Other "facts" quoted by Watson in "Aventis Pasteur MSD - Vaccines For Life" paper:

- Watson: "*national safety regulators require all side effects to be reported*". But this doesn't mean they actually are, especially in a novel syndrome with (up till 1998) no publicity, delayed onset, and an official refusal to count reports as an "adverse reaction"
- Watson: "*there have been over 500m doses given worldwide*". But there are also many hundreds of thousands of cases of autism worldwide, and none of these has been admitted by authorities to be consequence of MMR, thereby keeping its safety record relatively clean.....

- Watson: "*As anyone in clinical trials knows, all participants or their parents are very carefully informed and consented*". Yes, but this wouldn't have covered a warning to watch out for subsequent delayed degeneration into autism!
- Watson: "*Any unusual event that occurs in that child at any time after trial should be reported to MCA*". But this would almost certainly never have included autism pre-1997, when very first publicity was given in Pulse magazine and BBC Newsnight. (NB: In Oliver Thrower's case, the BBC TV Newsnight report of 8/97 was the first clue, nine years after vaccination, as to the cause of his autism. In his case, vaccination had never previously been mentioned or considered as a possibility by health professionals. He was added to the UK Medicines Control Agency database 11 years after vaccination. So much for the value of even a 63-day trial follow-up!)
- Watson: "*An unimmunised child is the infectious equivalent of a drunk driver*". This comment is a revealing insight of the industry's "MMR or be damned" culture.
- Watson: "*Giving vaccines separately would be more expensive*". More expensive than all the extra health costs, care costs, special education costs, special needs transport costs, lost earnings of the victim, lost tax revenues, parents' lost earnings and taxes?
- Quote from MSD product insert on MMR: "*Clinical studies of 279 triple seronegative children, 11 months to 7 years of age, demonstrate that MMR is highly immunogenic and generally well tolerated.*" (So is just 279 the number?)

68. UK Department of Health Statement, Combined MMR Vaccines - Response of the Medicines Control Agency and the Department of Health, UK (Repudiation of the Wakefield & Montgomery Through A Glass Darkly Paper)

The UK Department of Health's response was summarised in its press release of 21st January 2001. The main points (which are taken from the paper by the MCA and the DoH) are set out below, with the DoH's text in italics, and with my own responses following.

- The claim by Wakefield & Montgomery that there was insufficient research "*is factually incorrect, as many studies recorded safety data up to six weeks, which is standard for vaccines, and some studies recorded data for longer - up to a year in some cases*". Comment - Yes, but autism did not form part of this surveillance, the importance of gastrointestinal problems was not appreciated, the reference to six weeks being "standard for vaccines" doesn't address the autism/gut syndrome, and very few cases indeed, in very few studies indeed, were followed up for longer than a few weeks. Thus the syndrome was missed.
- "*Combined MMR vaccines had been extensively tried and tested in Scandinavia and the USA before they were introduced in the UK in 1988*". As a statement, this proves

nothing. Comment - The new syndrome of autistic enterocolitis was not suspected in these countries, either, and again was missed.

- *"Now MMR is successfully used in over 30 European countries as well as the USA, Canada, Australia and New Zealand"*. Comment - The same comments apply. There is an autism problem in all these countries too. Perhaps MMR is implicated elsewhere outside the UK.
- *"A publication in 1988 lists 30 published studies where combined MMR vaccines were studied and follow-up was extended up to ten years"*. Comment - The same comments again apply. (See also the Wakefield/Watson/Shattock rebuttals section)
- *"The safety of combined MMR vaccines has been reviewed repeatedly by the Government's independent expert scientific advisory committees including the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation"*. Comment - This is true in a purely literal sense, but the reviews have been mis-designed and halfhearted or inconclusive (Quote from the original source: *"It was impossible to prove or refute the suggested association between MMR vaccine and autism/pervasive development disorder or inflammatory bowel disease because of the nature of the information, the self-selection of cases and the lack of comparators"* - Committee on Safety of Medicines Report of the Working Party on MMR Vaccine, page 12, paragraph 5.5). Further comment - One can also strongly argue that the Committees quoted are neither wholly independent (see other references) nor expert in the field of gastroenterology, as opposed to immunology.
- *"The use of MMR vaccine is also endorsed by the World Health Organisation, the British Medical Association, the Royal College of General Practitioners and the Royal College of Nursing."* Comment - This in itself proves little in the context of an intense scientific debate about a new discovery in gastroenterology. The latter institutions may come to regret their endorsement in the fullness of time. Have their advisers read all the evidence, on both sides, first-hand? If the evidence either way is fuzzy, do they give the benefit of the doubt to the parents who allege their children degenerated, or to the vaccine manufacturers?
- *"By 2000, several hundred million doses will have been given worldwide"*. Comment - Yes, and there will also be several tens, or hundreds, of thousands of cases of autism worldwide, some of which may have been precipitated by MMR.

Overall comment - In short, the DoH's rebuttal sought to refute the Wakefield/Montgomery paper, but was almost entirely couched in generalities. The devil is in the detail of the Wakefield/Montgomery paper. And the Department of Health was unable to refute this detail - indeed, it largely avoided addressing it at all.

PART H - STUDIES THAT POINT TOWARDS THE PLAUSIBILITY OF AN MMR/GUT/AUTISM LINK

69. Paper by Eggers, *Autistic Syndrome (Kanners) and Vaccination Against Smallpox, Klinikal Paediatrics, 1st March 1976 (944354 PubMed, 76172565 Medline)*

This paper reported that 3-4 weeks following an otherwise uncomplicated first vaccination against smallpox, a boy then aged 15 months and last examined at age 5.5 years, gradually developed a complete Kanner syndrome (autism). The question whether vaccination and early infantile autism might be connected was being discussed.

It noted that "A causal relationship was considered extremely unlikely, but vaccination is recognised as having a starter function for the onset of autism" (my emphasis).

(Note: this paper is most notable for drawing attention to a possible vaccination/autism link as long ago as 1976. If such a link was recognised a quarter of a century ago, why has so little been done since to research it?).

70. Paper by Weizman, Weizman, Szekely, Livni and Wijsenbeek, published in the American Journal of Psychiatry 1982 Nov 139 (11) 1462-5

This reported a study by macrophage migration inhibition factor test, in seventeen autistic patients and a control group of eleven patients suffering from other mental diseases, of cell mediated immune response to human myelin basic protein. It found:

- of the seventeen autistic patients, thirteen demonstrated inhibition of macrophage migration
- none of the non-autistic patients showed such a response
- the results therefore indicate the existence of a cell-mediated immune response to brain tissues in autism

71. US paper, by Drs. Delgiudice-Asch (clinical instructor in psychiatry, Mount Sinai School of Medicine) and Hollander (Seaver Autism Research Centre)

This includes:

- the noting of the potential relevance of antimyelin autoantibodies
- reference to the work of Stubbs in the USA and the suggestion that an inflammatory reaction in the brain may contribute to the development of autism

- references to indirect evidence of immune activation in autism
- the reference to Singh's finding, also in the USA, that identified serum antibodies to myelin basic protein in 19 out of 33 autistic children, compared with only 9% in a control group
- reference to Todd and Ciaranello's detection of circulating antibodies in seven out of thirteen children with autism

72. Paper by Dr. H. Fudenburg, *Dialysable Lymphocyte Extract In Infantile Onset Autism: A Pilot Study*, has been published (date/journal not identified), NeuroImmuno-Therapeutics Research Foundation, 1092 Boiling Springs Road, Spartanburg, South Carolina (fax 803 591 0622)

This studied 40 infantile autistic patients ranging from 6-15 years, of which 22 were classical infantile autism ("true autism", or TA) and 18 lacking one or more defects associated with infantile autism and were therefore termed "pseudo-autism syndrome" (PAS). Medical histories focused on possible viral infection in the mother, especially during second trimester, whether the child had multiple infections, especially otitis media, in the first to fifteenth month of life, and the relation of onset of symptoms to immunisation. Results were:

- antibodies to myelin basic protein were present in 20 out of 22 TA and 4 out of 18 PAS children
- 12/22 TA and 6/18 PAS children had a decreased response to ConA and negative LIF response to PHA and a decrease in suppressor functional assay (later studies showed a good correlation of the above with low levels of CD8/CD28 and CD8/CD38 T-cells)
- 6/22 TA and 12/18 PAS children had increased toxic metal levels, usually aluminium) and decreased levels of trace minerals necessary for a normal immune response
- 10/22 TA and 6/18 PAS children had elevated thyroid stimulating immunoglobulin values
- titers to rubella were ten times normal in 11/22 TA and 5/18 PAS children
- several of the children had elevated IgM levels to measles, indicating a defect in immune regulation

Fudenberg states that:

- the very low IL-2 receptor/positive lymphocytes and the decrease in DR+, but not IL-2 receptor+ lymphocytes, suggests incomplete activation in the TA children, a finding seen in other autoimmune diseases; this suggests that TA may be an autoimmune disease

- it is possible that "auto-antibodies" are directed against various viruses and that the reaction to myelin basic protein, neuron axone filaments, one or other receptors for neurotransmitters, represent molecular mimicry
- TA is probably due to adverse reactions to live virus or live virus vaccine in a genetically-predisposed individual, one whose cell-mediated arm of his/her immune system is not yet mature, or, in a very young infant, by transplacental IgG antibodies from a mother with high titers of antibodies to one of the vaccine constituents, e.g. diphtheria toxin

73. Dr. Reed Warren, Professor of Biology at Utah State University in Logan, set out a pathogen-autoimmune hypothesis for autism (source details not known):

- some children are susceptible to an environmental pathogen, probably a virus or bacterium, resulting from an inherited deficiency of their immune system
- unable to clear the pathogen, the child is at higher risk for the pathogen to damage the developing brain or trigger an autoimmune response
- the pathogen would not necessarily create gross neuronal damage, but have more subtle effects on portions of the brain controlling behaviour
- although not a requirement, the pathogen might persist and replicate slowly or be maintained in homeostasis by the immune system

Dr. Warren outlined the possibility of several key factors, which included:

- exposure to a certain pathogen at a vulnerable time, i.e. at the time the central nervous system is undergoing rapid development
- the existence of an immune susceptibility or deficiency that would allow a pathogen to persist
- a genetic constitution that allowed certain T cells to react to the pathogen in such a way as to cause reactivity against the central nervous system or products of the central nervous system such as neurotransmitters
- in some cases an immune susceptibility or deficiency in the immune system of the mother that may permit a pathogen to be present in utero or allow an immune response within the foetus
- in some cases, a purported immune mechanism may have not caused irreversible damage to the central nervous system but is only interfering with brain function such as by binding to various neurotransmitters or their receptors

74. Warren and Singh Paper, Immunogenetics, 1992, 36: 203-207

In a study by Warren and Singh published in the journal *Immunogenetics*, it was noted that:

- of the 46 chromosomes of 23 patients, 27 chromosomes (58.7%) had an extended haplotype as compared to an unrelated control group in which 33/128 (only 25.8%) of chromosomes carried an extended haplotype
- the frequency of extended haplotypes on chromosomes of autistic children was much greater than that on family-parent normal chromosomes, the latter being only 30.7%
- in the initial and later studies, only eight out of 45 autistic subjects did not have an extended haplotype, and fifteen autistic subjects carried an extended haplotype on each of their chromosomes
- also, the mothers but not the fathers of the autistic children had an increased representation of extended haplotypes
- an additional control group of subjects with general severe learning difficulties had a haplotype frequency of 26%, similar to that of the earlier-mentioned unrelated controls

It was also noted that:

- many normal individuals possess one or more of the above factors, but it would only be those children that possessed all of these, plus probably others, simultaneously, where autism would occur
- four season-of-birth studies had found an excess of births in the month of March, and that, if a pathogen was involved in autism, it was conceivable that it was more prevalent during early winter so as to affect March babies
- four to five times more boys than girls were affected by autism, but that autoimmune diseases were often more common in one sex, with the influence of sex hormones on immune functions well-established.

It was further noted there was a link between genetic background and frequency of infections:

- the products of the C4A and C4B genes are crucial to the activation of the other vital components of complement involved in protection against viruses, bacteria and other infectious agents
- C4A proteins bind avidly to amino-rich surfaces and C4B proteins form linkages with hydroxyl-containing carbohydrate surfaces

- deficiency in the C4 proteins especially C4B has been associated with increased viral and bacterial infection
- inherited abnormalities of the complement C4 proteins are linked to certain autoimmune diseases

75. Paper by Singh, Warren, Odell, Warren and Cole, published in Brain Behaviour 1993 March 7(1) 97-103

This investigated the possible pathological relationship between autoimmunity and autism, and reported that:

- antibodies reactive with myelin basic protein (anti-MBP) had been investigated in the sera of autistic children
- nineteen out of 33 (58%) of sera of autistic children under or equal to age ten were found to be positive for anti-MBP
- in controls, only eight out of 88 (9%) were positive; controls were age-matched and included normal children and children with mental retardation or Downs Syndrome, as well as normal adults aged 20-40.

76. Paper by Dr. Vijendra Singh, College of Pharmacy, University of Michigan, Ann Arbor, joint with Professor Reed Warren, Professor of Biology, Centre for Persons with Disabilities, Utah State University in Logan and Adjunct Professor of Psychiatry, University of Utah, and also Dennis Odell, published in Brain Behaviour, March 1993

This studied the immune responses to myelin basic protein, which is a protein component of myelin. Defects in myelin would dramatically affect brain activity. The study of 33 autistic children at or over ten years old was compared with eighteen age-matched normal children. twenty children with unknown-cause mental retardation and twelve children with Down syndrome were also studied as controls, and testing for serum antibodies to MBP undertaken:

- antibodies were found in nineteen of the 33 (58%) of autistic children
- the corresponding level for controls was 7%, or over eight times higher
- testing of the autistic children showed features also found in patients with autoimmune diseases such as rheumatoid arthritis, insulin-dependent diabetes and multiple sclerosis

The features above included genetic predisposition, gender imbalance (four or five times higher frequency in boys than girls), major histocompatibility association, and immune activation.

- The authors suggest that autoimmunity may be a critical factor in the cause of autism.

- They note that an essential part of the autoimmune mechanism should involve antibody-mediated immune responses or antibodies against the brain, and that other recent studies have found evidence of antibodies to brain tissue antigens, such as myelin basic protein, neurofilament proteins and serotonin receptor.
- They also note that antibodies to MBP may have some pathological relevance since abnormal cell-mediated immune response involving a soluble factor but not antibodies to this protein has been detected by other researchers, suggesting that autistic children develop inappropriate immune responses to this brain protein.
- They conclude that at present (1992) the relationship between antibodies to MBP and autism was not understood, but they hypothesised that the development of the immune response could be the basis of autoimmune pathogenesis in some cases of autism. It was conceivable that if an immunological assault was to occur before birth or during infancy or early childhood, it could lead to poor myelin development or abnormal function of the nerve fibre myelin.

77. Unpublished US paper, by Dr. Oleske and Assistant Professor Zecca, New Jersey Medical School

This found that:

- among 16 children diagnosed with autism, there was a threefold increase in their serum rubeola titers over the expected normal range
- the unusually high and persistent titers of anti-measles antibodies in autistic children was statistically significant when compared with a similar group of non-autistic subjects
- it is suggested in the paper that MMR may play a role in the pathogenesis of autism because elevated titers of anti-measles antibodies may signify a chronic over-activation of the immune system

78. US paper by Theresa C. Binstock, Researcher in Developmental and Behavioural Neuroanatomy, IMI, Denver

This found that

- brain regions whose pre-vaccination neuronal damage had been relatively insignificant may, via vaccine-induced clonal expansions, suffer additional damage.....resulting in vaccination-enhanced neuropathy presenting clinically as autism
- recent research findings are instructive regarding autistic children for whom.....medical records show a history of infections, antibiotic treatments, vaccinations and temporally-associated onset of autistic traits.....

- nearly any vaccine may have the potential for inducing neuronal damage in persons with NdEs." (Source: *Hypothesis: Infection, Antibiotics, Vaccination-Induced Neuropathies; Mechanism Of Pathogenesis In Some Cases Of Autism, ADHD, Tourette's*, by Theresa C. Binstock, *bit.listserv.autism* 3rd January 1997)
- although presented as a hypothesis, a route is offered that demonstrates how a small subset of susceptible infants could be affected, that a variety of vaccines could be involved for this subset of cases, and that prior treatment with antibiotics may play a critical role

79. Letter by Anne-Marie Plesner, Department of Epidemiology, Statens Seruminstitut, Copenhagen, The Lancet, Vol 345, Feb 4th 1995

This letter reported:

- That there had been 24 notifications of temporary gait disturbances after MMR vaccination
- At a median of 6 days (range 3-25 days) after vaccination, the children developed unsteadiness. Usually the children recovered after a short time (median 8 days, range 1-100 days). One child had not recovered after three months.

A possible cerebral disorder was reported in 8 children, with unusual screaming in 5.

- In company reports of MMR vaccines, gait disturbance was mentioned as a rare complication.

Plesner et al later reported on a study of gait disturbance following MMR (*Acta Paediatrica*, 2000, 89, 58-63)

80. Paper by Thompson, Montgomery, Pounder & Wakefield, *Is Measles Vaccination A Risk Factor for Inflammatory Bowel Disease*, The Lancet, April 1995, 345: 1071-74

The summary of this paper was as follows:

- Measles virus may persist in intestinal tissue, particularly that affected by Crohn's Disease, and early exposure to measles may be a risk factor for the development of Crohn's. Crohn's Disease and ulcerative colitis occur in the same families and may share a common aetiology, in view of the rising incidence of inflammatory bowel disease (Crohn's Disease and ulcerative colitis), the study team examined the impact of measles vaccination upon these conditions.
- Prevalences of Crohn's Disease, ulcerative colitis, coeliac disease and peptic ulceration were determined in 3,545 people who had received live measles vaccine in 1964 as part of a measles vaccine trial

- A longitudinal birth cohort of 11,407 subjects was one unvaccinated comparison cohort, and 2,541 partners of those vaccinated was another
- Compared with the birth cohort, the relative risk of developing Crohn's Disease in the vaccinated group was 3.01, and of developing ulcerative colitis was 2.53. There was no significant difference between these two groups in coeliac disease prevalence.
- Increased prevalence of inflammatory bowel disease, but not coeliac disease or peptic ulceration, was found in the vaccinated cohort compared with their partners.

The study team concluded that these findings suggest that measles virus may play a part in the development, not only of Crohn's Disease but also of ulcerative colitis.

81. Paper by Gupta, Aggarwal and Heads, *Dysregulated Immune System in Children with Autism - Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics*, Journal of Autism and Developmental Disorders, vol. 26 no. 4 1996

This suggested a theory that high titers of rubella antibody present in mothers of children with autism could be transplacentally transferred and could persist in the child, and that when the child received MMR, rubella antigen may complex with pre-existing antibodies, thereby possibly playing a role in the pathogenesis of autistic features.

82. Paper by Montinari, Favoino and Roberto, *Role of Immunogenetics in the Diagnosis of Postvaccinal Central Nervous System Pathology*, presented at a conference at Naples held by the Associazione per la Libera Universita Internazionale de Medicina Omeopatica, 9th May 1996.

This study involved the observation of 30 patients with post-vaccinal pathology of the CNS and other symptoms, where the first symptoms appeared concomitantly with or immediately after administration of a vaccine. Patients were subjected to serological testing for herpes virus (IgG and IgM) and to HLA (A, B, C) and HLA-DR-DQ tissue typing to see if there was any correlation between the emergence of CNS pathology and these antigens, to show a possible autoimmune type immunogenetic basis for any demyelination process.

The authors reported that 30 Italian patients were observed between April 1994 and October 1995. Clinical signs were dermatitis, food allergies, constipation and reflux, and these followed vaccination with the Salk or Sabin polio vaccine, DT, measles, DPT, anti-tuberculosis or Hepatitis-B vaccines. All patients had had convulsions with or immediately after vaccination, with very high fever or diarrhoea. The patients were children 3-9 months old.

