Testimony before Congressional Oversight Committee on Autism and Immunisation

Dr Andrew J Wakefield MB.,BS FRCS

Mr Chairman and members of the Committee,

The purpose of this testimony is to report the results of the clinical and scientific investigation in a series of children with developmental disorders, principally autism. Nothing in this testimony should be construed as anti-vaccine; rather the author advocates the safest vaccination strategies for the protection of children and the control of communicable disease. The opinions expressed in both this text and the attendant presentation, represent those of the author. I am testifying on behalf of the children who have been referred to me for investigation, and am not here on behalf of, or representing, any institution.

These studies were undertaken against a collective background experience of the principal authors, of over 500 peer-reviewed clinical and scientific papers, published in reputable medical journals, and over 1000 peer reviewed abstracts presented to learned societies. The ongoing studies form part of an international, multidisciplinary research program including California's MIND Institute at UC Davis into inflammatory diseases of the intestine and childhood developmental disorders, involving the disciplines of pathology, immunology, virology (particularly, molecular detection of viral genes) and epidemiology. All studies were approved by the appropriate institutional Ethical Practices Committee.

We have now investigated over 150 affected children with autistic spectrum disorders. A preliminary report of the first 12 children has been published (*Lancet* 1998;351:637-641). A detailed analysis of the first 60 children in due to be published (*American Journal of Gastroenterology*). The clinical findings described in these reports have been reproduced in the extended study of more than 150 children. The latter group includes 4 children from the US. Independently, other centres investigating children with autism and gastrointestinal symptoms in the UK, Europe and the US, have confirmed the clinical findings that comprise the syndrome of *autistic enterocolitis*.

Our study was initiated at the request of parents, and was stimulated by the conviction that their children had; 1) developed normally during the first 1-2 years of life; 2) undergone developmental regression to autism, in the majority of cases following measles mumps rubella (MMR) vaccination, and; 3) developed gastrointestinal symptoms that, in the parents' opinion, were closely associated with the behavioral/developmental pathology. Almost without exception, the anxieties of the parents, as described above, had been dismissed by the medical and allied professions. Bowel symptoms had been disregarded without investigation. Raising the issue of the possible role of MMR vaccine in their child's autistic regression had led to an acrimonious breakdown of the doctor-parent relationship in many cases.

One of the fundamental rules of conventional clinical medicine is to listen; to listen to the patient or the patient's parents, and then to investigate the presenting symptoms, without prejudice, in order to determine whether or not they have an organic origin. In this context, the Committee should be aware that the parents' story is remarkably consistent whether, for example, they come from the US, Canada, the UK, mainland Europe, Asia or Australia. The pervasive features include developmental regression and gastrointestinal symptoms following MMR vaccination (Figure 1).

Figure 1 *New Straits Times*, Kuala Lumpur "After receiving his MMR inoculation at 18 months, Nicholas came down with a very bad case of gastroenteritis. From then on I noticed very distinct changes in his behavior," Ang recounts.

Accordingly, we have conducted a series of detailed studies on behalf of these children, the findings of which, in summary form, include:

1. A pattern of symptoms that comprise abdominal pain, abnormal bowel habit (constipation with overflow diarrhoea), bloating, reflux. The pattern and severity of behavioural and gastrointestinal symptoms appear to parallel each other.

2. A frequent history of atopy (asthma, eczema, hay fever)

3. Recurrent, refractory upper respiratory tract/ear infections.

4. A strong family history of autoimmune disease.

5. On direct visualisation of the lower intestine, ileo-colonic lymphoid nodular hyperplasia (swelling of the tonsil-like tissues in the small and large intestine; figure 2), plus inflammation of the colon and, to a lesser extent, the ileum.

Figure 2. Marked lymphoid nodular hyperplasia of the terminal ileum in a child with autistic enterocolitis

6. Low numbers of circulating immune cells (lymphocytes; figure 3) and an inability to respond <u>appropriately</u> to common antigens to which the children have been exposed previously (tetanus, diptheria, pertussis, house dust mite, candida). These differences are statistically significant compared with age-matched healthy controls.

