

**MMR Vaccine,**  
**Thimerosal and**  
**Regressive or Late Onset**  
**Autism**  
**(“Autistic Enterocolitis”)**

**A Review of the Evidence**  
**for a Link Between**  
**Vaccination and**  
**Regressive Autism**

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## EXECUTIVE SUMMARY

- ÿ This comprehensive review sets out the concerns of parents whose children have degenerated into an acquired-autistic state after MMR or other vaccines, and attempts to summarize the debate over thimerosal (or thiomersal) preservative used in vaccines other than MMR, and to highlight possible links between this mercury-based preservative and autism. It is possible, and increasingly likely, that the MMR and thimerosal factors overlap or interact in the cause of late-onset degenerative autism.
- ÿ These are immense and complex subjects. This review does not attempt to cover every single piece of the available scientific literature for or against an MMR/autism or thimerosal/autism link, but it reviews well over one hundred of the most recent, most pivotal, or most frequently-quoted studies and papers.
- ÿ 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 measles-containing vaccines, or thimerosal-containing vaccines.
- ÿ The concept of vaccination is not the issue. No attempt is made here to criticize the principle of vaccination. It has been argued that vaccines have saved millions of lives, and continue to do so, particularly in the developing world.
- ÿ The issue here is, have a small minority of children been damaged by vaccines, in a way that has yet to be fully understood? Specifically, is a subset of the autism spectrum causally linked to certain types of vaccine, or vaccine ingredients? These are the questions that must be addressed.
- ÿ This document therefore is in no way an "anti-vaccine" tirade. But if there is a problem, even for a small sub-set of children, it must be rigorously investigated, and its consequences faced up to. We do not shrug-off air travel fatalities, or deaths of passengers traveling by rail, because it might be bad for the travel business. Yet possible vaccine damage seems to have been largely ignored in the past, and the issue of safety treated as a taboo subject. Vaccine safety monitoring, and even the wider issue of drug and pharmaceuticals safety, has been in need of major reform, in many countries, and for many years.
- ÿ Each of the studies that seeks to "disprove" an MMR/autism link or a thimerosal/autism link can be argued to be flawed in design or ambiguous in results. These flaws are discussed in detail later in the text.

- ÿ It also notes that all but one of the studies that seek to disprove an MMR/autism or a thimerosal/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, and have indeed been criticized by professional statisticians.
- ÿ Such studies also fail to address the problem - what was it that damaged the specific children that became autistic after MMR or thimerosal-containing vaccines?
- ÿ The one MMR study that has both claimed there is no MMR/autism link and also actually looked at information extracted from the medical records of a sub-set of UK 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 still not a clinical study. No children were actually clinically examined.
- ÿ Parents who have scrutinised the studies quoted by the Department of Health as “proof” of there being no link between MMR or thiomersal and autism have found that such studies crumble away easily when pressed. To give just one example, the Finnish study by Patja, Peltola et al was very loudly heralded, as late as at the start of 2001, by the UK 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 subsequent 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. Yet the study still continues to be regularly quoted by medical commentators and professionals, and the media, as “proof” that MMR is safe. The study was still being quoted as “evidence” by BBC television news in mid-2005.
- ÿ In contrast, the parents find that there is a considerable, and growing, number of studies that suggest that MMR and/or thimerosal preservative (routinely used in very many vaccines until very recently, and still in widespread use in 2005-06) could be causing acquired autism (or “autistic enterocolitis”) in significant numbers of children.
- ÿ Completely contrary to the claims of the authorities, particularly in the UK, not all of these studies originate from only one group of researchers (the former Wakefield team at the Royal Free Hospital London, and then Dr. Wakefield since his departure), as has sometimes been inaccurately

asserted by those who defend MMR. The studies that point to a link have involved a significant and growing number of research teams, in a number of countries.

- ÿ Other studies, whilst not specifically targeting MMR or thimerosal-containing vaccines, offer further clues as to what may be happening, and are fully consistent with an MMR and/or thimerosal involvement, implicating vaccines.
- ÿ Furthermore, many of the studies that suggest that there is an MMR/autism or a thimerosal/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?”.
- ÿ It is now believed that a “house of cards” has thus been constructed by the UK Department of Health, the US Government health system and by other authorities and commentators in the medical establishment over the past eight or nine years, with repeated assurances being given to the public, but with these being based upon a lop-sided, highly partisan and culpably selective gathering and interpretation of the available evidence.
- ÿ This review also finds that there are other related concerns - from the regulatory bodies themselves - about the risk of permanent developmental damage from thimerosal-containing (or thiomersal-containing) vaccines, though it is not yet completely understood as to how these problems are directly interlinked biologically to the MMR/autism problems (we are told that MMR in itself does not contain thimerosal). Class-action lawsuits are now under way in the US (see later sections) over thimerosal/thiomersal and autism, just as they have been (or still are) in the UK and Ireland over MMR and autism.
- ÿ 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 six years and more - clues that all too often have been ignored, or, worse still, which have been rejected out of hand by the authorities.
- ÿ The medical establishment has repeatedly asked itself the wrong question. It has asked itself “Is MMR safe?”, and “is thimerosal safe?”, hoping for an affirmative answer. In contrast, researchers and parents have asked two very different questions: “What precisely is wrong with this child?”, and “Why did this child gradually or suddenly change from being healthy to being autistic?”. It is answering these latter two questions that should be the key issue.

- ÿ The safety trials of MMR were undoubtedly very poor. That is an established fact. The UK trials were recently described by a former senior Department of Health insider as “hopeless - a mess”. For the thimerosal issue, the picture is even more stark. The product appears to have had no proper safety trials at all since its introduction about 75 years ago, and its use also appears to have lacked even the most basic appropriate back-checks on safety.
- ÿ Much of the debate within the medical community appears to have been based around the simplistic assumption that, for example, if MMR caused autism, there should consequently be matching graphs showing the uptake of MMR and the uptake of autism. For example, in Spring 2005, Dr. William Barbaresi of the Mayo Clinic, Rochester, Minnesota, commented that children had been given MMR for almost twenty years before there was a marked increase in US autism. The possibility that children had, for example, been damaged in gradually-increasing numbers by the introduction of MMR and then the later acceleration of the vaccination schedule using increased total burdens of thimerosal for each child, in combination, producing a delayed-action increase in autism numbers, does not seem to occur to the medical establishment.
- ÿ It is rather like road accidents. Accidents are caused by driver behaviour, vehicle design, vehicle speeds, road design, road condition, weather and other factors, in combination. You do not simplistically expect to find a precise historic straight-line linear relationship over decades between (say) “numbers of drivers” and “numbers of deaths”. Life is much more complex than that.
- ÿ The children that have been damaged have had their lives ruined. They were previously completely healthy. They now have seventy or eighty years of mental handicap ahead.
- ÿ Their care will cost the taxpayer dear. Whether their sacrifice is justified in the interests of wider public health is not the point at issue.
- ÿ What is at issue is, what changed for these children, through what processes, involving what susceptibility factors and trigger factors. And how can further cases of damage be headed-off?
- ÿ This briefing note also poses a number of unanswered questions about MMR, about thimerosal, and about the children that are believed to have been severely damaged by vaccine administration. The damage involved is not confined to regressive autism.
- ÿ Finally, it is emphasized that this note is the result of a search of the published (and sometimes unpublished) studies and other information. It does not offer medical advice. Parents considering vaccinating their children with MMR or with thimerosal-containing vaccines must form

their own conclusions as to whether to proceed, and are urged to gather the maximum amount of hard information before making their own choice. It is hoped that this review offers a useful start, and is particularly useful for journalists.

## PART A

### A NOVEL SYNDROME

#### 1: What Is Acquired Autism/Autistic Enterocolitis?

- ÿ 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. It is an effect, and a consequence, not a cause in itself. Everything has a cause. Autism is not some mysterious illness that comes out of the sky, to strike children at random. It is a global term, all too loose, to describe a set of characteristics.
- ÿ The “classic” form of autism was first described by Dr. Leo Kanner. These children were different from normally-developing children from birth.
- ÿ However, a very different form of autism, formerly a minority variant, 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. This is not so much autism as brain damage.
- ÿ Often the damage is severe or very severe, and usually the damage appears to be permanent, although some remedial treatments are claimed to be able to reverse some aspects of damage to a modest degree.
- ÿ This late onset of autism typically follows the receipt of MMR vaccination, but also appears to sometimes follow measles-containing vaccines such as monovalent (so-called “single”) vaccine, or measles-rubella (MR) vaccine, and sometimes other vaccines such as DPT (diphtheria-pertussis-tetanus).
- ÿ It does not necessarily occur immediately after MMR - 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, quite possibly several or even many months, or even in some cases a longer period.

- ÿ The rate of deterioration seems to vary considerably. It has been a consistent error of the medical authorities to view autism as an alleged acute, immediate, reaction, although many parents have certainly reported that some form of immediate or near-immediate (within 24 hours) adverse reactions, such as high-pitched screaming and high temperatures, have occurred. Some parents have reported a rapid change in their child's behaviour, whereas others have seen a slower decline.
- ÿ Typically, the child's mood has changed, they have become quiet and withdrawn, speech has been lost and skills have vanished. Sleep patterns have often disintegrated.
- ÿ Crucially, the onset of this acquired form of regressive autism is accompanied by other visible and associated physical manifestations of problems. These include bright red ears and dark rings under the eyes after certain foods, acute gluten and casein intolerances, prolonged hyperactivity, night sweating and loss of temperature control, and chronically poor sleep patterns.
- ÿ The arrival of these problems and the degeneration of the child into autism as a "package" strongly suggests that they are interconnected
- ÿ The timing of onset following vaccination - not just MMR - is described by the UK Department of Health as a coincidence. Their argument is that autism is "noticed" around this time, because this is a time when child development is most rapid, and therefore any failure most noticeable. The thinking behind this stance appears to be that either autism was always there, all along, or that it is akin to some sort of delayed-action genetic "bomb", primed in certain individuals to coincidentally detonate just after receipt of MMR or thimerosal-containing vaccines, or around that time.
- ÿ The gross implausibility of this argument, that it is highly unlikely in the extreme that previous problems would have been missed, and at a time where children receive constant devoted attention and close scrutiny regarding their development, is ignored. The concept that genetics alone could be responsible for a sudden devastating decline in a developing infant is equally implausible.
- ÿ Photographic and video evidence, together with child health and developmental records and the accounts of relatives, friends and visitors, that contradicts the authorities' arguments, is also routinely ignored, without even a superficial investigation to verify their accuracy.
- ÿ However, very significantly, much older children have also degenerated into autism after MMR or other vaccination. 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.



- ÿ Also, no cases are known, at least to campaigning parents, of any children who have rapidly become autistic just before MMR or thimerosal-containing vaccines. This clearly implies that such cases are much fewer in number.
- ÿ 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. This is almost certainly not skewed development. It is likely to be damage, from an external cause.
- ÿ There is also the issue of double-regression, where children have been normal, have been vaccinated, have regressed, have made some remedial progress, have been re-vaccinated (as a booster) and have severely regressed again. This principle is known as “challenge-rechallenge”.
- ÿ The US Institute of Medicine has stated that evidence of challenge-rechallenge would constitute powerful support for a causal link between vaccines and regressive autism. There are many UK children (and presumably US children, too) who offer such evidence, but the IoM has still not yet accepted that its self-declared criteria has been fulfilled.
- ÿ 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. A growing number of scientists, as well as parents, believe that the trigger is either MMR, or thimerosal, or both acting in synergy.
- ÿ 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 patently is not. Research is being held up by the refusal of the medical establishment in the UK and US to recognise the problem, or even to recognise the reality of a steep increase in autism.
- ÿ Also coinciding with the late onset of autism in many of the children (or other severe 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.
- ÿ Examination of children, initially but not exclusively at the Royal Free Hospital, London, 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. The pioneer

research the Royal Free has now been confirmed by researchers at other centres in Ireland and the US.

- ÿ 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).
- ÿ Research reported by Dr. Jeff Bradstreet to the US Institute of Medicine on 9th February 2004 found that, when the cerebrospinal fluid of 28 regressive-autistic children was analysed, measles virus was found in 19 of the 28 cases. When 37 non-autistic control-group children were analysed, only one child was found to have measles virus.
- ÿ All 65 of these children had received MMR, and none had any recorded history of wild measles infection. This more recent research is powerful statistical evidence of a measles virus complicity in the pathogenesis of regressive autism. This research therefore strongly endorses the anecdotal evidence of the parents, that their children became autistic after MMR. For many children, MMR thus remains the prime suspect.
- ÿ In February 2006, Dr. Peter Fletcher, former Chief Scientific Officer at the Department of Health, strongly criticised the way that the UK Government and medical authorities were ignoring the mounting evidence for an MMR/autism link. A more detailed review of Dr. Fletcher’s comments appears elsewhere in this review. He stated that *“there are very powerful people, in positions of great authority in Britain and elsewhere, who have staked their reputations and careers on the safety of MMR, and they are willing to do almost anything to protect themselves”*. It is the source of this statement that makes such criticisms so powerful, as Dr. Fletcher was a UK Government senior medical adviser, responsible for advising as to whether medicines and vaccines were safe.

## 2: The New Syndrome

This is a very brief summary of the new syndromes of autistic enterocolitis and/or mercury damage:

- ÿ 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.

- ÿ The condition is believed to have developed in each case in the period following MMR immunisation
- ÿ Because of the swollen and hyperplastic condition of the intestinal wall, 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.
- ÿ 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 myelinisation. Comprehensive studies to determine this have also yet to be undertaken.
- ÿ It is also possible that thimerosal, a mercury-based preservative that has been routinely used in a number of vaccines, may have played a role. The resultant damage closely resembles that of mercury poisoning. Again, adequate research has not yet been done.
- ÿ Damage may in the event be via either, or a combination, of these pathways.

Further details are given in the text, and further evidence is emerging.

### 3. Evidence of Regression

One of the most frequent “explanations”, that has been quoted by the UK Department of Health, is that children who are reported as having regressed into autism between their first and second birthdays - usually after vaccination with measles-containing or MMR vaccine, and sometimes in combination with other vaccines - were always autistic, from birth, but that this had not been noticed by the parents.

For example, this letter was received from Baroness Jay of Paddington, Government Health Spokesman in the UK House of Lords, addressed to Helen Southworth, Member of Parliament for Warrington, Cheshire, UK, 10<sup>th</sup> October 1997:

“Autism is a condition with signs that are typically first noticed between the first and second birthdays: this coincides with the recommended age for MMR immunisation. Over 90% of children in the UK are immunised with MMR vaccine before their second birthday. Symptoms of autism, therefore, will be recognised by chance around the time that a child receives their MMR vaccine, or shortly afterwards.” (my underlining).

The implication of this attitude is that parents fail to “notice” or to “recognise” their child’s autism prior to MMR vaccination.

The parents' view - and parents know their children - is very different. They saw a child developing, a child that was healthy, that passed all its developmental milestones. Then they see that child's development falter, then stall completely. Then they see the child regress backwards, losing most of the skills it already had achieved possession of.

In August 2005, at long last, came a study finding that backed the parents. The Archives of General Psychiatry reported a study of home videotapes of children's first and second birthday parties. The study found that research at the University of Washington's Autism Center provided the first objective evidence for autistic regression. The Archives report stated that regressive autism was estimated to account for 25% of all autism cases in the United States. The study did not address possible causes of autism.

The study looked at 56 children, comprising:

- 15 who were later diagnosed with autism, and whose parents reported that their children experienced regression in the first year of life
- 21 whose parents reported that their child had symptoms early in life and did not experience regression
- 20 typically developing young children

Children's behaviour was coded by trained observers who were not aware of which children had later been subsequently diagnosed with autism or regression.

The study's lead author, Geraldine Dawson, stated: "Once again, this study provides an important lesson - that parents are good reporters on what is happening with their children. It underscores the importance of professionals to listen to parents". The study was funded by the US National Institute of Child Health and Human Development.

#### 4. Presentation by Dr. Andrew Wakefield, Thoughtful House conference, US, 3<sup>rd</sup> April 2005

A relatively recent presentation by Dr. Andrew Wakefield, on behalf of Thoughtful House, a charity established to assist in treating affected children, gave a very useful summary of the autistic enterocolitis problem as far as it is understood to date, and is set out here. This contains technical language. If readers are looking for non-technical information, they should skip this and the next section (sections 4 and 5):

- the starting point is that you listen to the patient, or in these cases the patient's parents

- one must go through the clinical history, and focus upon the investigation that derive from the clues found in the clinical history
- a second set of clues is what you find from the examination of the actual child
- the clinical history that first became apparent in 1995 at the Royal Free Hospital, London, was that children had developed normally, acquired skills, demonstrated social interaction and developed language, and then degenerated into autism
- at the same time that the children degenerated, they experienced the onset of neurological and gastroenterological problems
- therefore it seemed probable that some form of neurological problem was occurring in association with developmental regression and gastrointestinal problems
- the parents described these gastrointestinal problems as diahorrea, abdominal bloating, pain, posturing
- the children generally had received multiple course of antibiotics, which may have been a proxy for an immune system that was not working properly, or antibiotics may in some way have been instrumental in the initiation of the disease process
- at the Royal Free, numerous cases of children who had had upper respiratory tract and ear infections were seen within the autistic cases total
- children presented at the Royal Free lacked muscle mass, were thin, and had distended abdomens. Symptoms reflected inflammatory intestinal disease
- the team at the Royal Free then performed ileocolonoscopies. The hyperplasia found (analogous to the swelling of the lymph glands in the neck in the case of a sore throat) would readily cause pain and changes in bowel habit
- ulcerations found were similar to those one might find in the mouth. What was happening was the breakdown of the lining of the intestine. At first this was interpreted as Crohn's disease, but was in fact a new disease, ileal-lymphoid nodular hyperplasia (ILNH)
- by the time that Dr. Wakefield had left the Royal Free, some 200 children had been investigated, and had demonstrated a remarkably consistent pattern of intestinal pathology

- studies (detailed later in this review) showed that inflammation could be extensive, throughout the intestine, the stomach, the small bowel, the duodenum, the terminal ileum and the colon and rectum - a pan-enteric disease
- Functional abnormalities accompany the inflammation of the intestine, including digestive enzyme deficiencies and dysmotility. Commonly, reflux esophagitis is seen. Food and acid come back up into the esophagus from the stomach, particularly at night, when children will then wake up fractious and upset
- Children may also suffer from fecal impaction
- Defective digestive enzyme is evidenced by the presence of undigested food in stools
- Dr. Tim Buie at Harvard, Dr. Krigsman at a New York Medical School, and Dr. Balzola and colleagues at the University of Turin (see later for references) have all subsequently and independently confirmed these findings. The detection of autistic enterocolitis has thus now been found in British, American and Italian children
- A study by Drs. Sabra, Bellanti et al has looked at children with autism, ADHD or anorexia nervosa. There appears to be a common denominator to these conditions, somewhere in the gastrointestinal tract
- In a paper by Dr. Furlano and colleagues (see later), it was demonstrated that there was activation of the innate immune system in the gut, with the infiltration of the epithelium by gamma delta T-cells. There was also activation of the adaptive immune system
- There was also specific mucosal inflammation associated with an excess of CD8+ lymphocytes in the intestines of the children, providing evidence of an adaptive immune response
- There is also the deposition of IgG antibodies from the blood of affected children, in the tissues of the base-lateral membrane of the epithelial lining cells. The IgG antibodies co-localize with a protein C1Q which is part of the inflammatory response repertoire of the body
- These two elements, deposited together as an immune complex, may be associated with cell and tissue injury, and are indicative of possible autoimmune disease in the gut

- Further studies have confirmed the presence of a similar disease process that may occur throughout the intestine in affected children. This response appears to be driven by something specific
- When investigators are looking for something specific, such as a virus, they now have a clue as to where to look - it is in the swollen lymph glands - the lymphoid nodular hyperplasia (LNH) in the intestine - that we now expect to find evidence of whatever is driving this immune response
- So, what are the immune cells actually doing? They appear to be activated and causing damage.
- Cytokines (communication systems between cells that influence inflammation and immunity, and which communicate signals that stimulate or inhibit the immune response) have been studied by Dr. Ashwood and colleagues (see later), and show that the immune cells in the bowels of these children are “switched on” and have a rather unique pattern of cytokine expression
- Among the children with autism, the immune cells of the bowel are producing high levels of tumor necrosis factor (TNF) alpha. This is a powerful pro-inflammatory mediator
- In contrast, the interleukin-10 (IL-10), which acts like the aspirin of the immune system, switches off pro-inflammatory immune activation
- In the children with autism, IL-10 appears to be switched off
- So in summary, there is a novel intestinal disease. The entire intestine may be involved, and there is a characteristic pattern, with swollen lymph glands and inflammation
- In addition, there is IgG antibody and complement (immune-complex) deposition, suggesting activation of both the innate and adaptive immune systems
- A recent study by Dr. Jyonouchi (see later) compared innate and adaptive immune responses of blood lymphocytes, rather than intestinal lymphocytes, in children with autism, and in developmentally normal controls. In autistic cases, there was an excess risk of immunisation reactions and atopic disease - there was something about their immune systems that made them overly responsive, and for example developing adverse reactions to vaccines (prolonged fever, febrile seizure, lethargy, extreme irritability, loss of speech within one week, or systemic urticaria/angiodema).

- This may be an important clue as to the population at risk. In addition, Dr. Jyonouchi's previous paper showed that onset of developmental regression is associated with adverse vaccine reaction in 80% of the children studied
- Jyonouchi also observed excessive innate immune responses in a high proportion of autistic-spectrum disorder children, particularly in TNF-alpha production. She demonstrated that in the blood of affected children, there is a disorder innate immunity with excessive pro-inflammatory response (TNF-alpha), and inadequate counter-regulatory response (IL-10) to dietary proteins and bacterial toxins
- The cytokine response was particularly evident in children with gastrointestinal symptoms, but it was also notable that with dietary intervention (a gluten-free and casein-free diet), there was not only resolution of the GI symptoms but also a dampening of the cytokine response
- Jyonouchi suggests that there is a fundamental defect in innate immune responses in this population
- Is there a link between the inflammation of the intestine and brain injury or encephalopathy? There is nothing new about gut-brain interactions, but the question is, what is there relevance to some children with autism, and what is the mechanism?
- Potential mechanisms include toxicity, immune consequences of intestine inflammation, or direct infection of the brain from a primary source in the intestine, or somewhere outside the brain
- In a paper, *Neurological Activation and Neuroinflammation in the Brain of Patients with Autism*, by Vargas et al (Johns Hopkins), published in *Annals of Neurology* in November 2004, the authors demonstrate evidence of activation of the innate immune system in the brain in patients with autism. They examined tissues from post mortem brains of people with autism, and controls, for evidence of immune activation, looking for the proteins that reflect immune activation and inflammation in different areas of the brain
- They also examined cerebrospinal fluid cytokine profiles, using protein assays. They identified activation of the resident innate immune system of the brain, but found no evidence at all for activation of the adaptive immune system - no evidence of B- or T-cell infiltration or immunoglobulin deposition. This innate immune system activation is accompanied by tissue injury, with loss of the Purkinje cells in the cerebellum. They suggest that their observations provide evidence of a mechanism - through activation of the resident immune system of the brain - for brain injury. Since there is no activation of the



immune system, it doesn't appear to be a primary response. Rather, it appears to be a secondary response in the brain to something happening somewhere else

- In support of this, when they examined the cerebrospinal fluid, they found inflammatory cytokines of lymphocyte origin. Lymphocytes were not present in the brain, and they were not present in the CSF. So where were these cytokines coming from? Are they coming from outside the brain, causing inflammation and tissue damage within the brain? Does this disease reflect, therefore, a primary intestinal disease in these children, that leads to a secondary injury in the brain?
- In summary, there is evidence of a primary immune system activation in the gut, and a secondary immune system activation, with no obvious source, in the blood and brain
- Is this biologically plausible? We have seen it in celiac disease, where a primary mucosal immunopathology is associated with a wide variety of secondary neurological complications. There are some 50 papers on the neurological complications of celiac disease, including ataxia, seizures, autism and dementia. We have also become aware that the majority of patients with celiac disease may not have overt gastrointestinal symptoms, but are identified through population screening
- So, while in prospective studies it is apparent that GI symptoms are common with children with autism, one should not be misled by the lack of overt GI symptoms in some children, particularly when the ability to articulate these symptoms may be impaired (by loss of speech)
- In the face of an epidemic disease, with unambiguous implications for a major environmental influence in causation, what is disrupting the innate immune system, in children, such that they cannot then respond appropriately to other perhaps ordinarily-benign environmental exposures? How do we define that risk at a biochemical level?
- There is no better starting point than (as discussed at the beginning) the clinical history and a knowledge of known causes of autistic spectrum disorders including viral exposures in-utero or in the Perinatal period, including rubella and measles
- My (i.e. Dr. Wakefield's) belief is that the answer will come from examining the determinants of the innate immune system function that operates early in life. How is an increased risk determined at the biochemical level?

- For oxidative stress, we all produce what are called reactive oxygen species (ROS) during the normal processes of oxidative metabolism. Normally we get rid of them, and they don't cause us harm. But if there is excessive ROS production in situations of inflammation or infection, and/or if our capacity to get rid of them decreases because it is impaired in some way, either for genetic or environmental reasons, then we go into a state of oxidative stress. This in turn impairs immune system function and detoxification capacity
- In summary, many children with developmental disorders have an underlying and potentially primary inflammatory bowel disease. This disease is novel, and similar in different behavioural subsets, including autism, attention deficit disorder (ADD) and attention-deficit hyperactivity disorder (ADHD)
- The disease has the characteristics of an infectious cause
- There may be a link between the primary gastrointestinal inflammation and the secondary central nervous system inflammation with tissue injury
- There is growing evidence in the literature that suggests that toxicity through by-products or intermediates of diet and gut bacteria also play a role in abnormal central nervous system function
- Much of the answer to the autism puzzle will come from understanding the influences on the education and functioning of the innate immune system

5. Presentation by Dr. Arthur Krigsman, formerly of New York University Medial School, now of Thoughtful House charity, Thoughtful House conference, US, 3<sup>rd</sup> April 2005

This presentation was made at a conference hosted by the US charity Thoughtful House, by Dr. Arthur Krigsman, fellow in pediatric gastroenterology at Mount Sinai Medical Center, New York's Beth Israel Medical Center. In summary, Dr. Krigsman stated:

- children with ASD frequently have gastrointestinal complaints such as diahorrea, constipation and bloating
- the majority of these children will be found to have lesions in either the small or large intestine, or both
- lesions take the form of ulcerations, erosions, pathologic lymphoid nodular hyperplasia (LNH) and enterocolitis

- the lesions seem to represent an autoimmune response inappropriately directed against the gastrointestinal mucosa
- a leading conceptual model linking the gastrointestinal pathology to the cognitive deficits involves a biochemical sequence of events in which luminal contents (consisting primarily of ingested foodstuffs) is pathologically absorbed through the highly permeable inflamed intestine mucosa before having a chance to be broken intraluminally into smaller micro-molecules
- the absorbed macromolecules then undergo metabolic degradation and processing by pathways not normally employed, resulting in the production of byproducts that may be toxic to the developing brain
- these byproducts can be identified and quantified in the urine
- though ultimately theoretical, this proposed mechanism is supported in its separate steps, both by published scientific data and the observations of clinicians caring for these children
- treatment must therefore be directed towards the goal of minimizing the degree of mucosal inflammation. Doing so clearly results in the reduced intensity of the symptoms
- the proposed mechanism could thus explain the observed benefits (both gastrointestinal and cognitive) of such treatments as restrictive diets, digestive enzymes, secretin, antibiotics, probiotics and possibly anti-fungals
- the majority of ASD children have gastrointestinal symptoms. They need to be treated for them. When their ulcerations go away, the gastrointestinal symptoms go away too.

Krigsman's observations were based upon the evaluation of over 350 patients.

## 6. Some Wider Points

Space precludes a wider debate here about the medical profession, conflicts of interest and the difficulty of drawing the attention of the authorities to examples of potential vaccine damage. However, it is worth making a few very brief points:

- Government and the vaccine manufacturers work very closely together to counteract communicable diseases. Their powerful alliance makes it difficult for parents, or "dissident" researchers, to raise legitimate concerns.

- **Funding for independently researching possible vaccine damage is extremely scarce. There is no enthusiasm in Government for such research, and most certainly none within the industry.**
- **More ominously, there is little or none in academic circles. Academic funding is now almost totally reliant upon Governments or upon industry. There is therefore little or no academic research that is not tied in some general or specific way to Government or industry. Academic researchers therefore do not research vaccine damage.**
- **There is intense commercial pressure on manufacturers to seek profits from approved vaccines. Going back to look for cases of damage would imperil a company's commercial strategy.**
- **There is a constant moral imperative upon the medical establishment, Government, political opposition parties and the media not to undermine public confidence in vaccines, for fear that immunisation rates would then fall and communicable diseases would return. An illustration was during the UK BSE ("mad cow disease") crisis. The then Medicines Division (which is now part of the UK Health Protection Agency) met to urgently discuss sourcing bovine serum albumin (which is used in some vaccines) from outside the UK - they chose New Zealand - because there was real concern that BSE could be transmissible to humans through vaccines, leading to variant-CJD brain disease. But, despite this urgent switch of source, they also chose not to destroy existing stocks of vaccines, but instead agreed to use them up on UK infants. They did this because they did not want to disrupt the vaccination programme (through shortages), nor to undermine public confidence in vaccine safety (source: Evidence to the Phillips Inquiry, Draft Factual Account 17, Medicines & Medicinal Products). An instructive and revealing episode, that is fully detailed in the accounts and words of the then Medicines Agency management to the Phillips Inquiry.**
- **The subject of vaccine damage is technically complex, and it is extremely challenging for the media to understand it, particularly where hard evidence of damage is scarce or controversial**
- **The nature of commercial manufacturing makes the process secretive, and accountability of the industry is thus almost completely impaired**
- **The bodies that approve vaccines are focussed upon fighting communicable diseases. They are highly secretive, and very few details of their deliberations are made public**
- **Very few health practitioners out in the field have time or motivation to research vaccine damage for themselves. The very strong tendency is thus to repeatedly offer official reassurance**

- Those who publicly question vaccine safety are often blackballed or excluded from the profession, either informally or sometimes formally

These features, in combination, make it extremely difficult for parents of damaged children - who themselves usually lack funding, technical knowledge, and time, to challenge official assurances that their children were not damaged by a vaccine, and that any adverse event following vaccination must have been coincidence.

## **PART B**

### **THE SCALE OF THE AUTISM PROBLEM**

#### **7: The Financial Costs - Autism Is Going To Cost The Taxpayer £\$Billions**

Quite apart from the immense social costs of autism for individual families, there are the huge financial costs. Autism effects every UK and US taxpayer, not just the families with the children. In the UK, the costs comprise:

- ÿ Health costs - specialist hospital visits, GP visits, prescriptions, exclusion diet costs - passed on to the taxpayer
- ÿ Major education costs - special schools, extra teachers, extra teaching assistants, extra training, management - passed on to the taxpayer
- ÿ Transport costs for schooling and respite - taxis plus drivers and escorts, plus local authority management costs, plus environmental/congestion costs of extra traffic - passed on to the taxpayer
- ÿ Significant childhood social services costs - respite care staff costs, management, inspection, reviews - passed on to the taxpayer
- ÿ Later special transport costs in adult life (during lifelong care) - funded by the taxpayer, as the person with autism will almost certainly have no earned income of their own
- ÿ The immense costs of sheltered accommodation during adult life (lifelong costs), again including social services, management, inspection, and also including furniture and other allowances, all passed on to the taxpayer
- ÿ The immense loss of earnings of the affected person (lifelong)
- ÿ The loss to the Government of their national tax revenues (lifelong)

- ÿ The loss to local government of their Council Tax revenues (lifelong)
- ÿ Loss of earnings of parents whilst acting as carers
- ÿ Loss of the parents' tax revenues whilst caring
- ÿ Carers allowances (paid to parents when they are acting as carers), the costs of which are passed on to the taxpayer
- ÿ Disability living allowances, often at the higher rate (lifelong), including care and mobility components, passed on to the taxpayer
- ÿ Incapacity benefit (lifelong beyond age 16), passed on to the taxpayer
- ÿ Wider economic costs - other losses of gross domestic product and other non-financial contributions to the national economy

It would be interesting to know if the UK (or US) 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 massive loss to the local and national taxpayer and the national economy, stretching over decades.

These costs will grow as more and more children become autistic and as more of the existing children reach adulthood and leave home. The affected people almost certainly won't be paying these costs as children, nor even as adults, as they almost certainly won't have any income. And once the children reach adulthood, the parents won't be paying them, either.

As these costs soar, the question becomes, "is autism too important to be left to the Department of Health, a Department that has done virtually nothing to investigate its causes"? - or to its counterparts in the US and elsewhere? Is this just a private matter for the medical community, or a matter for a wider audience?

And, for the medical safety regulators, "who guards the guards"? Does a Government Minister control his/her advisers, or do his/her advisers control the Minister? And is a Minister, in giving reassurance to the public, acting on the best technical advice, or hiding behind it?