Results of tests showed that:

- Serologic investigation for herpetic virus (IgG and IgM) were positive in all patients for IgG and negative for all patients for IgM

- Seropositivity (IgG) for Epstein-Barr virus was estimated at 73.8%, for cytomegalovirus of 71.4%, for Herpes Simplex virus of 47.6%, and for Varicella-Zoster virus of 21.4%
- In all patients, diminished sideremia and a deficit of IgA and IgG were noted

All of the patients had been normal prior to administration of the first dose of vaccine. Physicians had administered follow-up doses of vaccines, leading to stabilisation of conditions presented, and progressive clinical deterioration.

Patients were also subjected to HLA tissue typing (A, B, C) and serologic HLA DR-DQ to check a possible correlation with the emergence of CNS pathology. These antigens indicated a possible autoimmune immunogenetic basis for the demyelination process.

- An increase in the HLA-A3 antigen was found (43.3% vs. 25% in the normal population) and the HLA-DR7 antigen (48.3% vs, 24.1% in the population).
- The presence of A3 and/or DR7 was observed in 22/30 (73.3%) of the patients.
- The authors noted the problems of molecular resemblance, of discriminating between self and non-self antigens, and of determining the function of the Class 2a CMI molecules.
- They noted that any interference with the process of presentation of the antigen can predispose to an autoimmune disease.
- They also noted that "alterations which do not occur can be due to the action of viral agents which compromise the specific immune response, because of their resemblance to the "self" tissue antigens.

The authors note that the consequence is persistence of the infective agents and a tendency to provoke - through a marked reaction - induction of an autoimmune disease. This can present in conditions of marked reactivity to some viruses and to myelin antigens.

In 66% of patients there was an obstinate constipation. In 31% there was proctitic symptomatology with emission of mucus and blood.

The authors concluded that autoimmune pathology was more frequent in countries where vaccination was more widespread, i.e. in countries defined as "clean" from the virologic or microbiologic point of view. They also noted that the use of thiomersal in vaccines (see elsewhere) could demonstrate the possibility of changes in the aminoacids of the molecules which preserve the antigen.

83. Paper by P. G. Auwaerter and Diane Griffin, (source: *Clinical Immunology and Immunopathology*, 79(2): 163-70, May 1996):

This found that:

- measles produces immune suppression which contributes to an increased susceptibility to other infections
- high-titred measles vaccines have been linked to increased long-term mortality among some female recipients
- vaccines can impair cell-mediated immunity by shifting cytokines release into a Th2 pattern, thereby allowing intracellular pathogens (e.g. many viruses) to be more successful

84. Paper by Cook, Courchesne et al, Laboratory of Developmental Neuroscience, University of Chicago, published in the May 1996 edition of Molecular Psychiatry

This noted that:

- it was a well-established finding that a significant number of people with autism have elevated levels of blood serotonin, and the successful use of medications (potent serotonin transporter inhibitors, or PSTIs) suggest the possibility that serotonin plays a role in autism
- the authors studied 86 people with autism and their parents to examine whether the gene for the serotonin transporter may contribute to the risk of autism. They found evidence of a significant relationship
- it was possible that the serotonin transporter gene HTT was serving as a marker in linkage disequilibrium with a genomic variant which was contributing to susceptibility to autistic disorder
- several lines of evidence suggested the serotonin transporter as the most logical candidate gene, based on existing evidence, but many other candidates could be considered on only slightly weaker evidence
- the short variant at the serotonin transporter locus was found to be preferentially transmitted from parents to children with autistic disorder, and this provides preliminary evidence that the serotonin transporter may serve as a susceptibility locus in autistic disorder. This finding may contribute to identification of other factors which add additively or in a multiplicative manner

85. Paper by Diane E. Griffin, D. E. Hussy et al, Johns Hopkins University, US, Journal of Infectious Diseases, 173 (6), 1320-26, June 1996)

This found that:

- measles virus and measles vaccinations impair cell-mediated immunity
- they also increase the likelihood of other viral infections

These researchers found that:

- of 88 children immunised at six or nine months with Edmonston-Zagreb or Schwarz SW6 or SW9 strain of measles vaccine, mitogen-induced lymphoproliferation was decreased at 2 weeks in the SW9 group and at 3 months in all groups
- this was negatively correlated with measles antibody level at 3 months
- CD8 T-cells, soluble CD8, neopterin and beta2-microglobulin were increased at 2 weeks in the SW9 group
- soluble CD8 and beta2-microglobulin remained elevated at three months
- therefore measles immunisation resulted in suppression of lymphoproliferation, which was most evident in infants with the highest antibody responses and most immune activation

86. Paper by Martinez et al, Proceedings of the National Academy of Sciences, 94.8726-31 1997:

This found that:

- relative deficiency of T-helper type 1 (Th1) and cytotoxic T lymphocyte (CTL) responses in early life is associated with an increased susceptibility to infections by intracellular microorganisms
- this is likely to reflect a preferential polarisation of immature CD4 T-cells towards a Th2 rather than a Th1 pattern upon immunisation with conventional vaccines

87. Paper By Zecca, Graffino et al, New Jersey Medical School, Children's Hospital of New Jersey, Newark NJ, Elevated Rubella Titers in Autistic Children, presented at a meeting of the National Institutes of Health, Bethesda, Maryland, September 1997

This paper reported that:

- The authors had evaluated the possible role of MMR in the pathogenesis of autism by comparing rubella titers in autistic and normal children.
- Amongst 16 children diagnosed with autism followed in their clinical practice, it had been found that these children had a threefold increase in their rubella titers over the

expected normal range. These had been compared with the rubeola titers from 13 normal controls.

- Subjectively, parents had stated that their children's developmental milestones deteriorated following MMR vaccination.
- The elevated titers of anti-measles antibodies in autistic children may signify a chronic activation of the immune system against this neurotropic virus. MMR may therefore play a role in the pathogenesis of autism.

88. Paper By Weibel, Caserta, Benor and Evans, *Acute Encephalopathy Followed By Permanent Brain Injury Or Death Associated With Further Attenuated Measles Vaccines: A Review of Claims Submitted to the National Vaccine Injury Compensation Program, Pediatrics, Vol 101 No. 3 March 1998.*

The purpose of this study was to determine any causal relationship between acute encephalopathy and subsequent permanent brain injury or death, following measles vaccine, mumps vaccine, rubella vaccine, MR or MMR. The conclusion was that a causal relationship may exist as a rare complication.

- The study looked at children who received the first dose of these vaccines 1970-93 and who then developed an encephalopathy with no determined cause within 15 days
- A total of 48 children (out of 403 claims submitted) aged 10-49 months met the criteria. Eight had died, the remainder had mental regression and retardation, chronic seizures, motor and sensory deficits and movement disorders. Symptoms were clustered on days 8 and 9 after vaccination. The clustering was accepted as suggesting a rare complication of measles immunisation.
- Of the 48, 1 child had MR, 30 had MMR, 2 had MMR plus DTP, 2 had MMR plus haemophilus influenzae type b (Hib), 4 had MMR plus DTP plus oral polio vaccine (OPV), 1 had MMR plus DTP plus OPV plus Hib
- Two of the deaths were in previously apparently normal healthy children, who then received MMR. Three deaths occurred 3 months to 4 years later. One non-fatal case reviewed had eventual hyperactivity and aggressive behaviour at age 5 years.
- The authors thought that (1) the 48 cases represented under-reporting from a passive system, but (2) most serious cases had been captured by the system - a self-comforting point?

89. Study by [Wakefield](#) et al, Inflammatory Bowel Disease Study Group at the Royal Free Hospital, London, *Ileal Lymphoid Nodular Hyperplasia, Non-Specific Colitis and Pervasive Developmental Disorder in Children*, Lancet, 28th February 1998

This is the "Early Report" that started the major public debate in the UK and beyond about a possible link between MMR and autism.

Dr. Wakefield and colleagues suggested that there could be the possibility of a linkage between vaccination and autism and other disorders. Although he was not in a position at that time to present the published evidence of comprehensive studies, initial findings suggested that the hypothesis was plausible.

The Royal Free Hospital group's report found:

- that there was patchy inflammation of the colon and swelling of the lymph glands in the last part of the small intestine in 39 out of 40 children studied that had developmental disorders.
- All the children had previously gone through periods of normal development, and most had acquired words and social skills which were subsequently lost
- most children had suffered either diarrhoea or alternating periods of diarrhoea or constipation, frequently associated with bloating, abdominal pain and poor appetite, and occasionally the passing of blood
- parents reported in some cases that certain foods made their child's symptoms markedly worse, and withholding those foods improved behaviour. This implied that there could be a syndrome that linked intestinal inflammation with developmental disorders of the autistic spectrum, and could offer a vital clue in understanding the origins of some forms of childhood autism

Dr. Wakefield also speculated that if the bowel was damaged during a critical period of brain growth, an excess of peptides could gain access to the developing brain, where these peptides may not only influence behaviour but also brain growth and development. The disease pathway was described as "speculative but biologically plausible".

No hard evidence (in terms of the examination of actual affected children or the disproving of this theory) to contradict this hypothesis has been offered to date by the UK Department of Health or others, and the Department has yet to offer evidence of its own that degeneration into autism or the onset of inflammatory bowel disease following vaccination is caused by some other source.

Note: the study only looked at 12 children. By the end of 2001, over 200 children had been examined. It has been reported in the UK press that virtually all fitted the same pattern as the original 12.

90. Paper by Montgomery, Morris, Pounder and Wakefield, Inflammatory Bowel Disease Study Group, Dept. Of Medicine, Royal Free Hospital, London, *Paramyxovirus Infections in Childhood*

and Subsequent Inflammatory Bowel Disease (full details of date and journal of publication not available)

This study investigated the patterns of infection that are risks for SSPE, early infection and a close temporal relationship between measles and another infection, as potential risks for IBD.

The data was from 7019 members of a nationally representative 1970 UK cohort study. The ages of five childhood infections were recorded before the onset of IBD symptoms. Diagnosis of IBD and insulin-dependent diabetes mellitus (IDDM) as a control disease were identified by age 26 years. The results were:

- Mumps infection before age 2 years was a risk factor for ulcerative colitis
- Measles and mumps infections in the same year of life were significantly associated with ulcerative colitis and Crohn's disease, but not with insulin-dependent diabetes mellitus
- These relationships were independent of each other and of sex, social class at birth, household crowding in childhood, and family history of IBD.

The study concluded that atypical paramyxovirus infections in childhood may be risk factors for later inflammatory bowel disease.

91. Letter published in The Lancet, Vol. 352, July 18th 1998, from Drs. Sabra, Bellanti and Colon of the International Centre for Interdisciplinary Studies of Immunology and the Department of Paediatrics, Georgetown University Medical Centre, Washington DC

This stated that:

- in support of the findings of Dr. Andrew Wakefield are several behavioural and clinical features known to be related to the central nervous system, such as infantile colic and attention-deficit hyperactivity disorder, which have been related to food allergy
- the US researchers had noted a striking appearance of ileal-lymphoid nodular hyperplasia in patients with non-IgE-mediated food allergy who had presented a range of conditions including asthma and attention-deficit-hyperactivity disorder
- examination of two cases with hyperactive disorders who were intolerant to various foods, by colonoscopy of their terminal ileum, had produced findings match those of Wakefield et al
- ileal-lymphoid nodular hyperplasia lesions of the gastrointestinal tract allowed the entry of antigens across the inflamed mucosa of the bowel as a result of the reactive inflammatory response in the adjacent lymphoid tissue of Peyer's patches in patients with non-IgE-mediated food allergies

- the researchers proposed that similar mechanism(s) may be involved in the pathogenesis of the central nervous system dysfunction in the patients described by Wakefield et al

92. Paper by [Singh](#) and Yang, Department of Biology and Biotechnology Center, Utah State University, University of Michigan College of Pharmacy, published *Clinical Immunology and Immunopathology*, October 1998, 89: 105-108

This paper suggested that:

- a significant number of autistic children have positive titers of measles and/or MMR autoantibody which is associated with the presence of myelin basic protein autoantibody
- Most autistic children with virus antibodies also had brain autoantibodies
- The more virus antibodies they had, the more likely they were to have the brain antibodies
- None of the non-autistic children had brain autoantibodies
- The strongest link was between measles virus antibodies and anti-MBP, suggesting that exposure to the measles virus may cause the immune systems of children with autism to attack myelin
- None of the autistic children in the study had had measles in the past, but all had had MMR vaccine
- a measles-related triggered autoimmune response to myelin may play a pathogenesis role in the cause of autism in at least a subset of cases

Singh commented that the most likely explanation for the connection between autism and measles virus was that some autistic people were genetically predisposed to the disorder. Measles or the MMR vaccine may somehow prompt their immune systems to act in a negative way whilst leaving other people unharmed.

Singh stated that, of 88 autistic cases that he had examined, 51% said that their child's autism had followed MMR vaccination, and 36% had said it had followed DPT vaccination.

93. Paper by Uhlmann, Sheils et al, *Measles Virus In Reactive Lympho-Nodular Hyperplasia and Ileo-Colitis of Children*, (publication date not known), Department of Pathology, Coombe Womens' Hospital, Dublin, Trinity College Dublin and Royal Free Hospital London.

This paper noted that measles virus nucleoprotein (N antigen) had been detected in association with follicular dendritic cells (FDC) in patients, and sought molecular confirmation of this result. It found that:

- Solution phase RT PCR yielded specific MV N gene amplification in affected children (10/10)
- Distinct measles virus genome was identified 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

94. Paper published by Bitnun et al, *Measles Inclusion-Body Encephalitis Caused By the Vaccine Strain of Measles Virus*, Clinical Infectious Diseases Journal, 1999; 29 855-61, (October)

This confirmed the presence of measles virus in the brain tissue of a previously-healthy 21-month-old boy, 8.5 months after he received MMR. The child had no history of exposure to measles or if immune deficiency.

The nucleotide sequence in the nucleoprotein and fusion gene regions was identical to that of the Moraten and Schwartz vaccine strains. The fusion gene differed from known genotype A wild-type viruses.

95. Paper by Dr. Vijendra Singh, University of Michigan College of Pharmacy, to the US House of Representatives Committee on Government Reform, 2000

Dr. Singh explained that he had set out in his studies to answer two questions:

- Do autistic children have a hyperimmune response (or increase of antibodies) for a specific virus?
- Is there a relationship between virus antibodies and brain autoantibodies in autism?

In his studies, he reported two important observations:

- There was indeed a hyperimmune response to a virus, and it was specifically for the measles virus, but not for the other viruses tested (human herpes virus 6 (HHV-6), rubella virus and cytomegalovirus)

- There was an association between measles virus antibodies and myelin basic protein autoantibodies (i.e. The higher the measles virus antibody level, the greater the chance of brain autoantibody)

Also:

- He had previously already found that many autistic children had antibodies to a specific protein of the MMR vaccine
- These viral antibodies were also related to positive titers of brain MBP autoantibodies.
- This was probably the very first laboratory-based evidence to link measles virus and/or MMR vaccine to autoimmunity in children with autism.

These observations led Dr. Singh to speculate that autism may be caused by a measles-induced, or MMR vaccine-induced, autoimmune response, but further research was being delayed by a lack of funding.

Dr. Singh reported his own anecdotal survey of apparently vaccine-injured children with regressive autism. He found that 93% of cases had autistic symptoms shortly after vaccinations. Of these, 52% were post-MMR, 8% post MMR and DPT, and 33% post-DPT. Just 7% were not linked by the parents to any vaccination. He acknowledged that the survey was non-scientific.

Dr. Singh's conclusion was that:

- Rapidly-accumulating evidence strongly implicated autoimmunity in autism
- In many, this may have resulted from a vaccine injury
- There was a possibility of an atypical measles infection in autism, but the evidence also suggested an MMR vaccine infection
- The Congressional Committee should explore the possibility that the manufacturers had never properly evaluated the safety of vaccines in the first place.

96. Paper Presented to US Congressional Oversight Committee on Autism and Immunisation, Professor John O'Leary, Dublin Womens Hospital, April 2000

This paper reported a study using biopsy material from children examined at the Royal Free in London. Dr. Wakefield at the Royal Free had posed three questions to the O'Leary team,

(1) was measles virus present in gut biopsies of affected children?

(2) where was measles virus located in the gut biopsies of the affected children?

(3) how much virus was present?

- The O'Leary team used in-situ hybridisation (with/without tyramide signal amplification), in-cell PCR, solution-phase PCR, TaqMan quantitative PCR and DNA sequencing to determine the answers to these questions.
- Using TaqMan PCR the team was able to quantify the measles virus copy number per 1,000 mucosal cells using gene dosage correction formulations. The copy number of measles virus in gut biopsies from children with autistic enterocolitis was low, at approx. 30-50 measles virus genomes per 2,000 mucosal cells (inc. Gut, epithelial, lymphoid and dendritic cells).
- Confirmation of the presence of measles virus genomes was achieved using positive and negative strand sequencing of cDNA measles amplicons.
- The results were that 24 out of 25 (96%) of the autistic children were positive for measles virus, including 2 children from the USA who were included in this analysis
- In the controls, only 1 of the 15 children (6.6%) was positive for measles virus.
- The study therefore localised, quantified and sequenced measles virus genomes in gut biopsies of children with autistic enterocolitis. The study team then posed the question, "how did it get there?".

97. Paper by Kawashima, Takayuki et al, *Detection and Sequencing of Measles Virus from Peripheral Mononuclear Cells from Patients with Inflammatory Bowel Disease and Autism*, *Digestive Diseases & Sciences* Vol. 45, No. 4, April 2000, pp723-729

Following reports that measles virus might be present in the intestines of children with Crohn's Disease, a new syndrome was reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases after MMR vaccine, was reported (see papers by Wakefield et al). It was not known whether the virus, if confirmed as present in these patients, derived from wild strain or vaccine strain.

This study carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in 8 patients with CD, 3 patients with UC and 9 patients with autistic enterocolitis. As controls, the study used 8 cases of either healthy children or children with SSPE, SLE or HIV-1. The results were:

- 1/8 patients with CD, 1/3 with UC and 3/9 with autism were positive. Controls were all negative
- The sequences from patients with CD shared the characteristics with wild-strain virus.

- Sequences from patients with UC and children with autism were consistent with vaccine strain measles.
- These results were consistent with the exposure history of the patient.

This study is obviously particularly important because it points to infection with vaccine-strain measles virus.

98. Paper by Hagenbuch, Kullak-Ublick et al, Department of Medicine, University Hospital, Zurich, *Transport of Opioid Peptides Across the Blood Brain Barrier*, Journal of Pharmacological Exp. The., July 2000,

This paper looked at organic anion-transporting polypeptides (OATPs), a rapidly growing gene family of polyspecific membrane transporters. The study looked at the human OATP. The results:

- demonstrated that OATP-A can mediate transport of the analgesic opioid peptides DPDPE and deltorphin II across the human BBB.
- indicated that members of the Oatp/OATP gene family of membrane transporters play an important role in carrier-mediated transport of opioid peptides across the BBB and blood-cerebrospinal fluid barrier of the mammalian brain.

These findings were not specifically linked to autism, but help to support the opioid-peptide theory aspect of autism.

99. Paper by Wakefield, Anthony et al, *Enterocolitis in Children With Developmental Disorders*, American Journal of Gastroenterology, September 2000, Vol. 95, No. 9, pp 2285-2295

This study described endoscopic and pathological characteristics in a group of children with developmental disorders that are associated with behavioural regression and bowel symptoms, and compares these with pediatric controls.

- Ileocolonoscopy and biopsy were performed on 60 affected children (median age 6 years, range 3-16, 53 male)
- Developmental diagnosis were autism (50), Aspergers (5), disintegrative disorder (2), attention deficit hyperactivity disorder/ADHD (1), schizophrenia (1), dyslexia (1).
- The results were that ileal-lymphoid nodular hyperplasia (ILNH) was found in 54/58 affected children (93%) but only 5/35 (14.3%) controls.
- Colonic LNH was present in 18/60 (30%) affected children but only 2/37 (5.4%) controls.