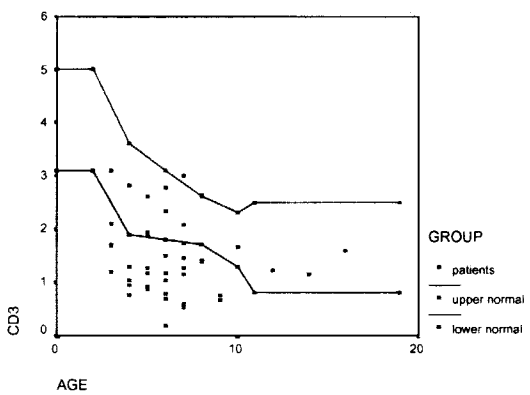


Figure 3. CD3+ lymphocyte counts in peripheral blood of autistic children (each blue square represents one child) compared with age-standardised reference ranges, showing the upper (green) and lower (red) limits of normal (5^{th} – 95^{th} centiles)

7. Microscopically, in intestinal biopsy tissue, a specific and subtle inflammatory pathology in the colon (figures 4 & 5) that, overall, appears distinct from that seen in patients with Crohn's disease, ulcerative colitis, idiopathic constipation, and histologically normal controls of a similar age.

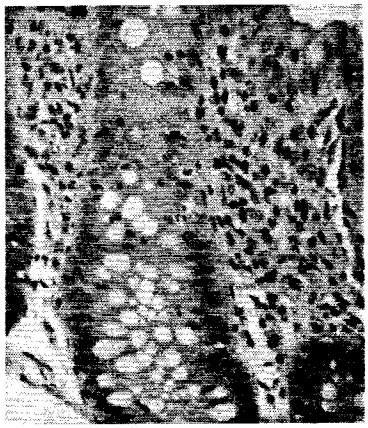


Figure 4. Autistic enterocolitis: acute inflammation in a colonic crypt

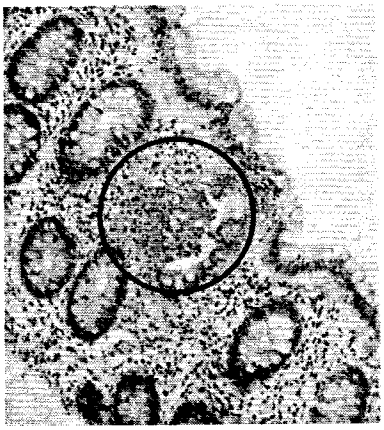


Figure 5. Autistic enterocolitis: colonic crypt abcess within the black circle

8. A pattern of colonic inflammation that distinguishes *autistic enterocolitis* from other common forms of inflammatory bowel disease, as demonstrated by the detection and quantification of specific immune and inflammatory molecules in the intestinal lining.

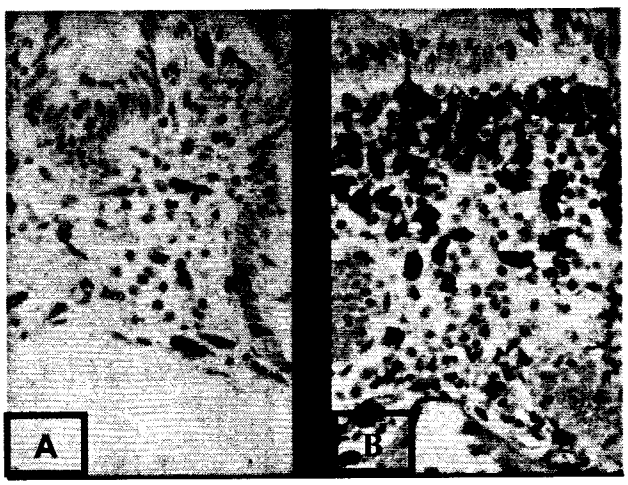


Figure 6. Activation of the immune system in the bowel lining in autistic enterocolitis. A = normal child; B = autistic enterocolitis. Staining represents Class II antigen expression (LN3)

1. In blood, a raised circulating IgG measles antibody titre that is statistically significant when compared with age-matched healthy controls. The same is not seen for antibodies to mumps, rubella or cytomegalovirus.