## 8: Overall Cost Estimates

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

- ÿ the annual costs of autistic disorder in the UK were at least £1 billion

Y 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. My own estimate is that they could run to £5m-£8m (\$8m-\$13m) over a lifetime, for proper care for one single case of severe autism.

If one reduces the £2.94m per child by an arbitrary 33%, to allow for the fact that many children are less severely damaged than the maximum, and will thus cost less to care for, one is still facing a bill of £2m for lifelong care, not counting other wider costs such as loss of tax revenues from the autistic person and (when their parents care for them) their carers, plus other costs such as carers' allowances (a UK scheme). The degree of severity and precise costings could be debated at length, but are clearly extremely large for severe cases.

Another way of looking at it is to compare the UK with the US, which has hard State-collected data. According to the Individuals With Disabilities Education Act data, the US autism numbers (with four times the population) stood at 166,000 in 2004-05 (amongst 6-21 year olds in full time education).

If UK cases currently run to around a quarter of this figure, say 35,000 to 40,000, then total economic costs for the UK could be immense. A reasonable estimate would be that (say) 35,000 cases would cost the UK taxpayer somewhere between £35 billion and £100 billion spread over perhaps seven decades, or between £500m and £1.4 billion per annum. A mid-range answer probably lies in the £20 billion to £40 billion-plus range, spread over five to six decades, and even that latter figure works out at £700 million per year. And that is only for the UK.

Even if these costs are being seriously overestimated here, they are still immense. And they could represent an underestimate, especially if there is economic damage from the milder cases that are probably not included in the statistics. There is also the prospect of cases being added to the total, all the time, now. Any annual increase in cases of, say, ten per cent would lead to all these estimates having to be re-doubled a decade on.

And this is wholly irrespective of any MMR-autism or thimerosal-autism link being proved, because the children already exist, even if the cause of their illness remains disputed. The children are out there, now, and these bills are being passed to the taxpayer, now, today.

The costs meter is thus already running, but the immense scale of the bill is partly obscured by it being spread amongst many central and local government (or Federal and State) budget headings, and amongst numerous lesser authorities.

The reader is invited to choose their preferred source of funding for resourcing the long term care of affected persons:

(a) the pharmaceuticals industry (which made the products that may eventually be proven to have been unsafe)

(b) the parents of each person with autism, who originally took their child to be immunised with what may have been an unsafe product - but remember, in the UK and US, at least, these persons have no legal liability to fund the care of their offspring once the latter have reached adulthood, so can be discounted for the long term as a funding source - and rightly so.

(c) the person with autism - who will probably be completely unable to earn any income, and who (at least whilst their parents are still alive) will not have any financial resources of their own, and so can also be discounted

(d) the taxpayer

If it is the last-mentioned, as seems likely, then autism will directly or indirectly affect every single member of the community - not just affected families. Taxpayers will save the cost from taxation of funding litigation against vaccine manufacturers, but will incur other much greater costs from taxation to fund care.

## 9. Failure To Monitor Increases In UK Autism Numbers

Y 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 have risen in far too short a timescale, to be credibly ascribed to better recognition alone.

Y 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, UK, 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.

Y 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.

- ÿ The UK Department of Health 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 historically been so?
- ÿ 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.
- ÿ In fact, most UK data is actually non-existent. In the year 2000, only 1 in 6 UK Boards/Authorities had any credible figures at all. Most used estimates from outdated textbooks.
- ÿ The Scottish schools census now includes autism. The census commenced in 1998. The 1998 figure was around 750, but by year 2000 this had climbed steeply to about 1,250, and by 2004 it stood at approaching 3,100, and still rising.
- ÿ 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.
- ÿ 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 only from a relatively-recent study in 1983. If you take a rate of 1 in 1830 as being the mid-point of these historic rates, then a rate of 1 in 166 is eleven times higher.

The repeated official line that the apparent increase is down to better recognition is 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 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 have been 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, as exposing sharp rises would attract unwanted media attention.
- Centrally-collated figures showing steep increases would beg uncomfortable questions as to the medical causes. The UK Department of Health seems to regard autism as a local problem for local education authorities - not for Government Departments.

It is understood that from January 2004, a first survey in England was to be undertaken of disabilities amongst children receiving special needs education. This will be the UK (England-only) Pupil Level Annual Schools Census (PLASC). English local education authorities and the schools in their areas have to supply data about the numbers of pupils with different types of special educational need, including autistic-spectrum disorders.

However, it may be some time before data is available, and obviously it will be several years before any clear trend emerges. Any past steep rise during the 1988-2004 period will therefore of course have been missed, although some idea of increases may be available if data is stratified by age (this is not known at time of writing).

It was also reported in November 2005 that very young children in English and Welsh nurseries will be assessed for learning skills, including imaginative play. This is also likely to act as a de facto form of screening, with ASD children being identified at least as requiring attention, even if it does not amount to formal data-gathering on ASD.

On 31<sup>st</sup> January 2006, the UK Department of Education stated in a reply to a parent that:

“The Department does not keep a list of all the children with ASDs throughout England. However, in the ASD Good Practice Guidance which (the Department) published with the Department of Health in 2002, we highlight policy and planning as one of the key principles of good autism provision, and recommend that at a local authority, regional and strategic level there should be close liaison between education, health and social services in order to build up a clear picture of the size of the ASD cohort locally, so that adequate provision can be planned and put in place to meet (needs).”

In other words, Government Departments are doing little or nothing themselves, and simply expect “good practice” locally. There is no coherent

data on ASD in England (or for that matter, the remainder of the UK, apart from the Scottish Schools Census).

There has been a similar failure to fully monitor numbers closely in the US, although the data position is considerably better, as will be explained later. The data position elsewhere in the world is not known, but is almost certainly either very poor or non-existent, though there are increasingly-frequent media reports, based upon local professional assessments, of steep increases.

#### 10. “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 at once in the past by parents, and recognised medically, and also reflected in much higher historic rates of prevalence/incidence. Regressive autism used to be a minority variant: Now it is clearly the predominant form, by a very wide margin.

Dr. Bernard Rimland, President of the US Autism Research Institute, has concluded, after a thorough analysis of the ARI database: “*Late onset autism (starting in the second year) was almost unheard of in the 1950s, 1960s and 1970s. Today, such cases outnumber early onset cases by five to one, with the increase paralleling the increase in required vaccines*”.

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

- ÿ **Some UK examples - an East Surrey 1 in 69 rate amongst three year old boys, a 1 in 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."***
- ÿ **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, UK)**
- ÿ **A local survey carried out in the Inverness area in 2003 found that 1 in 49 children was on the autistic spectrum.**
- ÿ **Wakefield LEA autism pupils rose 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, UK, 1999)**
- ÿ **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, UK)**
- ÿ **As noted, Scottish schools census, repeatedly up year-on-year, and by a large margin each year; from around 750 in 1998 to over 3,000 in 2004 (source: Scottish Annual School Censuses, available from Scottish Education Office, tel 0131 556 8400)**

**The problem isn't confined to autism. On December 22nd 2002, the (UK) Observer newspaper carried a report on the apparent epidemic of behavioural problems amongst UK schoolchildren. Whilst not 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. More recent press reports have confirmed continuing huge rises in UK Ritalin prescriptions.

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

ÿ 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

ÿ 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.

### 11. Is Autism Increasing Due To Changes In Criteria?

This has become a hotly-contested topic, as it is central to the vaccine/autism controversy. But gradually, sheer numbers are silencing, or at least weakening, the position of those who doubt that autism has greatly increased in a very short space of time.

It has frequently been asserted by Governments, some researchers and elements of the medical establishment that the apparent increases in numbers of children with autism can be ascribed to "looser" criteria for inclusion. This latter point is demonstrably not the case. The criteria have in fact tightened-up.

Kanner's original concept of autism included five diagnostic features:

- A profound lack of affective contact.
- obsessive desire for the preservation of sameness
- Fascination for objects
- mutism or language that does not seem suited to interpersonal communication

- feats of memory, or skills in performance tests

**Kanner and Eisenberg, in 1956, emphasized two diagnostic criteria:**

- profound lack of affective contact.
- repetitive ritualistic elaborate behaviour

**They considered that if these two key features were present, the other typical features would also be found.**

**In 1980, the DSM-III (Diagnostic and Statistical Manual III) criteria were introduced. These included:**

- “pervasive developmental disorder” for the general category of autism.
- “infantile autism”

**The category of infantile autism was defined as:**

- lack of responsiveness to others.
- language absence or abnormalities.
- resistance to change and/or attachment to objects.
- the absence of schizophrenic features.
- onset before age 30 months

**In 1994, DSM-IV criteria were introduced. These criteria are more restrictive than DSM-III, and so an increase in numbers between the DSM-III era and the DSM-IV era cannot be explained by looser criteria, as the very opposite is the case. For example, in Washington State, autism numbers actually fell when DSM-IV was introduced.**

**It is worth setting out in detail the criteria for autism and relating autistic-spectrum disorder (ASD) conditions, and this is done in the next sections.**

## **12. DSM-IV Autistic Disorder**

**For DSM-IV, a total of six or more items from the following lists of (1), (2) and (3) is necessary, with at least two items having to come from (1), and one each from (2) and (3):**

**(at least two from)**

**(1) Qualitative impairment in social interaction as manifested by:**

- \* marked impairment in the use of multiple non-verbal behaviours, such as eye-to-eye gaze, facial expression, body postures and gestures to regulate social interaction.**
- \* failure to develop peer relationships appropriate to developmental level.**
- \* a lack of spontaneous seeking to share enjoyment, interests or achievements with others (eg by a lack of showing, bringing or pointing-out objects of interest.**
  - \* lack of social or emotional reciprocity**

**(at least one from)**

**(2) Qualitative impairments in communication, as manifested by at least one of the following:**

- \* delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)**
- \* in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others**
- \* stereotyped and repetitive use of language or idiosyncratic language**
- \* lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level**

**(at least one from)**

**(3) Restricted, repetitive and stereotyped patterns of behaviour, interests and activities as manifested by at least one of the following:**

- \* encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus**
- \* apparent inflexible adherence to specific non-functional routines or rituals**
- \* stereotyped and repetitive motor mannerisms (eg hand or finger-flapping or twisting or complex whole-body movements)**
- \* persistent preoccupation with parts of objects**

### 13. Pervasive Development Disorder - Not Otherwise Specified (PDD-NOS)

The DSM-IV criteria also included criteria for “pervasive development disorder-not otherwise specified”, or PDD-NOS. This category applies to cases where there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and non-verbal communications skills, or when stereotyped behaviour, interests and activities are present, but the criteria are not met for a specific pervasive developmental disorder, or schizophrenia, or schizotypal personality disorder, or avoidant personality disorder.

For example, PDD-NOS includes “atypical autism”, presentations that do not meet the criteria for autistic disorder because of late age of onset, atypical symptomatology, or sub-threshold symptomatology, or all of these.

### 14. Asperger’s

The DSM-IV criteria for Asperger’s Disorder (or syndrome) are as follows:

Qualitative impairment in social interaction as manifested by at least two of the following:

- \* marked impairment in the use of multiple non-verbal behaviours such as eye-to-eye gaze, facial expression, body postures and gestures to regulate social interaction.
- \* failure to develop peer relationships appropriate to developmental level
- \* lack of spontaneous seeking to share enjoyment, interests or achievements with other people
- \* lack of social or emotional reciprocity

Restricted, repetitive and stereotyped patterns of behaviour, interests and activities as manifested by at least one of the following:

- \* encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal in intensity or focus
- \* apparently inflexible adherence to specific nonfunctional routines or rituals
- \* stereotyped and repetitive motor mannerisms such as hand or finger-flapping or twisting, or complex whole-body movements
- \* persistent preoccupation with parts of objects



The disturbance causes clinically-significant impairment in social, occupational or other important areas of functioning. There is no clinically-significant general delay in language, eg single words are used by age two years, communicative phrases used by age three years). There is no clinically-significant delay in cognitive development or in the development of age-appropriate self-help skills, in adaptive behaviour (other than in social interaction) and in curiosity about the environment in childhood. Criteria are not met for another specific pervasive developmental disorder, or schizophrenia.

#### 15. Paper by Mark Blaxill, June 2001

The issue of diagnostic criteria was also considered in a long and detailed paper, "The Rising Incidence of Autism", by a parent, Mark Blaxill, in June 2001. This paper covered a number of aspects of the vaccine/autism controversy, and is reported in several sections of this document. Coverage of diagnostic criteria - and whether changes in criteria have produced a "false impression" of an epidemic, were summarised in the paper.

The five most influential criteria groups that have formed a backdrop to the work of epidemiologists have been:

- \* Kanner's original work. Kanner's criteria were abandoned in the 1970s.
- \* Rutter's attempt to modify and refine Kanner's work with the introduction of a categorical approach
- \* the codification of Rutter's approach within the Diagnostic Statistical Manual (DSM) series, termed DSM-III
- \* the modification of DSM-III into DSM-III-R ("r" for revised)
- \* attempts at producing an international standard, with the use of DSM-IV and ICD-10 (International Disease Classification-10)

From Rutter onwards, all the criteria have attempted a categorical approach. A child must exhibit specific significant impairments. Of the above four categorical methods, differences can be compared as follows:

(Social category)

- \* Rutter 1978, "impaired social development which has a number of special characteristics (that are) out of keeping with the child's (normal expected) intellectual level"
- \* DSM-III 1980, "lack of responsiveness to others"

\* DSM-III-R 1987, “qualitative impairment in reciprocal social interaction”, defined more specifically by the fulfillment of at least two out of five criteria from a checklist

\* DSM-IV 1994 “qualitative impairments in social interaction” which are now defined by meeting two out of four criteria from a checklist. These criteria include lack of eye contact, inability to form friendships, lack of awareness of the feelings of others, and lack of spontaneous play

(Language/communication category)

\* Rutter 1978, “delayed and deviant language development that also has certain defined features and is out of keeping with the child’s intellectual level”

\* DSM-III 1980, “language absence or abnormalities”

\* DSM-III-R 1987, “qualitative impairment in verbal and non-verbal communication, and in imaginative activity”, which was defined as including at least one item from a list of six abnormalities. This included lack of language, abnormal speech patterns, lack of eye contact, abnormal play skills, abnormal conversation patterns and echolalia

\* DSM-IV 1994, “qualitative impairments in communication” which are now defined as any of four areas, including language absence or delay, abnormal conversation skills, echolalia or abnormal pretend play

(Behaviour category)

\* Rutter 1978, “insistence on sameness as shown by stereotyped play patterns, abnormal preoccupation or resistance to change

\* DSM-III 1980, “resistance to change or attachment to objects”

\* DSM-III-R 1987, “markedly restrictive repertoire of activities and interests”, which require meeting one of five conditions, including self-stimulatory body movements, unreasonable insistence upon routines, distress over small changes in the environment, preoccupation with parts of objects and unusual preoccupation with narrow subject areas”

\* DSM-IV 1994, “restricted repetitive and stereotyped patterns of behaviour interests and activities” which requires meeting one of four criteria, including self-stimulatory body movements, unreasonable insistence on routines, preoccupations with parts of objects or unreasonable preoccupation with narrow patterns of interest

Blaxill notes that all four of these approaches share a great deal in common and reflect relatively few differences. He concludes that it is very difficult to

make the case that a discontinuity in diagnostic concepts between 1978 (when Rutter's criteria replaced Kanner's) and the present time (then 2001) could produce increases of the magnitude recently reported.

In other words, the major rises in autism numbers cannot be solely explained by changes in the diagnostic criteria, as is so often asserted by the medical establishment and by the US and UK Governments.

#### 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:

- ÿ One in 175 (58/10,000) children was autistic, whereas previous studies had pointed to a rate of 1 in 2000 (5/10,000)
- ÿ 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.
- ÿ In responding mainstream schools, the prevalence was 1 in 300. In the responding special schools, the prevalence was 1 in 8.
- ÿ Extrapolated across the UK, that would imply 30,000 primary school (age 5-11) children with autism
- ÿ The overall sex ratio of the children was 4 to 1 male to female, but in mainstream schools it as 8 to 1.
- ÿ Linking these rates to estimated costs of education and care for sufferers would give a figure of as high as £5 billion per year, (\$8m), 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

Y 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

Y 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. UK National Autistic Society Estimates

The National Autistic Society (UK) estimates for autism have been quoted (BBC, 7/7/04) as having historically been:

- 1 in 2,222 (year 1966)
- 1 in 492 (year 1979)
- 1 in 141 (year 1993)
- 1 in 110 (year 2004 - but see below)

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

Y People with Kanner syndrome (IQ less than 70)	5/10,000, or 1 in
2,000	
Y Other spectrum disorders (IQ less than 70)	15/10,000, or 1 in
666	
Y Asperger’s (IQ 70 or above)	36/10,000, or 1 in
278	
Y Other spectrum disorders (IQ 70 or above)	35/10,000, or 1 in
286	
<b>Combined total of above four groups</b>	<b>91/10,000, or <u>1 in</u></b>
<b><u>110</u></b>	

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 approaching three decades old and grossly out of date, and also pre-dates MMR introduction into the UK.

### 18 Review By Blaxill of Rates, 2004

The US parent Mark Blaxill has reviewed published rates of autism in his 2004 paper “What’s Going On? - The Question of Time Trends in Autism”, reviewed elsewhere in this document.

Blaxill looked at 54 published studies, and their reported rates per 10,000 children. A 25% selection of the pre1996 rates, and the full list of post-1996 rates, that he covered in his paper, is produced below (readers should obtain the full paper, published in Public Health Reports, Nov-Dec 2004, Vol 119, pp536-551, for further details):

<i>(author/s)</i>	<i>Studied location</i>	<i>Year of Publication</i>	<i>No. of autism cases per 10,000 children</i>
Lotter	England	1966	4.1
Treffert	US	1970	0.7
Haga & Miyamoto	Japan	1971	1.1
Wing & Gould	England	1979	4.9
Bohman et al	Sweden	1981	6.1
McCarthy et al	Ireland	1984	4.3
Gillberg	Sweden	1984	2.0
Burd et al	US	1987	1.2
Matsuishi et al	Japan	1987	15.5
Aussiloux et al	France	1989	4.7
Fombonne et al	France	1992	4.9
Deb & Prasad	UK	1994	9.0
Honda et al	Japan	1996	21.1
Fombonne et al	France	1997	5.4
Wignyosumarto et al	Indonesia	1997	11.7
Webb et al	UK	1997	7.2
Arvidsson et al	Sweden	1997	10.0
Sponheim & Skejldal	Norway	1998	3.8
California DDS	US	1999-2003	31.2 (peak)

Taylor et al	UK	1999	5.3
Kadesjo et al	Sweden 1999	1999	24.0
Irie	Japan	1999	10.4
Kielenen et al	Finland	2000	5.6
Baird et al	UK	2000	30.8
Chakrabarti et al	UK	2001	16.8
Fombonne et al	UK	2001	26.1 (ASD)
Kaye et al	UK	2001	16.3
Bertrand et al	US	2001	40.0
Sturme & James	US	2001	16.0
Davidovitch et al	Israel	2001	9.9
Magnusson et al	Iceland	2001	8.6
Croen et al	US	2002	11.0
Scott et al	UK	2002	57.0 (ASD)
Lingham et al	UK	2003	14.9
Gurney et al	US	2003	3.0 - 52.0 (ASD)
Yeargin-Allsopp et al	US	2003	34.0 (ASD)

Despite the variation between studies, and between countries, the apparent steep increase in rates since the mid-1980s is obvious, and is very difficult to explain away through improved ascertainment or diagnostic switching..

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

The purposes of this report included:

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

The findings included the following:

- ÿ 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%.
- ÿ 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.

ÿ 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:

- ÿ 1 in 86 children in mainstream schools had special educational needs that were related to ASD.
- ÿ 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.
- ÿ This is in addition to children with ASD in special schools. In special schools, 1 in 3 children has ASD-related needs.

21. Autism In Scottish Schools

Although there is no proper UK database on autism, comparable to the US’s Individuals With Disabilities Education Act (IDEA) database, and the Department for Education and Employment does not have any breakdown of its total numbers of children in England with special educational needs, the position is rather better in Scotland. There, a Scottish Schools Census was implemented by the Scottish Executive in 1998, and this annual survey now gives a picture of rising numbers within Scottish schools - the only systematic monitoring of numbers in the UK to date.

The census covers both junior and senior schools, and identifies (by sex) scholars with special educational needs, counting those with a primary diagnosis of autism as “autistic” (they may also have other disabilities).

The data available is (totals):

<i>year</i>	<i>Number of cases counted primarily as autism</i>	<i>% increase over previous year</i>	<i>% increase over 1998 base figure</i>
1998	820		
1999	959	17%	17%
2000	1,245	30%	52%
2001	1,515	22%	85%
2002	2,204	45%	169%
2003	2,663	21%	225%
2004	3,090	16%	277%

2005	3,484	13%	325%
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This gives a rise over seven successive years after 1998 of 325%. For every case there was in 1998, by 2005 there were over four cases. Despite this, according to a report in the Scottish Daily Mail of 1<sup>st</sup> March 2006, the Scottish Health Minister insisted that the higher numbers were down to greater awareness and more accurate diagnoses.

However, the criteria for inclusion have not been changed during that time, and although greater awareness and improved diagnosis may have made a minority contribution to the increase, it seems inconceivable that there is not an underlying real increase in these figures, matching the similar steep rises reported in the US by the IDEA database.

## 22. Is Autism Increasing? - Some Official UK Pronouncements

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

- ÿ *“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)
- ÿ *“The true incidence of autism is uncertain”* - Sir Kenneth Calman, then Chief Medical Officer, March 1998
- ÿ *The apparent rise in autism in the UK began more than ten years before the introduction of MMR”* - Tessa Jowell, in June 1998
- ÿ *“Rates of autism are rising, but not because of MMR”* (Committee on Safety of Medicines, June 1999)
- ÿ *“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
- ÿ *“Numbers of cases of autism are rising, but the reason for this is unclear”* - John Hutton, Minister for Public Health, December 2000
- ÿ *“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.
- ÿ *“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)*

Y *“The vast majority of the increase is due to the fact that we’re much better at detecting autism now (and) we include many more things in the spectrum for autistic spectrum disorders.....There’s a far wider spectrum, so that’s one of the factors.” - Dr. Stephen Ladyman, the then Health Minister for England, in Epolitix, 14th October 2003*

But then Dr. Ladyman hedged his bets a little.....

Y *“And underlying that, I think there may well be some sort of underlying increase in the number as well.....But what I am as certain of as I can be is that it has nothing to do with MMR and there is no reliable piece of science that links MMR and autism.”*

and

Y *“In my view, it is clear from the literature available that more people with autism have bowel disorders compared to the rest of the population” (extract from All Party Parliamentary Group On Autism minutes, address by the Minister).*

### 23. Autism In The USA

The UK Department of Health is fond of saying how MMR is safely used in 32 countries, including the USA, almost as though its daily use elsewhere is proof, in itself, that it is safe. Recent claims have even referred to 100 countries, although many of these are very small. A similar attitude prevails over thimerosal.

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). The Act was passed in 1975 to ensure equal educational opportunities for children with disabilities. State and local education districts are mandated to provide a “free appropriate public education”, based upon an “individualized education program”, geared to each student’s needs. The US Department of Education is in turn mandated to report annually to Congress.

- Initially, autism cases were few, but as cases grew, in 1991 it was decided to specifically list autism separately. Numbers were (US-wide) 5,415 in 1991-92, but this early figure must be regarded as unreliable, as some States were slow to enumerate cases and establish a firm baseline figure. The baseline from the year 1992-93 has therefore been used in this review document

- This system therefore picks up numbers of schoolchildren with developmental problems, and illustrates a huge increase in autism numbers in a very short space of time. Autistic pupils ages 6-21 have now increased from 5,415 in 1991-92, and 12,222 in 1992-93, to 140,920 in 2003 and 166,302 by December 2004. (Source: US IDEA State data). Thus for every aged 6-21 years case that there was in the IDEA system in 1993, there were 14 cases by the end of 2004.
- Since the introduction of the more restrictive DSM-IV autism criteria from 1994 onwards, the rise in US numbers has continued unabated
- To the ages 6-21 totals also has to be added the cases of autism amongst children aged 3-5 years. As at year 2005, this was 25,901 (this number will have since increased further).
- Many of the increases in individual States (see later tables) can only be described as alarming.
- 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 West Yorkshire UK (up from 5 to 111 in seven years, 1992-99). 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 ages 6-21 served by IDEA who have autism. These are the latest statistics at time of writing (February 2006). The table compares the increases since 1993, in what is a very short space of time, and also shows the most recent year-on-year rises:

<i>State</i>	<i>Year ending Dec 1993</i>	<i>Year ending Dec 2001</i>	<i>Year ending Dec 2002</i>	<i>Year ending Dec 2003</i>	<i>Year ending Dec 2004</i>
<b>Alabama</b>	68	904	1,096	1,319	1,582
<b>Alaska</b>	8	223	259	291	353
<b>Arizona</b>	199	1,348	1,689	2,131	2,643
<b>Arkansas</b>	30	774	912	1,040	1,192

<b>California</b>	1,605	13,257	16,093	19,034	22,691
<b>Colorado</b>	14	538	688	879	1,072
<b>Connecticut</b>	164	1,470	1,754	2,041	2,377
<b>Delaware</b>	15	294	345	387	439
<b>Distr of Columbia</b>	0	144	179	208	199
<b>Florida</b>	582	4,328	5,117	5,915	6,902
<b>Georgia</b>	262	2,462	3,057	3,956	4,667
<b>Hawaii</b>	52	380	528	618	711
<b>Idaho</b>	39	356	480	571	695
<b>Illinois</b>	5	3,802	5,080	6,005	6,955
<b>Indiana</b>	273	3,262	3,975	4,755	5,562
<b>Iowa</b>	67	554	1,148	1,224	1,233
<b>Kansas</b>	74	743	878	993	1,149
<b>Kentucky</b>	38	1,022	1,171	1,358	1,551
<b>Louisiana</b>	409	1,297	1,493	1,640	1,871
<b>Maine</b>	37	552	675	815	985
<b>Maryland</b>	28	2,396	2,692	3,536	4,077
<b>Massachusetts</b>	493	2,681	3,193	4,007	4,564
<b>Michigan</b>	288	4,719	5,463	6,341	7,319
<b>Minnesota</b>	296	3,270	4,116	5,076	6,263
<b>Mississippi</b>	0	461	537	622	739
<b>Missouri</b>	336	1,953	2,254	2,664	3,138
<b>Montana</b>	20	197	232	247	257
<b>Nebraska</b>	4	415	481	557	694
<b>Nevada</b>	5	518	684	891	1,118
<b>New Hampshire</b>	0	404	491	585	696
<b>New Jersey</b>	446	3,526	4,180	4,933	5,753
<b>New Mexico</b>	16	265	311	359	416
<b>New York</b>	1,648	7,023	8,274	9,486	10,891
<b>North Carolina</b>	786	3,095	3,518	4,074	4,762
<b>North Dakota</b>	9	144	178	220	246
<b>Ohio</b>	22	3,057	4,017	5,146	6,308
<b>Oklahoma</b>	31	785	829	959	1,148
<b>Oregon</b>	37	2,847	3,339	3,759	4,341
<b>Pennsylvania</b>	346	3,969	4,836	5,805	7,034
<b>Puerto Rico</b>	266	518	531	666	775
<b>Rhode Island</b>	19	384	471	568	686
<b>South Carolina</b>	141	1,012	1,168	1,303	1,500
<b>South Dakota</b>	36	250	285	328	379
<b>Tennessee</b>	304	1,103	1,359	1,659	2,034
<b>Texas</b>	1,444	7,099	8,576	10,354	12,412
<b>Utah</b>	105	723	843	1,030	1,279
<b>Vermont</b>	6	248	247	280	306
<b>Virginia</b>	539	2,365	2,966	3,533	4,266
<b>Washington</b>	476	1,972	2,344	2,824	3,413

<b>West Virginia</b>	101	374	429	507	591
<b>Wisconsin</b>	18	2,247	2,739	3,259	3,876
<b>Wyoming</b>	15	117	132	162	192
<i>Total, all States</i>	12,222	97,847	118,602	140,920	166,302

(Source: Individuals With Disabilities Education Act data, US Department of Education)

The all-US nationwide totals for each school year since 1993 for children and students ages 6-21 enrolled in full time education in the US as a whole are as follows:

<i>School year</i>	<i>Nos of children/students</i>	<i>% increase over previous year</i>	<i>% increase over 1994 base*</i>
<b>1993</b>	<b>12,222*</b>		
<b>1994</b>	<b>22,780</b>	<b>See footnote*</b>	<b>See footnote*</b>
<b>1995</b>	<b>28,813</b>	<b>26%</b>	<b>26%</b>
<b>1996</b>	<b>34,082</b>	<b>18%</b>	<b>50%</b>
<b>1997</b>	<b>42,487</b>	<b>25%</b>	<b>87%</b>
<b>1998</b>	<b>53,561</b>	<b>26%</b>	<b>135%</b>
<b>1999</b>	<b>65,391</b>	<b>22%</b>	<b>187%</b>
<b>2000</b>	<b>78,717</b>	<b>20%</b>	<b>246%</b>
<b>2001</b>	<b>97,847</b>	<b>24%</b>	<b>330%</b>
<b>2002</b>	<b>118,603</b>	<b>21%</b>	<b>421%</b>
<b>2003</b>	<b>140,920</b>	<b>19%</b>	<b>519%</b>
<b>2004</b>	<b>166,302</b>	<b>18%</b>	<b>630%</b>

(source: Individuals with Disabilities Education Act, US. \*The 1993 figure may be significantly too low, as not all States were up to speed in compiling IDEA autism figures at this time, and so the percentage increase over the period 1993-94 may have become greatly inflated in relation to the unrealistically low 1993 base figure. For the right hand column's percentages, 1994 rather than 1993 is therefore used here as a baseline figure for calculating the percentage figures)

The figures show that the scale of each year's increase is immense. In the mid-1990s, each year saw an increase of around 5,000 children. By year 2000, the increases over the previous year had hit 13,000. By the year 2004-05, the annual increases had reached 24,000.

For the youngest ages, 3-5 years, the following data, highlighting the most recent one-year percentage increases, covers children classified as having a primary diagnosis of autism and enumerated by the Individuals With Disabilities Education Act database (a few States had yet to report at time of writing, so have been marked "n/a"):

<i>State</i>	<i>As at Dec 2003</i>	<i>As at Dec 2004</i>	<i>One-year percentage increase</i>

			<i>(rounded)</i>
Alabama	160	174	9%
Alaska	n/a	n/a	n/a
Arizona	157	223	42%
Arkansas	74	102	38%
California	5,829	6,598	13%
Colorado	99	121	22%
Connecticut	316	368	16%
Delaware	88	92	5%
Distr of Columbia	n/a	n/a	n/a
Florida	1,236	1,415	15%
Georgia	427	504	18%
Hawaii	152	157	3%
Idaho	64	69	8%
Illinois	n/a	n/a	n/a
Indiana	679	699	3%
Iowa	n/a	n/a	n/a
Kansas	137	153	12%
Kentucky	228	232	2%
Louisiana	284	332	17%
Maine	203	270	33%
Maryland	548	583	6%
Massachusetts	1,080	1,100	2%
Michigan	918	1,031	12.3%
Minnesota	762	963	26%
Mississippi	n/a	n/a	n/a
Missouri	199	255	28%
Montana	23	31	35%
Nebraska	n/a	n/a	n/a
Nevada	273	337	23%
New Hampshire	82	120	46%
New Jersey	570	650	14%
New Mexico	54	73	35%
New York	n/a	n/a	n/a
North Carolina	613	644	5%
North Dakota	20	32	60%
Ohio	344	366	6%
Oklahoma	32	34	6%
Oregon	630	686	9%
Pennsylvania	1,373	1,582	15%
Puerto Rico	n/a	n/a	n/a
Rhode Island	n/a	n/a	n/a
South Carolina	n/a	n/a	n/a
South Dakota	n/a	n/a	n/a
Tennessee	299	356	19%
Texas	1,586	1,824	15%
Utah	149	205	38%

<b>Vermont</b>	<b>n/a</b>	<b>n/a</b>	<b>n/a</b>
<b>Virginia</b>	<b>418</b>	<b>470</b>	<b>12%</b>
<b>Washington</b>	<b>288</b>	<b>333</b>	<b>16%</b>
<b>West Virginia</b>	<b>27</b>	<b>33</b>	<b>22%</b>
<b>Wisconsin</b>	<b>410</b>	<b>485</b>	<b>18%</b>
<b>Wyoming</b>	<b>n/a</b>	<b>n/a</b>	<b>n/a</b>
<b>Total</b>	<b>n/a</b>	<b>n/a</b>	<b>n/a</b>

(source: Individuals with Disabilities Education Act, relevant US State departments)

Some of the above base numbers are small, and increases may be being calculated against past numbers that represented an under-recording, and so individual percentage increases for individual States need to be treated with great caution. However, there are many States showing 10%-20% increases in a single year, and the overall trend seems reasonably clear.