- Reactive follicular hyperplasia was present in 46/52 (88.5%) ileal biopsies from affected children and only 4/14 (29%) UC controls, but not in IBD controls.
- Active ileitis was present in 4/51 (8%) affected children but not in controls.
- Chronic colitis was identified in 53/60 (88%) affected children compared with 1/22 (4.5%) controls and in 20/20 (100%) with UC.
- Scores of frequency and severity of inflammation were significantly greater in both affected children and those with UC, compared with controls.

100. Statement by Professor Walter O. Spitzer, Emeritus Professor of Epidemiology, McGill University, Montreal

Although not a study (but see later), the statement by Professor Spitzer deserves coverage. Professor Walter O. Spitzer, Emeritus Professor of Epidemiology, McGill University, Montreal, stated on December 6th 2000:

- *"The safety of MMR has been brought into question, both in the United Kingdom and in California. It is not possible to rule out the possibility that excessive rates of autism occur among children immunised with MMR"*
- *"The early epidemiological findings are worrisome. The clinical and laboratory data strongly suggest the biological plausibility of a link between MMR and autistic disorders"*
- (He) *".....strongly endorses immunisation as a pillar of public health strategy for most diseases. But one should never surrender caution".*

101. Furlano, Anthony et al Study, Colonic CD8 and T-Cell Infiltration With Epithelial Damage in Children With Autism, Journal of Pediatrics, 2001; 138: No. 3, 366-72

Following reported colitis with ileal lymphoid nodular hyperplasia (LNH) in children with regressive autism, this study was undertaken to characterise this lesion and determine whether LNH is specific for autism:

- Ileocolonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms.
- Blinded comparison was made with 8 children who had a histologically normal ileum and colon, 10 developmentally normal children with ileal LNH, 15 with Crohn's disease and 14 with ulcerative colitis.

- Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness.
- In the results, histology demonstrated lymphocytic colitis in the autistic children, less severe than classical inflammatory bowel disease. However, basement membrane thickness and mucosal cell density were significantly increased above those of all other groups, including patients with inflammatory bowel disease.
- CD8+ density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH and normal control groups
- CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups.
- Epithelial, but not lamina propria, glycosaminoglycans were disrupted.
- However, the epithelium was HLA-DR-, suggesting a predominantly TH2 response.

The interpretation of these results was that immunohistochemistry confirmed a distinct lymphocytic colitis in autistic spectrum disorders in which the epithelium appears particularly affected, and that this was consistent with increasing evidence for gut epithelial dysfunction in autism.

102. Jyonouchi, Sun and Le Study, *Innate and Adaptive Immune Responses in Children With Regression Autism: Evaluation of the Effects of Environmental Factors Including Vaccination*, Journal of Allergy and Clinical Immunology, February 2001, Part 2, Vol. 107 No. 2. Presented at the AAAA 57th Annual Meeting, New Orleans, March 2001

This study investigated the alleged causal association between the onset of regression/autistic behaviour and infant immunisation, viral infection and adverse reactions to common foods. In the study, the authors hypothesised that children with regressive autism may have an aberrant immune response against these common, usually benign, factors. The study:

- Determined innate and adaptive immune responses in children with autism spectrum disorders (n = 35, age = 2-14 years, median 6 years, 24 males, 9 females)
- It found that the autistic children produced a higher TNF- α , sTNFR II and IL-6, with a low dose of LPS, than controls. This was due to a subset of patients who produced large amounts of these cytokines
- 27/35 (77%) of the study cohort produced higher than the maximum levels of TNF- α , sTNFR II and IL-6 and/or IL-1 β observed in controls

- The study also observed elevated serum levels of these cytokines in 8 out of 18 autistic children
- Results indicated a high frequency of excessive innate immune responses in children with regressive autism
- These results may partly explain the apparent association between the onset of regression or autistic behaviour and immunisation in these children

The study also assessed T1/T2 responses:

- The ratio of IFN- γ /IL-5 did not differ between autistic children and controls
- 7 and 8 out of 35 autistic children produced significantly high IL-12p40 with recall antigens IL-12 and IL-18 respectively
- 10 and 11 out of 35 subjects produced high amounts of IL-10 with PHA and tetanus respectively
- 12/35 subjects produced significantly low IL-10 with PHA as compared to controls

The study team concluded that these results also indicated aberrant production of regulatory cytokines for T cell responses in subsets of autistic children.

103. Further Study by Jyonouchi, Sun and Le, Department of Pediatrics, University of Minnesota, *Proinflammatory and Regulatory Cytokine Production Associated With Innate and Adaptive Immune Responses in Children With Autism Spectrum Disorders and Developmental Regression*, Journal of Neuroimmunology, 120 (2001) 170-179

The study determined innate and adaptive immune responses in 71 children with developmental regression and autism spectrum disorders (ASD), in 23 developmentally normal siblings and in 17 controls. The study found:

- A number of ASD children produced excessive proinflammatory and regulatory cytokines associated with innate immunity compared to controls
- Some siblings of ASD patients showed abnormalities in production of these cytokines
- The findings may indicate the presence of aberrant immune responses in ASD children with developmental regression at high frequency

The study team also observed:

- Many parents report the onset of regressive autism following immunisation and/or benign childhood infections, and aggravation of symptoms following benign viral infection/immunisation.
- Data supporting the role of infection/immunisation/dietary protein Ag in ASD are scarce and inconclusive
- Many ASD patients also suffer from recurrent/chronic ear infection, sinusitis, viral infection and chronic diarrhoea/constipation

Jyonouchi et al commented: "*Vaccination was developed to provide protective immunity by stimulating the immune system with killed or attenuated microbes. It is well known that purified protein Ags are poor immunogens and will not induce immunity if not given with adjuvants. Adjuvants augment Ag-specific immune responses by activation of innate immunity, by facilitating co-stimulatory molecule expression, Ag processing and production of pro-inflammatory cytokines by APC*".

Jyonouchi et al hypothesise that ASD patients with developmental regression may have aberrant innate immune responses that could result in increased risk for adverse reactions to benign childhood infection, and even to immunisation. They also hypothesise that aberrant innate immunity results in abnormal adaptive immune response and intolerance to common environmental Ag such as dietary proteins

The study report concluded: "*Our results indicate for the first time that a number of ASD children with developmental regression are likely to demonstrate aberrant innate immune responses that may also result in aberrant adaptive immune responses*".

104. Paper By Spitzer, Aitken et al, *The Natural History of Autistic Syndrome in British Children Exposed to MMR*, Journal of Adverse Drug Reactions and Toxicology, 2001, 20(3) 160-163

This paper found that:

- Just over 900 families whose children had had MMR were seeking legal redress in the UK, and so reviewed a set of 493 of the children's National Health Service records. Some were ineligible for various reasons, and the study therefore focussed on 369 eligible cases.
- Of these cases, there was classic ICD-10 autism in 259 cases, atypical autism in 25, Aspergers in 30, specific language impairment in 10, disorders of attention, motor control and perception (non-ICD-10) in 2, and other childhood disintegrative disorders in 2. There were no cases of Rett's syndrome.
- Of the cases of classical and atypical disorders, 112 (39%) regressed, from "normal" function pre-MMR, to unequivocal major deficits in function that fit conventional

criteria. A further 115 (40%) were "failure to develop" following MMR immunisation. A further 30 (11%) manifested both regression and failure to develop.

- The median delay from first dose of MMR to diagnosis was 2.5 years, with the range being 0.5 years to 11.8 years. The interquartile interval was 1.8 years to 4.2 years. Virtually none of the cases would have been classifiable if followed for only six weeks after MMR.
- The project was acknowledged to be passive surveillance of an unrepresentative group of children, almost certainly affected by major underreporting.
- The key finding is the delay between exposure to MMR and the emergence of autistic symptoms or the delay to definitive diagnosis of an autistic syndrome.
- The median the authors report for delay to diagnosis is 2.5 years within an interquartile interval of 1.8 to 4.2 years. That means that the assumptions about delay and the distribution of delay in many published articles and safety assessments are invalid.

This paper was dismissed in a Parliamentary Written Answer by Lord Hunt, Government Health Spokesman in the UK House of Lords on 3rd January 2002. Lord Hunt stated that *".....it provides no scientific evidence to link MMR vaccine with autism, (it is) strongly suggestive that MMR played no role", and its findings "are also counter to the paper by Dr. Andrew Wakefield and colleagues published in the Lancet in 1988, which reported rapid onset of behavioural symptoms, median 6.3 days, after MMR"*.

105. Paper by Dr. Ken Aitken to the Scottish Society for Autism, published in the Society's "In Touch" magazine, 2001

In this paper, Dr. Aitken sets out several, possibly interacting, biologically plausible mechanisms to link autism with immunisation:

- An autoimmune reaction. This would be where the body's immune system raises antibodies to a vaccine virus, and those antibodies go on to directly affect the functioning of the central nervous system. A parallel might be drawn with disorders known as PANDAS, where a movement disorder (Sydenham's chorea) occurs after a streptococcal infection, and can be cured by removing the antibodies from the bloodstream. A number of recent autism papers point to autoimmune problems
- A gastrointestinal dysfunction, where interference with intestinal function leads to alteration to endogenous opiate systems or to food related opiate-like substances passing into the bloodstream, reaching the brain and causing autistic-like behaviour. The opioid hypothesis receives support from a range of studies. Endoscopic research published to date demonstrates abnormalities of both the oesophagus (Horvath et al) and the intestine (Wakefield et al)

- A direct viral infection of the central nervous system, although evidence for this is more limited, being to date three deaths from chronic measles infection of the nervous system (subacute sclerosing panencephalitis, or SSPE), which have been reported within the group of UK children whose cases are making their way to the High Court

106. Paper by Imani and Kehoe, Division of Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Asthma and Allergy Center, Baltimore, *Infection of Human B Lymphocytes with MMR Vaccine Induces IgE Class Switching*, published in *Clinical Immunology*, Vol 100, No. 3, September 2001, pp 355-361.

The authors noted that circulating immunoglobulin E (IgE) is one of the characteristics of human allergic diseases including allergic asthma. The authors had previously showed that infection of human B cells with rhinovirus or measles virus could lead to the initial steps of IgE class switching, and that, as many viral vaccines are live viruses, they speculated that live virus vaccines may also induce IgE class switching in human B cells. To examine this, they selected the MMR vaccine.

- In their study, they showed that infection of a human IgM+B cell line with MMR resulted in the expression of germline e transcript
- In addition, infection of freshly prepared human PBLs with MMR vaccine resulted in the expression of mature IgE mRNA transcript
- The authors concluded that their data suggested that a potential side effect of vaccination with live attenuated viruses - in this case, specifically MMR - may be an increase in the expression of immunoglobulin E

107. Paper by Dr. Timothy Buie, Harvard Massachusetts General Hospital, Presented to the Oasis 2001 Conference for Autism, Portland, Oregon, November 2001

Dr. Buie reported that he had performed over 400 gastrointestinal endoscopies with biopsies, and evaluation of digestive enzyme function in children diagnosed with autism. The results of his testing were reported to be similar to the observations of Dr. Andrew Wakefield and colleagues at the Royal Free Hospital, London. Buie had found:

- The presence of chronic inflammation of the intestinal tract, although the incidence was noted to be less frequent than in the RFH group.
- Biopsy results indicated the presence of chronic inflammation of the digestive tracts, including esophagitis, gastritis and enterocolitis
- Lymphoid nodular hyperplasia had been found in 15 of 89 children examined

- Results of enzyme testing had paralleled that of Dr. Karoly Horvath and colleagues at the University of Maryland School of Medicine
- The autistic children examined showed disaccharide/glucoamylase enzyme levels below normal
- Some 55% of the children had lactase deficiencies (which break down lactose in milk), as well as deficiencies of the enzyme sucrase (responsible for digestion of table sugar).

Buie shared the opinion of a growing number of clinical researchers: *"These children are ill, in distress and pain, and not just mentally, neurologically dysfunctional"*.

108. Paper By Uhlmann, Wakefield, O'Leary et al, *Potential Viral Pathogenic Mechanism For New Variant Inflammatory Bowel Disease*, Journal of Clinical Pathology, Molecular Pathology, 2002, 55, 0-6, published 6th February 2002

This study investigated the presence of persistent measles virus in the intestinal tissue of 91 patients with new variant inflammatory bowel disease, and examined a group of controls, using molecular analysis.

- Patient samples were provided by the Department of Gastroenterology, Royal free Hospital, London. The 91 patients had a median age of 7 years, age range 3-14, 77/91 were boys.
- The 70 developmentally normal controls had age range 0-17 years, 47/70 were boys. These included 19 children with normal ileal biopsies, 13 children with mild non-specific chronic inflammatory changes, 3 children with ILNH investigated for abdominal pain, 8 children with Crohn's disease, one child with ulcerative colitis, 26 children who had undergone appendectomy for abdominal pain including appendicitis.
- Biopsies from the terminal ileum of affected children and normal controls were examined. Measles virus fusion (F) and Haemagglutinin (H) genes were detected by Taqman reverse transcription polymerase chain reaction (RT-PCR) and the Nucleocapsid (N) gene by RT in-situ PCR. Localisation of the mRNA signal was performed using a specific follicular dendritic cell antibody.
- Measles virus positive control material included 2 cases of SSPE and MV-infected Vero cells. Negative control material included uninfected Vero cells and human tissues, control RNA extracted from Raji cells (Applied Biosystems, Foster City, California) and normal peripheral blood mononuclear cells.

The results of the study were:

- 75 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 of 70 controls.
- 70 of 91 affected children were positive for MV compared with 4 out of 70 controls as analysed by TaqMan RT-PCR
- Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300,000 copies/ng total RNA.
- Of the paediatric controls, MV was not detected in normal children or children with isolated ILNH. However, 4 out of 26 appendectomy samples harboured the MV genome. The study noted that the prevalence of MV in the general population is unknown, and that this warrants further investigation.
- The conclusion is that the data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder

The study did not exclude the presence of alternative infections to MV, and that viruses might exist elsewhere or exert a transient effect. The study concluded that its findings raised many questions - most importantly, does measles virus play an aetiological role in intestinal inflammation in developmental disorder? But the study raises for the first time an association between MV infection and ileocolonic lymphonodular hyperplasia and ileocolitis in children with developmental disorder.

109. Paper by Singh and Nelson, Utah State University, Logan, Utah, *Abnormal Measles Serology and Autoimmunity in Autistic Children*, abstract released online in January 2002 (no publication details available yet)

Following their finding that many autistic children have autoantibodies to brain myelin basic protein (MBP) and also elevated levels of measles virus antibodies, Singh and Nelson conducted further serological studies. These included measles virus (MV), mumps virus (MuV), rubella virus (RV) cytomegalovirus (CMV), human herpes virus-6 (HHV-6), MMR, DPT, diptheria-tetanus (DT), and hepatitis B (Hep-B). These were then studied for correlations with MBP autoantibodies.

Antibodies were assayed in the sera of autistic children (n = 125) and in normal children (n = 92) by ELISA or immunoblotting methods. The study findings were:

- Autistic children have significantly higher than normal levels of MV and MMR antibodies, compared with controls

- The antibody levels of MuV, RV, CMV, HHV-6, DPT, DT and Hep-B did not significantly differ between autistic and normal children
- Immunoblotting analysis showed the presence of an unusual MMR antibody in 60% (75 out of 125) of the autistic children, but in none of the 92 controls
- By using MMR blots and monoclonal antibodies, Singh and Nelson found that the specific increase of MV antibodies or MMR antibodies was related to measles hemagglutinin antigen (MV-HA), but not to mumps or rubella viral proteins, of the MMR vaccine
- In addition, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a causal association between MMR and brain autoimmunity in autism

The authors concluded by suggesting that an "atypical" measles infection, in the absence of a rash but with neurological symptoms, might be etiologically linked to autoimmunity in autism.

110. Review, *The Concept of Enterocolonic Encephalopathy, Autism and Opioid Receptor Ligands*, Wakefield, Pulestone, Montgomery et al, Inflammatory Bowel Disease Study Group Royal Free and University College Medical School London and Department of Pathology, Coombe Women's Hospital and Trinity College Dublin, Aliment Pharmacological Ther., 2002: 16: 663-674.

This review paper set out some of the background to the relevance of the gut-brain axis in understanding the pathogenesis of autism:

- In a proportion of affected children, gut-brain interactions may contribute to abnormal neural development and the subsequent expression of aberrant behaviours.
- The paper noted that a researcher, K. Soddy, had noted as early as 1986 that recurrent gastrointestinal upsets were a constant feature of autistic children and that although these observations had featured prominently in parental accounts, they had been largely ignored in the autism literature. 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 paediatric controls.
- It also noted the researcher D'Eufemia's finding that aberrant intestinal permeability in asymptomatic autistic children indicated that reliance upon symptomatology would substantially underestimate the proportion of autistic individuals with possible gastrointestinal pathology. The identification of increased intestinal permeability was also not in itself a diagnostic end-point, but indicated the need for further detailed investigation.
- Also, Bellanti and colleagues had presented evidence of similar findings to the 1998 Wakefield team findings, in children with attention deficit hyperactivity disorder,

suggesting that gastrointestinal pathology may be relevant to a broader spectrum of childhood developmental and behavioural disorders.

- In summary, within the autistic spectrum, there is a substantial group of children presenting with what may be a primary immune-mediated intestinal pathology. The constellation of developmental disorder and gastrointestinal pathology (autistic enterocolitis) combines the paradoxical elements of a motility disorder (oesophageal reflux plus constipation with spurious diarrhoea) and enterocolonic mucosal inflammation.
- In the central nervous system, exposure to opioid excess during a critical phase of early cerebral development may not only adversely influence that development, but may also increase the long-term susceptibility to systemic opioids, whether exogenous or endogenous in origin. It has been demonstrated in rodents that perinatal exposure to an opioid excess leads to a permanent increase in the active transport of systemic opioid across the blood-brain barrier.
- An opioid excess at a critical phase of cerebral development may produce enduring cognitive deficits that are not fully corrected by subsequent dietary restriction. The window of vulnerability for sustaining permanent impairment or susceptibility might be a neurotoxic exposure, such as an opioid excess, during a time of critical neuronal development during the first years of life.
- The mucosal lesion in the small and large intestine is consistent with an autoimmune pathology, and the presence in some affected children of antibodies to myelin basic protein, neurofilament protein and cerebrovascular endothelium, suggests the possibility of cerebral damage due to an autoimmune response to structural components of the CNS.
- The paper noted, however, that there were several inconsistencies in this hypothesis that required explanation. Autism is not progressive. Imaging and histopathological studies do not support an inflammatory CNS pathology in autism. No investigations have yet indicated cerebral inflammation that would be consistent with an autoimmune process, although a more subtle lesion remains a possibility.
- Alternatively, the finding of a variety of autoantibodies in affected children suggests that, due to underlying immune aberrations, they may overproduce such antibodies, but their pathogenetic significance (if any) has yet to be determined. The paper also noted that there could be "cross-talk" between opioid-mediated effects and autoimmunity.
- The paper finally noted the biological plausibility that exogenous gut-derived neurotoxins can enter the systemic circulation and, by operating during a critical window of vulnerability, could damage the developing CNS and cause autism, and that this is now widely accepted.

111. Report of Study by Comi et al, Johns Hopkins Hospital, Baltimore, US

This study looked at the background history of families of children with autism. It found that families of children with autism had an unusually high incidence of diseases of the immune system, in particular rheumatoid arthritis.

Comi and colleagues sent questionnaires to the families of 61 children with autism, and to 46 children without autism. The families were asked if they suffered from autoimmune diseases, such as rheumatoid arthritis, lupus, early-onset diabetes, multiple sclerosis and thyroid disorders.