2. In preliminary studies, the presence in intestinal tissues, of measles-specific antigens (protein), specifically in the follicular dendritic cells of the reactive ileal lymphoid tissue.

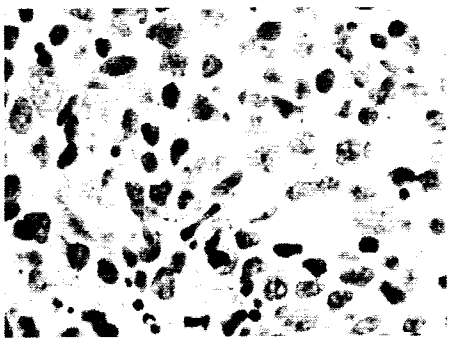


Figure 5. Measles virus nucleocapsid protein in the centre of a reactive lymphoid follicle in a child with autistic enterocolitis

3.The absence, in the same lymphoid tissues, of antigens specific for other common viruses including mumps, rubella, adenovirus, herpes simplex virus I and II and HIV.

4. The absence of measles antigen, in intestinal lymphoid tissue from developmentally normal children without inflammatory pathology.

5. Investigations including chromosome analysis, metabolic analysis, imaging studies of the central nervous system, electro-encephalography and analysis of cerebrospinal fluid did not reveal any alternative causes for developmental regression in these children.

6. The presence in 3 of the initial 9 children with autistic enterocolitis who were studied by gene amplification technology, of measles virus hemagglutinin (H)

gene in peripheral blood immune cells (Kawashima H et al. *Digestive Diseases and Sciences.* March 2000)

7. Subsequent molecular studies of the detection of measles virus genetic material will be described by Professor J.J. O'Leary.

The issue of coincidence

Many pediatricians have expressed the opinion that, for autism, any association between MMR vaccination and the parents' recognition of the child's behavioral problems is coincidental. Such an assumption is inappropriate in the absence of a thorough history and investigation. For example, symptoms of classical, early onset autism are often noticed initially, in the first and second years of life the child does not develop in the way of normal siblings and peers. Parental concerns about the child's development are often expressed in the second year, when these differences become evident. MMR vaccine is given routinely at this age, and coincidence is therefore inevitable. However, in children with autistic regression, the pattern is of loss of speech, language and social skills, accompanied by bizarre behaviors, in a previously developmentally normal child. This is consistent with an early onset disintegrative psychosis. Furthermore, loss of speech and language are accompanied by symptoms of excessive thirst, bowel disturbances, self-injury, and a self-limited diet associated with cravings for particular foods. Atopy and recurrent, refractory upper respiratory tract infections are prominent features. These symptoms do not feature in the exclusively behavioral descriptors of the diagnostic manual for autism - DSM-IV.

The issue of coincidence may be addressed, in part, by considering those children who have received more than one, measles containing vaccine. If the intestinal pathology and the associated behavioral problems are causally linked to a persistent viral infection of the intestine, then re-exposure to the same virus vaccine might be expected to exacerbate the condition by, for example, eliciting an immune response against virally infected cells. In the cohort of children with

autistic enterocolitis under our care, we have 10 children who have received more than one dose of a measles containing vaccine. Developmental/behavioral changes had to be identified contemporaneously, rather than retrospectively. The data for first and second vaccine doses, and initial and subsequent behavioral changes are shown graphically, below (Figure 7).