The picture for children ages 3-5 in the US as a whole shows similar steady rises:

<i>Year</i>	<i>Nos</i>	<i>% increase over previous year</i>	<i>% increase over 2000-01 base</i>
<b>2000-01</b>	15,581		
<b>2001-02</b>	17,032	9%	9.3%
<b>2002-03</b>	19,017	12%	22%
<b>2003-04</b>	22,724	20%	46%
<b>2004-05</b>	25,901	14%	66%

(source: Individuals with Disabilities Education Act, US)

Further confirmation of steep increases is provided by US Office of Special Education Programs (OSEP) data, for children ages 3 to 5 years:

<i>School year</i>	<i>Children ages 3-5 covered by OSEP</i>	<i>Percentage increase over previous year</i>
2000-01	15,581	-
2001-02	17,032	+9.3%
2002-03	19,017	+11.6%
2003-04	22,724	+19.5%

ÿ The 2002 MIND study by Byrd et al (see later) proved that these increases were not ascribable to either better recognition or greater awareness.

ÿ It seems obvious that the US has an autism epidemic.

ÿ The UK has a very similar health regime to the US, so it also seems reasonable to suppose that the UK probably has an autism epidemic, too,

but has failed to realise it. On a pro-rata basis, UK figures are probably between one-quarter and one-third of the US IDEA-based figures

- ÿ 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”.*

#### 24: Close-Up On 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 California Regional Center system is a system of centers that children showing developmental delay are referred to for assessment. The centers are under contract to the Department of Developmental Services. Their function is to provide services to persons with developmental disabilities. The CDDS system was initiated in 1969.

Originally, autism was not even included in the so-called Lanterman Developmental Disabilities Services Act, the act that established a State-wide system of services. Autism was only added in 1971, mainly because its effect on an individual child was serious and lifelong.

The CDDS system only recognises professionally diagnosed individuals with mental retardation, autism, epilepsy, cerebral palsy, and conditions similar to mental retardation, as being eligible for services.

It is noteworthy that persons diagnosed with other forms of pervasive developmental disorders, such as PDD-not otherwise specified (PDD-NOS), Asperger's, Rett's and Childhood Disintegrative Disorder, are not eligible for regional center services.

- ÿ The rise in autism in California 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.

- ÿ Department of Developmental Services data showed that a record number of professionally-diagnosed DSM-IV criteria autism cases are now entering the State system. The rate of increase actually appeared to be accelerating.

- ÿ Numbers had gone up 1994-2004 from 5,281 to 24,297.

- Y Between January 5th 2004 and April 2nd 2004, California added 795 new cases of professionally diagnosed DSM-IV full-syndrome autism to its recording system. Those 795 cases averages 11 new cases per day, seven days per week. The new cases do not include any children under three. They also do not include children with “autism spectrum disorder”, such as PDD, NOS, Aspergers etc.
- Y Historically, autism made up 3% of childhood disability in the State Developmental Services system. It now comprises 55% of new cases added to the system. Autism has been by far the fastest-growing disability, and is now the number one disability.
- Y Eight out of ten persons (of all ages, not just children) 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).

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 at each centre in the period 1998-2002:

<i>(regional centre)</i>	<i>At 7th Jan 1998</i>	<i>At 3rd Jan 2002</i>	<i>Increase %</i>
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%
Lanternman	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%



<b>S. Central LA</b>	<b>549</b>	<b>874</b>	<b>59%</b>
<b>Tri-Counties</b>	<b>352</b>	<b>725</b>	<b>106%</b>
<b>Valley Mountain</b>	<b>153</b>	<b>373</b>	<b>144%</b>
<b>Westside</b>	<b>613</b>	<b>986</b>	<b>61%</b>
<b>(Statewide Total)</b>	<b>8,781</b>	<b>16,802</b>	<b>91%</b>

**Comment: the above suggests a major rise in autism incidence in California, as elsewhere.**

**In April 2005, it was reported that California's autism epidemic now accounted for 57% of all new intake into the child developmental services system. In 1988, there had been 2,778 cases of autism in California. By April 2005, this had reached 27,312, a rise of 883% in seventeen years. For every case there was in 1988, there were nearly ten cases by 2005.**

**However, a notable development first reported in July 2004 was that new cases of autism had begun to reduce in California. On July 14<sup>th</sup>, the California Department of Developmental Services announced the first sustained nine-month reduction in numbers of professionally diagnosed new cases, for the three quarter-year periods October 2003 till June 2004. This was the first reduction in 35 years, with 197 fewer cases than the previous October-June period.**

**Furthermore, April 2004-June 2004 produced the all-time largest reduction (108 fewer cases) in the history of the California DDS system. There was speculation that this fall might be linked to California's ban of thimerosal in infant vaccines:**

**The turn-round was as follows:**

<b>Quarterly period</b>	<b>Number of new cases</b>	<b>Increase/decrease</b>
<b>Jan-Mar 2001</b>	<b>1930</b>	<b>+176</b>
<b>Jan-Mar 2002</b>	<b>2314</b>	<b>+182</b>
<b>Jan-Mar 2003</b>	<b>2391</b>	<b>- 15</b>
<b>Jan-Mar 2004</b>	<b>2194</b>	<b>- 108</b>

**In late 2005, the Californian State Department of Developmental Services released a fresh round of data. This showed that the number of new cases of professionally diagnosed full syndrome DSM-IV autism entering the State system declined from 734 new cases during the second quarter of 2005 (April-June) to 678 new cases during the third quarter (July-September). This represented a 7%-8% fall in the increases, in a single quarter.**

**The figures for the first three quarters (combined) of the previous/current three years were therefore:**

<b>Three quarters Jan-Mar, Apr-June and Jul-Sep, combined</b>	<b>Numbers of new cases</b>
---	-----------------------------

2003 (three quarters)	2,449
2004 (three quarters)	2,267
2005 (three quarters)	2,148

These reductions in the scale of the increase are set against two decades of record increases.

The numbers exclude children under age three years. They also comprise only those persons with professionally-diagnosed full syndrome autism, not including PDD, NOS, Asperger or other spectrum disorders. These cases are only full-blown DCM-IV autism cases.

Campaigner Rick Rollens of Sacramento commented that the new trend roughly corresponded to the removal of mercury preservatives from paediatric vaccines (source: Los Angeles Times, 13<sup>th</sup> July 2005).

At the start of 2006, the year-end figures for California for 2005 were announced. In 2001, the new admissions (DSM-IV cases only) stood at a record 2,725. In 2002, a new record of 3,132 was reached. But in 2005, the annual total of new admissions had fallen back again, to 2,848.

The cases are concentrated in the younger ages. Excluding cases under three years (which do not form part of the system), nearly two out of three cases are age 3-13 years.

Further details of the turnaround are included in the review by Geier and Geier, dated March 2006, detailed elsewhere.

## 25. Close-Up On 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 related to the position as at 1st January 2002:

<i>age</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>
<i>nos</i>	514	505	465	439	360	257	208	165

<i>age</i>	<i>14</i>	<i>15</i>	<i>16</i>	<i>17</i>	<i>18</i>	<i>19</i>	<i>20</i>	<i>21</i>
<i>nos</i>	145	124	81	73	58	63	30	14

The total number of cases was 3,501. This equated to an average of 219 for each age-year. One year later, the position had worsened noticeably:

<i>age</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>
<i>nos</i>	582	548	531	469	442	369	254	215

<i>age</i>	<i>14</i>	<i>15</i>	<i>16</i>	<i>17</i>	<i>18</i>	<i>19</i>	<i>20</i>	<i>21</i>
<b>nos</b>	<b>175</b>	<b>150</b>	<b>130</b>	<b>84</b>	<b>81</b>	<b>50</b>	<b>59</b>	<b>18</b>

- ÿ The total number of cases by this time was 4,157, an increase of 18% over the year before.
- ÿ The youngest three years average out at 554 cases.
- ÿ The oldest three years average out at 42 cases.
- ÿ The average numbers of autistic children diagnosed in the youngest three years is about 13 times that of the numbers in 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:

- ÿ 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.
- ÿ 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.
- ÿ 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.

## 26 “Explaining” The US Increases

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 some minority part, but the authorities seem to want to use these factors to explain-away all the increase, without having any hard evidence to support their stance.

The authorities are also quick to point to changes in the criteria for inclusion as being responsible. But, again, this does not stand up to

detailed scrutiny. In basic terms, the criteria changes since 1956 have been as follows:

• 1956, Kanner and Eisenberg propose that just two essential diagnostic features were required to make a diagnosis of autism. These were from areas covering profound lack of affective contact and repetitive ritualistic elaborate behaviour

• In 1978, Rutter proposed that a definition of autism in children required four criteria: (1) impaired social development out of keeping with the child's intellectual level; (2) impaired language development out of keeping with the child's intellectual level; (3) stereotyped play patters, abnormal preoccupations and resistance to change; and (4) onset before the age of 30 months.

• In 1980, DSM III (Diagnostic & Statistical Manual of Mental Disorders, third edition) criteria were introduced. Its classification for infantile autism required five criteria (1) lack of responsiveness to others, (2) language absence or abnormalities, (3) resistance to change or attachment to objects, (4) absence of schizophrenic features, and (5) onset before 30 months

• In 1980, the diagnostic criteria for autism were revised once again, to DSM III-R, and a definition of pervasive developmental disorder (PDD) was also introduced.

• Since 1994, the required criteria for autistic disorder has been set out in DSM IV, requiring the meeting of six criteria. Further detailed criteria were also set out for Asperger's Syndrome (AS) and PDD Not Otherwise Specified (PDD-NOS).

• DSM-IV criteria are more restrictive for autism than hitherto, and when they were introduced, figures for autism in some US States actually fell slightly.

The massive increases in US autism amongst young persons are in marked contrast to the moderate increase in other disabilities recorded by IDEA data:

	<i>1991-92</i>	<i>2001-02</i>	<i>% increase</i>
Autism	5,315	97,847	+1,700%
All disabilities (inc autism)	4,499,924	5,853,830	+30%

(Source for the above: *Autism In The United States: A Perspective*, by F. Edward Yazbak, MD, FAAP, *Journal of American Physicians and Surgeons*, vol 8 no 4 Winter 2003)

What this amounts to is that criteria for the mid-1990s onwards became more restrictive. The steep rise in autism witnessed in the US (on the IDEA

database) and elsewhere wherever DSM-IV criteria are used (which includes the UK) are thus in the face of this more restrictive eligibility. There is thus no possibility that increases can be fully explained away by suggesting that criteria have somehow widened. Although there may have been a small element of diagnostic switching, the vast bulk of the increases are real.

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 troubling) question, "What was causing the increase?".

By early 2003, other evidence that increases were real was also beginning to accumulate - see next main section. Readers should also see the later section on California.

In January 2004, after prolonged denial that autism was running at an unprecedentedly-high level, the US Department of Health and Human Services, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics conceded that 1 in 166 children in the US had been diagnosed with autism or ASD.

Data is also obtainable from the US Office of Special Education Programs (OSEP). This data was first used by Yazbak (see elsewhere), in his review "Autism 1999 - A National Emergency", to draw attention to the alarmingly-high autism rates that were manifesting themselves.

The scale of the apparent increases has forced some commentators to re-think their position. Autism specialist Dr. Eric Fombonne (a professional who is highly regarded within UK Government health circles on autism, and who agreed to act as a paid witness on behalf of the vaccine manufacturers

in the later-aborted UK MMR/autism legal action), originally stated that autism prevalence was between 1 in 5000 and 1 in 1000. However, Fombonne's subsequent work showed that autism had increased by between 600% and 3400% (the timeframe involved is 25 years), and could now be 68 per 10,000, or 1 in 147. This would represent a doubling every two years between 1976 and 2001.

## 27. The US Amish Community

As is well known, very few of the Amish community in the US - specifically, the community based in Lancaster County, Pennsylvania - vaccinate their children. This clearly offers the possibility of detailed study, to compare autism rates between the Amish and a comparable-sized US non-Amish community that does vaccinate its children to a high degree. The Amish have lived in Pennsylvania since fleeing Europe three centuries ago.

Such a study remains to be done. However, UPI columnist Dan Olmsted has reported on his search for autistic children amongst the Amish. His results suggest that autism is very rare indeed. In Lancaster County, he discovered just three children with autism, these being a girl aged 3 adopted from China, a girl aged 8 (described by her mother as resulting from a vaccine reaction at 15 months), and a boy of about 10. One further possible case was subsequently uncovered, and five others nationally, beyond Lancaster County.

The total population of the Lancaster County Amish community is put by Olmsted at 22,000. On that basis, Olmsted calculated that there should be at least several dozen autistic children. But he reported that there were only 3 or 4 at most.

Local commentators remarked on how one found autistic children in the non-Amish community, but had noted how they appeared virtually absent amongst the Amish. This clearly suggests that a properly-funded independent detailed study of autism amongst the Amish - or the apparent lack of it - should be undertaken.

Olmsted also reported in December 2005 that thousands of children cared for by Homefirst Health Services, a six-doctor healthcare practice in Rolling Meadows, north-west Chicago. Their medical director, Dr. Mayer Eisenstein, commented: "I don't think we have a single case of autism in children delivered by us who never received vaccines". Thousands of Homefirst's children have not received vaccines. "We do have enough of a sample. The numbers are too large to not see it. It's not something anyone would miss." Homefirst follows State immunization mandates, but Illinois allows religious objections, based either on the belief of the faith or on personal beliefs.

Again, it suggests that the cohort of unvaccinated children should be formally and rigorously studied.

## 28. Autism Elsewhere

(Canada)

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 steep 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.

In Canada's Province of Quebec, the number of children with pervasive developmental disorder (note, this is not full autism) in schools increased by 63% in two years, from 1,388 in September 2001 to 2,267 in September 2003, according to the Ministry of Education. (There is a paper on Quebec in the next section)

(New Zealand)

The issue is now being debated in 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."*

(Australia)

An early-2004 press report stated that there were 30,000 children in the country with autism, and that there had been a "dramatic increase of more than 200 per cent in diagnoses over the past ten years." Diagnoses of new cases were reported in 2004 to be running at 17 per week nationally.

In 2004, further information was received as follows: "Early in 1997, a TV information item stated a rate of 1 in 600 in Canberra. By mid-1997, diagnoses for the first six months of 1997 had exceeded the number for the whole of 1996, indicating a rate of 1 in 300. In January 2002 (press reports indicated) the rate to be 1 in 100.

In the most recent Canberra Autism Association newsletter, 60 diagnoses were reported to have been made in the previous nine months. With 4,617 births in Canberra for year 2002, that represents one diagnosis for every 58

births (Note: this would appear extremely high, but closely matches the Inverness, Scotland, rate of 1 in 49 being quoted in the Scottish press in early 2004).

A press report in April 2005 noted that the number of State school students with disabilities and language disorders in Victoria has (quote) “soared” by almost 10,000 in five years. State education data show that there were now 23,083 Victorian students in school-disability and language-disorder programmes, a rise of 74 per cent compared with 13,257 in year 2000. In Melbourne, the Catholic Education Office also confirmed that the number of disabled students at Catholic schools had risen by 58 per cent in five years.

(Denmark)

According to a 2004 paper by Dr. Fou Yazbak of the US, the prevalence of autism in children and teenagers under the age of 14 in Denmark, which was 13 per 10,000 in the seven years before MMR was introduced, increased by 542% to 84 per 10,000 in the years 1995-2002 (source: Danish Psychiatric Central Register). The Denmark situation is detailed elsewhere in this review.

(Finland)

There was a striking increase in the incidence of autism recorded in the Northern Provinces between 1991 and 1994, with a cumulative incidence in the 5-7 year age range of 20.7 per 10,000 (1 in 483).

(Saudi Arabia)

In Saudi Arabia, which has a population of just under 23 million, there were 42,500 confirmed cases of autism in 2002, and many more cases were believed to remain undiagnosed.

(Jersey, Channel Islands, UK)

Although part of the UK healthcare system, Jersey (a small island off the northern French coast) clearly offers a further insight. There were (as at October 2003) 64 children in Jersey with autism, of which 59 were 16 or under 16. It was reported that a decade earlier, there were only three cases. The under-16 population of the island is 15,664 (2001 census), giving a rate of incidence (discounting undiagnosed cases at the younger end of the age spectrum) of 1 in 265.

(China)

A 2004 press report from Xinhuanet stated that “Children suffering from autism.....have been rising rapidly in China, and now there are altogether 1.8m children with autism across the country.....Bai Xueguang, a professor



of neurology with the People's Hospital of Hubei Province (and based in Wuhan).....estimated the number of children with autism was growing at an annual rate of 20% in the country, even higher than the world average of 14%.”

## PART C:

### MMR

#### 29. The Introduction Of MMR

(some of this information relates to the UK only)

The recent focus of attention has been upon a subset of autism (particularly late onset autism) being linked causally to MMR vaccine and/or thimerosal in vaccines.

A combined measles mumps and rubella (MMR) vaccine, called MMR-I, was first licensed in the UK in 1972, but was not introduced. It was replaced by MMR-II. The difference between the two is reported to be in the rubella virus strain used.

MMR was introduced in the US in the 1970s, and later in other countries, such as Scandinavia in 1982. The widespread use of MMR began in the late 1970s. It is reported that by 1988, over 500m doses of MMR had been administered worldwide.

But, although that was taken at the time by the UK authorities as “evidence” of MMR’s safety, in fact virtually no-one had made any MMR/autism connection. Such a linkage had not been researched. Possible descent into autism was not officially recognised, anywhere in the world, as an adverse consequence of MMR, and so data on autism following MMR was not collected. Equally importantly, autism was not back-checked afterwards during follow-up monitoring, as a possible adverse outcome.

Initially in the UK, a single immunisation of MMR was given, but a two-dose schedule was introduced, with the first dose at age 12-15 months and the second dose at age 3-5 years.

Three brands of MMR were originally introduced into the UK childhood vaccination schedule in October 1988. The vaccines were claimed to be a one-off lifelong protection against the three serious diseases of measles, mumps and rubella. Although it was not made clear at the time, the vaccines’ advantages, according to previous published safety tests, were convenience and economy, rather than greater safety or effectiveness.

The vaccine manufacturers were SmithKline Beecham (brand name Pluserix), Merieux (brand name Immravax) and Merck Sharpe Dohme (brand name MMR-II).

SmithKline Beecham/Pluserix and Merieux/Immravax both used Schwartz strain measles virus, Urabe AM9 strain mumps virus and Wistar RA27/3 strain rubella virus. Merck Sharpe Dohme/MMR-II used Enders' Edmonston strain measles virus, Jeryl Lynn strain mumps virus and Wistar RA27/3 strain rubella virus.

In the US, monovalent measles vaccine was licensed from 1963, and was widely used from about 1965-66. In 1971-72, MMR was licensed, and from 1977-78, MMR was widely used. There was no interruption between the use of single measles vaccine and the use of MMR. Monovalent measles vaccine continued to be used in reduced amounts until the late 1970s.

The UK and US Governments, health authorities and medical establishments behave as though the very concept of vaccine damage does not exist. But it does, and there have been a number of very serious problems with a variety of vaccines, including in recent years, as was recently pointed out by the Congressional Committee on Government Reform in the US:

*“On three occasions in the last fifteen years, changes have been made to vaccine policies to reduce the risk of serious adverse effects. First, a transition from oral polio vaccine to injected polio was accomplished in the US to reduce the transmission of vaccine-induced polio. Second, an acellular pertussis vaccine was developed and a transition from DTP to DTaP was accomplished to reduce the risk of pertussis-induced seizures in children. And when the Rotashield vaccine for rotavirus was linked to a serious bowel condition (intersuception), it was removed from the US market” - quote from the report.*

MMR is now one (or three) of a lengthening list of vaccines that now make up the UK infant immunisation schedule. It is not the purpose of this review to criticize immunisation as a concept. However, it is useful to set MMR in the context of the overall UK programme.

In 2006, the UK infant schedule is now:

(at two months)

\* Five-in-one injection against diphtheria, tetanus, whooping cough, polio and Hib (an infection causing bacterial meningitis)

(at three months)

\* **Five-in-one injection against diphtheria, tetanus, whooping cough, polio and Hib**

\* **Meningitis C**

**(at four months)**

\* **Five-in-one injection against diphtheria, tetanus, whooping cough, polio and Hib**

\* **Meningitis C**

\* **Pneumococcal vaccine**

**(at one year)**

\* **Combined Hib/meningitis C vaccine**

**(at thirteen months)**

\* **measles, mumps, rubella (live vaccine)**

\* **pneumococcal vaccine**

Figures for the cost of a dose of MMR-II have not been obtained for the UK, but the US Centers for Disease Control are reported to pay manufacturers a discounted price of about \$17 per dose, whilst US private doctors pay a much higher amount, over \$40. The UK Department of Health therefore probably pays the equivalent of around \$20, say about £12, per dose.

### 30. Sudden UK Withdrawal of Pluserix and Immravax Vaccines

The debate about MMR's safety is sometimes held in an atmosphere of "Problems? There've never been any problems with MMR!" from the UK Department of Health.

But in the UK, there were to be serious problems with both the Pluserix and Immravax vaccines, two of the three versions of MMR introduced into the UK in 1988. It took the UK Department of Health a full four years to identify these and to withdraw the two brands, in September 1992, due to an emerging link between the Urabe strain mumps virus and aseptic meningitis. It is understood that withdrawal was carried out at just 48 hours' notice.

The vaccines use an attenuated (weakened) version of the virus to stimulate an immune-system response in the child. In a letter published on 9th February 2002 in The Times (UK), Dr. David Hall, President of the Royal College of Paediatrics and Child Health, stated: "Some children develop

encephalitis (brain swelling) when they catch measles, mumps or rubella virus, and may be left with a variety of handicaps, including physical and mental impairment, deafness, internal organ damage and autism.....”

So could an insufficiently-attenuated strain of these viruses, administered in the form of a vaccine, also cause autism?

The reason for the withdrawal of Pluserix and Immravax was that they contained the Urabe strain of mumps virus. These two Urabe-strain vaccines are suspected of comprising the majority of the total stock used of the three types, in those early years.

In 1992, the UK Chief Medical Officer suddenly announced “changes in the supply” of MMR, with Pluserix and Immravax being withdrawn, without explanation to the media or public. The withdrawal was because some children were experiencing febrile convulsions, which were a symptom of mumps meningitis.

In a UK Public Health Laboratory Service report published later in The Lancet, in 1995, the authors noted that the measles component of any MMR vaccine could also cause febrile convulsions, six to eleven days after administration of MMR, in 67% of a group of hospital admissions studied. The study did not look beyond eleven days after administration as that was the limit of the scope of the study. Questioned about these problems, by the JABS parents’ group, the then Chief Medical Officer, Sir Kenneth Calman, was unable to provide an answer.

However, according to a report in the British Medical Journal at the time, the problems with the Urabe strain MMR vaccines Pluserix and Immravax had been discovered purely by chance. A cluster of children had been found in the Nottingham area (East Midlands, UK), and had been traced back to MMR.

### 31. 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:

Y (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 subtle, insidious and unresearched - becomes much 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 (including

rare serious 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 reported adverse events are unconnected with prior vaccination.

The Department of Health’s line seems to be “only good can come from vaccination”. The manufacturers’ own warnings contradict this stance.

In the US, State health departments do acknowledge the basic concept of risk of adverse outcomes from receiving MMR. For example, the Texas Department of Health information sheet to parents of children about to receive MMR includes the following phrase in the agreement they have to sign: “I know the benefits and risks of the vaccine.”

### 32. US Vaccine Adverse Events Reporting System (VAERS)

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**
Diphther 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%

<b>Mumps</b>	<b>54</b>	<b>19</b>	<b>3</b>	<b>35%</b>	<b>6%</b>
<b>Polio live or</b>	<b>24,702</b>	<b>3,541</b>	<b>970</b>		
<b>Pneumococ</b>	<b>5,841</b>	<b>712</b>	<b>95</b>		
<b>Rubella</b>	<b>685</b>	<b>100</b>	<b>1</b>	<b>15%</b>	<b>0%</b>
<b>Tetanus Dip</b>	<b>9,566</b>	<b>520</b>	<b>12</b>		
<b>Varicella</b>	<b>12,635</b>	<b>590</b>	<b>31</b>		
<b>TOTALS*</b>	<b>201,815</b>	<b>27,768</b>	<b>4,965</b>	<b>14%</b>	<b>2%</b>

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) diphtheria tetanus, (2) diphtheria tetanus acellular pertussis, (3) diphtheria pertussis tetanus, (4) diphtheria 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.

More up-to-date information has been obtained in relation to years 1999-2002, covering adverse reactions, hospitalizations and deaths data on the US Vaccine Adverse Events Reporting System database:

(adverse reactions reported to VAERS 1999-2002 ages 0-6 years):

<i>(vaccine)</i>	<i>(number of adverse events reported)</i>
DTaP	16,544
Flu	419
HepB	13,363
Hib	22,463
MMR	18,680
OPV	22,915
Varc	11,246 (from 1995)

(hospitalizations reported to VAERS 1999-2002 ages 0-6 years)

<i>(vaccine)</i>	<i>(number of adverse events reported)</i>
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DTaP	1,631
Flu	41
HepB	1,840
Hib	3,224
MMR	1,736
OPV	2,868
Varc	576 (from 1995)

(deaths reported to VAERS 1999-2002 ages 0-6 years)

<i>(vaccine)</i>	<i>(number of adverse events reported)</i>
DTaP	394 deaths
Flu	11 deaths
HepB	642 deaths
Hib	843 deaths
MMR	110 deaths
OPV	866 deaths
Varc	34 deaths (from 1995)

It is interesting to note that 20,526 adverse events were reported 1999-2002 for MMR, including 110 deaths. The VAERS data is regarded as a gross underestimate of the true number of adverse events.

Adverse events from all causes (i.e. all types of vaccine) for the years 1990-2004 were:

<i>(year)</i>	<i>(number of adverse events reported)</i>
<b>1990</b>	<b>1,920</b>
<b>1991</b>	<b>9,873</b>
<b>1992</b>	<b>10,756</b>
<b>1993</b>	<b>9,637</b>
<b>1994</b>	<b>11,038</b>
<b>1995</b>	<b>9,478</b>
<b>1996</b>	<b>12,223</b>
<b>1997</b>	<b>11,686</b>
<b>1998</b>	<b>10,464</b>
<b>1999</b>	<b>12,287</b>
<b>2000</b>	<b>13,631</b>
<b>2001</b>	<b>14,694</b>
<b>2002</b>	<b>14,128</b>
<b>2003</b>	<b>16,868</b>
<b>2004</b>	<b>15,487</b>
<b>(total 1990-2004 inclusive)</b>	<b>174,170</b>

(source: Vaccine Adverse Events Reporting System, US)



### 33. Contra-indications to Receiving MMR

This list of potential contra-indications 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 by their healthcare professionals on these aspects before their child received MMR.

UK Department of Health leaflets are extremely uninformative about both adverse reactions and contra-indications, barely mentioning them. The moral pressure is always to press ahead with giving the child MMR, and indeed, doctors receive a significant financial bonus for achieving takeup targets. The bonus is not on a pro-rata sliding scale - if you are just short of the target, you receive a nil bonus. The pressure is therefore considerable, particularly where takeup rates hover just around the target threshold.

Contra-indications recognised by the manufacturers (but in almost all cases not passed on to the public by the UK Department of Health) include:

- ÿ Hypersensitivity to any component of MMR, including gelatine
- ÿ Anaphylactic or anaphylactoid reactions to neomycin
- ÿ Febrile respiratory illness or other active febrile infection
- ÿ Patients receiving immunosuppressive therapy
- ÿ Individuals with blood dyscrasias, leukemia, lymphomas of any type or other malignant neoplasms affecting the bone marrow or lymphatic system
- ÿ Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses
- ÿ 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"
- ÿ 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.

The US, too, warns of a long list of possible contraindications. The Centers for Disease Control, in 2005, included the following warnings in its checklist:

- \* antimicrobial therapy (current) - precaution for several vaccines
- \* illness, including moderate to severe acute illness, fever, otitis, diarrhea, vomiting - deferral of vaccination until recovery may be prudent
- \* immunodeficiency in recipient - contraindication of precaution for several vaccines
- \* thrombocytopenic purpura (history of) - precaution for MMR
- \* allergic reaction to any vaccine component - do not vaccinate

The full list is much more complex than this, and is on the CDC website.

#### 34. The UK Department of Health's Position On MMR And Autism

The UK Department of Health has energetically denied any link between vaccination and autism, a paradox when one considers that the causes(s) of autism are unknown.

- ÿ 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.
- ÿ 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.
- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ The DoH-sponsored impression of “a growing body of evidence” that there is no MMR/autism link is therefore illusory - the “house of cards”.
- ÿ The situation mirrors that in the US, where there is official Congressional recognition of it:

*“To date, studies conducted or funded by the CDC (US Centers for Disease Control) that purportedly dispute any correlation between autism and vaccine injury have been of poor design, under-powered and fatally flawed. The CDC’s rush to support and promote such research is reflective of a philosophical conflict in looking fairly at emerging theories and clinical data related to adverse reactions from vaccinations” - quote from the conclusions of a report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, US House of Representatives, May 2003*

- ÿ The UK 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.
- ÿ It is also unlikely that any of these bodies has met with parents or listened sufficiently attentively (or even at all) 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.
- ÿ 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.

### 35. Single Vaccines In The UK

- ÿ 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.
- ÿ 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. In the 1996 edition it states, page 135, 22.2.3, "single antigen measles mumps and rubella vaccines are available", so perhaps it was dropped some time after this date as stocks of single vaccines were reduced.

### 36. Measles Deaths In The UK and US

- ÿ There have also been numerous spurious claims about measles deaths, aimed at frightening parents into having MMR. For example, the Chief Medical Officer for England, Professor Sir Liam Donaldson, told the BBC Today programme that Dr. Andrew Wakefield's research had led to a loss of confidence in MMR, a vaccine "that had saved millions of children's lives". The implication was that a significant proportion of these "saved" lives was in the UK.
- ÿ The truth was very different. Dr. F. Edward Yazbak, in a letter to the *British Medical Journal* in March 2004, pointed out that UK measles deaths had decreased precipitously before the introduction of measles vaccines, because of better nutrition and hygiene. "The following can be checked with the (UK) Department of Health. In 1901 there were 9,019 deaths (see table below) attributed to measles, in a population of 32,612,000 in England and Wales, giving a mortality of 276.5 per million. In 1960 (before measles vaccination was introduced, using the single vaccine), there were just 80 deaths (see table below) and the total population was 45,775,000.
- ÿ The measles mortality rate in England and Wales was therefore 1.75 per million in 1960. In other words, the mortality rate from measles had decreased by 99.12% before the introduction of the (single) measles vaccine."
- ÿ It is also interesting to note that, bearing in mind that health officials routinely wave-away claims of potential damage from vaccines as being a "one in a million" chance, but that even as long ago as 1960, the actual

recorded death rate from measles was barely much more than the proverbial “one in a million”.