The results showed that

- in 46% of families with autism, two or more family members had autoimmune disorders, compared with 26% in controls
- Some 21 per cent of autistic children had at least one parent suffering from such a disorder, compared with 4% in controls
- A further finding was that 11% of children with autism had allergies, compared with 39% of controls

Dr. Comi urged that larger studies should be undertaken

112. Paper, *Small Intestinal Enteropathy With Epithelial IgG and Complement Deposition in Children with Regressive Autism*, by Torrente, Ashwood, Day et al, Lancet, May 2002

This study compared duodenal biopsies in 25 children with regressive autism to 11 with coeliac disease, five with cerebral palsy and mental retardation, and 18 histologically normal controls. The study was part of a continuing investigation into a novel gastrointestinal pathology in children with regressive autism. Inflammatory pathology had already been confirmed in these children in the large intestine and upper gastrointestinal tract.

Routine staining showed only minor differences between autistic children and controls, but immunochemistry highlighted striking abnormalities in the group with autism. The density of CD8 intraepithelial lymphocytes was significantly greater in autistic children than in normal controls or children with cerebral palsy, but was not as high as in children with coeliac disease.

This study:

- Confirmed the presence of immunopathology in the mucosal lining of the small intestine. It identifies the unique nature of the pathology when compared with developmentally normal children with normal intestinal tissues, those with known inflammatory pathologies, and children with mental retardation but without autism
- The most striking finding was the deposition of IgG1 and IgG4 on the basolateral enterocyte membrane and the subepithelial basement membrane in 23 out of 25 autistic children but in none of the other groups. The study reports IgG binding to the epithelial cell surface, lymphocyte infiltration, and increased crypt cell proliferation in the small bowel of these children with autism. It thus reports the detection of an antibody in the circulating blood of affected children that binds to a target (or targets) molecules on the membrane of the epithelial cells that line the intestine. The antibody

appears to bind in the same distribution as a chemical - complement component C1Q - that forms part of the activated inflammatory cascade.

- The co-localisation of these two molecules at this site is unique to the children with regressive autism, and indicates a likely autoimmune basis to the intestinal disease, in which the body's immune system turns upon itself and causes tissue injury.
- The study notes that autoimmune diseases tend to run in families and are often linked to a genetic susceptibility that requires an environmental trigger to initiate and propagate the disease. The study found that the pathology in these regressive-autism children is consistent with a virally-driven autoimmune enterocolitis (an intestinal inflammation).

This study adds a very important piece to the emerging jigsaw of autistic regression, intestinal disease and the presence of measles virus in many affected children. Dr. Simon Murch, one of the authors, commenting on the study, stated that "the big question is whether such unexpected gut involvement either causes or exacerbates the cognitive abnormalities that typify autism. If the answer is yes, then this may point towards the logical use of immune-based therapy in future children at the time of their first regression".

113. Paper, *Abnormal Measles Serology and Autoimmunity in Autistic Children*, by Singh, Nelson (Utah State University), Jensen and Bradstreet, published in the *Journal of Allergy and Clinical Immunology* 109 (1) S232, January 2002 and also presented to the 102nd General Meeting of the American Society for Microbiology, Salt Lake City, Utah, May 19th-23rd 2002

Autoimmunity to brain myelin protein (MBP) secondary to a measles infection may cause autistic regression in some children with this neurodevelopmental disorder.

The authors hypothesised that MMR immunisation is a source of measles infection, hence the serological link between MMR and MBP antibodies might exist in autistic children. To test the hypothesis, the authors conducted a serological study of MBP, MMR and neuro-axon filament protein (NAFP) in serum and cerebral spinal fluid (CSF) of autistic children. Antibodies were assayed by immunoblotting with MBP, NAFP and MMR as antigens.

The authors found that:

- A significant number of autistic children had antibodies to MBP (up to 88% positive) and antibodies to MMR (up to 65% positive) but not to NAFP
- Normal children did not harbour these antibodies
- The analysis of paired samples (serum and CSF) from seven autistic children also revealed a high degree of serological association between MMR and MBP. 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, as indicated by paired analysis of serum and CSF samples, there is a strong correlation between MMR antibodies and MBP autoantibodies in autism.
- By using monoclonal antibodies, the authors characterised that the MMR antibodies are due to the measles sub-unit, but not due to mumps or rubella sub-units of the polyvalent vaccine.
- Furthermore, the MMR and MBP antibodies are not cross-reactive, because the pre-incubation of MBP with MMR did not block the binding of MBP antibodies.

In the light of this new evidence, the authors suggest that in some cases of autism, the MMR vaccine might cause autoimmunity, and it might do so by bringing on an atypical measles infection that does not produce a typical measles rash but instead manifests neurological symptoms upon immunisation.

The authors add that the MMR antibody has been previously reported to be the hemagglutinin protein of the vaccine measles virus (MV-HA). Immunoblotting analysis showed the presence of an unusual MMR antibody in 60% (75 out of 125) of autistic children, but none of the 92 normal children had this antibody. Moreover, by using MMR blots and monoclonal antibodies, the authors had found that the specific increase of MV antibodies or "MMR" antibodies was related to measles hemagglutinin antigen (MV-HA).

114. Paper by O'Leary et al, Coombe Women's Hospital and Trinity College Dublin, presented July 2002 to a conference of the Pathological Society of Great Britain and Ireland

(these brief details are based upon reports in June 2002 in the UK press)

- The study has detected the strain of measles virus that is used in the MMR jab, in the tissue samples from the inflamed intestines of twelve children. The twelve are a pilot sample of a larger cohort of 75 children previously found to have persistent measles virus in the gut, and to have developed acquired autism following MMR vaccination.
- Each of the children developed autism after receiving MMR. None of the children had exhibited any signs of measles disease before becoming autistic.
- As controls, researchers used brain tissue from cases of SSPE, the rare brain disease associated with persistent measles infection.
- In their earlier study (see elsewhere) measles virus of then-unknown origin had been detected in the gut biopsies of 75 out of 91 autistic children with bowel problems. Virus had only been found in five of 70 developmentally-normal controls. The O'Leary research team suggests that the new study thus corroborates the earlier study linking measles virus with autism.

- The study used a commercially-available molecular probe to distinguish between wild-strain and vaccine-strain measles virus. The probe can distinguish a single difference in the genetic code of the viruses and to give off a fluorescent signal.

115. Paper by Dr Andrew Wakefield to US Committee on Government Reform Hearing, *The Status of Research into Vaccine Safety and Autism*, Washington DC, June 2002

Dr Wakefield updated the Committee with the state of his research into the causes of autistic enterocolitis:

- The Royal Free team, in conjunction with Professor John O'Leary of Coombe Women's Hospital Dublin and Dr. Simon Murch of the Royal Free Hospital London, has shown in a series of eight subsequent papers that the major findings of the Wakefield et al study of March 1998 had been correct
- Children with regressive autism and intestinal symptoms have a novel and characteristic inflammatory disease of their intestine
- The disease is not found in developmentally normal children
- The disease is entirely consistent with a viral cause
- The disease may be the source of toxic damage to the brain
- Measles virus has been identified in the diseased intestines of the majority of those children with regressive autism that had been studied
- Measles virus has only been found in a small minority of developmentally normal children.
- The measles virus in those with autism is vaccine strain
- Children with regressive autism appear to have an abnormal immune response to measles virus
- The findings are entirely consistent with parental reports that their normally-developing child regressed into autism following exposure to MMR
- Other researchers in the US have confirmed the presence of intestinal inflammation in children with regressive autism and, independently, the link with measles virus.
- The study (then) due to be presented at the Pathological Society of Great Britain and Ireland in Dublin, Eire, in July 2002 will confirm that measles vaccine virus is present in the diseased intestinal tissues of children with regressive autism.

Dr Wakefield also gave details of "re-challenge" deterioration, where children had experienced a double-hit from MMR or measles-containing vaccine, with acquisition of autistic symptoms first time around and then worsening of these symptoms after a second, later, immunisation. The researchers had observed that some children receiving the second dose had deteriorated, and this decline was referred to as "biological gradient" (i.e. Downhill).

He also noted that in its review of April 2001, the Vaccine Safety Committee of the US Institute of Medicine had stated, in the context of MMR, that "challenge/re-challenge" would constitute strong evidence of an association" (in other words, to degenerate once might be coincidence, but to worsen after a second vaccination was much stronger proof of an underlying causal association).

The researchers have now undertaken a systematic evaluation of the re-challenge and biological gradient effects in children with regressive autism. "Exposed" children with normal early development and regressive autism who had received more than one MMR/MR vaccination were compared with age- and sex-matched "unexposed" children who had normal early development, and also with children who had regressive autism but only one MMR (but otherwise similar baseline characteristics to the exposed group).

In a preliminary analysis, exposed children scored significantly higher than unexposed children for:

- Secondary regression. This group excluded those whose secondary regression had occurred after the publication of the March 1998 Wakefield et al paper, i.e. whose parents might then have made the association as a result of reading about it, and included only those with records that confirmed independent corroborative evidence of secondary regression
- Secondary physical symptoms
- Presence of severe ileal lymphoid nodular hyperplasia
- Presence and severity of acute mucosal inflammation

The preliminary study had also found that no measures of disease were worse in unexposed than exposed children. The data had identified a "re-challenge effect" on symptoms and a "biological gradient effect" on severity of intestinal inflammation.

Dr. Wakefield also stated that he had repeatedly requested a meeting with the UK Chief Medical Officer for England and Wales, Professor Liam Donaldson, to discuss this. The response had been a refusal to meet, and a demand for the children's samples. However, no scientific protocol had been offered indicating how these samples would be analysed. In any event, independent sample analysis was offered to the defendants' scientists as part of the forthcoming UK High Court cases.

116. Paper by Dr. Arthur Krigsman to US Committee on Government Reform Hearing, *The Status of Research into Vaccine Safety and Autism*, Washington DC, June 2002

Dr. Krigsman set out his findings from data drawn from his evaluation of gastro-intestinal symptoms of children with autism. He had observed that a large proportion of his autistic patients suffered from chronic unexplained gastrointestinal symptoms. His experience covered 43 consecutive children aged 2-10 years. Most had been referred by private practitioners, but others were self-referred. Some 42 patients had received a diagnosis of either autistic disorder or ASD, one was Aspergers.

Features were:

- The majority had a clear history of developmental regression. The children had developed in an entirely normal fashion, with a typical vocabulary of 15-25 words, maintained normal eye contact, were playful and interactive, and not overly irritable.
- At some point during the age interval 12-18 months, they had either a precipitous or gradual decline in all the above mentioned markers. Clear regression was seen in the social skills of the children. The ratio of males/females was 7/1.
- The most common gastrointestinal symptom noted by the parents was diahorrea. Stools were particularly malodorous and usually contained pieces of undigested food. Irritability often preceded bowel movements. Consistency of passed stools was not overly-hard, suggesting that this was not true constipation. Most patients experienced periods of diarrhoea alternating with periods of constipation. Abdominal pain was another frequent complaint.
- Most regressive children also showed poor growth, with the majority falling in the lower 10th %tile weight for their age. There did not seem to be a concomitant percentile deficit in height.
- Examination included history, physical examination, complete blood count with platelets, erythrocyte sedimentation rate, serum chemistries, celiac antibody panel with serum IgA, inflammatory bowel disease serology, stool examination for ova and parasites, culture and occult blood.
- Patients then underwent colonoscopy. Upper endoscopy was performed only if pain was a predominant complaint or if celiac disease was strongly suspected.

Dr. Krigsman's findings were as follows:

The lymphoid nodules of the terminal ileum were found to be markedly enlarged. This is in agreement with the previously published findings of Dr. Wakefield, in which a similar

proportion of patients were found to have abnormal lymphonodular hyperplasia of the terminal ileum.

The second significant finding was the histologic evaluation of the biopsy specimens:

- 28/43 (65%) had colitis
- 22/43 (51%) had active colitis
- 17/43 (40%) had chronic colitis
- 3/43 (7%) had eosinophilic colitis
- 36/40 (90%) had lymphoid nodular hyperplasia of the terminal ileum
- 15/43 (35%) had neither active nor chronic nor eosinophilic colitis
- Inflammation was not subjected to a uniform rating system. The patterns of inflammation were patchy and unpredictable in any given patient, but overall were noted in all parts of the colon and terminal ileum.
- Most patients with colitis had both chronic and active inflammation.
- Most patients had at least 3-4 distinct areas of histologic inflammation, with an equal number of biopsies that were histologically normal.
- The intensity of the inflammatory lesions varied as well, with many being subtle and somewhat focal, and others being more marked and diffuse. The latter included areas of cryptitis, crypt abscess, ulcerations and dense inflammatory infiltration. Most significantly, these findings were consistent and seen repeatedly amongst the majority of patients.

In regard to the last-mentioned group of patients listed earlier, the majority of these patients were found to have a heavy and diffuse lymphoid hyperplasia of the colon (macroscopic and microscopic), signifying an activation of the colon's internal immune system.

Krigsman's overall conclusion:

- In a series of 43 autistic children, mostly regressive with chronic gastrointestinal symptoms, the majority were found to have pathologic inflammation of the colon and terminal ileum
- 90% had pathologic lymphonodular hyperplasia of the terminal ileum

- The findings were similar and consistent from patient to patient within the affected group.

Krigsman posed four questions for further debate:

- Does autistic colitis occur equally in regressive vs non-regressive autism?
- Do differences in growth exist between the colitis and non-colitis group?
- Do differences in growth exist between the regressive vs non-regressive group?
- In a retrospective analysis of growth, will onset of growth failure coincide with the onset of regressive behaviours?

117. Unpublished Research by Dr Paul Shattock, University of Sunderland Autism Research Unit, June 2002

This research is continuing, but some details were released to the UK media at the end of June 2002. The basic details were:

- A survey of 4,000 cases of autism had been undertaken, and some preliminary findings had been drawn.
- One in ten autistic children analysed by the Autism Research Unit (ARU) appeared to have a distinctive form of autism. The children shared distinctive symptoms that made them stand apart from other children with autism. These children tended to suffer from bowel problems. They had an abnormal gait and were friendlier than other autistic children.
- Crucially, there were differences in the chemicals found in their urine. Around 80% of all people with autism have high levels of the compound indolyl acryloyl glycine (IAG) in their urine, thought to be produced when the body breaks down the amino acid tryptophan. But children whose parents had reported an observed link with MMR vaccination tended to have far lower levels.

Shattock commented that "In the group where parents stress that MMR caused the problem, we do not get abnormal levels of IAG and the researchers suspect that a different mechanism causes the autism. We believe it may be measles in the intestine which causes inflammation and permeability of the intestines. The numbers here are quite small, so any connection does not show up in epidemiological studies".

Shattock added that the latest reliable figures (for the UK) showed that 1 in every 150 children suffer from ASD. If his ARU's findings remained at the 10% mark, then 1 in every 1,500 MMR vaccinations will trigger autism.

118. Paper by Sheils, Smyth, Martin and O'Leary, *Development of an Allelic-Discrimination Type Assay to Differentiate between the Strain Origins of Measles Virus Detected in Intestinal Tissue of Children with Ileocolonic Lymphonodular Hyperplasia and Concomitant Developmental Disorder*, Department of Histopathology, Trinity College, Dublin, Ireland (full publication details not known)

The authors noted that in a recent study, their research group had described the presence of measles-virus RNA genes in a new form of inflammatory bowel disease with concomitant developmental disorder.

One of the many questions raised by that study was whether the measles virus detected was wild or vaccine type in origin.

The objective of this pilot study was to address this point. Several conserved amino acid coding changes have been identified in measles virus strains in the Edmonston Vaccine lineage, and it has been suggested that these represent a vaccine "strain signature".

One such site (nucleic acid position 7901, amino acid position 211) displays a consistent A-G mutation in Edmonston derived vaccines, compared with wild type strains. The site is reportedly located in the H gene region of the measles genome, and is associated with cellular CD46 interaction.

This single base mutation was used as the basis for the design of an allelic discrimination assay, using TaqMan MG8 probes (FAM labelled for wild type and VIC labelled for vaccine type). The assay was run on an ABI 7000 sequence detection system using total RNA extracted from intestinal biopsies amplified with TaqMan one-step PCR kit.

Synthetic oligonucleotides representing wild and vaccine strains were designed using published sequences from the NCBI database, and used as controls in the assay system.

The study found that:

- The assay identified wild type measles in three brain blocks from an SSPE patient
- The 12 gut biopsies from affected children were deemed to have vaccine strain present
- This pilot study further corroborates the team's previous findings of an association between the presence of measles virus and gut abnormalities in children with developmental disorder, and indicates the origins of the virus to be vaccine strain

119. Paper by Dr. Vijendra Singh, Utah State University, *Journal of Biomedical Science*, 2002; 9: 359-364

This was a further paper following the examination of blood samples from 125 autistic children and 92 controls. Singh's team had found an unusual MMR antibody in serum samples from 75 autistic children, but not in any of the normal controls.

The paper by Dr. Singh was attacked by Dr. Mary Ramsay, an epidemiologist at the UK Public Health Laboratory Service (and a colleague of Dr. Elizabeth Miller). Dr. Ramsay stated: We have problems with the methodology of the study. I find it a strange technique to use the vaccine as a combined antigen. The internationally-validated technique is to look at the vaccine as a combined antigen".

However, Dr. Singh's paper explained his reasoning for choosing this approach: "Antibodies to MMR will be a true measure of seroconversion for this triple or polyvalent vaccine, instead of antibodies to measles, mumps or rubella viral proteins that are individually used for measuring virus serology in routine practice".

Dr. Ramsay was reported to have later privately admitted that she had not actually read Dr. Singh's paper.

120. Paper, *Gastrointestinal Microflora Studies in Late-Onset Autism*, Finegold, Molitoris, Song et al, Infectious Diseases Section, Veterans Affairs Medical Center, West Los Angeles, California US, published *Journal of Clinical Infectious Diseases*, 2002, Sept. 1: 35 (Supl 1): S6-S16.

The authors noted that:

- Some cases of late-onset (regressive) autism may involve abnormal flora because oral vancomycin, which is poorly absorbed, may lead to significant improvement in these children
- Fecal flora of children with regressive autism was compared with that of control children, and clostridial counts were higher The number of clostridial species found in the stools of children with autism was greater than in the stools of control children. Children with autism had 9 species of clostridium not found in controls, whereas controls had only three species not found in the children with autism.
- In all, there were 25 different clostridial species found
- In gastric and duodenal specimens, the most striking finding was total absence of non-spore-forming anaerobes and microaerophilic bacteria from control children, and significant numbers of such bacteria from children with autism.

The authors concluded that these studies demonstrated significant alterations in the upper and lower intestinal flora of children with late-onset autism, and might provide an insight into the nature of the autism disorder.

121, Paper, *Innate Immunity Associated with Inflammatory Responses and Cytokine Production against Common Dietary Proteins in Patients with Autism Spectrum Disorder*, by Jyonouchi, Sun and Itokuzu, Department of Paediatrics, University of Minnesota, Minneapolis, US (full publication details not known)

The objective of this study was to examine the proposition that children with ASD frequently reveal various gastrointestinal symptoms that may resolve with an elimination diet, along with

apparent improvement of some of the behavioural problems. The evidence suggests that ASD may be accompanied by aberrant (inflammatory) innate immune responses.

The study measured IFN-gamma, IL-5 and TNF-alpha production against representative dietary proteins (DPs) such as gliadin, cow's milk protein and soy by peripheral blood mononuclear cells (PBMCs) from ASD children and controls (those with dietary protein intolerance, ASD siblings and healthy unrelated children).

The study evaluated the results in association with proinflammatory and counter-regulatory cytokine production with endotoxin (LPS), a microbial product of intestinal flora and a surrogate stimulant for innate immune responses.