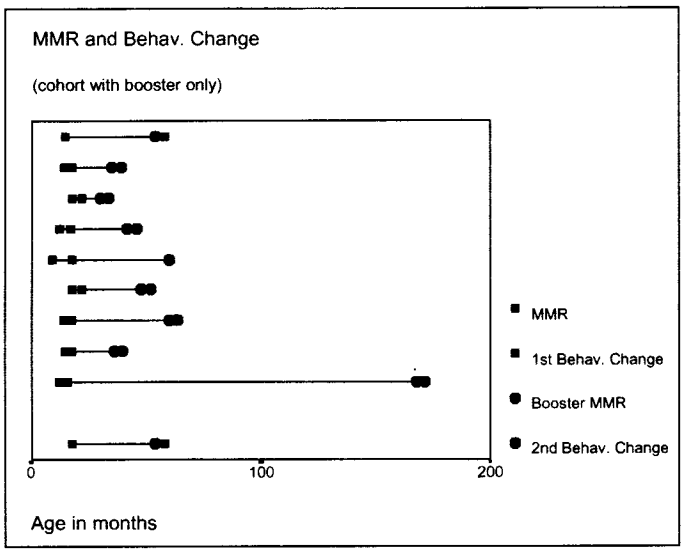
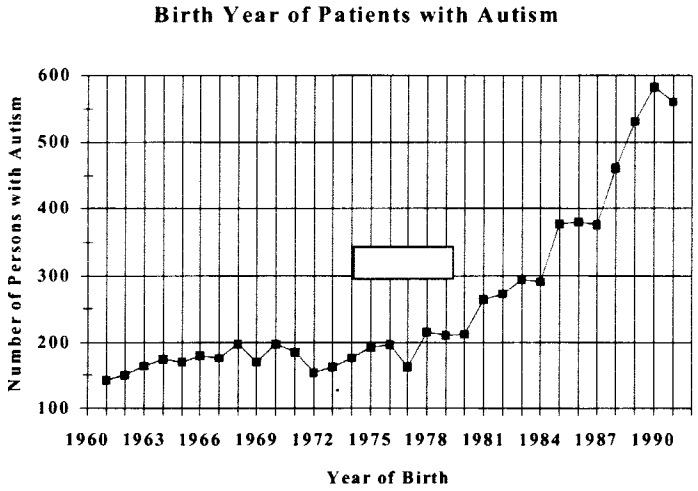


Figure 7. The graph, where each time line represents one child, shows that for 7 children (2-4 & 6-9) developmental regression accompanied both exposures. In 2 children (1 & 10) it followed the second dose, long after the second year of life. These data are not consistent with coincidence.

Temporal trends in autism

If MMR vaccine is causally related to autism and autistic enterocolitis, then there should have been an increase in the numbers of cases of autism following the introduction of MMR vaccine in different countries. Moreover, since MMR was introduced into different countries at different times, the effect should be one of

Is Incidence Increasing?



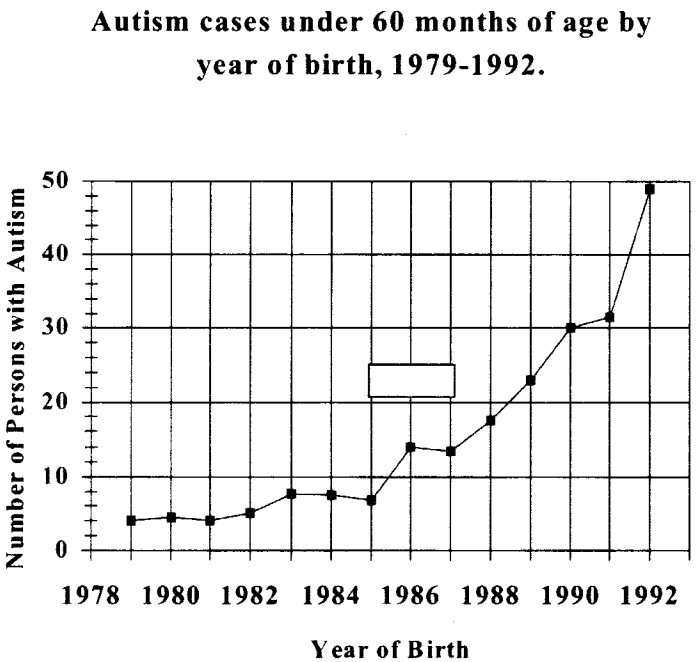
Temporal trends for autsim cases in California