The actual figures for measles deaths in the UK (this is for England and Wales only, excluding Scotland and Northern Ireland) for 1901-1979 are set out below. Since 1970, the numbers (although each undoubtedly representing personal and individual tragedies) have been extremely small. Bear in mind that MMR was only introduced in the UK well after these figures, in October 1988:

<i>(year)</i>	<i>(no. of recorded deaths from measles)</i>
<b>1901</b>	<b>9,019</b>
<b>1902</b>	<b>12,930</b>
<b>1903</b>	<b>9,150</b>
<b>1904</b>	<b>12,306</b>
<b>1905</b>	<b>11,076</b>
<b>1906</b>	<b>9,444</b>
<b>1907</b>	<b>12,625</b>
<b>1908</b>	<b>8,011</b>
<b>1909</b>	<b>12,618</b>
<b>1910</b>	<b>8,302</b>
<b>Ten-year total for 1901-1910</b>	<b>105,481</b>
<b>Annual average for 1901-1910</b>	<b>10,548</b>
<b>1911</b>	<b>13,128</b>
<b>1912</b>	<b>12,856</b>
<b>1913</b>	<b>10,644</b>
<b>1914</b>	<b>9,133</b>
<b>1915</b>	<b>16,445</b>
<b>1916</b>	<b>5,411</b>
<b>1917</b>	<b>10,814</b>
<b>1918</b>	<b>9,787</b>
<b>1919</b>	<b>3,532</b>
<b>1920</b>	<b>7,190</b>
<b>Ten-year total for 1911-1920</b>	<b>98,940</b>
<b>Annual average for 1911-1920</b>	<b>9,894</b>
<b>1921</b>	<b>2,241</b>
<b>1922</b>	<b>5,694</b>
<b>1923</b>	<b>5,316</b>
<b>1924</b>	<b>4,834</b>
<b>1925</b>	<b>5,337</b>
<b>1926</b>	<b>3,483</b>
<b>1927</b>	<b>3,622</b>

<b>1928</b>	<b>4,302</b>
<b>1929</b>	<b>3,388</b>
<b>1930</b>	<b>4,188</b>
<b>Ten-year total for 1921-1930</b>	<b>42,405</b>
<b>Annual average for 1921-1930</b>	<b>4,205</b>
<b>1931</b>	<b>3,288</b>
<b>1932</b>	<b>3,411</b>
<b>1933</b>	<b>1,937</b>
<b>1934</b>	<b>3,769</b>
<b>1935</b>	<b>1,349</b>
<b>1936</b>	<b>2,751</b>
<b>1937</b>	<b>1,052</b>
<b>1938</b>	<b>1,633</b>
<b>1939</b>	<b>310</b>
<b>1940</b>	<b>855</b>
<b>Ten-year total for 1931-1940</b>	<b>20,355</b>
<b>Annual average for 1931-1940</b>	<b>2,036</b>
<b>1941</b>	<b>1,144</b>
<b>1942</b>	<b>458</b>
<b>1943</b>	<b>769</b>
<b>1944</b>	<b>243</b>
<b>1945</b>	<b>728</b>
<b>1946</b>	<b>203</b>
<b>1947</b>	<b>644</b>
<b>1948</b>	<b>326</b>
<b>1949</b>	<b>307</b>
<b>1950</b>	<b>221</b>
<b>Ten-year total for 1941-1950</b>	<b>5,043</b>
<b>Annual average for 1941-1950</b>	<b>504</b>
<b>1951</b>	<b>317</b>
<b>1952</b>	<b>141</b>
<b>1953</b>	<b>245</b>
<b>1954</b>	<b>50</b>
<b>1955</b>	<b>176</b>
<b>1956</b>	<b>30</b>
<b>1957</b>	<b>95</b>
<b>1958</b>	<b>49</b>
<b>1959</b>	<b>98</b>
<b>1960</b>	<b>80</b>
<b>Ten-year total for 1951-1960</b>	<b>1,281</b>

<b>Annual average for 1951-1960</b>	<b>128</b>
<b>1961</b>	<b>152</b>
<b>1962</b>	<b>39</b>
<b>1963</b>	<b>166</b>
<b>1964</b>	<b>73</b>
<b>1965</b>	<b>115</b>
<b>1966</b>	<b>80</b>
<b>1967</b>	<b>99</b>
<b>1968 (single measles vaccine intro)</b>	<b>51</b>
<b>1969</b>	<b>36</b>
<b>1970</b>	<b>42</b>
<b>Ten-year total for 1961-1970</b>	<b>853</b>
<b>Annual average for 1961-1970</b>	<b>85</b>
<b>1971</b>	<b>28</b>
<b>1972</b>	<b>29</b>
<b>1973</b>	<b>33</b>
<b>1974</b>	<b>20</b>
<b>1975</b>	<b>16</b>
<b>1976</b>	<b>14</b>
<b>1977</b>	<b>23</b>
<b>1978</b>	<b>20</b>
<b>1979</b>	<b>6</b>
<b>Nine-year total for 1971-1979</b>	<b>189</b>
<b>Annual average for 1971-1979</b>	<b>19</b>

To summarize the above, average UK deaths from measles in each year across each of the ten-year bands (or nine-year band in the case of 1971-79) were as follows:

<i>(decade)</i>	<i>Average number of deaths per annum</i>
<b>In each year 1901-1910</b>	<b>10,548</b>
<b>In each year 1911-1920 (including war)</b>	<b>9,894</b>
<b>In each year 1921-1930</b>	<b>4,205</b>
<b>In each year 1931-1940 (including war)</b>	<b>2,036</b>
<b>In each year 1941-1950 (including war)</b>	<b>504</b>
<b>In each year 1951-1960</b>	<b>128</b>
<b>(single measles vaccine intro 1968)</b>	
<b>In each year 1961-1970</b>	<b>85</b>

<b>In each year 1971-1980</b>	<b>19</b>
<b>(MMR vaccine introduced 1988)</b>	

It is believed that monovalent measles vaccine was introduced in the UK in 1968. MMR was introduced in the UK in 1988.

There is therefore:

- no evidence that deaths from measles were a major problem in the years immediately before MMR was introduced. Justifying MMR on the basis of deaths from measles is clearly therefore a spurious argument. There is obvious evidence that deaths from measles were brought down, from a seriously-high level, before single measles vaccine was introduced, and long before MMR was introduced.
- This suggests that the key contributory factors that influence the number of recorded deaths from measles has very little to do with MMR immunization, and is much more closely linked to income, hygiene, nutrition, water supply, housing quality and general healthcare.

In November 2005, the UK lawyer Clifford G. Miller made the following statement, in BMJcom:

“In 1987, the year prior to the introduction of MMR, and when monovalent measles vaccine was in use (with its incomplete and lower coverage, according to the UK Office of National Statistics:

- out of 8,535 UK deaths from all causes in the age range of children up to 14 years, just one child died of measles, plus one from encephalitis and two from pneumonia post measles
- in 1989, the year following MMR’s introduction, out of a corresponding 8,061 UK deaths in this age range (0-14 years), there was one death from encephalitis and one from otitis post measles”

We now turn to the US. The situation in the US has followed a similar pattern:

(Deaths from measles, US, 1912-1983)

<i>(year)</i>	<i>(deaths from measles)</i>
<b>1912</b>	<b>3,974</b>
<b>1913</b>	<b>7,446</b>
<b>1914</b>	<b>4,149</b>
<b>1915</b>	<b>3,246</b>
<b>1916</b>	<b>7,663</b>



1917	9,906
1918	8,546
1919	3,251
1920	7,600
1921	3,694
1922	4,026
1923	10,314
1924	8,180
1925	2,357
1926	8,579
1927	4,345
1928	5,888
1929	2,907
1930	3,783
1931	3,523
1932	1,926
1933	2,813
1934	6,986
1935	3,907
1936	1,267
1937	1,501
1938	3,296
1939	1,174
1940	706
1941	2,279
1942	1,302
1943	1,301
1944	1,923
1945	307
1946	1,310
1947	472
1948	888
1949	949
1950	468
1951	683
1952	618
1953	462
1954	518
1955	345
1956	530
1957	389
1958	552
1959	385
1960	380
1961	434
1962	408
1963	364

1964 (single measles vacc introduced)	421
1965	296
1966	261
1967	81
1968	24
1969	41
1970	89
1971	90
1972	24
1973	23
1974	20
1975	20
1976	12
1977	15
1978	11
1979	6
1980	11
1981	2
1982	2
1983	4

Single measles vaccination was introduced in the US in 1963, when deaths were in the low hundreds. MMR was introduced in 1971. In the year before MMR, the deaths figure was 89. In the five years 1967-71, in the run up to MMR, it averaged just 65 per year, in a population of two hundred million.

These were tragic cases, but the risk of death from measles, at a time when only the single vaccine was being administered, was clearly extremely small.

Once again, the message is obvious - deaths in the US from measles sank to a very low level long before MMR was introduced. Deaths fell from several thousand per year to less than one hundred per year, before MMR.

Any claim that MMR is primarily responsible for tackling a formerly high level of measles deaths in the US is thus again demonstrably false.

### 37. Promotion Of MMR In The UK After The Wakefield “Early Report”

- ÿ During the years 1998-2004, 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.
- ÿ 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.

- Y 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. More recently, these have been supported by research from Denmark, but again emanating from one small group of researchers.
- Y 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 safely 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 eventually win in the High Court (as has occurred in Japan). It would therefore be prudent to think of this possibility, and permit choice now.
The evidence is that MMR does not cause autism or IBD (a number of studies are quoted, but only those which suit the Department's stance)	There is evidence that suggests that it may do. Every 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, far greater. And already, significant numbers of 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 most certainly 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 extremely 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

	<b>position.</b>
<b>Measles, mumps and rubella are rare in the UK so there is no need to immunise.</b>	<b>This is not the issue in dispute.</b>
<b>MMR causes autism and bowel disease.</b>	<b>There is now ample evidence pointing towards an MMR/autism/IBD connection. Until this area is thoroughly researched, it is scientifically untenable to rule it out.</b>
<b>There was a scientific paper that linked MMR and autism/IBD</b>	<b>There have now been a number of such papers. They form part of an unfolding story. Research in the US and Italy has endorsed the Wakefield findings.</b>
<b>Giving MMR as separate vaccines reduces the risk of side effects.</b>	<b>It is not possible to prove/disprove this until proper clinical research has been funded and conducted.</b>
<b>The vaccine was not properly tested.</b>	<b>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. The tests were recently described by the former senior medical adviser to the Department as “hopeless - a mess”.</b>
<b>My child has already received one dose, so does not need a second dose.</b>	<b>This is not the issue in dispute.</b>
<b>My son does not need protection against rubella, my daughter does not need protection against mumps.</b>	<b>This is not the issue in dispute.</b>

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 by far the greatest weight being attached to clinical findings. Its answer completely, and quite deliberately, ducked the issue of clinical studies, focussing solely on epidemiological studies (see later for a critical review of these).
- The Department’s position on measles as a disease is also open to question. The Chief Medical Officer for England, Professor Sir Liam Donaldson, claimed during a BBC Radio 4 Today Programme interview that Dr. Wakefield’s research had led to a loss of confidence in a vaccine that had claimed “millions” of children’s lives. But in a written response, Dr. F. Edward Yazbak has pointed out that measles deaths in the UK had declined precipitously before the introduction of the measles vaccine, because of better nutrition and improvements in hygiene (see previous relevant section).

### 38. Ten Thousand Vaccines?

Meanwhile, the UK Government’s Health Department’s Dr. David Salisbury maintains that children can deal with any number of vaccines - even a thousand at once!

- On BBC-2’s Newsnight programme, on 9<sup>th</sup> August 2004, Dr. Salisbury, head of the UK Department of Health’s Immunisation and Communicable Diseases department, asserted: “The immune system of a baby has got huge spare capacity to deal with challenge.....If we didn’t, the human race would not survive, but let’s look specifically at vaccines. This has been studied carefully. A baby’s immune system can actually tolerate perfectly well a thousand vaccines.”
- Dr. Salisbury was quoting - or rather, mis-quoting - Dr. Paul Offit in the US. Dr. Offit had stated that (in his view) a young infant was fully capable of generating protective humoral and cellular immune responses to multiple vaccines simultaneously. He then had concluded that an infant “would have the theoretical capacity to respond to about 10,000 vaccines at any one time” (source: Pediatrics, Vol 109, No. 1, Jan 2002 pp 124-129).
- It is not clear as to whether Offit was referring to live viruses or killed or attenuated viruses, but it seems inconceivable that he meant live viruses.
- The Pediatrics paper mentioned that “the only live vaccine that was routinely given in the US in the first year of life, the oral polio vaccine, has now been replaced with inactivated polio vaccine.

Therefore, children do not receive their first live viral vaccines until about 12-15 months of age.” Hence his reference to “10,000” vaccines clearly is not suggesting that children under 12 months could or should receive 10,000 live vaccines at once.

- It therefore seems highly likely that he was not suggesting that children over 12 months should, either. The actual text is imprecise in several areas, also loosely referring to “infants” and “children” at various points.
- The press also picked the Offit quote up, but again seemed to become confused by it. Mark Henderson of the (UK) Times, who has taken an consistent position in favour of MMR and against Dr. Wakefield and the parents’ viewpoint, stated on August 14<sup>th</sup> 2004: “Vaccines add a trivial load. It is estimated that babies’ (my emphasis) immune systems are robust enough to deal with 10,000 vaccines at once. Even if eleven were to be combined, they would engage just a thousandth of that capacity.”
- But Henderson did not qualify whether he meant 10,000 live vaccines, or 10,000 attenuated/killed vaccines. As the debate was about MMR, which contains live viruses, it was a crucial failure on his part.
- On 9<sup>th</sup> February 2006, the UK Daily Mail reported comments made by the Chief Medical Officer for England, Professor Sir Liam Donaldson, that “science shows that a baby’s immune system can cope with thousands of vaccines”.

The above demonstrates typical sloppy reporting (by The Times) and sloppy reading. Salisbury misquoted 10,000 as 1,000, and didn’t distinguish between live and attenuated/killed vaccines, and neither Donaldson nor Henderson did, either. None seemed to be sure whether they were referring to infants aged under 12 months, aged 12-15 months, children over 15 months, or all three. And Donaldson did not make it clear that Offit had only claimed the “theoretical” capacity - there had (of course) been no experiments to test the claim.

Such imprecision has characterized Government and other official or media “assurances” about MMR.

### 39. Position of US Centers 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 2006):

- Y 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.

ÿ 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.

ÿ 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

ÿ 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.

The position of the US health authorities on thimerosal is equally evasive. There is no admission of potential harm. The thimerosal issue is covered elsewhere in this review.

#### 40: 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, by definition, 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

ÿ (a) repeatedly overstating the dangers of diseases, vaguely citing experience of diseases without making it clear that they are referring to the disease amongst children from poor and underdeveloped countries, or are referring back to UK experiences from well over half a century ago,



or are pointing to recent deaths (e.g. Ireland) where other factors played a major part, or

- ÿ (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 almost any adverse outcome was the result of a vaccine. This is despite the indisputable existence of the UK Vaccine Damage Payment Scheme, and the US Vaccine Injury Compensation Program, both of which make payments for vaccine damage.

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.

- ÿ 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.
- ÿ But all the attention of the past upon possible adverse reactions to vaccines has focussed upon acute near-immediate events.
- ÿ 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.
- ÿ 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 scientific and investigative importance of this pattern has been ignored by the Department of Health, by the US Centers for Disease Control, and other health professionals..

This document attempts to focus upon hard fact, and so there are few anecdotes. However, a couple of parents' stories should be quoted, as they reflect the majority experience of affected families:

*“Russell began his life as a normal healthy and robust child, meeting his age-appropriate milestones. At seven months, after receiving his third DPT and first Hib vaccines, Russell began the slow and insidious process of slipping into the world of autism.....Within days after his first MMR vaccination, Russell began his final journey into the abyss of autism, losing most of his remaining skills, developing severe sleep disruption, chronic gastrointestinal problems, worsening of his already-disturbed behaviours and suffering pain exhibited by days of endless crying. Russell was officially diagnosed with*

*autism six months later.*” (testimony of Rick Rollens to the House Committee on Government Reform, US Congress, August 3<sup>rd</sup>, 1999)

*“June Cox-Smith says her son Edwards came home a different child after he had the MMR vaccination. He was vaccinated at the age of 13 months, and she says that he has never been the same since. He is six and a half now, and is severely autistic. He cannot communicate with other people in a normal way. His speech is very limited, he cannot talk to people and his handwriting is limited too, although his intelligence is high. He has problems with all kinds of communication. He has no social skills.....We have no doubt that the MMR is to blame. He was very sick (when he had it) and had a temperature straight away. He was ill for several days, almost two weeks, and he never recovered his old self. He was never the same boy again.”* (The Independent (UK), 2<sup>nd</sup> November 2003)

The subsequent view of affected parents can be summed up by two quotes from Canada:

*“Basically, I haven’t met a single person with autism who can’t trace it to the shots. Our stories are all the same. My kid had the DPT and he started getting sick. He had the MMR and we thought he went deaf. We gave him antibiotics for an ear infection.....and suddenly he’s going spinning and twirling and laughing for no reason. You’d have to be an idiot not to see the connection.”* (Cynthia Stark, Canadian parent)

*“How is it possible that (the medical establishment) can ignore it? They keep talking about environmental factors. What is this mysterious environmental factor? I hear the same stories over and over again. A few months after an MMR shot, a child begins to regress and to lose milestones. That’s the repeated “broken record” that keeps being told over and over. I see the MMR as the straw that breaks the child’s health.”* (Edda West, of the Vaccine Risk Awareness Network, Canada)

#### 41. Some Examples Of Suspected-Damaged Children

One also has to be very wary of tabulating a selection of examples of children believed to have become autistic after vaccination, as their listing does not in itself offer direct proof of a causal link between the two, particularly as the examples are selected from a list that included other forms of damage, and deaths.

However, the accounts of parents offer perhaps the first line of evidence that something may be amiss, and so - even if selected - this is an abbreviated summary of a small number of cases that have been reported to the UK parents’ group JABS, for interest. Only the autism-related cases are listed below (i.e. other cases, with non-autism forms of damage, have been omitted):

<i>(vaccine suspected)</i>	<i>(date of vaccination)</i>	<i>(main symptoms)</i>	<i>(elapse of time before onset)</i>
DPT + polio	1963 (3 dates)	Continual screaming, red hot, sweating, then autism , epilepsy, mute	immediate
Smallpox + P + DPT	1967	High fevers after all vaccinations, autism within one month of smallpox vaccination	immediate
DPT + polio + Hib	1994	Pallor, fever, difficulty rousing, high pitched cry, swollen injection sites, speech and language delay, hyperactive	immediate
M + MMR	1988 + 1991	High pitched crying, descent into autism, poor sleep, then subsequent worsening of autism, food allergies, aggression	days
M	1987	Slept 19 hours, screamed 5 hours, measles encephalopathy, learning and behavioural difficulties	One hour
DPT + MMR	1990-91	Encephalitis, temporal lobe epilepsy, learning difficulties	Slow onset
MMR	1994	Measles rash, high fever, lost speech and comprehension	Days
MMR	1996	Self-injuring, clumsiness, rage, aggression, extreme behavioural regression	Days
DPT + polio	1978	Screaming, autism, motor development delay	Days
DPT + polio + measles	1974	Behavioural changes, aggression, learning difficulties, ADD	Immediate
MMR	1996	Inconsolable screaming, rage, developmental regression, autism	One day
MMR	1992	Developmental regression, autism, hyperactivity, loss of all speech, tantrums, bizarre behaviour, irritable bowel syndrome	Two weeks
DPT	1992	Screaming for hours, ear infections, sickness,	Immediate

		concentration difficulties, head-banging (pain displacement), sensitive to noise	
Men C	2000	Hyperactive, tired, irritable, weepy, violent	Immediate
MMR + DPT + P + Hib, DPT + P + Hib	1998, 1999 (two dates)	Speech delay, withdrawn, clumsy, autistic spectrum	Gradual
MMR, DPT + P, DPT + P, DPT + P, DT + P, Hib	1990 to 1994 (six dates)	Fever and sickness, decline, withdrawn, tantrums, sleeping and eating problems, autism, bowel disorder	Immediate
Men C	2000	Obsessive-compulsive disorder, behavioural problems	Weeks
Measles, DPT	1984, 1982	Autism, bowel problems, measles virus in bowel	Gradual decline
MMR, DPT, DPT, DPT	1992, 1991 (three dates)	Loss of language and all communication, wild bizarre behaviour, destructive tantrums, no sense of pain, increased thirst, autism, irritable bowel syndrome	immediate
MMR + Hib	1992	Fever, convulsions, autistic spectrum, Aspergers	Ten days
MMR, DPT + P + Hib, DPT + P + Hib, DPT + P + Hib, Men C	1998-2000 (five dates)	Atypical autism, no speech, biting, sound-sensitive	Gradual
MMR, DPT + Polio + Hib + Men C, DPT + polio + Hib + Men C, DPT + polio + Hib + Men C	1997-98 (four dates)	Loss of speech, loss of eye contact, stopped playing with toys, loose stools, autism	gradual
MMR, MMR	1992, 1993	Screamed all night, withdrew, lost speech, diahorrea, lost sense of	Few days

		<b>pain, atypical autism</b>	
<b>MMR</b>	<b>1988</b>	<b>Fever, loss of eye and social contact, autism</b>	<b>Immediate</b>
<b>MMR, DPT + Hib + Polio, DPT + Hib + Polio, DPT + Hib + Polio</b>	<b>1999, 2001 (three dates)</b>	<b>Stopped forming words, social skills and speech delays, assessed for autism</b>	<b>Days</b>
<b>M, MMR</b>	<b>1984</b>	<b>High fever, slept a lot, gradual decline into autism</b>	<b>One day</b>
<b>MMR, DPT + polio, DPT + polio, DPT + Polio, DPT + polio</b>	<b>1988-92 (five dates)</b>	<b>Autism, severe learning difficulties</b>	<b>Gradual</b>
<b>MMR</b>	<b>1997</b>	<b>Autistic spectrum disorder, speech vanished, tantrums, loss of eye contact</b>	<b>Six weeks</b>
<b>MMR, DPT + Hib + Polio, DPT + Hib + Polio, DPT + Hib + Polio, Men C</b>	<b>2000-01 (five dates)</b>	<b>Measles, vomiting, diarrhoea, distress for two weeks, later diagnosed as autism (twin 1)</b>	<b>Ten days</b>
<b>MMR</b>	<b>1989</b>	<b>Behavioural changes, mood swings, became “monster”, personality change, violent, learning difficulties, diarrhoea, ADHD</b>	<b>gradual</b>
<b>MR</b>	<b>1996</b>	<b>Collapse, unconsciousness, personality change, obsessiveness, joints swollen, deteriorated over 2 years</b>	<b>Immediate</b>
<b>M</b>	<b>1969</b>	<b>High fever, breathing difficulties, speech stopped, smiling stopped, autism</b>	<b>Immediate</b>
<b>DPT?</b>	<b>1979</b>	<b>Chest infection, seizures,</b>	<b>Within one month</b>

		grand mal, epilepsy, severe brain damage	
MMR	1997	Prolonged screaming, inconsolable, lost eye contact, autism	Immediate
DPT + polio + Hib	2002	Screamed. Started screaming, fits every alternate day. After next vaccination, screaming every day. Slowed development	Immediate

## PART D

### THE THIMEROSAL/THIOMERSAL ISSUE

#### 42. Thiomersal's Possible Role

In addition to MMR, recent attention has focussed upon autism's possible links with thimerosal, either in combination with MMR-related damage or as a freestanding causal pathway.

This section commences with some more quotes:

*"My grandson received vaccines for nine different diseases in one day. He might have been exposed to 62.5 micrograms of mercury in one day through his (US Food and Drug Administration-approved) vaccines. According to his weight, the maximum safe level that he should be exposed to in one day (according to the US Environmental Protection Agency) is 1.51 micrograms. This is (therefore) 41 times the amount at which harm can be caused"* - letter from Rep. Dan Burton, then Chairman of the House of Representatives' Committee on Government Reform, to the then US Department of Health and Human Services Secretary Donna Shalala, October 2000

and.....

*"In 2001, the Institute of Medicine stated that it is "unclear whether ethylmercury (from vaccines) passes readily through the blood-brain barrier. The IoM recommended several biological and clinical studies to answer this question.....These studies were in a large part never done.....Even today, the IoM cannot tell you with any degree of certainty what happens to ethylmercury once injected into an infant. Does it go to the brain? Does it cause developmental problems?"* - Press Release by Representative David Weldon, US House of Representatives, May 2004

and.....

In 2003, the staff of Rep. Dan Burton, member of the US House of Representatives for Indiana, obtained a confidential internal US Government email written in June 1999 by former Food and Drug Administration scientist Peter Patriarca, offering an assessment of the impending statement in July 1999 by the US Public Health Service urging manufacturers of vaccines to reduce or eliminate thimerosal: *“(This) will raise questions about the FDA being asleep at the switch for decades, by allowing a potentially hazardous compound to remain in many childhood vaccines, and not forcing manufacturers to exclude it from new products. It will also raise questions about various advisory bodies about aggressive recommendations for use. We must keep in mind that the dose of ethylmercury was not generated by rocket science - conversion of the percentage of thimerosal to actual (micrograms) of mercury involves 9th grade algebra. What took the FDA so long to do the calculations? Why didn’t the Centers for Disease Control and the advisory bodies do these calculations while rapidly expanding the childhood immunisation schedule?”*

The currently-stalled UK litigation regarding autism and vaccination was proceeding on the basis of autism following MMR (or MR) vaccination. In contrast, in the US, cases are taking legal action over the link between autism and thimerosal, the mercury-based preservative used in many vaccines for several decades, both in the UK and US.

It is understood that thimerosal, 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.

In the US, in the 70 years since thimerosal/thiomersal/merthiolate preservative was developed, the Food and Drug Administration never required manufacturers Eli Lilly to conduct clinical studies of its safety. Even in 2004, the FDA still referred to the original 1931 Powell and Jamieson study (which offered no proof of thimerosal’s safety) as an indication of its “safety and effectiveness as a preservative.

Eli Lilly ceased manufacture of thimerosal-containing products in the mid-1980s, but thimerosal remained in widespread common use, including in vaccines, into the 21st century. Eli Lilly still has revenue from licensing agreements with other pharmaceuticals companies using thimerosal all around the world.

The key point about thimerosal is that no-one thought to check that, as more and more vaccines were recommended for infants, whether this produced a cumulative total that was in excess of safety guidelines.

The two suspected causes, MMR and thimerosal, 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.

- Y The thimerosal 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 thimerosal-containing vaccines at several visits may be exposed to more mercury than recommended by Federal guidelines for total mercury exposure”.
- Y 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.
- Y Worldwide, thimerosal has been used for about the past 60 years. Ethyl mercury constitutes about 49.6% of its weight, and mediates the antimicrobial effects. Thimerosal 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.
- Y It is believed that levels of thimerosal 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 thimerosal. In the US, in 2001, a free exchange system was instigated by the manufacturers, to remove stocks.
- Y In the UK, the Department of Health has refused to acknowledge that there might be a problem with thimerosal, and no free exchange system has been offered, or sought. Thimerosal 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 thimerosal, and this was not refuted by the Department of Health.
- Y In the US, a September 2001 survey of 65,909 vaccines at provider centres found that 5.5% still contained thimerosal. Some 36% of these were DtaP-Hib for the fourth dose. A depot survey of 837,174 vaccine doses found that 1% still contained thimerosal. Of these, 80% were for DtaP.



Y In early 2003, calls for all thimerosal to be removed from vaccine use were renewed. Michael Bender, Director of the Mercury Policy Project, stated that continued use was irresponsible and not worth the risk. Sallie Bernard, Director of the Safe Minds charity, said that there was no “safe” level for mercury in vaccines, and that use should cease unequivocally and without delay. Barbara Loe Fisher, President of the National Vaccine Information Center, said that all vaccines should be mercury-free.

It is also instructive that - as detailed later - the neurotoxic effects of some forms of mercury have been observed to be greater in male mice than female mice - which suggests that the similar imbalance of the sexes in autism may have this as a scientific basis. Observers have long noted that there are four or five times more autistic boys than girls, and we may now be beginning to understand why.

It is worth pointing out that thimerosal’s use is about cheapness. It is a cheap preservative, and its use enables multi-dose vials to be used - again, for cheapness.

#### 43. Thimerosal Safety Data Sheets

The thimerosal Safety Data Sheets issued by Eli Lilly, and dated 13<sup>th</sup> June 1991, state that it has the following occupational effects for humans:

“Effects, including signs and symptoms of exposure:

- \* topical allergic dermatitis has been reported
- \* Thimerosal contains mercury. Mercury poisoning can occur, and topical hypersensitivity reactions may be seen
- \* early signs of mercury poisoning in adults are nervous system effects, including narrowing of the visual field and numbness in the extremities
- \* exposure to mercury in utero and in children can cause mild to severe mental retardation and mild to severe motor co-ordination impairment
- \* based on animal data, may be irritating to the eyes
- \* the mercury component has caused nervous system effects in experimental animals, including mild to severe mental retardation and motor co-ordination impairment
- \* handling precautions - goggles or appropriate respirator with eye protection. (Use) laboratory fume hood or local exhaust ventilation.

Advice further stated:

\* “Poison.....harmful by inhalation and ingestion. May cause reproductive damage. May be harmful through skin contact.

\* Chemical hazard T+. = very toxic. Inhalation, swallowing or absorption through the skin in very small amounts can cause considerable damage to health, and may sometimes be lethal. In the event of exposure, serious evidence of severe, possibly irreversible damage to health by single, repeated or prolonged absorption

#### 44. 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 thimerosal 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:

ÿ “*Thiomersal has been used as an additive.....since the 1930s.....*”  
(Comment: so what?)

ÿ “*There is a significant safety margin incorporated into all the acceptable mercury exposure limits*” (Comment: but the toxicity of ethylmercury has not yet been accurately assessed, so the adequacy of any “safety” margin is not known)

ÿ “*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)

ÿ “*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).

ÿ “*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 a tautological statement, and is revealing. What the AAP/PHS are saying is, the risks from thimerosal 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 thimerosal 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).

ÿ “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”. (Comment: but they used up existing stocks on the kids, they denied there was any problem, and they still left thimerosal in certain vaccines)

Key action agreed was:

- ÿ A formal request to manufacturers for a clear commitment and a plan to eliminate or reduce mercury content of vaccines
- ÿ A review of data
- ÿ Expedited FDA review of manufacturers’ supplements to their product license applications, to eliminate or reduce mercury content
- ÿ Studies to better-understand the risks and benefits of this safety assessment

#### 45. Removal of Thimerosal

On July 31<sup>st</sup> 1999, John Jabara, the Vice-President of SmithKline Beecham (now GlaxoSmithKline) wrote to the US Centers for Disease Control stating that: “.....we agree that, despite the absence of any scientific data that thimerosal causes adverse effects, whenever possible thimerosal-containing vaccines should be removed as soon as possible” (my underlining).

If there wasn’t a problem, why the note of urgency?

The following is quoted from a paper, *Vaccination - An Analysis of the Health Risks*, Part 1, by Gary Null PhD and Martin Feldman MD: published in Townsend Letter for Doctors & Patients, October 2003

“Use of thimerosal - In July 1999, the American Academy of Pediatrics issued a statement urging the removal of the mercury-containing preservative thimerosal from vaccines. The Centers for Disease Control and Prevention (reported) that as of April 2001, all seven of the vaccines recommended for use in all children contain either no thimerosal or trace elements only. These vaccines include Hepatitis B, Haemophilus influenza B, and DTaP (Diphtheria tetanus acellular Pertussis) which formerly contained thimerosal as a preservative, and MMR, polio, varicella and pneumococcal (which have never contained thimerosal).

The FDA explained that the vaccines were now being produced as either thimerosal-free or thimerosal-reduced products. The term “thimerosal-reduced” indicated that trace amounts of mercury - less than 0.5mcg per 0.5ml vaccine dose - may remain from the use of thimerosal in the manufacturing process, but that thimerosal was no longer added as a preservative. The term “thimerosal-free” means that a vaccine does not have a preservative but, again, that trace amounts may remain from the manufacturing process”.

What this report did not make clear, as is explained later in the papers by Geier and Geier, was that large stocks of thimerosal-containing vaccines, some with expiry dates of 2005, remained in use, and were not recalled, but were being used up in children.

The key dates for thimerosal’s run-down, as set out by Geier & Geier in their March 2006 paper in the Journal of American Physicians and Surgeons, is as follows (this uses the US vaccination schedule):

- \* (mid-1980s) thimerosal present in virtually all whole-cell diphtheria tetanus whole-cell pertussis (DTP) vaccines administered to children four times, starting at age two months, during the first eighteen months of life (maximum 25 micrograms of mercury per dose)
- \* (late 1980s) thimerosal-containing haemophilus influenza type B (Hib) vaccine is administered to children at age 18 months (max of 25 micrograms of mercury per dose), bringing total exposure to 125 micrograms
- \* (early 1990s) four doses of Hib are recommended within first eighteen months of life, starting at age two months (max of 25 micrograms per dose), bringing total exposure to 200 micrograms
- \* (early 1990s) three doses of thimerosal-containing hepatitis B vaccine are recommended within the first six months of life, starting on the day of birth (max of 12.5 micrograms of mercury per dose), bringing maximum exposure by eighteen months to 237.5 micrograms
- \* (middle 1990s) some DTP and Hib vaccines are combined to produce DPTH vaccine, with only 25 micrograms of mercury per immunisation, thus reducing mercury levels of exposure for some children, but is rapidly replaced by diphtheria tetanus acellular pertussis vaccine (DtaP), beginning in the US in 1996
- \* (1996-97) GlaxoSmithKline introduces a new thimerosal-free DtaP vaccine (“Infarix”) that contains 2-phenoxyethanol as a preservative. Aventis Pasteur introduces a new Hib vaccine (ActHIB) that contains no preservative
- \* (late 1990s) three doses of thimerosal-containing influenza vaccine are increasingly recommended for administration during the first eighteen

months of life, starting at age 6 months (12.5 micrograms per dose), bringing maximum mercury exposure to 200 micrograms in the first six months and to 275 micrograms in the first eighteen months

\* (July 7<sup>th</sup> 1999) the AAP and PHS request removal of thimerosal from all pediatric vaccines as rapidly as possible, and the AAP suggests delaying Hep B vaccine until after age 6 months for children born to hepatitis B negative mothers

\* (August 27<sup>th</sup> 1999) thimerosal-containing formulations continue to be distributed, even following the licensing (on this date) of thimerosal-free alternatives such as thimerosal-free Recombivax HB (made by Merck)

\* (March 28<sup>th</sup> 2000) thimerosal-free Engerix-B by GSK is licensed by the FDA

\* (March 7<sup>th</sup> 2001) thimerosal-free Tripedia by Aventis Pasteur is licensed by the FDA

\* (late 2002/early 2003) the CDC and FDA claim that the last remaining doses of thimerosal-containing DtaP, Hep B or Hib vaccines are administered to US children

#### 46. Interview With Neal Halsey, Johns Hopkins University

In November 2002, the New York Times carried an interview with Dr. Neal Halsey, a Johns Hopkins University researcher. Halsey is a highly influential figure in the US vaccination industry, and chaired the American Academy of Pediatrics committee on infectious diseases from 1995 until 1999. These are some extracts from the NYT article:

“In June 1999.....Halsey attended a meeting (at the FDA) to discuss thimerosal.....Halsey would be forced to reckon with the hypothesis that thimerosal had damaged the brains of immunised infants.”