The results of this study were:

- ASD children's PBMCs produced elevated IFN-gamma and TNF-alpha but not IL-5, with common dietary proteins at high frequency as observed in dietary protein intolerant peripheral blood mononuclear cells.
- ASD children's PBMCs revealed increased proinflammatory cytokine responses with LPS at high frequency with positive correlation between proinflammatory cytokine production with LPS and IFN-gamma and TNF-alpha production against DPs
- Such correlation was less evident in DPI PBMCs

The study team's conclusion was that immune reactivity to dietary proteins may be associated with apparent dietary protein intolerance and gastrointestinal inflammation in ASD children that may be partly associated with aberrant innate response against endotoxin, a product of the gut bacteria

122. Paper, *Treatment of Late Onset Autism As A Consequence of Probable Autoimmune Processes Related to Chronic Bacterial Infection*, E. B. Matarazzo, Dept. Of Psychiatry, School of Medicine, University of Sao Paulo, Brazil, November 2002

Two cases were described, of children who first developed normally but before the age of three developed autistic symptoms following the reactivation of a chronic oto-rhinolaryngologic infection. The clinical and laboratory data of the cases supported the aetiological hypothesis of an autoimmune process.

Adrenocorticotrophic hormone (ACTH) was prescribed in one case within the first months, and the child was cured.

The other patient was two years old when autism presented, but was only treated six years later, showed a partial but definite improvement with immunosuppressive treatment.

The study report proposed that re-activation of a chronic bacterial infection be included among the aetiologies of late-onset autism. It also demonstrated that, when the aetiological

hypothesis of an autoimmune process based on clinical and laboratory data was considered, an immunosuppressive treatment could be effective and safe.

123. Unpublished letter by Dr. Wakefield to the New England Journal of Medicine, November 2002

In late 2002, in response to the Madsen et al (Denmark) study, Dr. Andrew Wakefield wrote to the New England Journal of Medicine. His letter included the following key points:

- The Madsen et al study had failed to disaggregate the relevant autism subset from the generality of autism cases
- The Wakefield team's studies had been concerned with examining the aetiology and pathogenesis of autism in a subset of children who became encephalopathic after a period of normal development, and who suffered an immune-mediated gastrointestinal pathology
- Within the relevant subset, the research team had observed frequent atopy (especially food allergy), antibiotic use, ear infections, receipt of multiple concurrent vaccines and a strong family history of atopic and autoimmune diseases
- Consistent with these observations, there appeared to be in many affected children a TH2-type mucosal and systemic immune bias
- Dysregulated mucosal immunity in affected children is accompanied by an excess of TNF a-positive lymphocytes, to an extent that distinguishes the autistic lesional mucosa from both inflammatory and non-inflammatory paediatric controls
- In controlled systematic studies, intestinal lymphoid hyperplasia of the degree seen in the affected children was clearly not (as anecdotal impression would have it) a normal variant
- A precursor to an adverse reaction to MMR may be a congenital or acquired aberrant TH2 immune programming. This would increase the likelihood of an inadequate antiviral immune response in the face of a live viral vaccine, and might facilitate viral persistence and immunopathology
- The key to defining the children at risk was the examination of the co-factors that might interfere with the appropriate TH2-TH1 transition, prior to, or concomitant with, MMR exposure. One such factor may be mercury, for which the immuno-toxicity of organic and inorganic derivatives is qualitatively similar.

Wakefield asked, in his letter, if a synergistic adverse interaction between mercury and a live viral vaccine was biologically plausible. He commented that the immunosuppressive and immunomodulatory effects associated with mercury exposure were accompanied by increased susceptibility to challenge with infectious agents.

He noted that in previously-resistant animals, sub-toxic doses of mercury chloride had induced an autoimmune syndrome characterised by the expansion of TH2 cells, IL-4 production by splenocytes and IgG1 and IgE production. This had been accompanied by a non-healing phenotype with increased footpad swelling and parasite burden. Methyl mercury enhanced the

immune damage and chronicity of coxsackie B3 myocarditis in mice, compared with mice infected without prior mercury exposure (the study he quoted was Ilback et al, Effects of Methyl Mercury on Cytokines, Inflammation and Virus Clearance in a Common Infection, Toxicology Letters, 1996 89: 19-28). And mercury was only one of several exposures to infants that might potentially influence the immune response to live viral vaccines.

124. Study by Croonenberghs, Wauters, Devreese, Verherk et al, In Autism - Increased Serum Albumin, Gamma Globulin, Immunoglobulin IgG and IgG2 and IgG4, University Center of Child & Adult Psychiatry and Department of Medical Biochemistry, University of Antwerp

This study noted that research on the biological pathophysiology of autism had found some evidence that immune alterations might play a role in the pathophysiology of the illness. The study team consequently expected to find that autism was accompanied by abnormalities in the pattern obtained in serum protein electrophoresis and in the serum immunoglobulin (Ig) and IgG subclass profile.

The team examined whether subjects with autism showed changes in total serum protein (TSP) and the serum concentrations of albumin, alpha globulin, alpha2 globulin, beta globulin and gamma globulins, IgA, IgM and IgG and the IgG subclasses IgG1, IgG2, IgG3 and IgG4, compared with normal controls.

The study found:

- Significantly increased concentrations of total serum protein in autistic subjects, which were attributable to increased serum concentrations of albumin and gamma globulin
- Significantly raised levels of serum IgG, IgG2 and IgG4
- Significant and positive correlations between social problems and TSP and serum gamma globulin
- Significant and positive correlations between withdrawal symptoms and TSP and serum albumin and IgG

The study concluded that:

- the results suggested that autism is characterised by increased total serum protein, a unique pattern obtained in serum protein electrophoresis, i.e. increased serum albumin and IgG, and by a specific IgG subclass profile, i.e. increased serum IgG2 and IgG4.
- The increased serum concentrations of IgGs in autism may point towards an underlying autoimmune disorder and/or an enhanced susceptibility to infections, resulting in chronic viral infections, whereas the IgG subclass skewing may reflect different cytokine-dependent influences on autoimmune B cells and their products.

PART H - OTHER RELEVANT PAPERS

125. US Developmental Delay Registry Report, 1994

A US parents' group, the Developmental Delay Registry, has reported that of nearly 700 children aged between one and twelve that had been surveyed in 1994:

- those that had taken more than 20 cycles of antibiotics in their lifetime were more than 50% more likely to suffer developmental delays
- nearly 75% of the developmentally-delayed children had been reported as developing normally in their first year of life
- developmentally-delayed children were 37% more likely to have had three or more ear infections than non-developmentally delayed children
- developmentally-affected children were nearly four times as likely to have had adverse reactions to immunisations

126. Paper by Stratton et al, *Adverse Events Associated With Childhood Vaccines*, National Academy Press 1994, 64-65)

This states "In the course of its review the committee encountered many gaps and limitations in knowledge.....(including) inadequate understanding of biological mechanisms underlying adverse events, insufficient information from case reports and case series, inadequate size or length of follow-up of many population-based epidemiologic studies".

127. Unpublished Paper by Kathryn M. Carbone, Laboratory of Pediatric & Respiratory Viral Diseases, Division of Viral Products, OVRP, Centre for Biologics Evaluation and Research, Food & Drug Administration, Bethesda, MD 20892, US, *Vaccine Safety Pathogenesis of Virus Vaccine Neurotoxicity*

The report received on this study, which is ongoing, states that:

- Since the developing nervous system is uniquely sensitive to damage following virus infection, postnatal CNS development during the first year of life provides continued susceptibility of the infant CNS to damage by viral infection after birth.
- Administering neurovirulent vaccines to infants also places the child's CNS at increased risk for injury.
- Wild type mumps virus, and some strains of mumps vaccine virus (Urabe Am9, Leningrad 3) are amongst the most neurotropic of the early childhood viruses, and new

MMR combinations continue to be proposed that include new strains of mumps vaccine virus.

- It is important to develop valid molecular biological, inn-vitro and in-vivo models to evaluate the pathogenesis of the neurotoxic effects of vaccine viruses. Information obtained in these studies about mumps virus vaccines will be likely to be useful in generalising to other potentially neurovirulent vaccines, e.g. Measles.

Study progress on molecular markers of neurotoxicity:

- We have identified vaccine virus related perturbations in CNS gene expression by standard semiquantative RT-PCR and by differential display techniques, including endogenous immune mediators of the CNS.
- We have recovered un-characterised gene products from new genes that are altered by virus infection of the brain.
- We have initiated RPA to compare changes in endogenous immune mediators in the CNS in animals infected with low and high neurovirulence strains of mumps virus

On animal models of CNS diseases following childhood virus infection:

- Viruses are known etiologic agents of autism (e.g. rubella). Therefore concerns are raised regarding a possible relationship between childhood vaccines and autism. Because no valid animal model exists to study the pathogenesis of the neuroanatomical and behavioural signs of autism, we developed a rat model of autism using neonatal infection with neurotropic viruses.
- We have characterised autistic-like changes in neuroanatomy, neurological disease and behaviour in these rates. In addition, we have identified regional and developmental changes in neurotransmitters, including serotonin and norepinephrine.
- A developmental study of damage to developing brains (e.g. Cerebellum) in virus infected rats was performed, demonstrating anatomical, behavioural and neurological consequences.

128. Iizuka, Saito et al Study, Akita Prefectural Institute of Public Health, Japan, *No Evidence of Persistent Mumps Virus Infection in Inflammatory Bowel Disease*, published Gut, 2001; 48; 637-641 (May)

This study was conducted to clarify the validity of a causal link between persistent mumps virus infection and inflammatory bowel disease.

- The study used amplification of the mumps virus genome by reverse transcription-polymerase chain reaction (RT-PCR).
- The mumps virus genome was not detected in intestinal specimens or peripheral blood lymphocytes.
- It concluded that it could not find any evidence to support a causal link with the mumps virus (note that this study did not look at the measles virus component of MMR)

129. Statement, *Is MMR Linked To Autism? - Epidemiological Perspectives, Testimony to the Congress of the United States of America, House of Representatives Committee on Government Reform, Walter O. Spitzer, April 25th 2001*

Spitzer's testimony included the following:

- (Commenting on safety studies) *"I have not found scientifically sound safety studies"*
- (On length of follow-up period) *"I shall present new data (see earlier) supporting the view that British evaluations on safety of MMR in respect to autism invoked inappropriately short lengths of follow-up"*.
- (On single vaccines) *"The intrusion of the authorities in the legitimate freedom of choice of responsible parents by proscribing monovalent products is self evident"*
- (On evidence for/against a link) *"The data about biological plausibility of an MMR/autism link has gradually become more persuasive."*
- (On the view held by Fombonne, described earlier, that there is no evidence of a rise in autism) *"Declaring a non-epidemic flies in the face of official statistics in government files and several published papers.....Fombonne's arguments do not explain away such steep rises in occurrence of AuS anywhere.....His letter gives inadequate attention to the rate changes of subsets of AuS, such as regressive autism. A worldwide epidemic of autism is in progress. That demands serious scientifically admissible inquiries about possible determinants."*
- (On the Kaye et al study, reviewed earlier, hailed by the UK Department of Health as evidence of no MMR/autism link) *"The Kaye-Jick study is the best published descriptive epidemiological study to date demonstrating that an epidemic of autism exists."*
- (On the UK Medicines Control Agency's Yellow Card passive reporting system for adverse events) *"Passive surveillance, pioneered by the British Yellow Card system and emulated world-wide, was designed to raise warning flags on safety. The system was never intended to be used the other way round, to confirm safety"*

- (On Patja, Peltola et al, the Finnish study) *"I find no evidence that the study was set up to be sensitive to AuS, nor that the surveyors or the reporters of events looked for autism events at any time.....A large scale study as was done in Finland is not automatically well designed or adequately reported because of its size.....There were no controls.....There was no discussion about such uncontrolled surveys.....There is no indication in the report about the length of follow-up.....There is no information about the nature or content of briefings to health care personnel before the study started, in relation to the types of reactions and the inclusion of autism as a reportable side effect.....Any assertion that the Patja-Peltola paper "clears" MMR is unfounded."*
- (On Taylor, Miller et al, reviewed earlier) *"The study and its report are seriously, if not fatally, flawed.....Complete ascertainment of all cases of autism in the eight districts (of North London) is uncertain.....(there is) inadequate classification of the various diagnoses within the autistic spectrum.....There is a failure to correct for "catch-up" components of the immunisation campaign (this is a reference to 7.5m older children immunised in the UK in 1994).....An incorrect analytic method was used. The case-series method used by Taylor, Miller, applies primarily to acute events.....One does not expect autism to develop acutely.....(There was a) failure to discriminate between types of MMR vaccine."*
- Spitzer concludes that the Taylor, Miller et al paper *".....which is incorrectly interpreted as demonstrating safety, provides much better evidence in the opposite direction, consistent with MMR being associated with some AuS categories. Moreover, an uncontrolled study is uninterpretable as the basis to demonstrate a link between MMR and AuS, or to dismiss it aside, unless the findings were dramatic and very clear."*

130. Statement by Dr. Tom Jefferson, Head of Vaccine Division, Cochrane Collaboration, Oxford, UK, October 2002

The repeated assurances of the medical establishment that there was strong evidence against any MMR/autism link were undermined by a statement by Dr. Tom Jefferson in late 2002. Dr. Jefferson has been funded to investigate vaccine safety by the European Commission. He is also a Board Member of the European Programme for Improved Vaccine Safety Surveillance, which has been set up by the European Commission.

Press reports quoted Dr. Jefferson as stating:

- Vaccine safety was the Cinderella of public health research. Government officials had failed to make it a high priority
- There was some good research, but it was overwhelmed by the bad
- The public had been let down because the proper studies had not been done.
- Although there was no evidence to suggest that any vaccine currently (in 2002) was dangerous, there was a dearth of sound studies on the risks and benefits. As a result,

the information available on the safety of vaccines that are routinely given to babies and toddlers was simply inadequate

- There was going to be a European-wide electronic register of children's vaccine exposure that would allow scientists to investigate the risks and benefits of inoculations, using data on thousands of participants. Pilot schemes would start soon in Sweden and Finland

He also offered the comment that Governments were "reluctant" to accept this, but that they owed it to future generations to back this idea. He was especially concerned because future vaccination programmes were likely to give children five, six or even seven vaccines all at once. He commented: "We have to think very carefully about how we will monitor these vaccines.....It is no use having a situation where someone suggests a possible harm and then everyone runs around frantically trying to find bits of evidence. What is required is good-quality information that has been systematically collated and assessed."

PART K - FUTURE PAPERS INVESTIGATING A LINK

The following are brief details about known UK studies investigating an MMR/autism link, but which have yet to report:

131. Unpublished Study by Fombonne et al, *A Case-Control Study of Autism In General Practice, UK, Study Period September 2000-August 2002*

This study, based at the Maudsley Hospital, Denmark Hill, London, is to assess if exposure to MMR immunisation is a risk factor for autism, and to assess the exposure to viral infections, both prenatally and postnatally.

The study will use UK GP data, hospital reports and a parents' questionnaire. It will use over 400 cases of autism and four times as many controls, selected from a GP database. It is funded by the Medical Research Council (£351,000). No date has been given for publication of the findings.

(Note: since this study commenced, Professor Fombonne has also agreed to appear at the forthcoming UK High Court cases as an expert witness on behalf of the manufacturers of MMR, against the children. His current role within the study is not known. It is also not known whether the control group will be "unvaccinated with MMR", "unvaccinated with MR", "unvaccinated with any measles-containing vaccine", "unvaccinated with thiomersal-containing vaccines" or "totally unvaccinated", or what the vaccination status of the control group children's mothers will be. These may affect any study findings).

132. Charman et al, *Epidemiological Study of Autism, Current Prevalence & Medical Risk Factors, Study Period February 2000-July 2003*

This study, based at the Behavioural Sciences Unit, Institute of Child Health, Guilford Street, London, will look at a representative population sample (but see caveats in previous section, final paragraph) of 8 year olds who have received a diagnosis of childhood autism or a related pervasive developmental disorder (PDD).

The study will address the following questions:

- Is the prevalence of autism in this population confirmed as five times the established figure?
- Alternatively, is the reported rate due to inaccurate over-diagnosis?
- What is the rate of metabolic medical risk factors in autism?

- To what extent are they specific to autism as opposed to other neurodevelopmental and learning problems?
- Do they distinguish between autism and related PDDs?
- What evidence is there in this representative sample that onset of symptoms is associated with MMR vaccination?

The study is funded by the Wellcome Trust (£461724).

133. Study By Hall, Smeeth & Fombonne, *A Case-Control Study of Autism and MMR Vaccination Using the General Practice Research Database*, London School of Hygiene and Tropical Medicine

This study, using the UK GP database, commenced in 2000, and was originally expected to report in 2002. The study, to investigate the causes of autism, including an assessment of the potential role of MMR, will use case-control and case-series statistical approaches. The electronic general practice records in the database will be supplemented by record interviews of all cases and questionnaires to both parents of affected children and of controls.

A protocol paper of this study was reported in BMC Public Health 2001, 1 (1): 2 in February 2001. The study is designed to determine:

- If autistic children are more likely to have received MMR vaccine prior to disease onset
- To examine whether there is any association between clinical onset of disease and the timing of MMR vaccination.

In July 2001, the research team, Hall, Smeeth and Fombonne, wrote to the British Medical Journal, stating that "*the failure (of other studies) to find an association between the time trends in vaccine coverage and the incidence of autism codes in children's electronic general practice records, does not exclude a causal association*".

(Note: Fombonne confirmed in summer 2001 that he was being retained as an expert witness on behalf of the manufacturers of MMR, and against the children, in the forthcoming UK High Court cases).

134. Study by Takahashi, Arai et al, Infectious Disease Surveillance Centre, National Institute of Infectious Diseases, Tokyo, *Autism and Infection/Immunisation Episodes in Japan*, Japanese Journal of Infectious Diseases, 54, 2001

The notification report of this current study (final reporting date not known) stated that:

- The prevalence of autism in Japan during the 1980s was 5-16 per 10,00, and was 21.1 in 1996. The apparent increase by 1996 was difficult to interpret, because it may have been due to recent improved screening and other factors.
- MMR was introduced in 1989 in Japan. The vaccination programme was unsuccessful, on account of the higher incidence of associated aseptic meningitis, and in 1993 the Ministry of Health & Welfare discontinued MMR
- During 1989-1992, 2.2 million doses of MMR and 3 million doses of monovalent measles vaccine were distributed in Japan
- The 1988-89 birth cohort received approximately 1.3 million doses of MMR and 1.7 million doses of monovalent measles vaccine
- It was noted that Kawashima et al had claimed that symptoms developed soon after MMR in the majority of autistic cases
- A case control study of the 1988-89 cohort would therefore be of value for elucidating a possible relation between autism and MMR

135. Study, *Role of Maternal Immunity in Susceptibility to Measles Virus Infection and Disease*, Glenn F. Rall, Fox Chase Cancer Center, US

The proposer of this study noted in early 2002 that it was increasingly apparent that the development of a child's immune response was strongly influenced by maternal immunity, both during gestation and postnatally through the transfer of antibodies in breast milk. Thus, if vaccines were involved in the etiology of autism, the possibility that altered immunity might contribute to increased risk seemed tenable. The study proposed:

- That it explore in an animal model of infection and immunity how previous maternal antigen exposure might either facilitate viral clearance or lead to immunological tolerance in newborns
- That experiments would take advantage of a novel transgenic mouse model of measles virus infection, using mice that had been genetically engineered to express the measles virus receptor CD46, specifically targeted to neurons, rendering them susceptible to measles virus infection and CNS disease
- While measles virus infected adult mice would mount a protective immune response which cleared the virus and afforded protection, neonates could not resolve the infection despite a similar induction of a robust immune response.
- The study would test the hypothesis that maternal antibodies were transferred to developing embryos to afford resistance against subsequent postnatal measles virus challenges.
- The overall theme of this work would be to explore the hypothesis that the immune response of a newborn mouse would be directly influenced by the exposure history of

its mother. The data will contribute to an understanding of how vaccines in some children may establish undetected smouldering infections that may initiate a cascade of events leading to neurodevelopmental damage.