A dramatic rise in the numbers of new cases of autism seen in the first birth cohorts eligible for MMR vaccination (bar)

There was a rather protracted period over which MMR was introduced in the US, because of the continued availability of monovalent vaccines. (F.Yazback. personal communication)

Source: Office of Developmental Services, Sacramento, Ca.

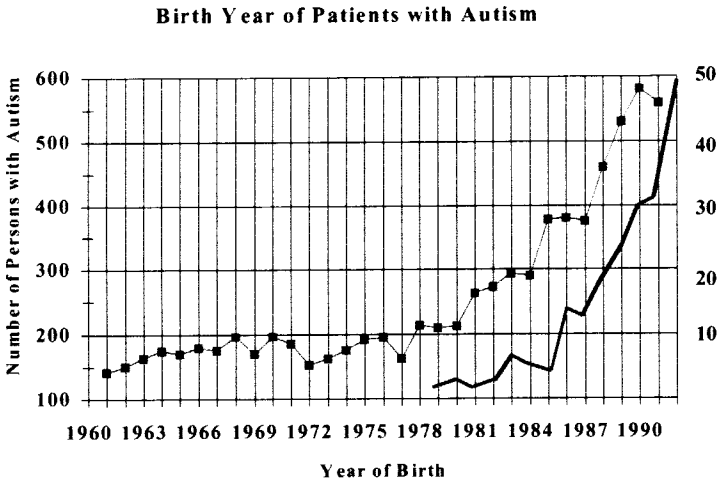
similar temporal trends in different countries, with any increase corresponding with the introduction of MMR.



Temporal trends for autism U.K. North London

Data published in the Lancet, compiled by the Public Health Laboratory Services and the Department of Community Paediatrics, Royal Free Hospital. Data show a doubling of autsim cases in the first birth cohorts eligible for MMR, with a dramatic and sustained rise thereafter. Bar shows first birth cohorts eligible for MMR

Source: Taylor et al. Lancet,



Temporal trend for autism: US and UK

Superimposing the data for the US and the UK analyses described above, identical time trends are seen, with a delay in the rise in the UK that corresponds to the later in introduction of the MMR vaccine in 1988

It is important to note that the UK and the US use exactly the same diagnostic criteria for autism and yet there is a 10-year delay in rise in the number of cases. These changes are very unlikely to reflect artefacts due to changing diagnostic criteria. This is confirmed by reviewing the temporal trends for autism and learning disabled children in the state of Illinois from 1991-1997.