“The numbers deeply troubled him. *‘From the beginning, I saw thimerosal as something different (to most vaccine scares). It was the first strong evidence of a causal association with neurological impairment. I was very concerned’.*

“The investigation into mercury vaccines was instigated in 1997 by Rep. Frank Pallone Jr., a New Jersey Democrat whose (constituency) includes a string of shore towns where mercury in fish is one of many environmental concerns Pallone.....attached an amendment to an FDA Bill requiring the Agency to inventory all mercury contained in licensed drugs and vaccines.”

“The job of adding up the amount of mercury in vaccines and assessing its risks fell to Robert Ball, an FDA scientist, and two FDA pediatricians, Leslie Ball and R. Douglass Pratt. The FDA team’s conclusions were frightening.

Vaccines added under Halsey's watch had tripled the dose of mercury that infants got in their first few months of life. As many as 30 million American children may have been exposed to mercury in excess of Environmental Protection Agency guidelines."

*"My first reaction was simply disbelief, which was the reaction of almost everybody involved in vaccines.....And what I believed, and what everybody else believed, was that it was truly a trace, a biologically insignificant amount. My honest belief is that if the labels had had the mercury content in micrograms, this would have been uncovered years ago. But the fact is, no-one did the calculation'."*

"Making matters worse, the latest science on mercury damage suggested that even small amounts of organic mercury could do harm to the foetal brain."

"The more Halsey learned about these mercury studies, the more he worried. *'My first concern was that it would harm the credibility of the immunisation program. But gradually it came home to me that maybe there was some real risk to the children'.*

"Halsey looked into the matter further and found only complexity. Although the thimerosal levels in vaccines exceeded EPA guidelines for methylmercury, thimerosal contained ethylmercury, a compound that behaves somewhat differently.....The EPA based its guidelines on (Faeroe Islands contaminated whalemeat studies). (Bit) the Faeroes studies, though they dealt with methylmercury, unnerved Halsey."

"Other researchers were troubled too. George Lucier, a toxicologist who led a White House 1998 review of mercury's dangers, went so far as to say it was 'very likely' that thimerosal had damaged some children. There was precious little data to back up that precise suspicion - and little to dismiss it - because of the lack of toxicology research on ethylmercury."

"On July 7<sup>th</sup> 1999, at Halsey's urging, the American Academy of Pediatrics and the Public Health Service released a statement urging vaccine manufacturers to remove thimerosal as quickly as possible, and advising pediatricians to postpone giving most newborns the birth dose of the hepatitis B vaccine."

"Halsey, who still heads the Hopkins Institute for Vaccine Safety, which he was a founder of in 1997, (remains) on the fence. *'I don't believe the evidence is convincing now that there has definitely been harm done by thimerosal'. If there is damage, 'there should be some kind of compensation.....I empathize with families of children with these disorders. How are you going to put a dollar value on that?.'*

The New York Times later carried a clarification that when Halsey described thimerosal injury as “a possibility that must be addressed”, he was referring to developmental delay, not to autism.

#### 47. 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:

- ÿ (1947) “It may be dangerous to inject a serum containing merthiolate into a patient sensitive to merthiolate”
- ÿ (1963) “It seems advisable to use a preservative other than merthiolate for injections into merthiolate-sensitive people”
- ÿ (1972) Merthiolate in vaccines caused six deaths - “The symptoms and clinical course of the six patients suggest subacute mercury poisoning”
- ÿ (1982) The (FDA) Panel concludes that thimerosal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin, and its allergy potential”.
- ÿ (1991) Lilly ceases manufacture or sale of thimerosal. Licensing agreements demonstrate continued profits from the product until at least 2010
- ÿ (1999) Lilly advice on thimerosal: “Mercury poisoning may occur.....Exposure in children may cause mild to severe mental retardation”.

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 thimerosal 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 thimerosal, 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:

Ÿ 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 thimerosal 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.”

Ÿ 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.

Ÿ 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”

Ÿ 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.”

Ÿ 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”

Ÿ 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”

Ÿ 17/8/1967, Medical/Science department requests that the claim “non-toxic” on thiomersal labels be deleted in next printing run

Ÿ 29/8/67, draft label changed to “non-irritating to body tissues”, non-toxic wording omitted



- ÿ 1972, British Medical Journal reports case of skin burns resulting from the chemical interaction of thimerosal 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 thimerosal have been informed” (thiomersal is being used in vaccines which also contain aluminium).
- ÿ 1972, article received by Lilly: “Merthiolate in vaccines caused six deaths? The symptoms and clinical course of the six patients suggest subacute mercury poisoning”
- ÿ 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?)
- ÿ 5/1/1982, Food & Drug Administration’s advance notice of proposed rule-making regarding thimerosal: “At the cellular level, thimerosal 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 thimerosal 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 bacteriostatic action can be reversed.”
- ÿ 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”
- ÿ 1991, Lilly ceases manufacture/sale of thimerosal. Licensing agreements demonstrate continued profits from the product until at least 2010
- ÿ 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”

The next pivotal event was the year-2000 Simpsonwood review by the US Centers For Disease Control. A detailed account of this event is set out later, in the section covering evidence for a thimerosal/autism link (note the “for”).

**48. Statement By Safe Minds (parents’ group), US, *Analysis & Critique of the Centers for Disease Control’s Handling of the Thimerosal Exposure Assessment Based Upon Vaccine Safety Datalink Information***

The parents’ group Safe Minds made the following comments:

- \* the Centers for Disease Control (CDC’s) approach to analysis of the Vaccine Safety Datalink (VSD) database demonstrates a pervasive pattern of bias and conscious manipulation of samples, statistics and findings to produce a negative finding, regarding the dangers of thimerosal exposure
- \* despite significant problems with study design and data quality, and contrary to public statements by the CDC, the VSD analyses of autism, neuro-developmental disorders and speech delay provide support for a causal relationship between thimerosal exposure and childhood developmental disorders
- \* comparisons at a population level across health management areas (in the US) suggest that compliance with the recommended vaccine schedule of thimerosal exposure was associated with high rates of neurological disorders and developmental delay
- \* full-compliance populations reporting disease frequencies to health management areas were at a level exceeding 5% of the birth populations. Extrapolating such rates to a national level suggests that the population harmed by thimerosal exposure could number in the millions

**49. United States Use of Thimerosal - Statement to the Institute of Medicine by Dr. Mark Geier, February 9th 2004**

As part of his submission on links between thimerosal and neurodevelopmental disorders, Dr. Mark Geier and David Geier provided the following useful profile of US thimerosal use:

- ÿ It is clear that, despite public perception that thimerosal has been removed from all US vaccines, it is obvious that thimerosal continues to be present in a number of vaccines at non-trace concentrations
- ÿ Additionally, the removal of thimerosal from the routinely recommended childhood immunisation schedule took considerably longer than is commonly acknowledged
- ÿ On July 17th 2003, the Associate Commissioner for Legislation for the FDA wrote a response letter to a March 12th 2003 letter written by

**Congressman Weldon inquiring about the presence of thimerosal in vaccines**

ÿ This response states that the routinely recommended pediatric vaccines (those recommended by the Advisory Committee on Immunisation Practices, the US equivalent of the UK's Joint Committee on Vaccination and Immunisation) that are administered during the first two years of life (hep B vaccine, inactivated polio vaccine, the 7-valent pneumococcal conjugate vaccine, the Hib vaccine, DTaP, MMR and varicella vaccine) have only been thimerosal-free or contained only trace amounts of mercury (<1mcg per dose) from thimerosal as a residual from the manufacturing process, since the end of 2002.

The letter reviews that there were many of the following vaccines containing thimerosal throughout 2002 including:

- ÿ Tripedia (DTaP, Aventis Pasteur, 25mcg per dose)
- ÿ Recombivax HB (hep B, Merck, 12.5 or 25mcg per dose)
- ÿ Energix B (hep B, 12.5 or 25mcg per dose)

The letter also reviews that the following thimerosal-containing vaccines were available in 2003:

- ÿ Thimerosal-containing DT vaccine (Aventis Pasteur, 25mcg per dose)
- ÿ Thimerosal-containing Td vaccine (Aventis Pasteur and Evans, for children 7 years of age or older, 25mcg per dose)

The Geiers had also stated that they had independently purchased vaccines to see which, if any, still contained non-trace amounts of thimerosal, and had found:

- ÿ Meningococcal polysaccharide vaccine (Aventis Pasteur, 10 dose vial, 25mcg per dose)
- ÿ Td vaccine (Aventis Pasteur, 10 dose vial, 25mcg per dose)
- ÿ Tetanus toxoid absorbed vaccine (Aventis Pasteur, 10 dose vial, 25mcg per dose)
- ÿ Tetanus toxoid vaccine (Aventis Pasteur, 15 dose vials, 25mcg per dose)
- ÿ Japanese encephalitis virus vaccine (Aventis Pasteur, 35.7mcg per dose)

- Y Influenza virus vaccine (Aventis Pasteur, 25mcg per dose)
- Y Td (Massachusetts PH Biological Laboratories, 8.3mcg per dose)
- Y Pediatric DT vaccine (Aventis Pasteur, 25mcg per dose)

Many of these vaccines had 2005 expiry dates, so were available long after the advice to remove thimerosal.

## 50. Thimerosal's Use In The US

The following list, headed "Mercury In Drug and Biologic Products" was published in the US by the FDA and the Center for Drug Evaluation and Research. This is an extract of the list, dated December 2002, which covers no fewer than 221 products apparently still in use at that time and still containing thimerosal or other mercury.

<i>manufacturer</i>	<i>product</i>	<i>mercury percentage</i>
Berna Products	Tetanus vaccine adsorbed	0.01
Bioport Corporation	Tetanus toxoid adsorbed	0.01
Bioport	Rabies vaccine adsorbed	0.01
Bioport	Pertussis vaccine adsorbed	0.01
Bioport	Diphtheria & tetanus toxoids adsorbed	0.01
Bioport	Diphtheria & tetanus toxoids & pertussis vaccine adsorbed	0.01
Connaught Labs	Diphtheria & tetanus toxoids adsorbed	0.01
Connaught	Diphtheria & tetanus toxoids & pertussis vaccine adsorbed	0.01
Connaught	Influenza virus vaccine, trivalent types A & B	0.01
Connaught	Tetanus toxoid for booster use only	0.01
Connaught	Influenza virus vaccine, trivalent types A & B	0.01
Connaught	Haemophilus B conjugate vaccine reconstituted with diphtheria & tetanus toxoids & acellular pertussis vaccines adsorbed	0.01
Connaught	Tetanus toxoid adsorbed	0.01
Connaught	Diphtheria & tetanus toxoids & acellular pertussis vaccine adsorbed	0.01
Connaught	Haemophilus B conjugate vaccine	0.01
Connaught	Tetanus & diphtheria toxoids adsorbed	0.01
Connaught	Japanese Encephalitis virus vaccine	0.007
Connaught	Diluent for meningococcal vaccine groups	0.1
Massachusetts Public Health Biologic Labs	Tetanus & diphtheria toxoids adsorbed	0.003
Mass Pub H Bio Labs	Diphtheria & tetanus toxoids adsorbed	0.01
Medeva Pharmaceuts	Influenza virus vaccine	0.01
North American Vacc.	Diphtheria & tetanus toxoids & pertussis	0.01
Parkedale Pharms.	Influenza virus vaccine, trivalent, types	0.01

	<b>A &amp; B</b>	
<b>SmithKline Beecham</b>	<b>Hepatitis B vaccine, recombinant</b>	<b>0.005</b>
<b>Wyeth Labs</b>	<b>Influenza virus vaccine, trivalent, types A and B</b>	<b>0.01</b>
<b>Wyeth</b>	<b>Diphtheria &amp; tetanus toxoids adsorbed</b>	<b>0.01</b>
<b>Wyeth</b>	<b>Tetanus &amp; diphtheria toxoids adsorbed</b>	<b>0.01</b>
<b>Wyeth</b>	<b>Tetanus toxoid, fluid</b>	<b>0.01</b>
<b>Wyeth</b>	<b>Tetanus toxoid, adsorbed</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Diphtheria &amp; tetanus toxoids &amp; acellular pertussis vaccine adsorbed</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Pneumococcal vaccine, polyvalent</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Diphtheria &amp; tetanus toxoids &amp; pertussis vaccine adsorbed &amp; haemophilus B conjugate vaccine</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Tetanus toxoid adsorbed</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Tetanus &amp; diphtheria toxoids adsorbed</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Diphtheria &amp; tetanus toxoids adsorbed</b>	<b>0.01</b>
<b>Wyeth-Lederle</b>	<b>Haemophilus conjugate vaccine</b>	<b>0.01</b>

### **51. UK Vaccines With Thimerosal**

**Vaccines in the UK that are believed to still contain, or until recently contained, thiomersal are:**

- ÿ DTaP (Diphtheria and Tetanus and acellular pertussis) made by Lederle Laboratories**
- ÿ HIB (haemophilus influenza type B) made by Connaught Laboratories**
- ÿ DPT (Diphtheria and tetanus and pertussis) made by Glaxo SmithKline**
- ÿ Energix-B (Hepatitis B) made by Glaxo SmithKline**
- ÿ HibTiter (Haemophilus influenza type B) made by Lederle**
- ÿ Fluvirin influenza virus vaccine made by Medeva Pharma**
- ÿ FluShield made by Wyeth-Ayerst**
- ÿ Menomune (Meningococcal polysaccharide vaccine) made by Connaught**
- ÿ Rabies vaccine made by Glaxo SmithKline**
- ÿ 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 thimerosal:**

- ÿ 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 thimerosal in vaccines”.

By early 2004, the UK was believed to be the last developed country in the world not to have acted to withdraw thimerosal from infant vaccines, and to be continuing to openly defend its use (but see later).

- The UK National Health Service stocks two DTP vaccines, DTwP, which contains thimerosal and which is routinely offered, without warning or advice, and DTaP, which is labelled Infanrix and which is thimerosal-free. Infanrix is available to parents who demand it, but DTwP, made by Aventis Pasteur, is cheaper, and so remains the standard issue.
- It is also understood that the UK introduced an accelerated schedule of DPT vaccination in 1991, which would have significantly increased the thimerosal intake of infants. From 1991, the age at which DPT was administered was lowered, to be given at monthly intervals at two, three and four months. The infant blood-brain barrier is not properly formed until six months, and so the acceleration of the schedule may prove critical to the increase in UK autism. As there is no proper autism database, it is still difficult to be precise on this point.
- It is known that MMR does not contain thiomersal, but it is thought that thimerosal may be used in its manufacturing process.
- When the thimerosal 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. Always, there is this overriding concern over maintaining public “confidence”.
- At what point should safety concerns be publicly debated? Safety concerns in other industries, such as air travel, are not swept under the mat to preserve public confidence, but are independently investigated. Why are vaccines so different?

## 52. UK Medicines & Healthcare Regulatory Agency Position On Thimerosal

- Y In May 2001, the UK Medicines Control Agency (now part of the Medicine & Healthcare Regulatory Agency) instructed manufacturers to warn doctors and patients of potential allergic reactions to vaccines containing thimerosal.
- Y However, unlike the US, the UK has not moved to remove existing stocks, which are being used up.
- Y The magazine Pulse also reported that the UK Government planned to reduce levels of thimerosal in infant vaccines, including DTP, HiB and the pre-school DT booster.
- Y 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 thimerosal levels in vaccines.

In June 2005, in correspondence, Dr. Philip Bryan, Senior Scientific Assessor at the Post-Licensing Division of the UK Medicine & Healthcare Products Regulatory Agency confirmed that he:

- \* had “not read the full transcript of the confidential meeting held by the US Centers for Disease Control (CDC) at Simpsonwood, Georgia, in June 2000” - detailed elsewhere in this review
- \* was unable to confirm if he had seen the report by Dr. Thomas Verstraeten to which (I had referred) - again, Verstraeten’s study is detailed elsewhere in this review

## 53. UK Joint Committee On Vaccination and Immunisation Position On Thimerosal

These are extracts from the JCVI minutes of 21<sup>st</sup> January 2000:

“The estimated potential thimerosal exposure through the UK (infant immunisation) programme was calculated to range between 0.15 and 0.30mg (equivalent to 75-150ug of mercury). In the US, the level of potential thimerosal exposure was calculated as 0.05 to 0.375mg (equivalent to 2.5-187.5ug of mercury.”

“The main problem (note the use of this latter word!) for the UK was that DTwP vaccine contained thimerosal. The DTwP/IPV did not contain thimerosal, neither did the DtaP vaccine. The effect of taking thimerosal out of vaccines on immunogenicity was not known, and more studies were needed.”

**“The manufacturers were concerned that, should the topic of thimerosal in vaccines lead to an unfounded safety scare, then they would have difficulties providing alternatives.”**

**These are extracts from the JCVI minutes of November 2001:**

**“Although the CSM (Committee on Safety of Medicines) had expressed some concerns about the limitations of the US study data (presumably this referred to Verstraeten), it had concluded that the preliminary results provided no coherent evidence of harm from thimerosal”**

**“They (the CSM) also felt that an extrapolation from methylmercury to ethylmercury (as contained in thimerosal) was not necessarily justified. Although CSM would continue to keep this issue under review, it had been reassured by what it had seen, and confirmed its view that there was no evidence that thimerosal in vaccines was harmful.”**

**“Further studies investigating the effect of thimerosal in vaccines were being conducted by the Public Health Laboratory Service (presumably Dr. Elizabeth Miller), one with WHO funding (Note: Dr. John Clements of the WHO had been part of the confidential Simpsonwood meeting to discuss the original Verstraeten study, where a 2.48 relative risk factor for autism after receipt of thimerosal-containing vaccines had been unveiled to a dismayed audience) and one with UK Department of Health funding. The Joint Committee would see the results of these studies when they were completed”.**

**“The Committee was reassured by the evidence that mercury exposure in the UK immunisation was very low. It confirmed its view that the available evidence did not indicate any hazard from the presence of thimerosal in vaccines, but that.....thimerosal should nevertheless be withdrawn from vaccines wherever possible.....”**

**But use of thimerosal continued:**

***“Based on the conclusions of (expert groups), there is no reason on the grounds of safety to change the current immunisation practices with thimerosal-containing vaccines.....The public should continue to have confidence in the immunisation programme, which has an enviable safety record” - Dr. Syed Ahmed, immunisation co-ordinator and Dr. Jim McMenamin, consultant in public health medicine, Greater Glasgow NHS Board, Glasgow, UK***

**This stance was endorsed in the Scottish press in June 2003 by Dr. Andrew Fraser, deputy chief medical officer, Scottish Health Department:**



**“Advice from the World Health Organisation (WHO) makes clear that the risk of death and complications from vaccine-preventable diseases is real, compared with the theoretical risk from side-effects of thimerosal”.**

**“No course of treatment is ever risk-free. The balance of risks, though, for the DTP vaccine (which had featured in adverse press comment) comes down strongly in favour of its use.”**

**Sallie Bernard of Safe Minds responded:**

*“Contrary to what Drs. Ahmed and McMenamin assert in their letter, in the October 2001 Institute of Medicine report, the thimerosal review committee concluded that “the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders.....is biologically plausible”.....(and) “the committee recommends the use of the thimerosal-free DTaP, Hib and Hep B vaccines in the US”.*

*She also pointed out a third conclusion: “The committee recommends that full consideration be given by professional societies and government agencies to removing thimerosal from vaccines administered to infants, children or pregnant women in the US”.*

**In an unpublished response to Dr. Fraser’s letter she further stated:**

*“As Dr. Fraser should know, the WHO in their investigation simply looked for existing studies on thimerosal safety. Finding none, since proper safety studies have never been conducted on this mercury compound, the WHO declared ‘no evidence of harm’”.*

*“The US report (from the Committee on Government Reform, in 2003) strongly criticised the FDA for its continued assurances to the public of thimerosal safety when in fact it had no supporting data. Now Dr. Fraser is using the same distortion to placate the Scottish public”.*

*“Dr. Fraser also misleads (Scottish) readers by suggesting that a little neurotoxic mercury is fine for babies because getting diphtheria, tetanus or pertussis disease is much worse. The argument is a false one, since the UK already has an effective licensed DTP vaccine (Infanrix) that does not contain thimerosal.....Thus to claim that Scottish parents must trade-off childhood diseases against mercury injections is absurd.”*

#### **54. UK Department of Health (England) Position on Thimerosal**

**According to correspondence between the Department of Health and a parent, John Stone, “The Department of Health, with advice from the Joint Committee on Vaccination and Immunisation, supported the recommendation as made by European Agency for the Evaluation of Medicinal Products (EMEA) in 1999 to move to thimerosal-free or reduced**

vaccines of equal or greater efficacy where possible. JCVI advised that until the alternatives to wP (whole cell pertussis) were available, the UK should continue to use wP (which contained thimerosal).”

In the House of Commons, in Parliamentary Question 169, the draft Written Answer was: “There is no evidence of harm caused by the level of exposure to mercury from the use of thimerosal-containing vaccines in the UK. However, as thimerosal contains mercury, both European and American regulatory authorities have recently recommended that vaccine manufacturers phase out its use wherever possible as a precautionary measure, to limit exposure to mercury. They have not recommended the withdrawal of any individual vaccines. The studies carried out by the US CDC do not demonstrate a causal connection between thimerosal and autism.”

The draft Written Answer to Parliamentary Question 170 stated that “Thimerosal has been used in vaccines for over sixty years. It has played an important role either as a preservative to prevent microbial contamination, or as an inactivating agent to produce killed vaccines”.....The thimerosal content of the UK routine childhood immunisation programme has not increased over the past decade.”

But then, it added, rather more ambiguously: “The World Health Organisation has stated that ‘thimerosal poses a theoretical low risk of neurodevelopmental toxicity in infants. The known risk of morbidity and mortality from vaccine-preventable diseases and of contaminated multi-dose vaccine vials far outweigh any potential risk posed by thimerosal.” (my underlining). (Comment: how can one say that a known risk outweighs an unknown risk, when the latter is unknown?)

The Written Answer also did not explain that use of multi-dose vials was an economy measure, to cut costs, and contamination risk thus should not be weighed into the risk equation, as it was an avoidable one.

The draft Written Answer to Written Question 172 stated that: “The Committee for Proprietary Medicinal Products (CPMP), a pan-European advisory committee, had recently made a recommendation that the use of thimerosal as a preservative in vaccines should be phased out wherever possible.”

It then went on, tautologically: “This is a precautionary measure to limit overall exposure to mercury, and is not due to concerns over long-term adverse effects of thimerosal-containing vaccines.”

A suggested reply (these “suggested replies” were obtained through Freedom of Information Act) to a Written Question from Dr. Phyllis Starkey, Labour MP, was: “In the UK, the only vaccines used in the routine childhood immunisation programme which contain thimerosal are diphtheria tetanus

pertussis (DPT) and diphtheria tetanus (DT) vaccines. There is no, and never has been, any thimerosal in MMR, Hib, oral polio, Meningitis C conjugate or BCG vaccines used in the UK.” (however, the Medicines Control Agency confirmed on 7<sup>th</sup> June 2001 that Hib-DTP contained thimerosal).

On 7<sup>th</sup> August 2004, the Department of Health announced that it was moving towards using thimerosal-free vaccines, although there would be no withdrawal of existing stocks.

The line taken was that thimerosal was completely safe, but that non-thimerosal vaccines would be “even safer”, a tautological statement in itself. Dr. David Salisbury, head of immunisation at the Department, was quoted in the Daily Telegraph of 8<sup>th</sup> August 2004 as saying that the decision had nothing to do with concerns over a link between the preservative thimerosal and autism.

However, Professor Graham George of the University of Saskatchewan, Saskatoon, was reported to be studying the effects of mercury in the body. Professor George stated that preliminary findings “indicated that mercury administered to rabbits as thimerosal does accumulate in the brain in a relatively short time.....about an hour, and was chemically modified, though the work had yet to be published at that stage. “It is a very good thing that it is coming out.....It shocked me when I found out it is in vaccines. If you wanted to choose something to put into a vaccine, and you were doing it fresh (ie from scratch) thimerosal would be the last thing. It is known to be neurotoxic and would never get approval for drug use these days. It is only because it has been ‘grandfathered in’ (ie has approval from the distant past) since the 1930s that it is in use at all.” Professor George “would not be surprised” if there was a link with autism.

#### 55. US Centers 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 Thimerosal 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 thimerosal and neurodevelopmental disorders such as language and speech delays, attention deficit hyperactivity disorder, stuttering and tics. No association was found with autism. (The study is detailed elsewhere in this review).

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 Thimerosal 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 were 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:

- ÿ 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
- ÿ Only researchers whom the CDC approves will be allowed this restricted access
- ÿ Researchers must come to the CDC's Center for Health Statistics to conduct their work
- ÿ Before leaving, researchers must submit their analyses for review by CDC personnel, who will edit their findings

56. Report, *Mercury in Medicine - Taking Unnecessary Risks*, prepared by the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, May 2003, As A Result Of A Three-Year Investigation

This is a summary of the report's key sections, verbatim:

- ÿ In 1999, following up on the FDA evaluation.....the House Committee on Government Reform initiated an investigation into the dangers of exposure to mercury through vaccination.....In January 2003, the investigation continued in the newly-formed Subcommittee on Human Rights and Wellness

- ÿ In July 2000, it was estimated that 8,000 children a day were being exposed to mercury in excess of Federal guidelines, through their mandatory vaccines
- ÿ According to the (FDA), “at the heart of all FDA’s product evaluation decisions is a judgment about whether a new product’s benefits to users will outweigh its risks. No regulated product is totally risk-free, so these judgments are important. FDA will allow a product to present more of a risk when its potential benefit is great - especially for products used to treat serious, life-threatening conditions”
- ÿ This argument - that the known risks of infectious diseases outweigh a potential risk of neurological damage from exposure to thimerosal in vaccines - is one that has continuously been presented to the Committee by Government officials. FDA officials have stressed that any possible risk from thimerosal was theoretical, and that no proof of harm existed.
- ÿ The Committee did in fact find evidence that thimerosal posed a risk. The possible risk for harm from either low-dose chronic or one-time high-level (bolus dose) exposure to thimerosal is not “theoretical” but very real and documented in the medical literature
- ÿ Congress has long been concerned about the human exposure to mercury through medical applications. As a result of these concerns, in 1997 Congress instructed the FDA to evaluate the human exposure to mercury through drugs and foods. The FDA realised that the amount of ethylmercury that infants were exposed to in the first six months of life through their mandatory vaccinations exceeded the Environmental Protection Agency’s (EPA’s) limit for a closely associated compound methylmercury
- ÿ The FDA and other Federal agencies determined that in the absence of a specific standard for ethylmercury, the limits for ingested methylmercury should be used for injected ethylmercury. The Institute of Medicine, in 2000, evaluated the EPA’s methylmercury standard and determined that, based upon scientific data, its own, rather than the FDA’s, was the scientifically validated safe exposure standard.
- ÿ Rather than acting aggressively to remove thimerosal from children’s vaccines, the FDA and other agencies within the Department of Health and Human Services (HHS) adopted an incremental approach that allowed children to continue to be exposed to ethylmercury from vaccines for more than two additional years. In fact, in 2001, the Centers for Disease Control and Prevention (CDC) refused even to express a preference for thimerosal-free vaccines.

ÿ Many parents, and a growing number of scientists, believe that this mercury exposure may have contributed to the explosive growth in autism spectrum disorders and neurological and behavioural disorders that this country has experienced....The Federal government has an obligation to vigorously pursue the necessary research to determine the extent of the impact of these heightened exposures to ethylmercury on our population

The Committee's findings and recommendations included:

ÿ Manufacturers of vaccines and thimerosal....have never conducted adequate testing on the safety of thimerosal. The FDA has never required manufacturers to conduct adequate safety testing on thimerosal and ethylmercury compounds

ÿ Studies and papers documenting the hypoallergenicity and toxicity of thimerosal have existed for decades

ÿ Autism in the US has grown at epidemic proportions during the last decade....At the same time that the incidence of autism was growing, the number of childhood vaccines containing thimerosal was growing

ÿ A growing number of scientists and researchers believe that a relationship between the increase in neurodevelopmental disorders of autism, attention deficit hyperactivity disorder and speech or language delay, and the increased use of thimerosal in vaccines, is plausible and deserves more scrutiny

ÿ The amount of ethylmercury to which children were exposed through vaccines prior to the 1999 announcement exceeded two safety thresholds established by the Federal government for a closely-related substance, methylmercury

ÿ While the Federal Government has established no safety threshold for ethylmercury, experts agree that the methylmercury guidelines are a good substitute. Federal health officials have conceded that the amount of thimerosal in vaccines exceeded the EPA threshold of 0.1mcg per kilogram of body weight. In fact, the amount of mercury in one dose of DTaP or Hep B vaccines (25mcg each) exceeded this threshold many times over.

ÿ Federal health officials have not conceded that this amount of thimerosal in vaccines exceeded the FDA's more relaxed threshold of 0.4mcg per kilogram of body weight. In most cases, however, it clearly did (Note: and using body weight as a measure is very crude - what about genetic susceptibility, difficult to measure but probably far more crucial?)

- ÿ The CDC's failure to state a preference for thimerosal-free vaccines in 2000 and again in 2001 was an abdication of their responsibility. As a result, many children received vaccines containing thimerosal when thimerosal-free alternatives were available
- ÿ No amount of mercury is appropriate in any childhood vaccine
- ÿ The CDC in general and the National Immunisation Program in particular are conflicted in their duties to monitor the safety of vaccines, while also charged with the responsibility of purchasing vaccines for resale as well as promoting increased immunisation rates
- ÿ There is inadequate research regarding ethylmercury neurotoxicity and nephrotoxicity
- ÿ There is inadequate research regarding the relationship between autism and the use of mercury-containing vaccines
- ÿ To date, studies conducted or funded by the CDC that purportedly dispute any correlation between autism and vaccine injury have been of poor design, under-powered and fatally flawed. The CDC's rush to support and promote such research is reflective of a philosophical conflict in looking fairly at emerging theories and clinical data to adverse reactions from vaccines
- ÿ Access by independent researchers to the Vaccine Safety Datalink database is needed for independent replication and validation of CDC studies regarding exposure of infants to mercury-containing vaccines and autism. The current process to allow access remains inadequate.
- ÿ Congress should enact legislation that prohibits Federal funds from being used to provide products or pharmaceuticals that contain mercury, methylmercury or ethylmercury, unless no reasonable alternative is available
- ÿ Congress should direct the National Institutes of Health (NIH) to give priority to research projects studying causal relationships between exposure to mercury, methylmercury and ethylmercury to autism spectrum disorders, attention deficit disorders, Gulf War Syndrome and Alzheimer's Disease

**57. Letter to Congress by the US Office of Special Counsel, Washington**

A major development in May 2004 was the issuing of a letter to Congress by the US Office of Special Counsel. The letter, from Special Counsel Scott J. Bloch, was directed to the Honorable Judd Gregg, Chairman, Committee on Health, Education, Labor and Pensions and to the Honorable Joe Barton,

**Chairman, Committee on Energy and Commerce, US House of Representatives.**

The letter included the following verbatim quotes:

*“As Special Counsel, if I find on the basis of the information disclosed, that there is a substantial likelihood that one of these conditions (Note: this referred to alleged violations of law, rule or regulation, gross mismanagement, gross waste of funds, abuse of authority or a substantial and specific danger to public health or safety)...I am required to advise the appropriate agency head of my findings, and the agency head is required to conduct an investigation of allegations and prepare a report*

*“I have recently received hundreds of disclosures from private citizens alleging a widespread danger to the public health, specifically to infants and toddlers, caused by childhood vaccines which include thimerosal*

*It appears there may be sufficient evidence to find substantial likelihood of a substantial and specific danger to public health caused by the use of thimerosal/mercury in vaccines because of its inherent toxicity*

*“Due to the gravity of the allegations, I.....hope that you will review these important issues and press Health and Human Services for a response to this very serious public health danger.*

*“The disclosures allege, amongst other things, that:*

*ÿ some datasets showing a relationship between thimerosal/mercury and neurological disorders no longer exist*

*ÿ That independent researchers have been arbitrarily denied access to Centers for Disease Control and Prevention databases*

*ÿ That Government-sponsored studies have not assessed the genetic vulnerabilities of sub-populations*

*ÿ That the Food and Drug Administration colluded with pharmaceuticals companies at a conference at Norcross Georgia (Note: this was the Simpsonwood meeting) in June 2000 to prevent the release of a study which showed a statistical correlation between thimerosal/mercury exposure through pediatric vaccines and neurological disorders, including autism*

*ÿ The author of the study, Dr. Thomas Verstraeten, later published a different version of the study in the November 2003 issue of Pediatrics (Note: the original and re-worked versions are both detailed elsewhere in this review), which then did not show a statistical correlation. No explanation has been provided for this discrepancy*



*Y There is an increasing body of clinical evidence on the connection of thimerosal/mercury exposure to neurological disorders which is being ignored by Government public health agencies*

*“Based on what is known to date about mercury as a deadly neurotoxin and because thimerosal is not an essential component to the vaccine, there is no reason to continue to purposefully inject it into the bloodstream of infants*

*“I believe these allegations raise serious continuing concerns about the administration of the nation’s vaccine program and the Government’s possibly inadequate response to the growing body of scientific research on the public health danger of mercury in vaccines.”*

The Office of the Special Counsel does not have jurisdiction over disclosures from private citizens. In the event, however, that a federal employee comes forward with information on this issue, the OSC would then have jurisdiction to determine whether there is a substantial likelihood that the information discloses a violation of any law, rule or regulation, or a substantial and specific danger to public health and safety.