136. Studies Commissioned by the US Center for Disease Control

At the hearing in June 2002 by the US House of Representatives Committee on Government Reform (see elsewhere in the document), Dr. Roger Bernier, Associate Director for Science, National Immunization Program, CDC, outlined five studies planned or underway to investigate the causes of autism:

- (study one) Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) MMR/Autism study. This is a large case-control study assessing the relationship between the timing of receipt of the first MMR and risk for developing autism. It is due to report in autumn 2002 (*comment - this is only an epidemiological study. It will not clinically examine children*). See earlier section for further details.
- (study two) CDC and National Institutes of Child Health and Human Development (NICHD) MMR/Regression Autism Study. This will examine the association between regressive autism and the timing of first receipt of the MMR vaccine. Results are expected in Spring 2004 (*comment: this too is only an epidemiological study, no children will be examined*)
- (study three was Madsen et al study, Denmark - see earlier section)
- (study four) Four Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) Study, supported by the CDC. This is a large epidemiological study to identify risk factors and biological markers of autistic spectrum disorder. No date for reporting was given (*comment: yet another epidemiological study, again without clinical examination of children*).
- (study five) Dr. Bernier reported that the CDC was in the early stages of planning a study to investigate whether or not measles vaccine-strain virus was present in the intestines of some children with ASD. An independent multi-center study was being designed to determine the prevalence of measles vaccine-strain virus gene sequences in bowel biopsy tissue taken from children with gastrointestinal tract complaints, with and without ASD. The study would be designed to ensure use of standardized clinical and laboratory protocols, appropriate enrolment of controls, "blinding" of specimens, use of standardized laboratory reagents and assays, and appropriate statistical evaluation (*comment: this would be a clinical study. But there would need to be a truly independent outside scrutiny - not just by the CDC - of both design protocols and research practice, to ensure full objectivity throughout*).

The CDC also discussed studies to look at possible links with thimerosal - this is dealt with in the next section.

137. Study by the UK National Institute for Biological Standards and Control (NIBSC)

This is a £300,000 study funded by the UK Department of Health. Work commenced in September 2002. Virologists at NIBSC will work in collaboration with the Paediatric Gastroenterology Department at the Royal free Hospital, London (the department where Dr. Andrew Wakefield formerly worked). The hospital retains samples of bowel tissue from the autistic children used in the original 1998 Wakefield et al study.

In addition to these samples of bowel tissue, the study will also use other samples. The study is being led by Dr. Muhammed Afzal, principal scientist at NIBSC, and Dr. Phil Minor. Dr. Minor also criticised the study by Dr. Vijendra Singh (reported elsewhere in this note) as "fundamentally flawed".

On 23rd August 2002, the London Evening Standard newspaper reported that Dr. Minor was also being paid by Glaxo SmithKline, manufacturers of MMR, to act as an expert witness in the impending UK High Court MMR/autism cases. GSK is one of three UK companies that are the subject of this litigation, the other two being Aventis Pasteur MSD and Merck & Co. Campaigners described Dr. Minor's dual role as "disgraceful". The Conservative Member of Parliament, Julie Kirkbride MP, who had unsuccessfully attempted to sponsor a private Parliamentary Bill to allow single-antigen vaccines, commented "This news will hardly inspire public confidence".

The London Evening Standard report also confirmed that Dr. Minor had also sat on the 2001 Medical Research Council review into the MMR/autism issue (reported elsewhere in this Briefing Note). In documents seen by the Evening Standard, covering declaring interests as part of the MRC Review, Dr. Minor had stated that he had no commercial or academic interests to declare, but that he was "an expert adviser on molecular virology in MMR/autism cases".

Dr. Minor had previously authored a paper in the "Mill Hill Essays" series, in 1998, published by the National Institute for Medical Research. This review paper concluded: "There is no evidence currently available that stands up to examination that measles virus is present in tissue from Crohn's Disease.....Autism occurred before MMR vaccine was introduced, and it would be surprising if it did not occur after. To find out.....needs a large carefully-designed study, but.....there is no scientific reason to believe that there is a connection based on the knowledge that is available now.....At the moment, the scientific consensus is that there is nothing in it."

138. Study by the University of California at Davis into Environmental Factors

This study was ready to be launched at the start of 2003. The study will be the first-ever major epidemiological case-control study of US autism, and will:

- Examine the histories of up to 2,000 Californian children

- Examine the potential role of genetic and environmental factors that may affect developmental delay, autism and mental retardation
- Establish a database, the Childhood Autism Risks from Genetics and the Environment (CHARGE), looking at children aged between 2 and 5 years. The database will be recruited over the next three years (2003-5) as newly-diagnosed children enter the Regional Center system for assessment of development. The study will be carried out in Los Angeles and North-Central California.

The study is one of three projects within the University of California at Davis Center for Children's Environmental Health and Disease Prevention. The Center was created in autumn 2001 with grants from the National Institute of Environmental Health Sciences, the US Environmental Protection Agency, and the MIND Institute at UC Davis.

Researchers will review regional-center records for children with autism and children with mental retardation or developmental delay. Families will complete questionnaires and their children will give specimens, and the research team will examine exposure to toxins, diet, genetic background, chemical and cellular markers from tissue samples and other information relating to both before-birth and after-birth periods.

139. Other UK Studies Funded By the Medical Research Council, London

A number of studies into autism are currently funded by the UK Medical Research Council. It is instructive to note that not one of these involves the clinical examination of children affected by autism following vaccination, nor explores the alleged MMR/autism link in any way, nor examines the potential role of viral infections.

Current (as at July 2002) studies are:

- Dr. Simon Baron-Cohen, University of Cambridge, study into the development of social intelligence in children with and without high functioning autism, 2000-2005
- Professor P Jacobs, University of Cambridge, study into the effects of duplications and triplications of chromosome 15q11-q13 with special reference to autism, 1999-2004
- Professor U Frith, University College London, study into cognitive deficits in developmental disorders, 1998-2003
- Dr Francesca Happé, Institute of Psychiatry, London, study into local-global processing and cognitive style in autism and normal development, 2000-2005
- Dr K Plaisted, University of Cambridge, investigation of the mechanisms underlying the deficits in contextual processing in autism, 2002-2006
- Professor Andrew Hall, London School of Hygiene and Tropical Medicine, case-control study of autism in UK general practice, 2000-2002
- Dr A Bailey, Institute of Psychiatry, London, international collaborative study into the molecular genetic basis of autism, 1999-2003
- Dr. Tony Bailey, Institute of Psychiatry, London, morphometric study of the neuropathology of autism, no date given but believed to start 2003

140. Study by Autism Center, University of Medicine & Dentistry, New Jersey, US

This is a study researching the physical symptoms common to many autistic children, including allergy, asthma, eczema, epilepsy, sleep problems and gastrointestinal disorders. Total value \$1.5m. No further details are available.

141. Study by Center for Disease Control, New Jersey, US

This CDC study is assessing autism prevalence in New Jersey, and will seek to identify every autistic child born between 1992 and 1998 in four counties, Ocean, Essex, Union and Hudson. Total value \$1m. No other details are available.

142. Study by Robert Wood Johnson Medical School, New Brunswick, US

This study is being undertaken at the Center for Neurotoxicology and Exposure Assessment at the Robert Wood Johnson Medical School. Researchers are examining neurological toxins amongst autistic children aged 24 months to 36 months. No further details available.

143. Survey by New Jersey Answers for Autism

This is a study seeking information from all families in the area with autism, to identify patterns common to child developmental backgrounds including immunisation, medication during pregnancy, viruses and toxins. No other information is to hand, but the value of the study is \$160,000.

PART L - THE THIOMERSAL ISSUE

144. Thiomersal's Possible Role

An obvious feature of the current litigation situation regarding autism and vaccination is that the UK cases are proceeding on the basis of autism following MMR (or MR) vaccination, whereas the US cases are over the link between autism and thiomersal.

However, the two suspected causes are not mutually exclusive. It has never been suggested that MMR causes all autism, and the two factors may in any case be working in concert.

- It is understood that thiomersal, a mercury-based preservative, has been used in a number of UK and US vaccines over many years. It is believed that it is not used in MMR itself, but it may yet prove to have been used in the manufacturing process. If this is the case, it is believed that no declaration has to be made on the manufacturer's information sheet, as it is not an actual MMR constituent.
- The thiomersal issue emerged when the 1997 US Food & Drugs Administration Bill was passed, a re-authorisation bill that required the FDA to compile a list of drugs and foods that contained intentionally-introduced mercury compounds. In June 1999, the FDA issued a report indicating that "infants who receive thiomersal-containing vaccines at several visits may be exposed to more mercury than recommended by Federal guidelines for total mercury exposure".
- Despite the FDA's report, there was no ordered recall of the vaccines. However, the FDA asked the manufacturers to reduce the mercury content, and they complied.
- Worldwide, thiomersal has been used for about the past 60 years. Ethyl mercury constitutes about 49.6% of its weight, and mediates the antimicrobial effects. Thiomersal has been used to prevent bacterial contamination during the vaccine manufacturing process, as well as in vials where repeated puncture may allow contamination to occur.
- It is believed that levels of thiomersal have been reduced over the years in vaccines, and removed altogether in some cases. In April 2001, the US Food & Drug Administration announced that they supported the reduction of mercury exposure from any source. The FDA then encouraged vaccine manufacturers to develop new vaccines without thiomersal. In the US, in 2001, a free exchange system was instigated by the manufacturers, to remove stocks.
- In the UK, the Department of Health has refused to acknowledge that there might be a problem with thiomersal, and no free exchange system has been offered, or sought. Thiomersal continues in use in a number of vaccines, not just those for children. As

recently as January 2003, press reports in The Scotsman newspaper indicated that four out of the seven influenza vaccines in use in the UK contained thiomersal, and this was not refuted by the Department of Health.

- In the US, a September 2001 survey of 65,909 vaccines at provider centres found that 5.5% still contained thiomersal. Some 36% of these were DtaP-Hib for the fourth dose. A depot survey of 837,174 vaccine doses found that 1% still contained thiomersal. Of these, 80% were for DtaP.

145. Joint Statement of American Academy of Pediatrics and Public Health Service, Thiomersal In Vaccines, July 1999

In 1999, researchers calculated that a low-birthweight baby could receive a cumulative dose of mercury (187ug) that would have exceeded the safety recommendations of the US Environmental Protection Agency.

In July 1999 the AAP and the PHS issued a joint statement on thiomersal in vaccines, noting that the US Food & Drug Administration Modernization Act of 1997 called for the FDA to review and assess the risk of all mercury-containing food and drugs.

The joint statement was generous in its self-reassurance:

- *"Thiomersal has been used as an additive.....since the 1930s....."*
- *"There is a significant safety margin incorporated into all the acceptable mercury exposure limits"*
- *"There are no data or evidence of any harm caused by the level of exposure that some children may have encountered"* (Comment - but this may reflect lack of studies or lack of monitoring, not lack of harm)
- *"Infants and children who have received thiomersal-containing vaccines do not need to be tested for mercury exposure"* (Comment - as an example of complacency, this statement is in a class of its own).
- *"The recognition that some children could be exposed to a cumulative level of mercury over the first six months of life that exceeds one of the federal guidelines on methyl mercury now requires a weighing of two different types of risk.....The large risks of not vaccinating children far outweigh the unknown and probably much smaller risk, if any, of cumulative exposure to thiomersal-containing vaccines"* (Comment - this is an tautological statement, and is revealing. What the AAP/PHS are saying is, the risks from thiomersal are unknown, are probably small, and are far outweighed by another risk - which of course is an impossible deduction to draw if the risks from thiomersal are unknown. One cannot say for certain that A is larger than B if there is no way of

determining the size of B, or if the size of B is unknown because it has been historically overlooked, and thus not measured).

- *"Nevertheless, because any potential risk is of concern, the PHS, the AAP and the vaccine manufacturers agree that thiomersal-containing vaccines should be removed as soon as possible".*

Key action agreed was:

- A formal request to manufacturers for a clear commitment and a plan to eliminate or reduce mercury content of vaccines
- A review of data
- Expedited FDA review of manufacturers' supplements to their product license applications, to eliminate or reduce mercury content
- Studies to better-understand the risks and benefits of this safety assessment

146. UK Vaccines With Thiomersal

Vaccines in the UK that are believed to still contain, or until recently contained, thiomersal are:

- DTaP (Diphtheria and Tetanus and acellular pertussis) made by Lederle Laboratories
- Hib (haemophilus influenza type B) made by Connaught Laboratories
- DPT (Diphtheria and tetanus and pertussis) made by Glaxo SmithKline
- Energix-B (Hepatitis B) made by Glaxo SmithKline
- HibTiter (Haemophilus influenza type B) made by Lederle
- Fluvirin influenza virus vaccine made by Medeva Pharma
- FluShield made by Wyeth-Ayerst
- Menomune (Meningococcal polysaccharide vaccine) made by Connaught
- Rabies vaccine made by Glaxo SmithKline
- Recombivax (Hep B recombinant vaccine) made by Merck & Co.

In January 2003, a detailed report in The Scotsman newspaper listed four influenza vaccines in use in the UK (out of a total of seven) that still used thiomersal:

- Fluvirin
- Fluarix
- Influvac
- Agrippal

The UK Department of Health was quoted in the report, "There is no evidence of long-term adverse effects due to the exposure levels of thiomersal in vaccines".

It is also understood that the UK introduced an accelerated schedule of DPT vaccination in the late 1980s/early 1990s, which would have significantly increased the thiomersal intake of infants.

It is known that MMR does not contain thiomersal, but it is thought that thiomersal may be used in its manufacturing process.

When the thiomersal issue was reviewed in the UK general practitioners' magazine *Pulse*, the report concluded: "*Another drawn-out public debate might damage public confidence, and falling vaccine uptake rates could cause the resurgence of preventable diseases*". This may be true, but this approach is also a potential charter for complacency and secrecy. At what point should safety concerns be publicly debated?

147. Scientific Review of Vaccine Safety Datalink Information By The US Centre for Disease Control, Simpsonwood Retreat Center, Norcross, Georgia, June 7th-8th 2000.

This meeting was convened by the US CDC to discuss the findings of Dr. Verstraeten in relation to the positive statistical association between thiomersal-containing vaccines and neurodevelopmental disorders (thiomersal is a mercury-based preservative that has been extensively used in the UK and US, and elsewhere).

The confidential version of the study reviewed at this meeting clearly demonstrated that an exposure to more than 62.5 micrograms of mercury within the first three months of life significantly increased a child's risk of developing autism. Specifically, the study found a 2.48 times increased risk of autism.

In the US, courts of law have held that a relative increased risk of 2.0 or higher is sufficient to substantiate that a given exposure causes disease (in the case of *Cook v. United States*, 545 F. Supp. 306, at 308, Northern District, California, 1982, the Court stated that "in a vaccine case, a relative risk greater than 2.0 establishes that there is greater than a 50% chance that the injury was caused by the vaccine").

The key findings of the Vaccine Safety Datalink analysis were that there was a statistically significant association between:

- A cumulative exposure to thiomersal-containing vaccines at 2 months of age and unspecified developmental delay
- A cumulative exposure at three months of age and tics
- A cumulative exposure at six months of age and attention deficit disorder
- A cumulative exposure at 1, 3 and 6 months of age and language and speech delay
- A cumulative exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general

The report noted that "*the consultants were unanimous in their opinion that further investigations should be pursued with a degree of urgency*".

These are some extracted comments from some of the key participants:

- Dr. Weil: "*There are just a host of neurodevelopmental data that would suggest that we've got a serious problem*"
- Dr. Verstraeten: "*We have found statistically significant relationships between the exposures and outcomes for these different exposures and outcomes. First, for two months of age, an unspecified developmental delay which has its own specific ICD9 code. Exposure at three months of age, Tics. Exposure at six months of age, an attention deficit disorder. Exposure at one, three and six months of age, the entire category of neurodevelopmental delays, which includes all of these plus a number of other disorders.*"
- "*Now for speech delays, which is the largest single disorder in this category of neurologic delays. The results are suggestive of a trend with a small dip. The overall test for trend is highly statically significant above one*".
- "*After excluding this speech group, the trend is also apparent in this group (developmental delays, less those with speech delays) and the test for trend is also significant for this category excluding speech*".
- Dr. Davis: "*In terms of a search for pre-disposing factors.....serious and chronic otitis media by history, being mentioned by the pediatrician or the specialist, was present 38% of the time*". (US parents' note: doesn't this sound familiar to all of you parents with autistic children?)
- Dr. Johnson: "*This association leads me to favour a recommendation that infants up to two years old not be immunised with thiomersal-containing vaccines if suitable*"

alternative preparations are available.....there are probably implications for this internationally".

Congress also ordered the Institute of Medicine (IoM) to investigate the autism/MMR link, or identify another cause(s). The IoM is a division of the National Academy of Sciences, whose members serve as advisers to Congress. The IoM met in 2001, and also looked at eight other vaccine-related safety concerns.

There was an interesting postscript to the Simpsonwood review above. In a letter to the US National Law Journal, following earlier coverage in its issue of 20th March 2002 of this subject, Mike Weathersby, a lawyer involved in the US thiomersal lawsuits, pointed out that:

- The key CDC researcher (Dr. Verstraeten was hired by GlaxoSmithKline prior to his delivering a "modified" study to the IoM.
- According to US lawyers Waters & Kraus, the original report to the IoM "never saw the light of day", though it was later obtained by the lawyers. Waters said that Verstraeten added more children into the epidemiological study. In its original form, the study had demonstrated that children who received mercury-containing vaccines were statistically 2.48 times more likely to be diagnosed with autism. After the report was modified, this statistical association fell well below the critical 2.0 barrier, where causality is accepted, to 1.69. It was the latter figure that was cited in the final IoM report.
- In reality, the IoM's only reservation in concluding that autism was linked to the mercury in thiomersal was the lack of associative conclusiveness to confirm or to rule out causality. In reality, the undisclosed-version results by Verstraeten exceeded the benchmark 2.0 relative risk (doubling of risk) that would virtually seal a finding of causality
- other problems with the Verstraeten study make it likely that the true relative risk in the age groups at which one would consider regressive autism ascertainable will be well in excess of three times the risk in an unexposed population

148. Waters & Kraus Press Release of March 17th 2002

In March 2002, the lawyers Waters and Kraus, acting on behalf of US children in the thiomersal/autism class action, stated that their discovery process in their case of Counter v. Eli Lilly (manufacturers of thiomersal) had demonstrated that thiomersal was known by Lilly as early as April 1930 to be dangerous. These included the following studies/warnings deposited with Lilly:

- (1947) "It may be dangerous to inject a serum containing merthiolate into a patient sensitive to merthiolate"
- (1963) "It seems advisable to use a preservative other than merthiolate for injections into merthiolate-sensitive people"

- (1972) Merthiolate in vaccines caused six deaths - "The symptoms and clinical course of the six patients suggest subacute mercury poisoning"
- (1982) The (FDA) Panel concludes that thiomersal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin, and its allergy potential".

In July 2002, the Indianapolis Star newspaper quoted the lawyers Waters and Kraus as saying that "Lilly flim-flammed scientists for years with a 1931 study that concluded thiomersal wasn't harmful to humans". The Star went on: "The study, published in the American Journal of Hygiene, reported that merthiolate has a very low order of toxicity.....for man".

Digging further, Waters found out that the study's toxicity data came from experimental use of thiomersal by doctors from Lilly and Indianapolis City Hospital on meningitis patients during a severe outbreak in 1929-30. 'The 1931 study on a cohort of severely ill people (who all died) ended up being quoted in Lilly brochures into the 1980s', Waters said. 'It very clearly demonstrates an effort to do an unethical study and then paint the results in a certain way that helps them sell this product'. Lilly ignored or covered up later evidence that thiomersal, which contains 50 per cent mercury by weight, can be dangerous to humans", Waters said.