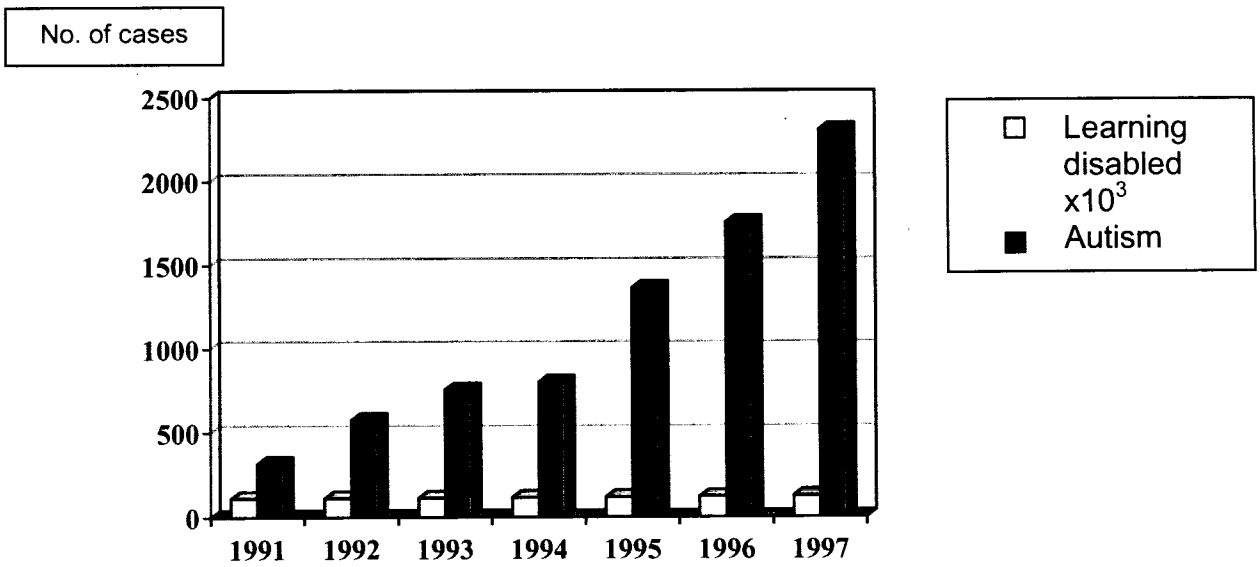


Figure 12. Temporal trends for autism and learning disabled ($x10^3$) in Illinois. In 1994 the broader autism criteria of DSM.III Revised (DSM.III-R) were amended

to the more exclusive DSM-IV. Had the increase been an artefact of diagnosis, then the numbers should have levelled off beyond 1994.

The Finnish paper

No evidence for MMR-associated inflammatory bowel disease or autism in a 14-year prospective study. Peltola et al, *Lancet* 1998; **351**: 1327-1328.

The study:

- Identified adverse events following 3 million doses of MMR in Finland during the 3 weeks post-vaccination
- Traced those individuals with severe gastrointestinal symptoms (diarrhea /vomiting) after MMR, lasting 24hrs or more. There were 31 recorded episodes.
- Followed up those 31 individuals from 1 to 14 years (mean=9 years) after MMR
- None of the 31 children had a diagnosis of autism or inflammatory bowel disease

The problems

- No one has ever suggested that acute gastrointestinal symptoms within 3 weeks of MMR is a risk for autism or inflammatory bowel disease.
- Parents reported **behavioural changes** as the initial presenting feature in their children
- 31 children is far too small a number, and the children are still too young to assess risk of inflammatory bowel disease.

Conclusion

- Peltola et al tested the wrong hypothesis

The Taylor paper

Taylor B et al (Royal Free & University College Medical School & the Public Health Laboratory Service) published a paper (*Lancet* 1999;353:2026-2029) that sought to dispel any relationship between MMR vaccine and autism. They performed a Case-Series analysis of children with autism in North West Thames. **Reasoning:** If there is a causal association between MMR and autism, there should have been a step-up in the numbers of children with autism in the first birth cohorts eligible for MMR. The authors stated that such a step-up should have occurred in those born in 1987 since these were the first children eligible to receive MMR in the second year of life. There was a crucial omission from the paper by Taylor et al. In 1988 – with the introduction of the MMR in the UK – a "Catch-Up" campaign was instituted which targeted pre-school children of one to four years of age who had not previously received monovalent measles, mumps or rubella vaccines irrespective of their immunity to the three infections.