#### 58. California Votes To Ban Thimerosal, June 2004

In June 2004, the State of California’s Senate Health and Human Services Committee voted 9 votes to 1 to ban the administration of mercury-containing vaccines that contain more than trace amounts of mercury (as per the US Food and Drug Administration’s definition) in pregnant women and children under three years of age.

#### 59. Other US States

Other US States have also acted to ban thimerosal in vaccines. For example:

- In Colorado, a Bill has been introduced that prohibits the administration of vaccines containing more than a specified amount of mercury to pregnant women and children under three years of age - and requires insurers to pay for vaccines that do not contain mercury - and allows (the health department) to exempt the use of vaccines that contain mercury if the executive director finds, and the Governor concurs, that (an emergency) exists
- In Maryland, Senate Bill 365 has been introduced - prohibiting individuals from being vaccinated with vaccines containing specified amounts of mercury per dose, on or after 1<sup>st</sup> January 2007 - prohibiting individuals from being vaccinated or injected with vaccines or other products containing any amount of mercury on or after 1<sup>st</sup> June 2009 - granting the Secretary of Health and Mental

Hygiene Authority to authorize the use of vaccines that may contain mercury in the event of (bioterrorism or public health emergencies)

- In Virginia, in 2006, Delegate Robert Bell has introduced a House Joint Resolution that calls for the Joint Committee on Health Care to study the reasons for continued use of mercury in some child and adult vaccines, the safety risks associated with such use, and whether or not mercury-free vaccines are equally effective, in terms of preventing disease and costs

Several other States are understood to have enacted or to be considering similar measures, including Iowa, Missouri and New York.

#### 60. US Centers For Disease Control's Current Position On Thimerosal

In October 2004, Dr. Julie Gerberding, director of the US Centers for Disease Control, stated that the CDC was committed to the elimination of thimerosal-containing vaccines for infants, but offered no timetable for doing so. She stated that at best, thimerosal would be eliminated by 2009.

The CDC has maintained that there is no thimerosal/autism link. In 2004, Dr. Marie McCormack, chair of the Institute of Medicine panel, stated: "It's really terrifying, the scientific illiteracy that supports these suspicions" (New York Times, June 2004).

The review panel dealing with the issue, stated: "Further research to find the cause of autism should be directed towards other lines of inquiry."

The head of the US CDC's immunization programme stated: "Only junk scientists and charlatans.....(take such a link seriously)."

However, behind the scenes, the CDC's actions do not square with its words. The CDC is continuing to investigate whether thimerosal in vaccines has caused cases of autism. This was confirmed by spokesman Glen Nowak in early 2006. "Dr. Gerberding (Director of the CDC) has made it clear that the CDC has not ruled out anything as possible causes of autism, including thimerosal.....We have continued to fund studies to look at the role, if any, of thimerosal." The study was designed in 2003, and data collection is under way.

#### 61. Memo by Merck

In February 2005, US press reports detailed how a memo had been leaked from within vaccine manufacturer Merck, expressing concern at the mercury burden being placed upon infants via the vaccination schedule.

The Los Angeles Times of 8<sup>th</sup> February stated that: "A memo.....shows that nearly a decade before the first public executives were concerned that

infants were getting an elevated dose of mercury.....The March 1991 memo obtained by the Los Angeles Times said that 6-month-old children who receive their shots on schedule would get a mercury dose as much as 87 times higher than guidelines for the maximum daily consumption of mercury from fish. ‘When viewed in this way, the mercury load appears rather large’, said the memo from Maurice R. Hilleman (now deceased, and known as “father” of the MMR vaccine).

## **PART E: EVIDENCE THAT AUTISM INCREASES ARE REAL**

### **62. Paper By Mark Blaxill, US Parent, The Rising Incidence of Autism, June 2001**

This was a major contribution by a parent to the debate, and was the first comprehensive assessment as to how autism was increasing. The paper included the following assessment of prevalence as indicated by past studies:

(Japan, in order of birth years studied))

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
Haga 1971	Kyoto	Kanner	1953-62	1.1
Nakai 1971	Gifu	Kanner	1953-62 estim	1.7
Tanino 1971	Toyama	Kanner	1956-61 & 1962-64	0.9 1.8
Hoshino 1982	Fukushima	Kanner	1960-76 & 1968-74	2.3 5.0
Yamazaki 1982	Hokkaido	Kanner	1961-63	5.0
Ishii/Takahashi 1983	Toyota	other	1970-76	16.0
Matsuishi 1987	Kurume City	DSM III	1971-79	15.5
Tanoue 1988	South Ibaraki	DSM III	1972-78	11.3 native, 13.9 total
Sugiyama/Abe 1989	Nagoya	DSM III	1978-82	13.0
Honda 1996	Yokohama	ICD 10	1988	16.2 native, 21.1 total

(Sweden)

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
Bohman	Vasterbotten	Rutter	1959-79	6.1

<b>1981</b>				
<b>Gillberg 1984</b>	<b>Goteburg</b>	<b>Rutter</b>	<b>1962-76</b>	<b>4.0</b>
<b>Steffenburg &amp; Gillberg 1986</b>	<b>Goteburg &amp; Bohuslan</b>	<b>DSM III</b>	<b>1975-84</b>	<b>6.6</b>
<b>Gillberg 1991</b>	<b>Goteburg &amp; Bohuslan</b>	<b>DSM III</b>	<b>1975-84</b>	<b>9.5</b>
<b>Kadesjo, 1999</b>	<b>Karlstad</b>	<b>DSM IIIR</b>	<b>1985</b>	<b>60 autism, 72 PDD, 121 ASD</b>

**(Other Scandinavian)**

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
<b>Brask 1970</b>	<b>Aarhus Denmark</b>	<b>Kanner</b>	<b>1949-60</b>	<b>4.3</b>
<b>Herder 1993</b>	<b>Nordland Norway</b>	<b>n/a</b>	<b>1975-91</b>	<b>5.5</b>
<b>Sponheim 1998</b>	<b>Akershus Norway</b>	<b>ICD-10</b>	<b>1978-89</b>	<b>5.2</b>
<b>Keilinen 2000</b>	<b>Oulu Lapland</b>	<b>DSM IV</b>	<b>1979-92</b>	<b>12.2</b>

**(USA & Canada)**

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
<b>Treffert 1970</b>	<b>Wisconsin</b>	<b>Kanner</b>	<b>1954-64</b>	<b>3.1</b>
<b>Ritvo 1989</b>	<b>Utah</b>	<b>DSM III</b>	<b>1960-84, 1975-79</b>	<b>2.47 total, 3.5 estimate</b>
<b>California 1999</b>	<b>California</b>	<b>DSM IV</b>	<b>1960-95</b>	<b>7.6 estimate</b>
<b>Burd 1987</b>	<b>North Dakota</b>	<b>DSM III</b>	<b>1967-83</b>	<b>3.26</b>
<b>Bryson 1988</b>	<b>Nova Scotia</b>	<b>DSM IIIR/other</b>	<b>1971-79</b>	<b>10.1</b>
<b>CDC 2000</b>	<b>Brick Tnship New Jersey</b>	<b>DSM IV</b>	<b>1988-95</b>	<b>40 autism, 67 ASD</b>

**(UK & Ireland)**

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
<b>Lotter 1966</b>	<b>Middlesex</b>	<b>Kanner</b>	<b>1953-55</b>	<b>4.1</b>
<b>Wing 1979</b>	<b>Camberwell</b>	<b>Kanner</b>	<b>1956-70</b>	<b>4.9</b>
<b>McCarthy 1984</b>	<b>East Ireland</b>	<b>Kanner</b>	<b>1965-68</b>	<b>4.3</b>
<b>Deb 1994</b>	<b>NE Scotland</b>	<b>DSM IIIR</b>	<b>1969-83</b>	<b>9</b>
<b>Webb 1997</b>	<b>S. Glamorgan</b>	<b>DSM IIIR</b>	<b>1977-89</b>	<b>7.2</b>

Taylor 1999	N Thames	ICD 10	1979-92	5.3 autism, 8.7 PDD, 10.1 ASD
Kaye 2001	UK GP data	n/a	1988-93	16.3
Scott 2001	Cambridge	ICD 10	1988-94	57 ASD
Baird 2000	SE Thames	ICD 10	1993	30.8 autism, 57.9 ASD

(France)

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
Fombonne 1992	Aquitaine, Lorraine, Ile de France, Picardie	“clinical”	1972 & 1976	4.9
Cialdella 1989	Rhone	“clinical”	1976-82	10.8
Fombonne 1997	Haute-Garonne, Isere, Saone et Loire	“clinical”	1976-85	5.35 autism, 16.3 PDD
Rumeau-Rusquette 1994	Aquitaine, Lorraine, Ile de France, Picardie	“clinical”	1981	3.1

(Other)

These were developed countries where a single study had been reported:

<i>(author/date)</i>	<i>location</i>	<i>criteria</i>	<i>Birth years</i>	<i>Prevalence per 10,000</i>
Magnusson (date not known)	Iceland	ICD 9 ICD 10	1964-83 1984-93 1964-93	3.8 8.6 6.2 (total)
Steinhausen 1986	W Berlin	Rutter	1968-79	1.9
Wignyo-sumarto 1992	Yogyakarta, Indonesia	CARS	1984-91	11.7
Davidovitch 2000	Haifa	DSM IIIR DSM IV	1989-93	9.9

It was the conclusion of Blaxill that these studies confirmed a sharp real rise in the incidence of autism. Further aspects of his detailed paper are considered in a later section of this document, reviewing the evidence to link autism with thimerosal exposure.

### 63. 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:

- ÿ 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
- ÿ The observed increase cannot be explained by a loosening in the criteria
- ÿ 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
- ÿ 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
- ÿ A diagnosis of mental retardation associated with autism had declined significantly between the two age groups studied.
- ÿ The percentage of parent-reported regression (loss of milestones) does not differ between the two age groups studied
- ÿ 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.

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

ÿ 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.

ÿ 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.

ÿ The results were that 987 children were identified, displaying behaviour consistent with DSM-IV criteria for autistic disorder, PDD-NOS or Asperger disorder.

ÿ The prevalence for autism was found to be 34 cases per 10,000

ÿ 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.

**65. Paper by Gurney, Fritz, Ness et al, *Analysis of Prevalence Trends of Autism Spectrum Disorder in Minnesota*, published in *Archives of Pediatric Adolescent Medicine*, 2003, 157, 622-627**

The purpose of this study was to quantify and characterise prevalence trends over time in ASD in Minnesota. The study conducted an age-period-birth cohort analysis of special educational disability data from the Minnesota Department of Children, Families and Learning from 1981-82 through the 2001-02 school years.

The study results were:

- ÿ Prevalence rates of autism spectrum disorder rose substantially over time within single-age groups and increased from year to year within birth cohorts
- ÿ Autism spectrum disorder prevalence among children aged 6 to 11 years increased from 3 per 10,000 in 1991-92 to 52 per 10,000 in 2001-02
- ÿ All other special educational disability categories also increased during this period, except for mild mental handicap, which decreased slightly from 24 per 10,000 to 23 per 10,000
- ÿ The study found that Federal and State administrative changes favouring identification of ASD corresponded in time with the increasing rates.

The study concluded that there were dramatic increases in the prevalence of ASD as a primary special educational disability, and that the trends show no sign of abatement. The study found no corresponding decrease in any special educational disability category to suggest diagnostic substitution as an explanation for the autism trends in Minnesota.

As to the extent that increases were real, the study sat on the fence. It confirmed huge rises, but suggested that there may have been underdiagnosis in the past. However, it did confirm that reassignment from other categories of disorder did not explain the increase, nor did it ascribe increases to criteria changes.

66. Paper by Dr. F. Edward Yazbak, *Autism In The United States - A Perspective*, published in the *Journal of American Physicians and Surgeons*, vol 8 No. 4 Winter 2003

This paper brought together much of the evidence of an autism epidemic for the first time in a peer-review publication:

- ÿ Autism has reached epidemic proportions in the United States. The increase cannot be attributed to changes in diagnostic criteria, which have actually become more restrictive.
- ÿ The increasing number of patients afflicted with this serious disability will have an enormous effect on the economy
- ÿ Studies of a potential relationship to childhood vaccines have been limited and flawed
- ÿ The autism explosion since 1994 and DSM-IV is best documented in California.....Autism has become the predominant disability for which services are accessed in California. According to the most recent (note -



at that time) California Autism Report released in March 2003, cases of Type 1 autism increased by 97% in the last four years compared to 16% for cerebral palsy and 29% for mental retardation

- ÿ There is every reason to believe that more children will develop autism in the coming years
- ÿ When the children become adults and the parents are no longer there, the impact on society will be even greater, and the burden on the US economy will mount into trillions of dollars
- ÿ To date, the US Centers for Disease Control and other US Government health authorities have not given enough attention to this serious epidemic (the same allegation could most certainly be levelled at UK Government agencies).
- ÿ According to Bernard Rimland of the US Autism Research Institute, two clear trends have emerged. First, the incidence of autism has increased remarkably, becoming an 'explosion' in recent years, and secondly, there has been a distinct shift in the time of onset of autistic symptoms
- ÿ According to Rimland, late-onset autism was almost unheard of in the 1950s, 1960s and 1970s, but today, such cases outnumber early onset cases by five to one
- ÿ Parents in increasing numbers are reporting similar stories. A child....who is developing socially and verbally on par for his age, suddenly stops acquiring new words and skills in the second year of life and then regresses, losing speech, cognitive abilities and social dexterity
- ÿ Suggesting that a sudden and exponential increase in autistic disorders is not real, and results only from better diagnosis, amounts to denial
- ÿ Genetic disorders have never presented as epidemics, and investing the scant available (research) resources solely in genetic research diverts them from the scientific exploration of more plausible environmental etiological factors
- ÿ In accordance with the US Individuals With Disabilities Education Act....the number of children aged 6 to 21 with autism in US schools rose steadily from 5,415 in 1991-92 to 118,602 in 2002
- ÿ Autism is not a diagnosis that parents accept readily, or physicians make lightly, or that school authorities approve easily. It is probable that autism in US schools is actually under-diagnosed and that many less

severe cases are labelled behaviour and communication disorders, in order to avoid the stigma and/or the added cost

ÿ In spite of all the above, some “experts” still claim that the spectacular increases in autism reported lately are simply the result of more liberal or less stringent diagnostic criteria

ÿ The only reasonable conclusion from this review is that the recent increase in autism in the US is real and significant

Dr. Yazbak’s conclusion was that emerging evidence suggested some relationship between MMR and thimerosal-containing vaccines and regressive autism, and that additional independent and unbiased clinical studies must be conducted in order to determine all causes involved.

67. Paper by Dr. F. Edward Yazbak, *Autism Skyrockets In Quebec - A Secret No More*, published by Red Flags Weekly, 25th January 2004

Dr. Yazbak also carried out research into the apparent steep rise in autism in Quebec. In this paper, he suggests that:

ÿ The recent 150% increase in autism in all school age groups, in itself disturbing, does not do justice to the seriousness of the situation facing the Province

ÿ The percentage of pre-schoolers with autism is almost double that of students in primary grades, and almost quadruple that in secondary grades, a clear indication that younger children are being diagnosed in increasing numbers

ÿ Although some of the increase will be due to better and earlier diagnosis, the number of young children with autistic disorders accessing the special education system and requiring specialised educational services has risen dramatically.

ÿ A total of 1,388 students with pervasive developmental disorders were registered in schools in the Province of Quebec in September of 2000. By September 2002 this had increased to 2,267, an increase of 63% in just two years.

ÿ There were 91 children with autism in Montreal schools in 1998. By 2003, this number had risen to 307, an increase of 237% in five years.

The autism situation for 2003 makes a disturbing comparison with that in 1971. In 2003, the estimated population of Canada was approximately 31.4m, of whom 25.1% were under the age of 19, divided-up as follows:

(age)	(percentage of total population)
-------	----------------------------------

0-4	5.4%
5-9	6.3%
10-14	6.7%
15-19	6.7%

The approximate population of Quebec was slightly under 7.5m in 2003, compared with slightly over 6m in 1971. Using prevalence estimates appropriate to the years in question, one can estimate that there were somewhere between 300 and 400 individuals with autistic disorders in the Province in 1971, compared with over 10,000 in 2003:

(year)	(population)	(pop. 0-18 yrs)	(prevalence)	(autism/PDD)
Year 1971	6,028,000	1,513,028	2/10,000	303
Year 2003	7,455,000	1,871,255	60/10,000	11,228

The most conservative evaluation should show that the increase in autistic disorders in Quebec has probably exceeded 3,000% in the last thirty years. It is unlikely that any other childhood disease has increased at anything like the same rate.

68. Paper by Blaxill, *What's Going On? - The Question of Time Trends in Autism*, published in *Public Health Reports*, Nov-Dec 2004, Vol 119, pp 536-551

This was an important and very detailed review of whether there were autism increases. The author reviewed the available survey literature and found evidence of large increases in prevalence in both the US and UK. These could not be explained away by changes in diagnostic criteria or improved case assessment. He reported that:

- incomplete ascertainment of autism cases in young child population is the largest source of predictable bias in prevalence surveys; however, this bias has if anything worked against the detection of an upward trend.
- Comparison of autism rates by year of birth for specific geographies provides the strongest basis for trend assessments. Such comparisons show large recent increases in rates of autism and ASD
- Reported rates of autism in the US increased from less than 3 per 10,000 children in the 1970s to greater than 30 per 10,000 in the 1990s, a ten-fold increase
- In the UK, autism rates rose from less than 10 per 10,000 in the 1980s to roughly 30 per 10,000 in the 1990s.

- Reported rates for the full spectrum of ASD rose from the 5 to 10 per 10,000 range to the 50 to 80 per 10,000 range in the two countries
- A precautionary approach suggests that the rising incidence of autism should be a matter of urgent public concern

The rates that Blaxill reviewed in his study are reported earlier in this document.

Blaxill concludes that:

- the evidence that supports an increasing rate of autism in the UK and US has gathered strength
- reviews that have downplayed the rising trend have over-emphasized unimportant methodological problems, employed flawed methods and failed to take into account the most relevant biases in methodology
- a comparison of UK and US surveys, taking into account changing definitions, ascertainment bias and case-finding methods, provides strong support for a conclusion of rising disease frequency
- the review has found little evidence that systematic changes in survey methods can explain these increases, although better ascertainment may still account for part of the observed changes

69. Study by Newschaffer, Falb and Gurney, Center for Autism and Developmental Disabilities Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore and Divisions of Epidemiology and Clinical Research, University of Minnesota, Minneapolis, US, *National Autism Prevalence Trends From United States Special Education Data*, published in *Pediatrics*, Vol 115 No 3 March 2005 ppe277-e282

This was an important paper, as it re-confirmed the findings of the MIND study by Dr. Robert Byrd, that autism really had increased significantly, and it was not a case of past misdiagnosis, greater awareness or diagnostic switching.

The objective of the study was to use national (US) data sources to compare the prevalence of autism with that of other disabilities amongst successive birth cohorts of US school-age children. The study used a comparison of birth-cohort curves constructed from administrative data, for children aged 6 to 17 years between the years 1992 and 2001.

The study reported the following results:

- clear cohort differences are apparent for autism, i.e. prevalence increases with successive younger birth cohorts

- this effect is greatest for cohorts born between 1987 and 1992. For cohorts born after 1992, the rate of increase in prevalence for successive birth years does not appear to be as great as for the previous birth cohorts
- it has been suggested that increased substitution of the autism diagnosis in place of mental retardation and/or language impairment diagnoses might account for some of the apparent increase in autism prevalence. If this substitution occurred with special educational classifications, then increases in autism prevalence with subsequent birth cohorts would be accompanied by decreases in mental retardation and/or speech/language impairment prevalences. It was found that mental retardation prevalence shows no birth cohort effect, in other words there is no suggestion that prevalence of the latter is decreasing or increasing amongst younger birth cohorts
- similarly, the data for speech/language impairment indicated no cohort differences
- prevalence trends for the mental retardation and speech/language categories have not increased over time. This is of particular interest because it has been speculated that children who in past years might have been classified in one or other of these categories are now being classified in the “autism” category, and that this “diagnostic shifting” could be responsible for observed apparent prevalence increases
- Because there was no indication of decreases in one or other of mental retardation/speech/language impairment categories concomitant with (and of similar magnitude to) increases in autism classification prevalence, these data do not support the hypothesis of diagnostic shifting
- Like autism, other health impairment classification prevalence has increased dramatically in successive birth cohorts during the past decade. Several State Departments commented that increases in other health impairment counts are being driven primarily by increasing numbers of children with ADHD
- Recent data have generally continued to suggest ASD prevalence growth (Jick et al, Yeargin-Allsopp et al 2003), with one exception. Lingham, Miller, Taylor et al (2003) used data on autism in East London UK in 2000 to predict expected numbers of cases according to birth cohort, correcting for under-ascertainment among younger children using a statistical model, and the data suggested prevalence leveling, beginning with the 1993 birth cohort

The authors did acknowledge a number of limitations to their study. Numerators were incomplete as some US school-age children with ASD and/or the other conditions considered in the study had not acquired special education classifications and/or were educated outside the State school system.

Also, data were more susceptible to diagnosis/classification bias than were data from research studies incorporating rigorous case definitions and case-confirmation criteria. The Individuals With Disabilities Education Act (IDEA) definition of autism was considered general enough to encompass all ASD, but State eligibility criteria and the way they were implemented could limit, for instance, the extent to which higher-functioning children on the autism spectrum received autism special educational classification. However, these limitations did not alter the outcome of the study.

The authors concluded that “the drastic increase in the prevalence of the autism classification (my emphasis) presents a major challenge to the nation’s special education service.”

## PART F:

# 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. Summaries of their studies, and criticisms of them, are set out here.

70. 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.....*”

ÿ 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.

Y 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 a penetrating 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

71. 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:

Y 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.

Y 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”.

72. 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:

ÿ 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.

ÿ Changing social attitudes have shifted stigma away from autism and onto mental retardation

ÿ 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

ÿ 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:

ÿ The views of parents, professionals and others, who testify that autism is now being seen in unprecedented numbers

ÿ 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

ÿ 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

### 73. 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.

ÿ 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

ÿ During the study period, prevalence of autism increased from 5.8 per 10,000 to 14.9 per 10,000

ÿ During the same period, the prevalence of mental retardation without autism decreased from 28.8 per 10,000 to 19.5 per 10,000.

ÿ 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.

A detailed commentary on the Croen et al study was published by Blaxill et al in the *Journal of Autism and Developmental Disorders*, Vol 33, No. 2, April 2003, criticising the following errors:

- \* they did not consider the trend information within their own dataset
- \* they did not consider obvious ascertainment biases within their youngest autism cohorts
- \* They did not consider similar ascertainment biases in the mental retardation category
- \* they did not analyse the implications of their own records review
- \* they did not define a key element of their principal disease frequency measure prevalence

And that correcting the first four of these errors is sufficient to controvert the authors' argument.

**74. 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:

- ÿ 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.
- ÿ The lower reported prevalence in 3- and 4-year olds might reflect lower sensitivity of case identification for disorders, which were often diagnosed later
- ÿ 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:

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

75. Jick et al, Boston University School of Medicine, *Increase in Autism is Due to Changes in Diagnosis, Pharmacotherapy, 2003; 23; 1524-30, December 2003*

This study set out to identify whether the number of diagnosed cases of autism had progressively increased over the previous decade, and, if it had, what environmental factors were related to any increase.

The study documented numbers of children in the UK diagnosed with behaviour and developmental disorders and with autism. It found that numbers of children with behaviour and developmental disorders tended to decrease by about 20% per year, 1992-2000, whereas the diagnosis of autism increased by 20% per year during the same time period.

The conclusion of the study was that increased incidence of diagnosed autism is primarily a reflection of changes in diagnostic practices, such as

improved identification. The authors did acknowledge that there had been a major increase in autism diagnoses.

The researchers also compared 126 autistic boys with non-autistic male controls. It found that there was no difference in the frequency of medicines or vaccines received by autistic cases compared with controls. There was no differences in medicines or illnesses between mothers of the two groups.

The study concluded that neither medicines (including vaccines) nor medical illnesses were responsible for the increase in autistic children. The study author, Jick, claimed that it “provides compelling evidence that vaccines, including MMR, are not the cause of the rise (in autism)”.

The study prompted comforting headlines in the UK press, such as “Autism Rise May Be A Myth” (Sunday Times, UK, January 2004). Jick commented: *“This represents compelling evidence that the children haven’t changed but the diagnosis has”*. However, there was a note of caution, that the authors *“do not rule out the possibility that MMR or another drug might trigger autism in an individual child, but that it cannot be responsible for the large rise.”*

Comment: it is mathematically impossible for cases of developmental disorders to decrease 20% year-on-year as cases of autism increase year-on-year as a consequence of the decrease. The numbers will not fit. This suggests that either the data of this study is suspect, or its interpretation is flawed, or that the claims being made of it are not supported by the data.

Comparing administration of medicines and vaccines between autistic/non-autistic groups proves nothing, and is irrelevant to the MMR debate. No one is claiming that giving MMR, in itself, causes autism. There have to be other co-factors, such as the state of health of the child, the state of its immune system, and genetic susceptibility due to familial background.

The Jick study appears to hinge upon a simplistic and erroneous hypothesis. It therefore offers no evidence in relation to links with MMR. To describe this study as “compelling evidence” is wholly unwarranted. That such a study should be so highly acclaimed is in itself revealing.

The US parent Mark Blaxill commented:

- \* Jick et al mischaracterize their “key measures”, erring by calling them either “year of diagnosis” or “year of birth
- \* they contradict their own previously-reported autism rates
- \* they fail to match the age ranges, diagnosis periods and birth years in their study population, introducing unnecessary biases in trend assessment

- \* they ignore the absence of diagnostic substitution during most of their study period
- \* they make no attempt to identify misreported cases of autism or developmental delay

These criticisms render the Jick et al study as unreliable and inconclusive.

76. Study by Smeeth, Fombonne, Hall et al, Department of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Department of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, and Department of Psychiatry, McGill University, Montreal, *Rate of First Recorded Diagnosis of Autism and Other Pervasive Developmental Disorders in United Kingdom General Practice, 1988 to 2001*, published in *BMC Medicine*, 2: 39, November 2004

This study analysed the rates of first diagnosis of pervasive developmental disorders amongst people registered with GP practices that were part of the UK GP Database during 1988-2001. It included 1,410 cases drawn from over 14 million person-years of observation. The main outcome measures were the rates of diagnosis of PDD, by the year of diagnosis, the year of birth, by gender and by geographical region.

The study found that:

- the rate increased progressively from 0.40/10,000 person years in 1991 to 2.98 per 10,000 person years in 2001
- there was a similar increase in standardized incidence ratios, from 35 in 1991 to 365 in 2001
- the temporal increase was not limited to children born during specific years, nor to children diagnosed in a specific time period
- the rate of diagnosis of PDDs other than autism rose from zero for 1988-92 to 1.06 per 10,000 person-years in 2001
- the rate of diagnosis of autism also increased, but to a lesser extent
- there was marked geographical variation in rates, with standardized incidence ratios varying from 66 in Wales to 141 for SE England

The study concluded that better ascertainment of diagnosis was likely to have contributed to the observed temporal increase in rates of diagnosis of PDD, but the authors could not rule out a real increase. The study claimed to be on of the largest undertaken of trends in the incidence of autism

The study authors had to admit to a considerable number of uncertainties, and make a number of suppositions. Uncertainties included:

- it was “likely” that a proportion of cases in the “autism” diagnostic category had a form of PDD other than autism
- the inaccuracy of diagnosis within the GP research database was “likely” to reflect changes in the definition of PDD
- inflation in the number of cases in later years “could have” occurred as other PDD diagnoses came into widespread use and some previously-undiagnosed children were diagnosed
- greater ascertainment of high functioning autism “may partly explain” the increased incidence of autism
- better detection of less severe cases alone cannot explain all the increases
- geographical variation “may” reflect differences in service provision and parental awareness in different regions
- the accuracy of the data “may” have changed during the study period
- these factors “could explain only a very small part” of the increased rates observed
- the nature of the study precluded the authors from assessing how often children with PDDs were not diagnosed

The study team concluded that the extent to which the increase in incidence that were documented was uncertain.

Comment - there are many criticisms that can be made of this study, many of which are identified by the study team themselves as potential confounding factors.

The study clearly found large increases, and attempted to shrug these off by linking them to factors such as better diagnosis and greater awareness. However, it was unable to accurately weigh these factors and quantify their individual influence. It is therefore the case that the study has very limited value. It is again interesting that the study authors seem anxious to avoid reaching the conclusion that there has been a large real increase in autism.

77. Study by Barbaresi, Katusic et al, *Incidence of Autism In Olmsted County Minnesota, 1976-1997 - Results From A Population-Based Study*, published in *Archives of Pediatrics and Adolescent Medicine*, January 2005, vol 159 pp37-44

**This study examined whether there was any connection between immunization and increases in autism. It examined data from the Rochester Epidemiology Project, a database of all inpatient and outpatient records in Olmsted County, Minnesota, US. It reviewed the medical and school history of a group of children with autism.**

**It found that autism was stable until 1988-1991, and then increased. Autism was found by the study to be 5.5 cases per 100,000 children from 1980 to 1983 - this seems extraordinarily low, but may provide evidence that autism was extremely rare before the mid-1980s.**

**It then found that cases were 44.9 per 100,000 for 1997. This was reported as an 8.2-fold increase. The increase was “confined to children younger than 10 years old who were born after 1997.”**

**Its lead author claimed that This study is the first to measure the incidence - the occurrence of new cases - of autism by applying consistent contemporary criteria for autism to a specific population over a long period of time.....In doing so, the study accounts for improvements in the diagnostic criteria for autism, the medical community’s improved understanding of this disease, and changes in Federal education laws.”**

**Barbaresi et al argued that prior to the introduction of new autism criteria in 1987, children affected may have been given less precise diagnoses such as developmental delay or mental retardation. They also argued that milder cases may not have been identified at all.**

**Reviewing the medical and school histories of a group of Olmsted County (Minnesota) schoolchildren showed that the incidence of autism “was stable until 1988-91, then increased after new laws and new diagnostic criteria were implemented.**

**The study concluded that:**

- increased incidence of autism in Olmsted County coincided with broadening of the diagnostic criteria for autism in 1987**
- it also coincided with the introduction of federal special education laws that included autism as a disability**
- the study speculated that prior to the new criteria, children with autism might have been given less precise diagnoses such as developmental delay or mental retardation, with children with mild autism not being identified at all**

**Comment: the problem with the Barbaresi study is that it is not up to date. For example, it argues that “the incidence of autism was stable until 1988-**

1991, then increased after new laws and new diagnostic criteria were introduced.” But this does not explain why numbers of children and young people ages 6-21 diagnosed under IDEA as autistic increased from 22,780 in 1994 to 166,302 in 2004. The timeframe of these latter figures is largely missed by Barbaresi.

The criteria did not change repeatedly during the decade 1994-2004. And the scale of the increase - an over six-fold increase, up 630% in a decade - remains unexplained.

Barbaresi et al's study is useful in explaining much, or even most, of early increases in the 1980s, although the study's finding that increases were concentrated at the under 10 years age group is compatible with the theory that high rates of autism are or have been affecting this younger age group from the late 1980s - a hypothesis that in turn is compatible with damage from an accelerated vaccination schedule and either increased intake of thimerosal or some other vaccine-related causal mechanism.

**Conclusion** - this study cannot be taken as evidence that autism did not markedly increase during the late 1980s and subsequently. Nor can it be taken as evidence that any increases could not be vaccination-related. Diagnostic switching and altered criteria may play a part in part-explaining increases, but the study does not provide accurate evidence as to what extent this might be true.

78. Study by Laidler, Department of Biology, Portland State University, Portland, Oregon, US Department of Education Data on Autism Are Not Reliable for Tracking Autism Prevalence, published Pediatrics Vol 116 No 1 July 2005 pp e120-e124

This study examined the Individuals with Disabilities Education Act (IDEA) data - see earlier - which is collated by the United States Department of Education (USDE), and whether it gave an accurate assessment of autism numbers and increases. The paper found:

- examination of data reveals anomalies within the data on autism
- diagnosis of autism is completely subjective. There are no objective findings (or tests) that are diagnostic for autism
- USDE data show not only a rise in overall autism prevalence, with time, but also a significant and nearly-linear rise in autism prevalence within a birth-year cohort as it ages, with significant numbers of new cases as late as 17 years of age
- There are indications that the increasing awareness of autism in the medical and educational communities may have led to a gradual shift in diagnosis to include less disabled individuals who would not have



previously been described as autistic, or who would have received a different diagnosis

- The guidelines for educational assessment of autism vary from State to State (Oregon is cited as an extreme example of divergence from DSM-IV)
- In addition, an unexpected reduction in the rise of autism prevalence occurs in most cohorts at 12 years of age
- These problems point to anomalies in USDE data, making them unsuitable for tracking autism prevalence
- USDE data are at odds with studies of autism prevalence

The study referred to an earlier review by Wing and Potter as “excellent”. The deficiencies in that study are described elsewhere in the review.