The detailed sequence uncovered by Waters (the wording is taken directly from their press release) is as follows:

- September 1930, Lilly secretly sponsor a "human toxicity" study on patients dying of meningococcal meningitis. Waters then states: "Lilly then cited this study repeatedly as proof that thiomersal was of low toxicity and harmless to humans. They never revealed to the scientific community or the public the highly questionable nature of the original research."
- Numerous articles since the 1930s indicated concerns about thiomersal and its potential hazard to humans. The evidence clearly demonstrates (according to Waters & Kraus) that Eli Lilly was advised repeatedly that their conclusions on low toxicity were not warranted, and they failed to pass the information on to appropriate Federal and public health authorities.
- 1947, article received by Lilly states: "No eruptions or reactions have been observed or reported to merthiolate internally, but it may be dangerous to inject a serum containing merthiolate into a patient sensitive to merthiolate"
- 1948, article received by Lilly, "Merthiolate is such a commonly-used preservative for biologicals, plasma, cartilage etc. that it would seem important to determine whether harm would result following its subcutaneous or intravenous injection in skin-sensitive individuals."
- 1950, New York Academy of Science article, "Mercurials as Antiseptics", states "It (merthiolate) is toxic when injected parenterally and therefore cannot be used in chemotherapy"
- 1963, article received by Lilly, "There is another point of practical significance: does the parenteral injection of merthiolate-containing fluids cause disturbance in merthiolate-

sensitive patients?" "It is known that persons that are contact-sensitive to a drug may tolerate the same medications internally, but it seems advisable to use a preservative other than merthiolate for injections in merthiolate-sensitive people"

- 17/8/1967, Medical/Science department requests that the claim "non-toxic" on thiomersal labels be deleted in next printing run
- 29/8/67, draft label changed to "non-irritating to body tissues", non-toxic wording omitted
- 1972, British Medical Journal reports case of skin burns resulting from the chemical interaction of thiomersal and aluminium. "Mercury is known to act as a catalyst and to cause aluminium to oxidize rapidly, with the production of heat". "The manufacturers who supply us with thiomersal have been informed" (thiomersal is being used in vaccines which also contain aluminium).
- 1972, article received by Lilly: "Merthiolate in vaccines caused six deaths? The symptoms and clinical course of the six patients suggest subacute mercury poisoning"
- 27/4/76, Lilly responds to Rexal Drug Company's efforts to place the following warning on merthiolate product: "Frequent or prolonged use or application to large areas may cause mercury poisoning" - Lilly objects to this proposed warning, stating: "We object to the connection of our trademark with the unjustified alarm and concern on the part of the user which the statement is likely to cause. We are not aware of any instance of 'mercury poisoning' after decades of marketing this product. This is because the mercury in the product is organically bound ethylmercury as a completely non-toxic nature, not ethylmercury." (Comment: this wording does not make complete sense?)
- 5/1/1982, Food & Drug Administration's advance notice of proposed rule-making regarding thiomersal: "At the cellular level, thiomersal has been found to be more toxic for human epithelial cells in vitro than mercuric chloride, mercuric nitrate, and merbromim (mercurichrom). It was found to be 35.3 times more toxic for embryonic chick heart tissue than for staphylococcus areas". A 1950 study showed that thiomersal was no better than water in protecting mice from potential fatal streptococcal infection. The panel concludes that thiomersal is not safe for over-the-counter topical use because of its potential for cell damage if applied to broken skin, and its allergy potential. It is not effective as a topical antimicrobial because its bacteriastatic action can be reversed."
- 7/4/1983, additional language added to some Lilly labels: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product"
- 1991, Lilly ceases manufacture/sale of thiomersal. Licensing agreements demonstrate continued profits from the product until at least 2010
- 8/12/99, Lilly notes include: "Primary physical and reproduction effects. Nervous system and reproduction effects. Effects of exposure include fetal changes. Mercury poisoning may occur. Exposure in children may cause mild to severe mental retardation. Hypersensitivity to mercury is a medical condition, aggravated by exposure"

149. UK Medicines Control Agency Position On Thiomersal

- In May 2001, the UK MCA instructed manufacturers to warn doctors and patients of potential allergic reactions to vaccines containing thiomersal.
- However, unlike the US, the UK has not moved to remove existing stocks, which are being used up.
- The magazine Pulse also reported that the UK Government planned to reduce levels of thiomersal in infant vaccines, including DTP, HiB and the pre-school DT booster.
- It also reported that the UK Government was set to adopt guidance from the European committee for proprietary medicinal products, urging manufacturers to implement a stepwise reduction in thiomersal levels in vaccines.

150. US Center for Disease Control Thiomersal Studies

At the hearing of the US House of Representatives Committee on Government Reform in June 2002 (see elsewhere for further details), several studies on the thiomersal issue were outlined by the US CDC representative, Dr. Roger Bernier:

(study one) This is the thiomersal Screening Analysis in the US Vaccine Safety Datalink (VSD) Project, which commenced Autumn 1999. Data from two health management organisations (HMOs) with automated outpatient data is screened. The CDC and VSD researchers found statistically significant associations between thiomersal and neurodevelopmental disorders such as language and speech delays, attention deficit hyperactivity disorder, stuttering and tics. No association was found with autism. The associations were weak and varied between HMOs. A third HMO has since been examined. This did not confirm the results of the first study phase. These results require further examination.

(study two) This is the Thiomersal Follow-Up Study. This will be designed to assess whether preliminary results from automated data used in study one can be confirmed using objective neuropsychological testing. The study will focus on the same developmental disorders as study one. Results are expected by the end of 2003.

Three other studies are planned, with results not available until 2005 or later.

The US CDC has been heavily criticised by parents' groups over its stance on access to the Vaccine Safety Datalink (VSD) database. The US group Safe Minds openly challenged the CDC to open VSD data to all qualified university-based researchers, but the CDC refused. The current position is that:

- The CDC's National Immunization Program has offered to provide limited access to selected areas of data which CDC personnel will choose and manually extract
- Only researchers whom the CDC approves will be allowed this restricted access
- Researchers must come to the CDC's Center for Health Statistics to conduct their work

- Before leaving, researchers must submit their analyses for review by CDC personnel, who will edit their findings

151. Study, *Mercury Concentrations and Metabolism in Infants Receiving Vaccines Containing Thiomersal - A Descriptive Study*, by Pichichero, Cernichiari, Lopreiato and Treanor, University of Rochester Medical Center, US, published in The Lancet, November 30th 2002.

[Review by Helen Tucker](#)

[Review by Sallie Bernard at Safeminds.org](#)

[Review by Sandy Mintz at Vaccinationnews.com](#)

This was a study published in The Lancet, conducted by Michael Pichichero and colleagues. Its appearance was hailed with relief by the medical community as "proof" that there was not a potential thiomersal role in the vaccine/autism debate, and that thiomersal-containing vaccines were safe.

Dr. Pichichero was interviewed by Dr. Laurie Barclay for Medscape. He summarised his study as follows:

- We looked at the blood levels of mercury in children who received thiomersal-containing vaccines. Not a single child had a blood mercury level approaching the lower safety limit established by the US Environmental Protection Agency
- Former predictions of possible paediatric problems with mercury in vaccines, which led to the removal of thiomersal from US vaccines (comment - it was only phased out, not removed, and other countries, eg the UK, did not even phase it out), were based on the notion that metabolism of ethyl mercury in the vaccine was the same as that of methyl mercury in fish. But our (the Pichichero) study showed that elimination (from the body) of ethyl mercury from vaccines was about six times as fast as that of methylmercury. The rapid metabolism was thought to "probably" account for the very low blood levels in the children studied
- The study accounted for virtually all the mercury contained in the vaccines in the stools of the children, with not much excretion in the urine, so there was "really no evidence" that there was any mercury unaccounted for which could be accumulating in the bones or elsewhere. (However, Pichichero then admitted that the study "was not a toxicity study and so did not examine this issue directly").

Asked if there were any study limitations, Pichichero responded that this was a small study of 61 children, comprising 20 two month olds who received thiomersal, 20 six month olds who got thiomersal, and 21 controls. He explained that because the study had not anticipated the rapid clearance of ethylmercury with a half-life of only 6-7 days, the study had predicted the sampling times on the basis of an assumed 45-day half-life. (Comment - but this doesn't address the drawback that the study was only small).

Asked about the basis of the EPA's public safety limits for mercury levels, Pichichero responded that the EPA levels were based on studies in the Faroes which had looked at the toxicity of methyl mercury ingestion from whalemeat. Mild neurological problems had occurred at levels in the blood of 200-300 ng/mL, and the mildest detectable neurodevelopmental toxicity had occurred at levels of 58ng/mL. The EPA had therefore added in a safety factor of ten, and taken the view that levels should not exceed 5.8ng/mL to be totally safe.

In the Pichichero study, most children had had levels of 1 to 2ng/mL, and two had had 2-3ng/mL. One child had had 4ng/mL. No child had approached the 5.8ng/mL EPA limit. (Comment: isn't a level of 4ng/mL "approaching" the 5.8ng/mL level? - it is almost 70% of it. And remember, this was a very small study indeed. What if they had measured levels in 1,000 children. Mightn't that have produced a few examples well in excess of the EPA limit?).

Pichichero also made three other revealing statements:

* "Our findings were (also) pivotal in the World Health Organisation's recommendation that thiomersal will remain in all vaccines provided by them to other countries", and

* (in answer to the question, "What are the advantages of using thiomersal in vaccines", he responded "Cost is a major issue. If you don't use preservatives at all, you have to dispense vaccines in single-dose vials, which is not only more expensive but which may lead to more errors in administration", and

* "The potential toxicity of using newer (non-thiomersal) preservatives is unknown, so we are trading the very small known risk (his words) of thiomersal for an unknown one". (Comment: why does Pichichero imply the assumption that the "unknown" risks of other vaccines would be higher?)

The study was critically reviewed by Sally Bernard of the US parents' group Safe Minds. Bernard's comments were as follows:

- The article and accompanying commentary made a number of sweeping statements about thiomersal's safety. The design and results of the study did not support these statements.
- Pichichero has acknowledged financial links with Eli Lilly & Company, the developers of thiomersal and the main target (to date) of US autism litigation. In an article back in April 2000 in the American Academy of Family Physicians newsletter, Dr. Pichichero made the following disclosures of interest: he had received research grants from Abbott Laboratories, Bristol-Myers Squibb Company, Eli Lilly (note), Merck, Pasteur Merieux Connaught, Pfizer Laboratories, Roche Laboratories, Roussel-Uclaf, Schering Corporation, SmithKline Beecham, Upjohn, and Wyeth-Lederle.

- Pichichero's earlier work has been cited in at least 21 vaccine patent applications. Many of his previous published papers deal with vaccines containing thiomersal. The University of Rochester (US) website describes him as an immunologist.
- The sample size of the Pichichero et al Lancet study was very small. Only 33 children were used for the blood mercury assessment work that the study conclusions hinged upon. The small sample means that the study lacks statistical power.
- The study sample was not drawn at random, but reflected convenience.
- Given that the half-life of ethylmercury appears to be 6 to 7 days, virtually all (if not all) blood samples drawn would have missed the peak blood concentrations of mercury
- It is impossible to state what the peak values actually were, as they were not measured. It was also impossible to calculate average blood concentrations unless the peak concentrations were accurately measured.
- Sally Bernard argues that it is disingenuous to compare the blood levels in this study with past methylmercury levels without using any adjustment factor, because the latter incorporated peak levels into their values, whereas the Pichichero et al study only included the smaller values.
- The dose of ethylmercury given to subjects varied greatly and was less than what a typical child in the 1990s could be expected to have received. In the Pichichero study, the two-month-old subjects were injected with between 37.5 and 62.5 mcg of ethylmercury, giving a 67% variation between the lowest and the highest doses. A typical child in the 1990s might receive 62.5mcg of mercury at age two months, then an additional 12.5mcg at birth (from the HepB vaccine), in other words between 37% and 64% more than the children in the study. The six-month-olds in the study were injected with between 87.5mcg and 175mcg of ethylmercury, reflecting a 100% difference between the lowest/highest levels. By six months of age, a 1990s child would have received 187.5mcg, or 68% more than the Pichichero study group average.
- In the Pichichero data, when the study characterizes blood samples drawn as being at "X" days after the mercury exposure, this is in fact misleading, because it refers only to the very last injection, and the reader actually cannot tell from the study data exactly how much dosage each infant received at the last exposure.
- In this study, there was a single blood sample drawn from each child, and the collection times varied between 3 and 21 days for the two-month-old infants (giving a 700% variation) and from 4 to 27 days for the six-month-old infants (giving a 675% difference).

In concluding, Sally Bernard also makes a number of other profound criticisms of this study:

- It makes improper use of methylmercury safety levels as a marker for ethylmercury risk
- There has never been any full assessment of thiomersal safety. This has been admitted by the US Food & Drug Administration.
- The Pichichero study does not address adverse outcomes (eg autism)

Her conclusion is that the Pichichero study does not offer the reassurance on thiomersal safety that is so widely claimed of it by the medical establishment. It is a small-scale descriptive study with many methodological limitations. It has little or no value regarding thiomersal safety.

PART M - FLAWED REGULATION AND MONITORING

152. Fighting Measles, Missing Autism, Overlooking Damage

The UK DoH has traditionally failed to commission research into the causes of autism. It seemingly prefers uncontroversial research into detailed behavioural manifestations, or genetic research that offers little insight into triggers. Also:

- The UK Medicines Control Agency (MCA) has failed to properly monitor adverse reactions to all vaccines, including MMR
- The DoH repeatedly demonstrates an entrenched bias in favour of maintaining public confidence in the vaccination programme, and against investigating the causes of autism
- The DoH repeatedly demonstrates dual standards of robustness of evidence for/against an MMR/autism link, and repeatedly shows this in its embracing of studies and findings that suit its case
- The studies that the DoH quotes (Taylor, Miller, the Committee on Safety of Medicines study, Gillberg, Peltola) are, when critically examined, inconclusive or largely irrelevant in terms of disproving any MMR/autism link.
- The adverse reaction monitoring system has never been properly reformed, because it would probably greatly increase adverse reaction statistics, and this in turn would prompt political pressure over possible vaccine damage, which in turn might undermine public confidence
- Autism has never been recognised as an adverse reaction, so has not been reported as such (thereby potentially giving false reassurance about vaccine safety records)

There also appears to be a very determined resistance on the part of the UK DoH to understanding that slow descent into autism takes place - it is not an acute adverse reaction, like other alleged adverse drug reactions. The DoH is determined to continue to ignore this, because acknowledging it would invalidate many of the studies it quotes as "proof" of MMR's safety, eg the original safety trials, the Peltola study, etc.

The greater their resistance, the stronger the suggestion is that the DoH understands rather more about this syndrome than it wishes to acknowledge publicly.

The problem should be seen in the wider context of lack of comprehensive monitoring of adverse outcomes from medical care in the UK National Health Service. In June 2002, it was reported that the newly-created National Patient Safety Agency had received 27,000

confidential reports from staff concerning minor or major incidents of medical error in a pilot study of 28 health trusts. However, the data system was so poor that no fewer than 62% of incidents could not be classified. Some 2% of errors were described as "catastrophic". It is not known whether any involved MMR or other vaccines, or degeneration into autism.

153. Has The UK Medicines Control Agency Missed The Syndrome?

The (then) Medicines Division, predecessor of the MCA, was admitted by its then management to have been in a disorganised and dysfunctional state in 1988, the year that the MMR programme commenced in the UK (see Draft Factual Account 17 of Evidence to the BSE Inquiry, pp 31-33).

- It had no effective method of finding files
- It had severe staff shortages in key areas
- Product licence renewals were handled purely administratively without scientific input. MMR wasn't a renewal, but may have been treated as little more than one, as the single vaccines were already licensed, and the long-term complications and link with autism were not foreseen. It is therefore very possible that MMR obtained its UK licence "on the nod", with minimal investigation.
- The Medicines Control Agency's adverse reaction warning system, known as the Yellow Card system, by their own admission only picks up 10-15% of even serious adverse reactions (source: Guidance on Interpretation of Yellow Card Data, MCA, 1997). The system is thus officially acknowledged to be woefully weak.
- Yellow Card was unable to identify the potential problem over autism because it must be shown that an adverse event occurs more frequently in a vaccinated than unvaccinated population. This is very difficult to do when almost all children are vaccinated. (source: personal communication of the MCA of 21/8/98)
- Yellow Card depends on doctors, dentists, coroners and hospital pharmacists to file reports (source: MCA). But these are unlikely to be able to make the link between autism and MMR.
- Adverse reaction reports are added to the ADROIT database, introduced in 1991. However, the database can only deal with the data it actually receives. If a syndrome is missed completely, then there will be no data in the database.
- Yellow Card is voluntary for health professionals, but compulsory for pharmaceutical manufacturers. But this depends on adverse reactions being reported to manufacturers - again, unlikely.

- Parents must also be able to make link between MMR/autism. This was not possible pre-1998, as publicity had never been given to a connection between vaccination and later degeneration into autism
- In any case, *"it has been estimated.....that only 10-15% of serious ADRs (adverse drug reactions) are reported"* (1997 Guidance Sheet issued by MCA), and *"....it is accepted that spontaneous reporting schemes have limitations"* (source: personal communication of the MCA of 29/3/99).
- And more telling still, *"Autism has been very rarely reported as an adverse drug reaction.....These figures are unsurprising since autism is not a recognised ADR to any particular medicinal substance"* (Source: personal communication of the MCA of 29/3/99). Once again, this is a chicken-and-egg argument.
- And a potentially-significant admission, *"Evidence from the Yellow Card scheme is unlikely to resolve the issue as to whether or not autism could be causally associated with MMR vaccine"* (Source: personal communication of the MCA of 29/3/99)
- The MCA's estimate of only 10-15% of ADRs being reported may even itself be optimistic. The West Midlands Centre for Adverse Drug Reactions Reporting did a survey and found a rate of only 6.3% of all ADRs being reported.
- All recent improvements to Yellow Card have been irrelevant to autism detection (extension of the system to hospital pharmacists, GP prescribing systems, community pharmacists, nurses)
- A similar situation appears to apply in the USA - *"On the basis of Vaccine Adverse Event Reporting System alone, we don't have proof that vaccines are not contributing to (vaccine-related problems)*(source: Caveats to Interpretation of VAERS Data, Centre for Biologics Evaluation & Research, VAERS, 1998)

The whole monitoring system is therefore highly passive, and potentially 100% irrelevant to detecting a link between immunisation and autism, in the way it has operated.

154. UK Department of Health Re-Launch of MMR, 22nd January 2001

On 22/1/01, the UK DoH launched a £3m publicity campaign for MMR and rejected the Wakefield & Montgomery "Through A Glass Darkly" MMR safety-test paper, without:

- announcing any investigation into the affected children
- offering any explanation as to why autism is rising so steeply in UK and around the developed world (although the Medical Research Council's 2001 review was announced soon afterwards - in the event, the latter proved to be yet another missed opportunity)

The DoH also released the 15-page paper, "Combined MMR Vaccines: Response of the Medicines Control Agency and DoH" referred to above, to attempt to refute the Wakefield and Montgomery paper. However, the DoH paper merely re-assembles previous studies quoted by the Department, and adds nothing new of note.

- The Chairman of the Committee on Safety of Medicines, Professor Alasdair Breckenridge, said "*MMR vaccination is very safe. There is no question-mark whatever over its licensing*".
- Professor Michael Langman, chairman of the JCVI, said "*My Committee has independently considered all the issues and reached the same position as the Committee on Safety of Medicines*".
- The Chief Medical Officer, Professor Liam Donaldson, said "*We are very pleased to have this further confirmation from the two independent expert committees*".

Some parents feel that, in the absence of conclusive evidence, either way, and taking all the surrounding factors into account, the re-launch of MMR was a serious error, leaving the authorities no escape should the test cases win in the High Court.

The Department of Health's high-risk strategy would, if this was the outcome, severely damage public confidence, probably in all forms of immunisation. The repercussions for the Department, and for child health generally, would be very significant. The Department's actions seem to have not countenanced this potential future scenario.