Corroboration of this comes in the form of a contemporaneous paper from Dr Christine Miller, previously of the PHLS, who stated: "Although the program will be aimed mainly at the **one to four** year age groups, where it will have the maximum effect, MMR vaccine can be given at any age." (Miller C. Introduction of measles/mumps/rubella vaccine. *Health Visitor* 1988;61:116-117)

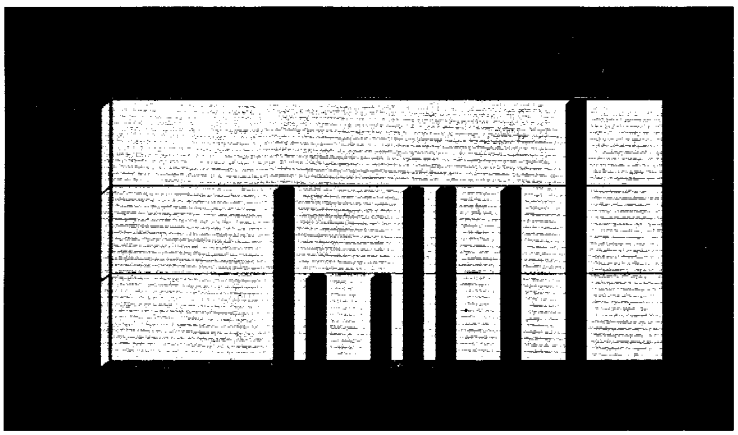
Taylor et al noted that the rise in autism occurred in children born in the few years before 1987 and concluded, therefore, that since this rise had started before the introduction of MMR it could not have been caused by MMR. This paper has been cited by various vaccine officials as definitive proof of the safety of MMR in this context.

Taylor et al's omission of the crucial information on the catch-up campaign, led the reader to believe that those, and only those, born in 1987 were the first children eligible for MMR. They were challenged on this omission in a subsequent letter to the Lancet (1999;354). In their reply they acknowledged that they were aware of the catch-up campaign and admitted that no fewer than 36 autistic children in their data-set were born before 1987 and had, therefore, received their MMR over the age of 2 years. They claimed that this was not

relevant since symptoms had apparently started in these children before MMR. This is not relevant; testing of a "step up" hypothesis is not based upon analysis of individual case notes, other than to confirm diagnosis. Since they were aware that their cohort contained children who received the MMR after the age of 2 years **it was not scientifically legitimate to test the hypothesis that a step up should be seen in those born in 1987**. The fact that the step up occurs in those born in 1986 is alarming, and would be consistent with an association with MMR.

Such were the anxieties about the quality of this study that it was recently the subject of a special, and highly critical debate at the *Royal Statistical Society* in London. The conclusion reached was that Taylor et al's study design was wrong.

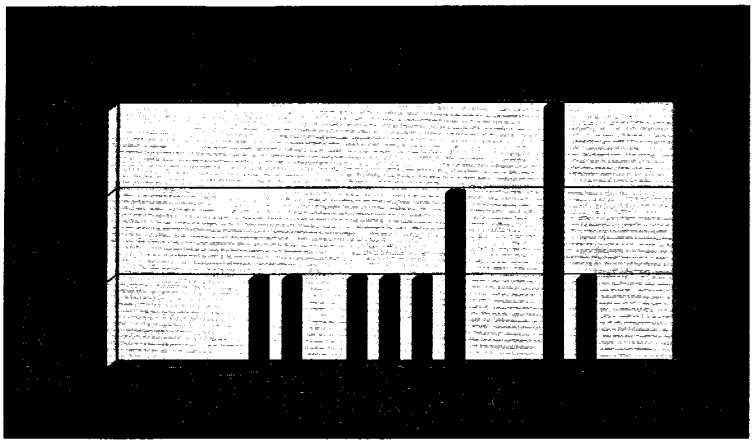
Further evidence for a temporal association between the introduction of MMR and an increase in the numbers of cases of autism comes from a current study of autism in island populations. The data for Shetland are shown below.



Year of Birth

Shetland Islands, Scotland.

A birth cohort effect for autism is seen in those born after the mid 1980's, corresponding with the introduction of MMR vaccine.
Source Thrower D.



Year of Birth

Figure . A similar birth cohort effect is seen for those born in the Western Isles of Scotland, a geographically distinct group from the Shetlands.