Comment: it is acknowledged that IDEA data were never designed to track autism prevalence in the community, and contain inaccuracies due to varying approaches to diagnosis at the local level. However, questioning the accuracy of the IDEA data does not neutralize the data’s evidence of a soaring increase in autism amongst young US residents.

Some of Laidler’s criticisms are vague (“may have led to a gradual shift”). Laidler also does not address the findings of other researchers who have found historically record-high rates of autism. For instance, Laidler does not explain, or mention, the 1 in 166 figure quoted by the Centers for Disease Control, a figure not based upon education data.

## **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.)

**79. 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:

- ÿ The Buynak study identified viral “interference”. The follow-up period was only 12 days
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ The Minekawa study confirmed viral interference. The follow-up period was only 15 days.
- ÿ 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.
- ÿ 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.
- ÿ 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.

- ÿ 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)
- ÿ The Stokes, Schwartz, Miller and Eddes studies were therefore all too small or too superficial to pick up uncommon adverse events.
- ÿ 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.

80. 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:

- ÿ *“Evidence on safety was very thin”, and “Too few children were followed for a sufficient time”*
- ÿ *“Big numbers were necessary, and computerised databases were already in place to permit this, but it was not done”*
- ÿ *“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)*
- ÿ *“The granting of a product licence was premature”*

81. 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:

- ÿ 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
- ÿ 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
- ÿ 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
- ÿ Autism that might be produced will not necessarily appear at a specific point after vaccination
- ÿ Complex long term control trials may be required to show MMR to not be involved in the pathogenesis of autism
- ÿ Research into the background pathogenesis of autism is currently shockingly inadequate

82. 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:

- ÿ 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
- ÿ These children actually lose previously-acquired skills
- ÿ Children with the new autism have gastrointestinal, neurological, sensory and endocrine difficulties
- ÿ 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

- ÿ 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
- ÿ 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.

### 83. 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.

- ÿ 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.
- ÿ 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. Immruvax also tested in seven studies. But Shattock questions whether studies are published or secret. Wakefield & Montgomery can only comment on what is published.
- ÿ 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.

- ÿ 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.
- ÿ 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?
- ÿ Watson: the “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.
- ÿ 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.
- ÿ 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?
- ÿ 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:

- ÿ 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”
- ÿ 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.....

- ÿ 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!
- ÿ 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!)
- ÿ 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.
- ÿ 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?
- ÿ 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 involved in the original trials?)

**84. 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.

- ÿ 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.

- ÿ “*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.
- ÿ “*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.
- ÿ “*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)
- ÿ “*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.
- ÿ “*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?
- ÿ “*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.

#### 85. Failure to Properly Test Vaccines

In late 2005, the Cochrane Collaboration reported on the absence to date of proper testing of the safety and effectiveness of MMR. The Cochrane study is reported elsewhere.

On 20<sup>th</sup> November 2005, writing in BMJ.com rapid responses, the New Zealand freelance journalist Hilary Butler pointed to a systematic failure to test new vaccines against a cross-section of the population. In evidence to support this charge, he quoted contemporary (2005) advertising for participants for safety trials of a new smallpox vaccine, who had to be:

- in good general health
- not pregnant or lactating

but the trial did not want applicants who:

- did military service prior to 1989
- had a history of previous smallpox vaccination
- had a known or suspected history of immunodeficiency, or with current radiation treatment or use of immunosuppressive or antineoplastic drugs
- had a household member or intimate contact with any of those conditions
- had known or suspected impairment of other immunologic function
- had malignancy including squamous cell or basal cell skin cancer at vaccination site
- had active autoimmune disease
- were subjects with known eye diseases or other conditions that required the use of corticosteroid eye drops
- had known/history of cardiac disease
- were subjects who had been diagnosed with three or more of the following risk factors: high blood pressure, elevated blood cholesterol levels, diabetes, high blood sugar, first-degree relative who had a heart condition before age 50 years, or smoked cigarettes
- were subjects with a history of palpitations or abnormalities of cardiac rhythm
- were subjects with odd ECG patterns
- were subjects with a 10% or greater risk of developing a myocardial infarction or coronary death within the next 10 years

- had positive or elevated creatinine kinase, CK-MB or Troponin I lab test levels
- had abnormalities of various other assessments
- had a current diagnosis or past history of eczema
- were subjects with a household member or intimate contact with the conditions listed above
- had any presence of acute, chronic or exfoliative skin conditions, open wounds or burns
- any history of keloid formation
- had known allergies to MVA or any known components (neomycin, gentamycin) of the vaccine
- had known allergies to eggs or egg products
- had known allergies to a number of other vaccine components
- had known allergies to antibiotics such as neomycin, streptomycin, chlortetracycline and polymixin B

## PART H

### STUDIES THAT POINT TOWARDS THE PLAUSIBILITY OF A GUT/AUTISM, MMR/GUT/AUTISM, THIMEROSAL/AUTISM OR AUTOIMMUNE/AUTISM LINK

86. Paper by Nelson and Gottshall, *Enhanced Toxicity for Mice of Pertussis Vaccines When Preserved With Merthiolate*, Applied Microbiology May 1967 pp590-593

The summary of this article stated: “Pertussis vaccines preserved with 0.01% merthiolate are more toxic for mice than unpreserved vaccines prepared from the same parent concentrate and containing the same number of organisms

The toxicities of both merthiolate (0.01%) preserved and unpreserved vaccines increased when the number of organisms injected was increased. An increase in mortality was observed when merthiolate was injected separately, before or after an unpreserved saline suspension of pertussis vaccine.”

The discussion section noted: “The greater toxicity in mice of merthiolate preserved pertussis vaccine compared with unpreserved vaccine may be due to (1) reactivation by merthiolate of an atoxic bacterial toxin, (2) lysis of bacterial cells by merthiolate with liberation of an endotoxin, (3) increase in susceptibility of the mice to the toxicity of merthiolate induced by pertussis

vaccine, or (4) increase in susceptibility to the toxicity of pertussis vaccine induced by merthiolate.”

“In all of the experiments, deaths were distributed throughout the seven-day observation period, and the times of death gave no clue as to whether the vaccine injected was slightly toxic or was one which was atoxic with the toxicity being due to the addition of merthiolate.”

87. Paper by Eggers, *Autistic Syndrome (Kanners) and Vaccination Against Smallpox*, *Klinical 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, fully 22 years before the Wakefield team’s Lancet paper of February 1998. If such a link was recognised a quarter of a century ago, why has so little been done since to research it?).

88. Paper by Weizman, Weizman, Szekely, Livni and Wijzenbeek, 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

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

This includes:

- ÿ the noting of the potential relevance of antimyelin autoantibodies
- ÿ 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
- ÿ references to indirect evidence of immune activation in autism
- ÿ 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
- ÿ reference to Todd and Ciaranello's detection of circulating antibodies in seven out of thirteen children with autism

90. 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:

- ÿ antibodies to myelin basic protein were present in 20 out of 22 TA and 4 out of 18 PAS children
- ÿ 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)
- ÿ 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
- ÿ 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

91. 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

92. 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

93. 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.

94. 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:

- ÿ antibodies were found in nineteen of the 33 (58%) of autistic children
- ÿ the corresponding level for controls was 7%, or over eight times higher
- ÿ 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.

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

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

This found that:

- ÿ among 16 children diagnosed with autism, there was a threefold increase in their serum rubeola titers over the expected normal range



- ÿ 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
- ÿ 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

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

This found that

- ÿ 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
- ÿ 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.....
- ÿ 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*)
- ÿ 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

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

This letter reported:

- ÿ That there had been 24 notifications of temporary gait disturbances after MMR vaccination
- ÿ 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.

ÿ 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)

98. 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:

ÿ 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.

ÿ 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

ÿ A longitudinal birth cohort of 11,407 subjects was one unvaccinated comparison cohort, and 2,541 partners of those vaccinated was another

ÿ 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.

ÿ 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.

99. 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.

100. 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 Università 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:

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

- ÿ 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).
- ÿ The presence of A3 and/or DR7 was observed in 22/30 (73.3%) of the patients.
- ÿ 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.
- ÿ They noted that any interference with the process of presentation of the antigen can predispose to an autoimmune disease.
- ÿ 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.

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

This found that:

- ÿ measles produces immune suppression which contributes to an increased susceptibility to other infections
- ÿ high-titred measles vaccines have been linked to increased long-term mortality among some female recipients

ÿ 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

102. 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:

- ÿ 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
- ÿ 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
- ÿ 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
- ÿ 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
- ÿ 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

103. 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:

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

These researchers found that:

- ÿ 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

- ÿ this was negatively correlated with measles antibody level at 3 months
- ÿ CD8 T-cells, soluble CD8, neopterin and beta2-microglobulin were increased at 2 weeks in the SW9 group
- ÿ soluble CD8 and beta2-microglobulin remained elevated at three months
- ÿ therefore measles immunisation resulted in suppression of lymphoproliferation, which was most evident in infants with the highest antibody responses and most immune activation

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

This found that:

- ÿ 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
- ÿ 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

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

This paper reported that:

- ÿ The authors had evaluated the possible role of MMR in the pathogenesis of autism by comparing rubeola titers in autistic and normal children.
- ÿ Amongst 16 children diagnosed with autism followed in their clinical practice, it had been found that these children had a threefold increase in their rubeola titers over the expected normal range. These had been compared with the rubeola titers from 13 normal controls.
- ÿ Subjectively, parents had stated that their children's developmental milestones deteriorated following MMR vaccination.
- ÿ 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.

**106. 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.

- Y 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
- Y 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.
- Y 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
- Y 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.
- Y 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?

**107. 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.

In March 2004, six years after the paper was published, 10 of the 13 original authors issued a statement:

*"The main thrust of the paper was the first description of an unexpected intestinal lesion in the children reported.... We wish to make it clear that in this paper, no causal link was established between MMR vaccine and autism*



*as the data were insufficient. However, the possibility of such a link was raised and consequent events have had major implications for public health. In view of this, we consider now is the appropriate time that we should together formally retract the interpretation placed upon these findings in the paper.”*

This statement was widely and erroneously publicised as a retraction of the paper, rather than a retraction of the interpretation of the paper - a crucial misunderstanding. Also, the remaining three authors, messrs. Wakefield, Linnell and Harvey - not just Dr. Wakefield alone - did not sign the statement, and indeed argued strongly to the contrary. However, the press subsequently referred to the paper as “discredited”, again a crucial misrepresentation.

The link between autism and a novel intestinal condition was not retracted, by any author. Again, the lay media largely missed this crucial point.

In a subsequent letter to the Sunday Times, which led the attack on Wakefield at the time of the above statement, Dr. Wakefield stated:

“Your (the Sunday Times’s) investigation suggested that I had a conflict of interest due to the fact that a subsequent and separate study, involving some of the same children from the first case report, was part-funded by the (UK) Legal Aid Board - funding that went into the research, not to me. Subsequently, the Lancet editor and ten of my former colleagues, who had collaborated on the original research, wrote in The Lancet to state their view that the reference to the timing of the MMR vaccination and the onset of the children’s symptoms (as given in the history by the parents of these children) should not have been included in the case report. These are matters of opinion.

“What they (the ten authors) do not dispute is the fact that these children have a form of inflammatory bowel disease. It is therefore simply not the case that the original Lancet report has been discredited or “fatally flawed”. Every aspect of this report has been supported by subsequent clinical and laboratory studies.”

Dr. Wakefield further commented, in The Lancet:

“Various claims were made by agents of The Sunday Times (UK newspaper) of February 22nd 2004 against those of us involved in The Lancet 1998 report. These claims included inappropriate patient referral, inappropriate use of legal aid funding, lack of ethics approval, unmerited clinical investigation, and keeping secret for six years the involvement of the Legal Aid Board in a separate study. All of these claims have been investigated and we know they are unfounded, and vigorously deny them.”

The Lancet commented, in response to allegations by journalist Brian Deer in The Sunday Times (UK):

<i>(original Sunday Times allegation, as quoted by The Lancet)</i>	<i>(Lancet's own response, in their Statement)</i>
1. "Ethics approval for the investigations conducted on the children reported in the study, some of them highly invasive (eg lumbar puncture) had not been given"	"The evidence we have seen indicates that ethics committee approval was given for data collection from clinically-inducated investigations in the children with an initially undiagnosed illness and who were described in the 1998 Lancet paper.....In summary, the evidence does not support this allegation"
2. "That the study reported in The Lancet was completed under the cover of ethics approval for an entirely different study"	"The evidence we have seen indicates that there was no attempt by investigators to conduct the study of children reported in The Lancet in 1998 under cover of an entirely different investigation.....The evidence does not support this allegation"
3. "Children were invited to participate in the study by Dr. Andrew Wakefield and Professor John Walker-Smith, thus biasing the selection of children in favour of families reporting an association between their child's illness and the MMR vaccine"	"The children were indeed consecutively referred.....As far as the facts can be ascertained by a review of the case notes and from memory, children reported in the 1998 Lancet paper were consecutively referred to the Royal Free and were not deliberately sought by the authors for inclusion in their study based on parents' beliefs about an association between their child's illness and the MMR vaccine" (In other words, the evidence as far as can be ascertained does not support this allegation)
4. "That the children who were reported in the Lancet study were also part of a Legal Aid Board funded pilot project, led by Dr. Wakefield.....the existence of which was not disclosed to the editors of The Lancet"	"Dr. Wakefield had two roles in this work. First, he was the lead investigator of a Royal Free study into the nature of a new syndrome with bowel and psychiatric symptoms. Second, he was commissioned through a lawyer to undertake virological investigations as part of a study funded by the

	<p>Legal Aid Board. At the time of submission and eventual publication of his Lancet paper, this second study had not been disclosed to the editors of The Lancet. We judge that it should have been so disclosed.....We believe that our conflict of interest guidelines at the time should have triggered such a disclosure.....(Despite Dr. Wakefield's response that) 'this Lancet publication.....adds nothing further to the issue of causation than that that was already well known to the lawyers').....the perception of a potential conflict of interest remains.....(and) this funding source should, we judge, have been disclosed to the editors of the journal"</p>
<p>5. "That the results eventually reported in the 1998 Lancet paper were passed to lawyers and used to justify the multi-party legal action prior to publication, a fact that was not disclosed to the editors of The Lancet"</p>	<p>(As above)</p>
<p>6. "That Dr. Wakefield received £55,000 from the Legal Aid Board to conduct this pilot project and that, since there was a substantial overlap of children, in both the Legal Aid Board funded project and the Lancet paper, there was a financial conflict of interest that should have been declared to the editors and was not"</p>	<p>(As above)</p>

The Lancet further commented: "we do not judge that there was any intention to conceal information or deceive editors, reviewers or readers about the ethical justification for this work"

Dr. Wakefield, amongst others, responded as follows:

"Allegation (4) completely misrepresents the facts. There were two quite distinct issues, the first a clinical report of 12 cases, and the second a hypothesis-testing laboratory study to examine for the presence or absence of measles virus in autistic children when compared with appropriate controls."

**“A minority of the children described in the 1998 Lancet report were part of the second study that was funded in part by the Legal Aid Board.....At the time that the children reported in the 1998 Lancet paper were referred to Professor Walker-Smith for investigations.....none of the 12 reported children were in fact legally aided, i.e. in receipt of legal aid certificates and therefore legal aid funding.”**

**“Whether parents perceived an association with MMR vaccine or not, whether parents had approached lawyers with the intent to seek legal redress, or whether children were in receipt of legal aid funding or not, had no bearing whatsoever on their selection for clinical investigation or inclusion in the Lancet report.”**

**“At the time the children underwent ileocolonoscopy.....one child had been granted a legal aid certificate. The authors had no knowledge of this fact until now.”**

**“Parents of children in the 1998 Lancet report have provided a written signed statement that (i) they contacted me for help, given their child’s gastrointestinal symptoms (ii) their referral to the Department of Pediatric Gastroenterology at the Royal Free was through their child’s doctor, (iii) that at no time did I encourage them to seek legal redress through the courts in the MMR class action, and (iv) that their child formed part of the initial study of 12 children reported in The Lancet in 1998.”**

**“Independently, I was commissioned through a solicitor, Richard Barr, to undertake quite separate virological studies on ten children. This is entirely in line with other university-based studies that have been similarly funded by the Legal Services Commission.....The list of children provided to me by Richard Barr was based upon his knowledge of an overlap between patients referred to in the Royal free and those whose parents had made contact with Richard Barr. I could not have constructed such a list since I had no knowledge of the litigation cohort or the legal status of the children within this cohort.....I had no specific knowledge of the legal status of the ten children on the list, other than as described above.”**

**“If and when.....studies are finally published, due acknowledgement will be made of all sources of funding, including that from the Legal Services Commission.”**

**“Allegation 5 is a complete misrepresentation of the facts. The results eventually reported in the 1998 Lancet paper were in the public domain long before their publication in February 1998.....There was no attempt to conceal these data.”**

(On allegation 6) “Funds received from the Legal Aid Board were paid into, and properly administered through, a research account with the special trustees of the Royal Free Hampstead NHS Trust.”

“If and when the relevant virological studies are finally published, due acknowledgement will be made of all sources of funding, including that from the Legal Services Commission.”

“The clinical and pathological findings in these children stand as reported.”

In fact, the Legal Aid Board funding, that was at the centre of the Sunday Times’ allegations, had actually been made public within the columns of The Lancet itself, by Dr. Wakefield, as early as May 1998, nearly six years before the Sunday Times ran its media story. In a letter in The Lancet of 2<sup>nd</sup> May 1998, Dr. Wakefield wrote: “*Only one author (AJW) has agreed to help evaluate a small number of these children on behalf of the Legal Aid Board. These children have all been seen expressly on the basis that they were referred through the normal channels (e.g. from general practitioners, child psychiatrists or community paediatricians) on the merits of their symptoms.*”

This letter thus directly addressed two of the Sunday Times’s eventual allegations of February 2004. Seemingly, and incomprehensibly, the Sunday Times was unaware of this letter when it ran its story.

The above information has been included here because there is a widely-held misapprehension that the 1998 Wakefield et al paper has been “fatally flawed” and compromised by these allegations. The controversial paper, and the science in it, stands.

108. 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:

ÿ Mumps infection before age 2 years was a risk factor for ulcerative colitis

- ÿ 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
- ÿ 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.

109. 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:

- ÿ 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
- ÿ 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
- ÿ 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
- ÿ 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
- ÿ 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

110. 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:

- ÿ 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
- ÿ Most autistic children with virus antibodies also had brain autoantibodies
- ÿ The more virus antibodies they had, the more likely they were to have the brain antibodies
- ÿ None of the non-autistic children had brain autoantibodies
- ÿ 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
- ÿ None of the autistic children in the study had had measles in the past, but all had had MMR vaccine
- ÿ 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.

111. 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:

- ÿ Solution phase RT PCR yielded specific MV N gene amplification in affected children (10/10)
- ÿ Distinct measles virus genome was identified in FDC reactive follicular centres by in-cell RNA amplification

- ÿ None of the normal controls showed any evidence of measles virus genome
- ÿ The data highlighted a possible causal link between measles virus infection and ileo-colonic lymphoid nodular hyperplasia in affected children

112. 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 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.

113. Paper by Horvath, Papadimitriou, Rabsztyl et al, *Gastrointestinal Abnormalities in Children With Autistic Disorder*, Department of Pediatrics, University of Maryland School of Medicine, Baltimore US, published in the *Journal of Pediatrics*, 1999 November, vol 135(5), pp559-563

The aim of this study was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms

- ÿ 36 children age 5.7 years +/- 2 years with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhoea, gaseousness and abdominal discomfort and distension
- ÿ The results were that histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15 and chronic duodenitis in 24
- ÿ The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects
- ÿ Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function
- ÿ 75% of the autistic children (27 out of 36) had an increased pancreatico-biliary fluid output after intravenous secretin administration



ÿ 19 out of 21 patients with diarrhoea had significantly higher fluid output than those without diarrhoea

The conclusions of this study were that:

ÿ Unrecognised gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioural problems of the non-verbal autistic patients

ÿ The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver

ÿ Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder

114. 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:

ÿ Do autistic children have a hyperimmune response (or increase of antibodies) for a specific virus?

ÿ Is there a relationship between virus antibodies and brain autoantibodies in autism?

In his studies, he reported two important observations:

ÿ 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)

ÿ 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:

ÿ He had previously already found that many autistic children had antibodies to a specific protein of the MMR vaccine

ÿ These viral antibodies were also related to positive titers of brain MBP autoantibodies.

Y 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:

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

115. Paper Presented to US Congressional Oversight Committee on Autism and Immunisation, Professor John O'Leary, Dublin Women's 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,

- (i) was measles virus present in gut biopsies of affected children?
- (ii) where was measles virus located in the gut biopsies of the affected children?
- (iii) how much virus was present?

Y 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.

- ÿ 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).
- ÿ Confirmation of the presence of measles virus genomes was achieved using positive and negative strand sequencing of cDNA measles amplicons.
- ÿ 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
- ÿ In the controls, only 1 of the 15 children (6.6%) was positive for measles virus.
- ÿ 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?”.

116. 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:

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

Y Sequences from patients with UC and children with autism were consistent with vaccine strain measles.

Y 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.

117. Scientific Review of Vaccine Safety Datalink Information By The US Centre for Disease Control, Simpsonwood Retreat Center, Norcross, Georgia, June 7th-8th 2000.

This paper, an early version of which is dated 29th February 2000 and which was titled “Thimerosal VSD Study Phase I” - with every page marked “Confidential - do not copy or release” - has since become widely known as the Verstraeten study. The paper was actually by Thomas Verstraeten, Robert Davis and Frank DeStefano. DeStefano will be remembered as one of the critical co-reviewers (along with Dr. Robert Chen) of the original 1998 Wakefield et al “Early Report” MMR paper in The Lancet.

This Simpsonwood 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.

The paper was suppressed, and a much later paper issued, with re-worked figures, to “prove” that there was no thimerosal/autism link. This earlier confidential paper proved that there was just such a statistical link, hence the inclusion here of this paper in a section reviewing evidence for a vaccine/autism association.

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, which itself was based upon US Health Management data from outpatient records from

Group Health Cooperative and from North California Kaiser, were that there was a statistically significant association between:

- ÿ A cumulative exposure to thiomersal-containing vaccines at 2 months of age and unspecified developmental delay
- ÿ A cumulative exposure at three months of age and tics
- ÿ A cumulative exposure at six months of age and attention deficit disorder
- ÿ A cumulative exposure at 1, 3 and 6 months of age and language and speech delay
- ÿ A cumulative exposure at 1, 3 and 6 months of age and neurodevelopmental delays in general

The key section of the discussion text from the Simpsonwood meeting is reproduced here, verbatim:

“The highest proportion of children in our cohort exceeded the Environmental Protection Agency limits (for mercury) at one and three months of age.....As for the exposure evaluated at 1 month of age, which is basically an evaluation of the neonatal hepatitis B dose, we have found a significant relationship to the outcome only for misery and unhappiness disorder (ICD code 313.1). We were not able to produce a graph for the relative risks at three months of this condition as no or few cases occur in the two lower categories. The relative risk for this condition was significantly increased (2.04) when comparing those with a cumulative exposure above 62.5ug at three months compared to those with cumulative exposure equal to or less than 62.5ug”.

“There is a nearly significant increased risk for the category exceeding 12.5ug at 1 month for attention deficit disorder. This group includes children that received two doses of hepB or their first dose of Hib or DTP in the first month of life. At three months, this positive relationship is no longer significant for any category”.

“As for the exposure evaluated at 3 months of age, we found increasing risks of neurologic developmental disorders with increasing cumulative exposure to thimerosal”.

“Within the group of developmental disorders, similar though not statistically significant increases were seen for the sub-group called specific delays (ICD9 code 315) and within this sub-group, for the specific disorder developmental speech disorder (dyslalia, ICD code 315.39) and for autism (ICD code 299.0), stuttering (ICD9 code 307.0) and attention deficit disorder (ICD9 code 314.0). This increase, when comparing each category of exposure to the lowest exposure group, was significant only for the entire category of

developmental disorders. For specific delays and speech disorders, this increase occurs only above 25ug.”

The background to these findings was the statement in the original study protocol that *“A relationship (between thimerosal and neurological damage) will be considered plausible if statistically significant or a relative risk of 1.5 or higher is found. This would allow weak suggestive findings to be further investigated, as we expect a bias towards the null of the relative risk, caused by the lack of sensitivity of the automated data”*. This was an acknowledgment that the findings were highly significant, given a background bias against the statistics revealing a link.

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 the transcript of some of the key participants’ discussion:

- ÿ Dr. Weil: *“There are just a host of neurodevelopmental data that would suggest that we’ve got a serious problem”*
- ÿ 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.”*
- ÿ *“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”*.
- ÿ *“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”*.
- ÿ 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”*. (a US parents’ note commented: doesn’t this sound familiar to all of you parents with autistic children?)
- ÿ 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”*.

The reaction of those present to these acutely-uncomfortable findings is best summed up by the comments of Dr. John Clements of the World Health Organisation, who was the WHO delegate to the meeting:

*"I really want to risk offending everyone in the room by saying that perhaps this study should not have been done at all, because the outcome of it could have , to some extent, been predicted, (my emphasis) and we have all reached this point now where we are left hanging, even though I hear the majority of consultants say to the Board that they are not convinced there is a causality direct link between thimerosal and various neurological outcomes. I know how we handle it from here is extremely problematic."*

The Simpsonwood participants also discussed how they could further manipulate the data to produce a different (one assumes, a less-disconcerting) outcome.

Verstraeten himself, the lead author, commented: *"Personally, I have three hypotheses. The first hypothesis is it is parental bias. The children that are more likely to be vaccinated are more likely to be picked up and diagnosed. Second hypothesis - I don't know. There is a bias I have not yet recognised, and nobody has yet told me about it" Third hypothesis. It's true. It's thimerosal."*

Congress had 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:

ÿ The key CDC researcher (Dr. Verstraeten) was subsequently hired by GlaxoSmithKline prior to his delivering a "modified" study to the IoM.

ÿ 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.

ÿ 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

ÿ 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

The Verstraeten study, and the discussion of it at Simpsonwood, is a revealing insight into how the authorities (including the World Health Organisation) "manage" uncomfortable study findings:

- \* keep them strictly confidential
- \* order further studies, but without sounding any alarms
- \* quietly act to reduce risk by recommending the removal of thimerosal, as a precautionary measure, whilst not announcing that there was/is a problem
- \* subsequently deny there was a problem

These actions enable the experts present to discharge their responsibilities and clear their consciences without damaging confidence in immunisation.

118. 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:

- ÿ demonstrated that OATP-A can mediate transport of the analgesic opioid peptides DPDPE and deltorphin II across the human BBB.
- ÿ 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.



119. 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.

- ÿ Ileocolonoscopy and biopsy were performed on 60 affected children (median age 6 years, range 3-16, 53 male)
- ÿ Developmental diagnosis were autism (50), Aspergers (5), disintegrative disorder (2), attention deficit hyperactivity disorder/ADHD (1), schizophrenia (1), dyslexia (1).
- ÿ The results were that ileal-lymphoid nodular hyperplasia (ILNH) was found in 54/58 affected children (93%) but only 5/35 (14.3%) controls.
- ÿ Colonic LNH was present in 18/60 (30%) affected children but only 2/37 (5.4%) controls.
- ÿ 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.
- ÿ Active ileitis was present in 4/51 (8%) affected children but not in controls.
- ÿ Chronic colitis was identified in 53/60 (88%) affected children compared with 1/22 (4.5%) controls and in 20/20 (100%) with UC.
- ÿ Scores of frequency and severity of inflammation were significantly greater in both affected children and those with UC, compared with controls.

120. 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:

- ÿ *“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”*

ÿ *“The early epidemiological findings are worrisome. The clinical and laboratory data strongly suggest the biological plausibility of a link between MMR and autistic disorders”*

ÿ (He) *“.....strongly endorses immunisation as a pillar of public health strategy for most diseases. But one should never surrender caution”.*

121. 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:

ÿ Ileocolonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms.

ÿ 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.

ÿ Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness.

ÿ 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.

ÿ CD8+ density and intraepithelial lymphocyte numbers were higher than those in the Crohn’s disease, LNH and normal control groups

ÿ CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups.

ÿ Epithelial, but not lamina propria, glycosaminoglycans were disrupted.

ÿ 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.

122. Paper by Bernard, Enayati, Redwood et al, AARC Research, Cranford, New Jersey, *Autism: A Novel Form of Mercury Poisoning*, published in *Medical Hypothesis*, 2001, 56 (4), 462-471

This paper was an important milestone in the mercury/vaccine/autism debate. The paper noted that:

- in 1999, the FDA and the American Academy of Pediatrics had determined that the typical amount of Hg (mercury) injected into infants and toddlers via childhood immunizations exceeded government safety guidelines for an individual. The detail on this was set out by Halsey at the National Vaccine Advisory Committee Workshop on thimerosal and vaccines, August 11<sup>th</sup>-12<sup>th</sup> 1999
- Past cases of mercury poisoning presented with considerable variation, depending on dose, type of mercury, method of administration, duration of exposure and individual sensitivity
- It was hypothesized by the paper's authors that the regressive form of autism represents a further form of mercury poisoning. This was based upon an analysis of both the traits of mercury poisoning and the traits of regressive autism, and the acknowledged existence of mercury exposure through vaccination (through thimerosal preservative)
- Other phenomena were consistent with a causal Hg/ASD link. These included (a) symptom onset shortly after vaccination, (b) ASD prevalence increases corresponding to vaccination increases, (c) similar sex ratios of affected individuals, (d) a high heritability rate for autism paralleling a genetic predisposition to Hg sensitivity at low doses, and finally (e) parental reports of autistic children having elevated Hg levels

The respective traits of autism and of mercury poisoning are described in the paper as follows:

<i>Autism</i>	<i>Mercury poisoning</i>
Impairments in sociality, most commonly social withdrawal or aloofness	Extreme shyness, indifference to others, active avoidance of others, desire to be alone
Variety of stereotypical behaviours	Problems with stereotypical behaviours
Need for sameness and exhibition of obsessive-compulsive tendencies	Schizoid and obsessive-compulsive traits
Diagnoses that include childhood schizophrenia, depression, anxiety disorder	Diagnosis is sometimes "psychiatric disorder". Other manifestations are depression, lack of interest, mental confusion

<b>Irrational fear</b>	<b>Anxiety and fearfulness</b>
<b>Poor eye contact</b>	<b>Poor eye contact</b>
<b>Aggressive behaviour, temper tantrums, irritability, inexplicable changes in mood</b>	<b>Irritability, aggression, tantrums, emotionability</b>
<b>Failure to develop meaningful speech</b>	<b>Marked difficulty with speech</b>
<b>Some clumsiness and lack of co-ordination</b>	<b>Movement disturbances, poor co-ordination</b>
<b>Unusual behaviours such as toe-walking, rocking, abnormal postures, spinning, hand-flapping</b>	<b>Rocking, unusual postures, hand-flapping (an unusual and thus significant marker)</b>
<b>Over- or under-reaction to sound</b>	<b>Sensory issues reported in virtually all cases</b>
<b>Deficit in language comprehension</b>	<b>Ditto</b>
<b>Pain sensitivity or insensitivity</b>	<b>Ditto</b>
<b>General aversion to touch</b>	<b>Ditto</b>
<b>Visual disturbances including sensitivity to light</b>	<b>Ditto</b>

The paper noted:

- **organic mercury, which readily crosses the blood-brain barrier, preferentially targets nerve cells and nerve fibres**
- **primates accumulate the greatest Hg levels in the brain relative to other organs**
- **although most cells respond to mercurial injury by modulating levels of glutathione, metallothionein, hemoxygenase and other stress proteins, neurons tend to be markedly deficient in these responses and are thus less able to remove Hg and are more prone to Hg-induced injury**
- **in the developing brain, mercury interferes with neuronal migration, depresses cell division, disrupts microtubule function and reduces neural cell adhesion molecules, which are critical during brain development for proper synaptic structuring**
- **whilst damage has been observed in a number of brain areas in autism, many nuclei and functions are spared. Mercury poisoning's damage is similarly selective**

Also:

- **some autistic children show a low capacity to oxidize sulphur compounds and have low levels of sulphate. This may be linked with Hg poisoning because Hg preferentially binds to sulfhydryl molecules**

such as cysteine and glutathione, thereby impairing various cellular functions

- mercury can irreversibly block the sulphate transporter NaSicotransporter NaSi-1, present in kidneys and intestines, thus reducing sulphate absorption
- besides low sulphate, many autistic children have low glutathione levels, abnormal glutathione-peroxidase activity within erythrocytes and decreased hepatic ability to detoxify xenobiotics
- glutathione participates in cellular detoxification of heavy metals
- hepatic glutathione is a primary substrate for organic-Hg clearance from humans
- intra-neuronal glutathione participates in various protective responses against Hg in the central nervous system
- by preferentially binding with glutathione, preventing absorption of sulphate, or by inhibiting the enzymes of glutathione metabolism, Hg might diminish glutathione bioavailability
- low glutathione can also derive from chronic infection, which would be more likely in the presence of immune impairments arising from mercury
- mercury also disrupts purine and pyrimidine metabolism. Altered purine or pyrimidine metabolism can induce autistic features and classical autism, suggesting another mechanism by which mercury can contribute to autistic traits

Children with autism are also more likely to have allergies, asthma, selective IgA deficiency, enhanced expression of HLA-DR antigen and an absence of interleukin-2 receptors, as well as familial autoimmunity and a variety of autoimmune phenomena, including elevated serum IgG and ANA titers, IgM and IgG brain antibodies, and myelin basic protein antibodies.