The Medicines Control Agency has attempted to prevent single vaccines from being administered, banning the importing of further supplies and threatening any GP who administers single vaccines with prosecution for breaching laws on importation, sale or supply of unlicensed vaccines

In early 2002, press reports indicated a fresh major "push" for MMR take-up:

- North Cheshire Health Authority launched a major advertising campaign
- In both Scotland and Wales, there were press reports that consideration was being given to making MMR compulsory for all children starting at nursery schools. Any such move would be highly controversial, and probably capable of successful legal challenge.
- In February 2002, the UK Health Minister, England & Wales Chief Medical Officer and Scottish Medical Officer announced an intensification of the programme of persuasion that there was no link between MMR and autism.

However, at the same time, there also appeared to be a shift of policy in early 2002 as to the actual threat of a measles outbreak.

- In 2001, the Public Health Laboratory Service's Communicable Diseases Surveillance Centre stated: "*We are below the critical threshold at which point we run the risk of getting a large number of cases. We will have to reverse that trend because there is a significant chance we will get a major measles outbreak or an epidemic*".
- Then, in January 2002, the Chief Medical Officer for England and Wales stated: "*There is no epidemic of measles and there is no concern that there will be. There are not large numbers of children dying of this disease*".

PART N - UK AND US POLITICAL INITIATIVES

155. House of Commons Health Committee, Westminster

- The House of Commons Health Committee strongly urged in 1997 that a register be established of numbers of children with autism. This was ignored by the Department of Health.
- Written and oral evidence to the Health Committee was given (by myself) on the MMR/autism issue, at its hearing on 24th June 1999, as part of its wide-ranging Inquiry into Adverse Outcomes From Medical Care. However, the Committee's final report did not make any specific recommendation in relation to the issue.
- The Health Committee Chairman, David Hinchliffe MP, says he still has questions over MMR issue, that there have been serious concerns raised in his own constituency, and that he needed to look for answers, and was to team up with members of Scottish Health Committee to further investigate the MMR issue (report in Daily Express 21/1/01)

The thiomersal issue does not appear to have been formally considered by the Select Committee. The possible link with autism had not surfaced publicly at the time of my evidence to the Committee.

156. UK All Party Parliamentary Group On Autism (APPGA), Westminster

- An All Party Parliamentary Group on Autism has been formed at Westminster. It is currently looking at diagnosis, education, care and causation issues. The Chair is Dr. Stephen Ladyman MP (Labour, Thanet South). Vice-Chairs are Lord Clement-Jones (LibDem), Stephen Hesford MP (Labour), and Tim Loughton MP (Conservative). The Treasurer is Brian Cotter MP (Labour). Some 150 Members of Parliament are members of the APPGA.
- The All-Party Group has called for clear progress on data-gathering by Government. However, the APPGA has not implied that there is any reason to question MMR's safety at this stage. No real progress has yet been made in collecting data in any coherent nationwide manner by the UK Government as at February 2003. Some parents regard this neglect as quite deliberate.

157. Scottish Parliament, Edinburgh

- The Health Committee of the Scottish Parliament appointed a Reporter, Mary Scanlon MSP, in Autumn 2000, to examine the issues surrounding the MMR/autism link and to report back to the Committee. The Committee subsequently requested further work,

and set up an Expert Group to give advice. The Group reported in April 2002 (see earlier). As expected by the parents, it rejected an MMR/autism link, as to have done otherwise would have prompted a major controversy.

- In February 2002, the Scottish Chief Medical Officer stated that calls to research the link between MMR and autism would be "resisted".
- Susan Deacon MSP, the then Scottish Health Minister, has said that the issue of single vaccines is a "reserved matter", ie the power remains in Whitehall. However, Scottish MPs at Westminster no longer cover health. So the Scottish democratic representation is in Edinburgh, but the power is largely still in London.
- The Scottish National Party, Scottish Conservatives and Tommy Sheridan MSP of the Scottish Socialist Party have all called for the re-introduction of single (monovalent) vaccines in Scotland. This has been opposed by Scottish Labour and Scottish Liberal Democrats.
- On 14th January 2003, a further petition was presented to the Scottish Parliament by Action Against Autism, a charity. This called for the setting-up of a medical treatment facility within a hospital in Scotland.

158. UK Liberal Democrats

- In February 2001, Nick Harvey MP, Liberal Democrat health spokesperson, stated in a personal communication that *"We do not doubt the integrity with which (Dr. Wakefield) approaches his work, which is still at an interim stage. We note that Dr. Wakefield's opinions are not currently shared by the vast majority (of the medical establishment). However, there are also a number of parents who are convinced that the MMR vaccine has been the cause of their children developing autism.....Liberal Democrats.....respect the right of parents to choose to have the vaccinations administered separately, this being preferable to children slipping through the net entirely"*.
- However, the current Liberal Democrat Health Spokesman in the UK House of Commons, Dr. Evan Harris, has repeatedly insisted that MMR is safe, and has also repeatedly opposed calls for the re-introduction of single vaccines.
- On December 22nd 2002, the Liberal Democrat MP Paul Burstow, commenting on the huge increase in the prescribing of the drug Ritalin for child behavioural disorders, said: "I am concerned that the prevalence of these disorders seems to be on the rise.....We need to look at why the prescription rates have gone up so steeply."

159. UK Conservatives

- The Conservative health spokesman, Dr. Liam Fox, has expressed his support for MMR but has also expressed his view that the provision of single vaccines would be preferable to children being unimmunised at all, and would reflect the wishes of parents for being offered a choice. In February 2002, this became Conservative policy. The usual cross-party consensus on vaccination policy has therefore broken down. This is without known precedent in the context of vaccine policy.
- A Conservative MP, Ms. Julie Kirkbride, has vigorously promoted a Private Member's Bill to bring about the re-introduction of single vaccines. In February 2002, her call for the re-introduction of single vaccines to give parental choice was publicly endorsed by another Conservative MP, George Osborne.

160. US House of Representatives Committee on Government Reform

In April 2000, Rep. Dan Burton, Chairman of the US House of Representatives Committee on Government Reform, initiated a series of hearings into the relationship between vaccination and autism. Some of the submissions of evidence to the hearings have been described in earlier sections.

In a statement on 15th June 2000, Burton criticised the Food & Drug Administration's Vaccines and Related Biological Products Advisory Committee (VRBPAC) and the Centers for Disease Control and Prevention's Advisory Committee on Immunisation Practices (ACIP)

- Members of these committees, including chairmen, were found to own stocks/shares in the companies that make the vaccines.
- Individuals held patents for vaccines under consideration
- The CDC granted conflict-of-interest waivers, a year at a time, to its committee members
- The CDC's committee had no public members, and the FDA's committee had only one.

Burton concluded that "*conflict of interest rules employed by the Food and Drug Administration and the Centre for Disease Control have been weak, enforcement has been lax, and committee members with substantial ties to pharmaceutical companies have been given waivers to participate in committee meetings*".

- The Committee on Government Reform found that the majority of members of both the FDA and CDC committees had financial ties to vaccine manufacturers or held patents on vaccines under development.
- The Committee Chairman, Rep. Dan Burton, said: "*For the public to have confidence in the decisions made by their government, they must be assured that those decisions are*

not being affected by conflict of interest. It has become clear over the course of this investigation that the FDA's Vaccines & Related Biological Products Advisory Committee and the CDC's Advisory Committee on Immunisation Practices are dominated by individuals with close working relationships with the vaccine producers. This was never the intent of the Federal Advisory Committee Act, which requires that a diversity of views be represented on advisory committees" (my emphasis).

- Parents giving evidence to the Committee on Government Reform told repeatedly-similar stories of how their child had developed normally, then received triple vaccines (MMR or DPT) and had gradually become autistic.
- A number of researchers in the field gave detailed evidence on autism incidence and its steep climb to near-epidemic (for a supposedly-rare condition) proportions
- The cause of autism could not be explained away by genetics, because genetics do not cause epidemics within only two decades - the two decades that multiple vaccines have become standard
- The US agencies defending MMR made their own presentations. Some acknowledged financial links with vaccine manufacturers. Others said they were "looking into" the MMR/autism connection, but their stance suggested an entrenched hostility to the concept of any link.
- Overall, these agency representatives displayed indifference and an unconvincing grasp of the facts. (Note: an entire industry of "looking into it" has developed, both in the US and the UK. In the US, this has reported to have consumed \$100m in two decades of lack of progress).
- Controversial areas of research are being avoided, in favour of more abstract genetic-background research. Key leads are not followed up, so progress is understandably very poor.
- At every turn, the researchers try to prove that MMR and DPT are not involved. Obvious approaches, such as comparing significant-sized cohorts of triple-vaccine-immunised and unimmunised children - the most promising line of any scientific exploration - are not taken.

In a hearing on 19th June 2002. In his opening address, Rep. Dan Burton stated:

- That the US CDC and National Institute for Health had not provided adequate funding to address the autism issue in the manner that public health service agencies had used to address other epidemics
- High quality clinical and laboratory research was needed now, not five or ten years from now

- Independent analysis of previous epidemiological and case control studies was needed as well
- The US CDC had attempted to refute the Wakefield clinical findings through an epidemiological review. Whilst epidemiological research is very important, it cannot be used to disprove laboratory and clinical findings.
- Official at the US Department of Health and Human Services had aggressively denied any possible connection between vaccines and autism. They had waged an information campaign endorsing one conclusion, on an issue where the science is still "out".

Some of the evidence to this hearing has been outlined earlier in this document.

Further hearings by the Government Reform Committee are planned. Other relevant points are:

- In February 2002, Rep. David Weldon, a Florida physician and member of the US House of Representatives, urged the American Academy of Pediatrics to fully inform parents of their choice in having MMR separated-out and administered at different times. He stated that he was "very disturbed" by the recent Uhlmann, Wakefield, O'Leary et al paper, and that there was an "epidemic" of autism among US children.
- There has been strong criticism of the US regulatory mechanisms for drugs and adverse drug reactions by the Committee on Government Reform, and by others. The consumer group Public Citizen found that only 13% of 88 follow-up studies required as a condition for the licensing of drugs launched in the early 1990s were actually completed. Public Citizen's Health Research Group said that the neglect of follow-up studies could mean that side effects are going undetected.
- A "USA Today" investigation of FDA advisory committees between 1/1/98 and 30/6/00 found that at 55% of meetings, half or more of the FDA advisors present had conflicts of interest. At some meetings, over 90% of advisors present had conflicts of interest.
- Federal law generally prohibits the FDA from using experts with financial conflicts of interest, but this has been side-stepped by using waivers. The FDA issued more than 800 waivers between 1998 and late 2000. Some 300 advisors serve on 18 advisory committees.

On 30th December 2002, Rep. Dan Burton wrote to the Indianapolis Star, setting out some key points in response to an editorial in the newspaper on 11th December. Samples of Burton's key arguments included:

- In 1990, Indiana schools had 116 requests for services for autistic children. By 2001, the number had risen to nearly 3,800.
- Despite the claims of safety by the US and UK authorities, it had not been demonstrated that thiomersal was safe. The US Institute of Medicine had concluded that a

thiomersal/autism link was biologically plausible, and that existing evidence was inadequate to either accept or reject a causal association.

- The US Food & Drug Administration had in fact ordered the removal of thiomersal from over-the-counter ointments as long ago as 1985, on the grounds of safety and the risk of cell damage.
- In September 1998, almost a full year before the FDA took action over thiomersal in child vaccines, the FDA's Maternal Immunisations Working Group had recorded: "For investigational vaccines indicated for maternal immunisation, the use of single-dose vials should be required, to avoid the need for preservative in multi-dose vials"
- In October 1998, the FDA official responsible for reviewing all scientific literature on the safety of thiomersal in vaccines observed "I disagree with the conclusion regarding no basis for removal of thiomersal".
- In an internal briefing document from 2000, a (US) Government researcher had stated: "Preliminary screening for possible neurologic and renal conditions following exposures to vaccines containing thiomersal before three months of age showed a statistical association for the overall category of neurological developmental disorders and for two conditions within the category, speech delay and attention-deficit disorder".

Some of the evidence submitted to the Committee has been summarised in earlier sections. Evidence can also be read on the Committee on Government Reform's website.

PART P - SOME BROAD CONCLUSIONS AND QUESTIONS

161. Some Broad Conclusions

The above puts "under one roof" a considerable amount of information on the MMR/autism and the thiomersal/autism issues (which are likely to prove to be interlinked), though it cannot possibly be an exhaustive coverage, given the many issues involved and the ongoing scientific debate. However, it demonstrates that:

- There is considerable evidence of (in relative terms) an autism epidemic, with large increases being reported, though being dismissed by some observers. It also begs the question "how large an increase in the numbers is needed before the authorities accept there really is an increase?". But common sense suggests a sharp rise.
- There are many studies that seek to deny an MMR/autism link, but it is possible to demonstrate that each is flawed in several ways. These studies are also statistical/epidemiological-type studies - not studies of the actual children involved. They are also based upon small (for statistical-type studies) samples.
- There are strong grounds for believing that the safety studies of MMR were cursory, that the potential for damage was not recognised, and that subsequent safety follow-up has been conspicuously lacking
- There are many papers that point - some of them powerfully - to an MMR/autism link. Some of these studies involve analysis of samples of the actual children involved
- The inclusion in the US Homeland Security Bill of December 2002 of clauses debarring parents from initiating litigation against Eli Lilly over thiomersal suggests that the manufacturers felt that such litigation had a reasonable chance of success, and that they therefore needed protection. This gives further weight to the credibility of a vaccine/autism link
- Putting the above conclusions together, there appears to be strong grounds for believing that children have been damaged, and are still being damaged, by MMR, and probably by other vaccines. No alternative credible explanation has been put forward for these children's condition. The explanation that their degeneration into autism is biologically linked to MMR or thiomersal, or both, is also supported by the consistent accounts of the parents of the actual children.

162. Some Unanswered Questions

Some outstanding questions, which the media may find useful to bear in mind, are offered here...

- (Q1) Does the Department of Health/Minister accept that parents' reports are to a consistent pattern?
- (Q2) Why was autism rare a couple of decades ago but now much more common?
- (Q3) Why do UK Health Ministers claim in debates that the apparent rise can be explained through "greater awareness" or "better diagnosis", when studies from the US point to the increases being real, and not explainable through these factors?
- (Q4) Why are papers/editorials that suggest that there has been no real rise in autism given a high profile (e.g. by being copied out to members of the public), whilst detailed studies that demonstrate a real increase in autism are routinely disregarded?
- (Q5) Why do reviews such as the 2001 review by the Medical Research Council stretch out so hard to reach the comforting explanation that it's mainly a matter of better recognition and improved diagnosis, when they have no scientific justification or hard data for doing so?
- (Q6) Just how large an increase in autism numbers is required for it to be recognised as a real increase? A ten-fold increase (as per Cambridge) isn't enough, apparently. Is the Department/Minister's threshold of acceptance a twenty-fold increase? A fifty-fold increase? A hundred-fold?
- (Q7) why were most autism cases prior to the late 1980s, the time of introduction of MMR, of children who failed to develop in very early infancy, whereas very many cases nowadays - paradoxically, when there is now much better recognition of the condition (i.e. when it is much less likely to be missed in early infancy) are now of acquired autism, after a normal infancy?
- (Q8) does the DoH etc accept that the alleged new syndrome involves slow degeneration over many weeks/many months/several years, rather than an acute event within a few days, or at most three weeks, of MMR vaccination?
- (Q9) does the DoH accept that many autistic children have extreme multiple food allergies, and that the onset of these approximately coincided with the onset of their autism?
- (Q10) Ditto question for bowel conditions.
- (Q11) related question: does the DoH etc accept that simultaneous or sequential onset of gut/bowel/autism problems could be interlinked causationally?
- (Q12) does the DoH accept the principles of "re-challenge", with children suffering a "double-hit" after their first and then second MMR/MR vaccination, and then the consequent downhill "biological gradient" effect, as outlined by Dr. Andrew Wakefield to the Government Reform Committee, US House of Representatives, in June 2002? (The US Institute of Medicine accepted in advance of June 2002 that evidence of this would be persuasive).

- (Q13) is the DoH monitoring England/Wales autism numbers centrally? (they are not!)
- (Q14) are UK health authorities/Boards monitoring autism locally, to a consistent degree? (it is known that they are not)
- (Q15) is the UK DoH aware of the well-documented huge increase in autistic pupils in the US, 1993-2001 up from 12,222 to 78,717? (the current year-end estimate for 2002 is 94,000-95,000). The UK DoH likes to quote that "MMR is safely used in the US". Does the DoH now accept that the increase is real?
- (Q16) what explanation does the Scottish Executive have for the consistent steep rise in numbers of school pupils with autism enumerated by the Scottish Schools census over the past four years? Do they have any scientific evidence to support their assertion that it is purely a matter of better recognition and greater awareness?
- (Q17) what research has the UK Department of Health etc commissioned into possible causes (as opposed to the genetic susceptibility aspect) of autism.
- (Q18) what is its £ value over how many years? How does this compare with US expenditure?
- (Q19) Why has so little clinical research into potential causes - particularly the gut/brain vaccine/autism link - been commissioned? (the only known study in the UK is the NIBSC study). And why is this study using researchers who are being paid by the manufacturers as expert witnesses in the impending UK High Court cases?
- (Q20) has the DoH (or anyone in the UK Government?) made any estimate of the national financial costs of autism? (health, education, social services care, etc multiplied by numbers of cases multiplied by years of life expectancy)?
- (Q21) was the UK Medicines Division in complete disarray and chronically understaffed in 1988, the year MMR was introduced into the UK? (it was - see BSE Inquiry evidence, Draft Factual Account 17, pp 31-33). Was there any critical scientific input into its UK licensing and introduction, and if so, what?
- (Q22) did the Taylor, Miller et al North London study find that autism was increasing?
- (Q23) did the 2001 Medical Research Council review into autism find that autism was running at a rate of 1/166?
- (Q24) is it admitted that the Patja, Peltola et al (Finland) study only followed up 173 of the 1.8m children/troops/other persons long-term? And is it true that all these 173 cases were only those with acute gastrointestinal or other problems (vomiting etc), not slow long-term degenerative problems?

- (Q25) was the study designed to look at autism? (Peltola has publicly admitted it wasn't), and would local paediatricians in Finland have connected autism with vaccination at all at that time? (they certainly wouldn't, virtually no-one had ever suggested it then in epidemiological circles, 15 years ago)
- (Q26) does the DoH etc concede that long-term (six months plus) follow-up was not undertaken of a sufficiently convincingly large sample (10,000-plus) children prior to MMR licensing, and that the UK was in effect trusting to safety because MMR was already widely used elsewhere, eg the US? (they'll never admit this, but keep trying)
- (Q27) did the Medicines Division license MMR on the basis that it was apparently only the amalgamation of three existing licensed vaccines, without considering that their combination could have a synergistic effect?
- (Q28) is autism now recognised and recorded even as a *potential* adverse reaction, nowadays, by the Medicines Control Agency as part of the Yellow Card warning scheme? (very important question)
- (Q29) are UK doctors now specifically advised by the DoH to look out for degeneration as a *potential* adverse consequence of immunisation? (Lord Hunt recently confirmed in a Parliamentary Written Answer to Lord Clement-Jones that they are not).
- (Q30) Has there been any further recent guidance on this, in the light of the study by Spitzer, Aitken et al? (there has not).
- (Q31) why has the UK Medicines Control Agency not instructed health authorities to replace existing stocks of thiomersal-containing vaccines with non-thiomersal containing vaccines, when there is concern over adverse reactions to thiomersal, and when the manufacturers are operating a free-exchange scheme in the US, and when US litigation is under way?
- (Q32) how will the Department of Health/whoever rebuild confidence in the immunisation programme if the children win in the forthcoming UK 2003-4 High Court cases?
- (Q33) will the England & Wales/Scotland Chief Medical Officers, Ministers for Public Health (whoever), resign if MMR children win in the High Court?

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