MMR and Compound effects

Parental reports have implicated the polyvalent MMR vaccine, but rarely the monovalent measles vaccine, in autistic regression. Is such a causal association consistent with what is known of the risks for acquired forms of this syndrome? Atypical patterns of exposure to common childhood infections - measles, mumps, rubella and chickenpox - have been associated with autism and autistic regression. *In utero* and infant exposures have been identified as periods of apparent susceptibility, when both the brain and the immune system are undergoing rapid development (Deykin EY and MacMahon B. *American Journal of Epidemiology* 1979;109:628-638). It is notable that a close temporal relationship in the exposure to two of these infections during the periods of susceptibility may compound both the risk and severity of autism. Although historically, these rare patterns of exposure may have accounted for only a small proportion of autism, the widespread use of a combination of the candidate agents in a single vaccine may have changed this. Recently, measles containing

vaccines were linked to developmental regression (Weibel RE et al. *Paediatrics* 1998;101:383-387).

In order to understand why autsistic enterocolitis might result from a compound effect – where the interaction of multiple concurrent viral exposures is important - it is helpful to examine the patterns of childhood infection that have been identified as risk factors for persistent measles virus infection and delayed disease. One important pattern of infection that may increase the risk of delayed disease is where different viruses interact, either with each other or both interact with the host immune system simultaneously. A close temporal exposure to measles virus and another infection, including chickenpox or an encephalitogenic enterovirus, is associated with an excess risk for a rare fatal encephalitis (subacute sclerosing panencephalitis), the onset of which may be delayed for many years. Similarly, atypical patterns of measles infection, including a close temporal exposure to mumps infection, but not other common childhood infections, have been identified as a significant risk factor for chronic intestinal inflammation - Crohn's disease and ulcerative colitis.

Clues that the component viruses of MMR could interfere, one with another, were provided in the very first pilot studies of this vaccine in 1969 (Buynak et al. *JAMA* 1969;207:2259-2262). However, despite providing compelling evidence of the potential for dose- and strain-dependent interactions between the component viruses in the MMR vaccine, both in the context of adverse reactions and antiviral immune responses, the matter was left in abeyance.

Six years later, in 1974, the potential for viral interference in MMR was the subject of a more detailed follow-up to the Buynak study, by Minekawa et al (*Biken Journal* 1974;17:161-167). The most striking observation was of a dose-dependent influence of the mumps vaccine upon not only clinical reactions to the measles component, but also seroconversion to rubella vaccine.

The ability of mumps virus to interfere with the cellular immune response to certain strains of measles virus and, thereby, in particular combinations

potentially to reduce viral clearance and increase the risk of persistent infection, is an intriguing hypothesis to some of those involved in the current debate. Whatever the ultimate merits of this hypothesis, the contemporaneous interpretation of Minekawa et al was that further studies were necessary. However, it does not appear, from the published literature, that these further studies were undertaken.

Summary

- Autistic enterocolitis is a real syndrome
- The swollen intestinal lymphoid tissue provides a focus for searching for the cause(s) of this syndrome.
- The virological data indicate that this may be measles virus in some children.
- It would be imprudent to interpret the temporal relationship with MMR as coincidence, in the absence of thorough investigation.
- Epidemiologic and virologic data support the possibility of a compound effect of multiple concurrent viral exposures influencing: the clinical and immunologic response to MMR; the risk of autism; and, the risk of delayed sequelae, including chronic intestinal inflammation.
- Autistic enterocolitis appears to be important part of the current epidemic of autism and autistic spectrum disorders.

Conclusions

- If, following thorough independent scientific investigation, it emerges that autistic enterocolitis and other related disorders are causally related to a compound influence of the component viruses of MMR, whether these viruses have been encountered naturally or in the vaccine, then through judicious use of the vaccines, one may have a means for preventing the disease. Spacing the single vaccines, thereby dissociating the exposures that, together, may constitute the risk, provides a way of not only preventing the acute measles, mumps and rubella infections, but also,

potentially, the risk of one of the most devastating diseases that it has been our misfortune to encounter.