The paper also noted that similar atypical responses to Hg have been ascribed to allergic or autoimmune reactions, and genetic predisposition to such reactions may explain why Hg sensitivity varies so widely by individual.

The paper also commented that IgG, brain autoantibodies, myelin basic protein and ANA have been found in mercury-poisoned subjects, and mice genetically prone to developing autoimmune diseases are highly susceptible to mercury-induced immunopathological alterations even at low doses.

In addition, many autistics have reduced natural killer cell function, as well as immune-cell subsets altered in a Th2 direction, and increased urine neopterin levels, indicating immune system activation. Depending on genetic disposition, Hg can induce immune activation, an expansion of Th2 subsets, and decreased NK activity.

The authors note that the discovery and rise in prevalence of ASD mirrors the introduction and spread of thimerosal in vaccines. Autism was first described in 1943, amongst children born in the 1930s, and thimerosal was first introduced into vaccines in the 1930s.

Autism increased during the 1980s and 1990s as the use of thimerosal-containing vaccines increased. In the late 1980s and early 1990s, for example, two new thimerosal-containing vaccines were introduced into the US immunisation schedule, these being HIB and Hepatitis-B.

An obvious criticism of the thimerosal/autism link is that most children do not become autistic after vaccination. However, the authors draw attention to the characteristic of mercury, in its great variability of effect on individuals. At the same exposure levels, some children will be affected severely whilst others will be asymptomatic. This was the experience with acrodynia, caused by mercury in teething powder in the early twentieth century, which affected only 1/500 or 1/1000 children given the same low dose. Susceptibility to Hg arises from genetic status, including a propensity for autoimmune disorders.

In addition, the authors note that ASD is more prevalent amongst boys than girls. Mercury studies in mice and in humans consistently report a greater effect upon males than females, other than for kidney damage. At high doses, both sexes are equally affected, but at low doses only males are affected.

The authors concluded that:

- \* the history of acrodynia (damage caused by mercury in teeth powder) illustrates that a severe disorder affecting a small percentage of children can arise from a seemingly-benign application of low doses of mercury
- \* the authors' paper established the likelihood that Hg may likewise be etiologically significant in ASD, with the mercury dose being derived from thimerosal in vaccines
- \* due to the extensive parallels between ASD and mercury poisoning, the likelihood of a causal relationship is great
- \* thimerosal should be removed from all childhood vaccines

- \* the mechanisms of mercury toxicity in autism should be thoroughly investigated
- \* developments of Hg poisoning-related treatments, such as chelation, would be beneficial

123. 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- $\alpha$ , sTNFR $\text{II}$  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- $\alpha$ , sTNFR $\text{II}$  and IL-6 and/or IL-1 $\beta$  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- $\gamma$ /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.

124. 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 pro-inflammatory 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 hypothesize 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 hypothesize 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*”.

125. 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:

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ The project was acknowledged to be passive surveillance of an unrepresentative group of children, almost certainly affected by major underreporting.

- Y 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.
- Y 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”.

126. Study by Holmes, Cave et al, Open Trial of Chelation With MESO-2, 3-Dimercapto Succinic Acid (DMSA) and Lipoic Acid (LA) In Children With Autism, submitted to IMFAR, June 2001

Over 400 children were being treated for removal of heavy metals. Patients were treated with DMSA alone at doses of 10mg/kg/dose three times per day for three days in a row (shorter than the lead protocol, to decrease side effects), with 11 days off to allow metals to re-equilibrate.

After at least two rounds of DMSA alone, the thiol antioxidant lipoic acid was added to each dose of DMSA at 2-3mg/kg/dose.

In general, noticeable improvements in language, self help skills, interaction and core autistic features are not seen until the patient has been on DMSA with LA for two to three months.

Of patients who had been on DMSA for four months plus, results had been noted as follows:

- \* For ages 1 to 5 (n = 40): marked improvement 35%, moderate improvement 39%, slight improvement 15%, none 11%.
- \* For ages 6-12 (n = 25), the results were marked improvement 4%, moderate 28%, slight 52%, none 16%.
- \* For ages 13-17 (n = 16), the results were moderate improvement 6%, slight 68% none 26%.
- \* For ages 18+ (n = 4), results were slight improvement 25%, none 75%.

The majority of children excreted mercury, lead and other metals, suggesting a possible general problem with metals metabolism. Side effects included transient increased hyperactivity, self-stimulatory behaviour, loose stools.

127. Paper by Mark Blaxill (parent), *The Rising Incidence of Autism: Associations With Thimerosal*, presented to the Institute of Medicine, US, July 2001

This paper has already been covered earlier in this document, under the section reviewing whether there has been an increase in autism, but is considered further here in terms of the thimerosal debate.

It noted that:

- \* the incidence of autism is rising sharply in the US and elsewhere
- \* US infants were exposed to sharply-higher amounts of mercury (via thimerosal-containing vaccines), starting around 1990
- \* the timing of the increases in autism rates, and the increases in infant mercury exposures (via thimerosal-containing vaccines) are closely associated

The paper argued that past studies, in the US, UK and elsewhere, had indicated steeply-rising rates of ASD incidence.

Blaxill then reviewed the apparent evidence that pointed to a link between these

Increased rates and changes in the immunization schedule of the relevant countries, specifically the changed intake of thimerosal and the increased mercury burden that might constitute an environmental insult to a genetically-susceptible subset of the population. He also reviewed the introduction of MMR (which does not contain mercury but which has been implicated in the potentially-causative pathway of degenerative autism). He commented as follows:

(USA)

- \* The date of introduction of MMR into the US appeared to have been the late 1970s
- \* 1978 was when autism rates in California (the only State with reliable historic data, due to the Reagan legislation of the time, that required children with delayed development to be referred to a child development centre for assessment) began to rise. Between 1961 and 1977, cases had varied little, ranging from 104 in 1969 and in 1972 and peaks of 141 in 1968 and in 1976. Starting in 1978, cases then rose sharply

\* Data by Dales et al show US MMR take-up rising sharply between 1980 and 1994, with an especially sharp “spike” in 1988. And in California, autism prevalence rates began a sharp upward increase from 1987-92, averaging nearly 21% per year, compared with increases averaging only 5.7% during the preceding decade 1977-87. The data from California therefore is consistent with an MMR implication. However, MMR coverage alone does not explain California’s recorded increases in autism

\* The mercury/autism hypothesis also seems to provide a linear relationship. Starting in the late 1980s, a number of significant events may have combined to create a sharp intensification in the childhood immunization programme.

\* The Hib vaccine was approved for inclusion in the schedule from October 1990, with immunization of infants at 2, 4, 6 and 15 months

\* The Hepatitis B vaccine was recommended for inclusion in November 1991, for administration at birth, one month and 9 months

\* DPT coverage was improved.

\* the Childhood Immunisation Initiative (the CII) was formally launched in 1993. When combined with the DPT increase, it meant that three thimerosal-containing vaccines all began a significant increase in coverage during the 1990s

Blaxill set out the resulting vaccine take-up increases across the US during the years 1991-99 as follows:

(coverage rates for thimerosal-containing vaccines in 19-month to 35-month old children, percentages)

<i>year</i>	<i>DPT/3 dose</i>	<i>DPT/4 dose</i>	<i>Hib/3 dose</i>	<i>Hepatitis B</i>
1991	68	n/a	-	-
1992	83	59	28	8
1993	88	72	55	16
1994	93	77	86	37
1995	95	79	92	68
1996	95	81	92	82
1997	96	84	93	84
1998	96	84	93	87
1999	95	83	93	88

(source: Centers for Disease Control, “Vaccination Coverage of Two Year Old Children, US”, via Mark Blaxill)

Blaxill noted that:

- the combined coverage rates for these three vaccines was to increase the cumulative mercury burden in two-year-olds from 100mcg to 237.5mcg and in six-month-olds from 75mcg to 175mcg. These increases are understated as there is no compliance data for Hib vaccine.
- The level of mercury introduced to infants via thimerosal in the 1990s exceeded the EPA limits of 0.1mcg/kg/day for every day in the first six months of infant life
- Mercury exposure via vaccines that contain thimerosal show a striking correlation with changing levels of reported autism in California

(UK)

The date of MMR introduction in the UK was October 1988. Blaxill again illustrates how autism data in the UK is consistent with an MMR trigger:

- On an aggregate basis, the UK immunization schedule has exposed children to lower mercury levels than the US schedule above. But early exposures have included an important 1990 policy shift.
- In two respects, UK exposures to thimerosal have been low or modest. Firstly, universal infant hepatitis B immunization has never been recommended in the UK (although this was changing in 2005, with a call from the British Medical Association to introduce it as part of the standard schedule)
- Secondly, although Hib was introduced to the infant immunization schedule, starting in 1991, the specific vaccine product used in most infant immunizations, PRP-T, does not contain thimerosal. However, there was a one year catch-up programme starting in October 1992, implemented amongst children aged 13-24 months. The vaccine used in this programme, HbOC, did contain thimerosal
- The change in DPT policy had the effect of dramatically increasing mercury exposure amongst children aged 4 months and younger. A number of changes in practice were implemented, starting in 1990. Accelerating the DPT schedule from a 3, 4.5 and 8-11 months sequence to a 2, 3 and 4 month sequence was intended to increase coverage rates, but had the effect of giving UK children the world's most aggressive DPT immunization schedule. Without thimerosal exposure from any other vaccine, this new schedule led to mercury exposures during the first four months of life that were comparable to US exposure levels during the same time-period, but from a single source

- Simultaneously, doctors were incentivised with a move to lump sum payments based upon achieving high coverage targets. Lump-sum payments totaling 5% or 7.5% of a GP's salary, if targets of 70% and 90% were achieved. For under 70%, the doctor received no payment at all.
- These two initiatives are believed by Blaxill to have resulted in a sharp increase in mercury exposure in the UK infant population. Before 1990, a 4-month-old infant would have received 25mcg. After 1990, this trebled to 75mcg.
- Almost every UK autism study shows low rates pre-1990. Almost every study involving children born post-1990 shows high rates. This in itself is only suggestive, but is consistent with a mercury/autism link. The increases in autism appear to tie in with increasing rates of DPT compliance
- The MMR vaccine was introduced in advance of the most significant increases in autism in the UK. This is consistent with MMR's role as a trigger or "primer".

128. 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

129. 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.

- Y In their study, they showed that infection of a human IgM+B cell line with MMR resulted in the expression of germline e transcript
- Y In addition, infection of freshly prepared human PBLs with MMR vaccine resulted in the expression of mature IgE mRNA transcript
- Y 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

130. Paper by Redwood, Bernard and Brown, *Predicted Mercury Concentrations in Hair From Infant Immunisations; Cause For Concern*, published in *Neurotoxicology*, 2001, October; 22 (5) 691-7

This paper reported that:

- thimerosal, used in numerous infant vaccines, contains 49.6% ethylmercury by weight
- it typically contributes 25 micrograms of ethylmercury per dose of infant vaccine
- in 1999, the FDA advised that infants who received multiple thimerosal-preserved vaccines may have been exposed to cumulative Hg in excess of FDA guidelines
- infants may have been exposed to 12.5 micrograms of Hg at birth, 62.5 micrograms EtHg at 2 months, 50 micrograms EtHg at 4 months, 62.5 micrograms EtHg at 6 months and 50 micrograms EtHg

at approximately 18 months, totaling 237.5 micrograms during the first 18 months of life

- neurobehavioural alterations, especially to the more susceptible foetus and infant, are known to occur after relatively low dose exposures to organic mercury compounds
- the study team estimated hair Hg concentrations expected to result from the recommended CDC schedule utilizing a pharmacokinetic model that had been developed to estimate hair concentrations from acute exposure to methylmercury from fish
- modeled hair Hg concentrations in infants exposed to vaccine thimerosal are in excess of Environmental Protection Agency safety guidelines of one part per million (1 ppm) for up to 365 days, with several peak concentrations within this period
- more sensitive individuals and those with additional sources of exposure would have higher Hg concentrations
- given that exposure to low levels of mercury during critical stages of development has been associated with neurologic disorders in children, including attention deficit disorder, learning difficulties and speech delays, the predicted hair Hg concentration resulting from childhood immunisations is a cause for concern
- based on these findings, the impact that vaccinal mercury has had upon the health of children warrants further investigation

131. 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:

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



- ÿ Results of enzyme testing had paralleled that of Dr. Karoly Horvath and colleagues at the University of Maryland School of Medicine
- ÿ The autistic children examined showed disaccharide/glucoamylase enzyme levels below normal
- ÿ 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”*.

132. 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.

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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:

- ÿ 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.
- ÿ 70 of 91 affected children were positive for MV compared with 4 out of 70 controls as analysed by TaqMan RT-PCR
- ÿ 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.
- ÿ Of the paediatric controls, MV was not detected in normal children or children with isolated ILNH. However, 4 out of 26 appendicectomy 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.
- ÿ 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.

**133. 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)**

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, diphtheria-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:

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

- ÿ The antibody levels of MuV, RV, CMV, HHV-6, DPT, DT and Hep-B did not significantly differ between autistic and normal children
- ÿ 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
- ÿ 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
- ÿ 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.

134. 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:

- ÿ In a proportion of affected children, gut-brain interactions may contribute to abnormal neural development and the subsequent expression of aberrant behaviours.
- ÿ 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.
- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.

ÿ 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.

135. 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

ÿ in 46% of families with autism, two or more family members had autoimmune disorders, compared with 26% in controls

ÿ Some 21 per cent of autistic children had at least one parent suffering from such a disorder, compared with 4% in controls

ÿ 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

136. 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".

137. 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

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:

- ÿ 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
- ÿ Normal children did not harbour these antibodies
- ÿ 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.
- ÿ Therefore, as indicated by paired analysis of serum and CSF samples, there is a strong correlation between MMR antibodies and MBP autoantibodies in autism.
- ÿ 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.
- ÿ 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).

138. 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)

ÿ 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.

ÿ Each of the children developed autism after receiving MMR. None of the children had exhibited any signs of measles disease before becoming autistic.

ÿ As controls, researchers used brain tissue from cases of SSPE, the rare brain disease associated with persistent measles infection.

ÿ 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.

ÿ 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.

139. 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:



- ÿ 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
- ÿ Children with regressive autism and intestinal symptoms have a novel and characteristic inflammatory disease of their intestine
- ÿ The disease is not found in developmentally normal children
- ÿ The disease is entirely consistent with a viral cause
- ÿ The disease may be the source of toxic damage to the brain
- ÿ Measles virus has been identified in the diseased intestines of the majority of those children with regressive autism that had been studied
- ÿ Measles virus has only been found in a small minority of developmentally normal children.
- ÿ The measles virus in those with autism is vaccine strain
- ÿ Children with regressive autism appear to have an abnormal immune response to measles virus
- ÿ The findings are entirely consistent with parental reports that their normally-developing child regressed into autism following exposure to MMR
- ÿ Other researchers in the US have confirmed the presence of intestinal inflammation in children with regressive autism and, independently, the link with measles virus.
- ÿ 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 associated” (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:

- ÿ 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
- ÿ Secondary physical symptoms
- ÿ Presence of severe ileal lymphoid nodular hyperplasia
- ÿ 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.

140. 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:

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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:**

- ÿ 28/43 (65%) had colitis**
- ÿ 22/43 (51%) had active colitis**
- ÿ 17/43 (40%) had chronic colitis**
- ÿ 3/43 (7%) had eosinophilic colitis**
- ÿ 36/40 (90%) had lymphoid nodular hyperplasia of the terminal ileum**
- ÿ 15/43 (35%) had neither active nor chronic nor eosinophilic colitis**
- ÿ 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.**
- ÿ Most patients with colitis had both chronic and active inflammation.**
- ÿ Most patients had at least 3-4 distinct areas of histologic inflammation, with an equal number of biopsies that were histologically normal.**
- ÿ 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:**

- ÿ 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**
- ÿ 90% had pathologic lymphonodular hyperplasia of the terminal ileum**
- ÿ The findings were similar and consistent from patient to patient within the affected group.**

Krigsman posed four questions for further debate:

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

In a press interview in the UK Daily Telegraph, Dr. Krigsman commented: “Our findings, which are independent of Dr. Wakefield’s findings, completely support his explanation and his observations of the abnormalities in the bowels of these children”. He added that the intestines of the children were not normal. One 13-year-old boy who had become so violent that his parents had wanted to institutionalize him, had “the worst case” of inflammation of the colon that Krigsman had ever seen.

141. 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:

- ÿ A survey of 4,000 cases of autism had been undertaken, and some preliminary findings had been drawn.
- ÿ 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.
- ÿ 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 acrylol 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.

**142. 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:

- Y The assay identified wild type measles in three brain blocks from an SSPE patient
- Y The 12 gut biopsies from affected children were deemed to have vaccine strain present

ÿ 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

143. 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”.

However, Dr. Singh’s paper explained his reasoning for choosing his 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, and had been putting out a ‘holding statement’ at Dr. Miller’s request.

144. 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:

ÿ 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

ÿ 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.

ÿ In all, there were 25 different clostridial species found

ÿ 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.

145. Paper by Jyonouchi, Sun and Itokuzu, Department of Paediatrics, University of Minnesota, Minneapolis, *Innate Immunity Associated with Inflammatory Responses and Cytokine Production against Common Dietary Proteins in Patients with Autism Spectrum Disorder* (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:

ÿ 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.

ÿ 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

ÿ 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

146. 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.

147. Paper, *Biochemical and Molecular Basis of Thimerosal-Induced Apoptosis in T Cells - A Major Role of Mitochondrial Pathway*, by Makani, Gollapudi et al, published in *Genes and Immunity*, 2002, 3, 270-278

This paper examined the effects of thimerosal on the biochemical and molecular steps of mitochondrial pathway of apoptosis in Jurkat T cells.

ÿ Thimerosal and not thiosalicylic acid (non-mercury component of thimerosal) in a concentration-dependent manner, induced apoptosis in T cells as determined by TUNEL and propidium iodide assays, suggesting a role of mercury in T cell apoptosis.

ÿ Apoptosis was associated with depolarisation of mitochondrial membrane, release of cytochrome c and apoptosis inducing factor (AIF) from the mitochondria, and activation of caspase-9 and caspase-3, but not of caspase-8.

ÿ In addition, thimerosal in a concentration-dependent manner inhibited the expression of XIAP, cIAP-1 but did not influence cIAP-2 expression.

- ÿ Furthermore, thimerosal-enhanced intracellular reactive oxygen species and reduced intracellular glutathione (GSH).
- ÿ Finally, exogenous glutathione protected T cells from thimerosal-induced apoptosis by upregulation of XIAP and cIAP1 and by inhibiting activation of both caspase-9 and caspase-3.

The study concluded that thimerosal induces apoptosis in T cells via mitochondrial pathway, by inducing oxidative stress and depletion of GSH.

148. Paper by Westphal, Asgari et al, *Thimerosal Induces Micronuclei In The Cytochalasin B Block Micronucleus Test With Human Lymphocytes*, Department of Occupational Health, Georg-August University, Gottingen, Germany, published in Archives of Toxicology, August 2002 (received date)

The study re-investigated thimerosal in the cytochalasin B block micronucleus test. Glutathione S-transferases were proposed to be involved in the detoxification of thimerosal or its decomposition products. Blood samples of six healthy donors of different glutathione S-transferase genotypes were included in the study. At least two independent experiments were performed for each donor.

The study reported that:

- ÿ significant induction of micronuclei was seen at concentrations between 0.05-0.5ug/ml in 14 out of 16 experiments
- ÿ Thus, genotoxic effects were seen even at concentrations which can occur at the injection site
- ÿ Toxicity and toxicity-related elevation of micronuclei was seen at and above 0.6ug/ml thimerosal
- ÿ marked individual and intra-individual variations in the in-vitro response to thimerosal among the different blood donors occurred
- ÿ however, there was no association observed with any of the glutathione S-transferase polymorphism investigated.

The study conclusion was that thimerosal is genotoxic in the cytochalasin B block micronucleus test with human lymphocytes. The results raised concern on the widespread use of thimerosal, and also did not rule out a possible carcinogenic effect.

149. 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  $\alpha$ -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.

**150. 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:

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

The study concluded that:

Y 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.

Y 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.

151. Paper by Holmes, Blaxill and Haley, of Baton Rouge, Louisiana, US, of Safe Minds, Cambridge Massachusetts US, and of the Department of Chemistry, University of Kentucky, Lexington US, *Reduced Levels of Mercury in First Baby Haircuts of Autistic Children*, published in the International Journal of Toxicology, 22, 277-285, 2003

This important paper was a defining moment in bringing a spotlight to bear upon a putative mercury/autism link.

The authors postulated that differential rates of post-natal mercury elimination might explain why similar gestational and infant exposures produced variable neurological effects.

Baby haircut samples were obtained from 94 children diagnosed with autism using the 4<sup>th</sup> edition of Diagnostic & Statistical Manual of Mental Disorders (DSM IV) criteria and 45 age- and gender-matched controls.

Information on diet, dental amalgam fillings, vaccine history Rho D immunoglobulin administration and autism symptom severity was collected through a maternal survey questionnaire and through clinical observation.

The results of the study were that:

- hair mercury levels in the autistic group were 0.47 parts per million (ppm), versus 3.63ppm in controls, a significant difference
- the mothers in the autistic group had significantly higher levels of mercury exposure through Rho D immunoglobulin injections than did control mothers
- within the autistic group, hair mercury levels varied significantly across mildly, moderately and severely autistic children, with mean group levels of 0.79, 0.46 and 0.21ppm respectively
- hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish

consumption, as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group

- hair excretion patterns among autistic infants were significantly reduced relative to controls
- these data cast doubt on the efficacy of traditional hair analysis as a measure of total mercury exposure in a subset of the population
- in the light of the biological plausibility of mercury's role in neurodevelopmental disorders, the present study provides further insight into one possible mechanism by which early mercury exposure could increase the risk of autism

The study report commented:

**“Our findings are consistent with the hypothesis connecting mercury exposure with autism. Autistic infants released dramatically lower levels of mercury into hair than control infants (my emphasis).”**

**“In our autistic group, this reduced level was not associated with lower levels of overall exposure, quite the contrary. In many, though not all, exposure categories, autistic infants experienced higher levels of mercury exposure.”**

**“Autistic infants in our sample experienced increased exposure levels through maternal Rho D immunoglobulin injections (as discussed above). The large majority of licensed preparations sold during the study period used thimerosal as a preservative. Forty-three out of 94, or 46%, of the children in our sample were exposed to mercury through these injections, as compared to 4 out of 45, or 9%, of controls. Several of the (mothers of autistic children) received multiple injections.”**

**“The control group showed a very strong correlation between measurable mercury exposure and the amount released into hair. This suggests that normal children have an ability to defend themselves against potentially toxic exposures and may demonstrate little negative effect, despite exposures that were relatively large.”**

**“By contrast, autistic infants who experienced comparable exposure to mercury were completely incapable of excreting mercury through hair at the levels that might have been predicted (when) based on the excretion patterns of the control infants.”**

**“Our study suggests two reasons why ‘low dose’ (where ‘low’ is relative to demonstrably harmful or even fatal doses and not the modified Environmental Protection Agency standard) exposures might raise the risk of developmental damage.”**

“First, vaccine exposures do not occur in isolation, but rather represent one amongst several pathways of exposure through which the fetal and infant brain might accumulate toxic levels of mercury. These pathways must therefore be evaluated in the context of cumulative exposures, any one of which might be harmless on its own but when combined with other sources might contribute to harmful overall levels. Both the autistic and the control children in our study showed increased mercury risk based upon multiple sources of exposure.”

“Secondly, the risk of any exposure will be greater if a larger fraction of the toxin is retained in tissue and not excreted quickly. Although hair is a minor pathway for mercury excretion and is far less important than faeces and urine, the low levels of mercury in the hair of autistic infants support a hypothesis that these infants were retaining mercury in tissue at a higher rate than control infants.”

“The lack of mercury in the hair of autistic (infants) ,ay be due to a decrease in blood mercury levels feeding the hair follicles. This decrease is likely caused by the retention of the mercury inside the cells where it most likely causes its major biological damage.”

“If we presume that a portion of the tissue mercury retention is sequestered in the central nervous system and is available to cause neurological damage at sensitive points in brain development, then it is plausible that mercury-associated damage might be a meaningful element in the pathological process that leads to an outcome of autism.”

152. Paper by Singh and Jensen, *Elevated Levels of Measles Antibodies in Children with Autism*, Department of Biology and Biotechnology Center, Utah State University, Logan, Utah, published Pediatric Neurology Vol 28 No 4 2003

This reported on further progress with the Singh and Jensen research:

- ÿ Virus-induced autoimmunity may play a causal role in autism. To examine the role of viruses, Singh and Jensen conducted a serological study of measles virus, mumps virus and rubella virus.
- ÿ Viral antibodies were measured by enzyme-linked immunosorbent assay in the serum of autistic children, non-autistic children and siblings of autistic children
- ÿ The level of measles antibody, but not mumps or rubella antibodies, was significantly higher in autistic children as compared to normal children or siblings.

Ÿ Furthermore, immunoblotting of measles vaccine virus showed that the antibody was directed against a protein of approximately 74kd molecular weight. The antibody to this antigen was found in 83% of autistic children but not in normal children or siblings of autistic children

Ÿ Thus autistic children have a hyperimmune response to measles virus, which in the absence of a wild-type measles infection might be a sign of an abnormal immune reaction to the vaccine strain or virus re-activation

**153. Paper by Dr. Mark Geier and David Geier, Genetics Centers of America, Silver Spring, Maryland US, *Neurodevelopmental Disorders After Thimerosal-Containing Vaccines: A Brief Communication*, published by the Society for Experimental Biology and Medicine (precise volume not known), 2003, pp660-664**

This study presented the first epidemiologic evidence, based upon tens of millions of doses of vaccines administered in the US, that associates increasing thimerosal from vaccines with neurodevelopmental disorders.

Specifically:

Ÿ An analysis of the US Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (relative risk 6.0), mental retardation (rr 6.1), and speech disorders (rr 2.2) after thimerosal-containing diphtheria tetanus and acellular pertussis (DTaP) vaccines in comparison with thimerosal-free DTaP vaccines.

Ÿ The male/female ratio indicated that autism ()and speech disorders were reported more in males than females after thimerosal-containing DTaP vaccines, whereas mental retardation was more evenly reported among male and female vaccine recipients

Ÿ Controls were employed to determine if biases were present in the data, but none were found

Ÿ It was determined that overall adverse reactions were reported in similar-aged populations after thimerosal-containing DTaP vaccinations

Ÿ Acute control adverse reactions such as deaths (rr 1.0), vasculitis (rr 1.2), seizures (rr 1.6) ED visits rr 1.4), total adverse reactions rr 1.4) and gastroenteritis (rr 1.1) were reported similarly after thimerosal-containing and thimerosal-free DTaP vaccines.

The conclusion of this pioneering study was that an association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but that additional studies should be conducted.



**154. Study by Dr. Mark Geier and David Geier, *Pediatric MMR Vaccination Safety*, published in *International Pediatrics*, May 2003, vol 18, No. 2, 2003, pp 203-208**

**This study examined the possible link between MMR and serious neurological disease including autism, cerebellar ataxia (loss of coordination due to damage to the cerebellum), mental retardation and permanent brain damage. The study used the database established and maintained by the Centers for Disease Controls and Prevention (CDC) in the US, known as VAERS (Vaccine Adverse Events Reporting System).**

**VAERS is designed to act as an early warning system for detection of adverse events after childhood vaccines. It is comparable to the UK Yellow Card system, and like the UK system, it is believed that only a very small percentage of even serious adverse events are actually reported and recorded. The UK system is admitted to pick up 10-15% of even serious events. It has been alleged elsewhere that the US system picks up much less than this, perhaps only one per cent.**

**The authors compared the incidence of reports of serious neurological diseases following MMR with the incidence of the same serious neurological diseases following the thiomersal-containing DTP vaccine.**

**The overall mean age of children was approximately 1.8 years and the mean onset time ranged from 5 to 10 days following MMR immunisation. Serious neurologic illnesses were reported following DTWcP vaccine as follows: 0.22 per million DTWcP vaccines for cerebellar ataxia, 0.29 per million DTWcP vaccines for autism, 0.84 per million DTWcP vaccines for mental retardation and 0.30 per million DTWcP vaccines for permanent brain damage. Cerebellar ataxia, autism, mental retardation and permanent brain damage were all statistically significantly increased following primary MMR vaccination in comparison with DTWcP vaccination.**

**The results therefore found a highly-significant association between MMR and autism, compared with DTP. The increased risk for MMR/autism was over five times that for DTP. Whilst the study acknowledged the limitations of passive reporting, it marked a significant milestone in the MMR debate.**

**The study authors commented: "In order to alleviate many of the difficulties encountered with the MMR vaccine, we suggest that a killed MMR vaccine should be made available as it may reduce the number and severity of adverse reactions following live MMR vaccine.....We also suggest that if the current live MMR vaccine is to remain in use, that parents should have the option to have each of the components of MMR vaccine administered individually at different times."**

The authors were aware of the potential for reporting bias, due to the high profile of the MMR/autism debate after February 1998, but confirmed that reporting bias did not appear to account for their findings.

155. Further paper by Geier and Geier, *An Assessment of the Impact of Thimerosal On Childhood Neurodevelopmental Disorders*, published in *Pediatric Rehabilitation*, April-June 2003, Vol 6, No. 2, 97-102

This paper was a further report on the Geiers' pioneering work.

ÿ The prevalence of autism in the US has risen from 1 in 2500 in the mid-1980s to 1 in 300 children in the mid-1990s.

ÿ The purpose of the study was to evaluate whether mercury from thimerosal in childhood vaccines contributed to neurodevelopmental disorders

ÿ Neurodevelopmental disorder dose-response curves for increasing mercury doses of thimerosal in childhood vaccines were determined, based upon examination of the Vaccine Adverse Events Reporting System database and the 2001 US Department of Education report.

ÿ The instantaneous dosage of mercury that children received in comparison to the Food & Drug Administration maximum permissible dose for the oral ingestion of methylmercury was also determined

ÿ The dose-response curves showed increases in odds ratios of neurodevelopmental disorders from both the VAERS and US Department of Education data closely linearly correlated with increasing doses of mercury from thimerosal-containing childhood vaccines and that for overall odds ratios statistical significance was achieved

ÿ Similar slopes and linear regression coefficients for autism odds ratios in VAERS and the US Department of Education data help to mutually validate each other

ÿ Controls employed in the VAERS and US Department of Education data showed minimal biases

The study paper concluded that the evidence showed that the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines did not appear to be coincidental.

156. Further study by Geier and Geier, *Thimerosal In Childhood Vaccines, Neurodevelopmental Disorders and Heart Disease in the United States*, *Journal of American Physicians and Surgeons*, Vol 8, No. 1, Spring 2003

The study team evaluated the doses of mercury that children received from thimerosal-containing vaccines as part of the routine US childhood immunisation schedule, in comparison to the US Federal Safety Guidelines for the oral ingestion of methylmercury.

Also, in order to analyze the effects of thimerosal in vaccine recipients, they analysed the incidence rates of neurodevelopmental disorders and heart disease reported following thimerosal-containing vaccines in comparison to thimerosal-free vaccines, based upon analysis of the Vaccine Adverse Events Reporting System (VAERS) database. They analysed thimerosal-containing diphtheria-tetanus-whole-cell-pertussis (DTwcp) and diphtheria-tetanus-acellular-pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines.

The study also analysed data from the US Department of Education on the number of children of various ages in US schools who were reported with various types of disabilities in comparison to the mercury dose that children received from thimerosal in their childhood vaccines.

The neurodevelopment disorders and heart disease conditions the study analysed were autism, speech disorders and heart arrest.

The study team hypothesised that DTaP or DTwcp vaccines, whether containing thimerosal or not, should have a similar incidence rate of adverse events. The assumption of similar reactogenicity following the vaccines under study forms the basis of their null hypothesis.

The team analysed DTaP and DTwcp vaccines so as to compare thimerosal-containing DTaP and DTwcp vaccines administered from 1992 through 2000 against thimerosal-free DTaP vaccines administered from 1997 through 2000. They compared incidence rates to determine relative risk.

The conclusions were that it was clear from their analysis that US infants had been exposed to mercury levels from childhood immunisations that far exceeded US Environmental Protection Agency and Food & Drug Administration-established maximum permissible levels for the daily oral ingestion of ethylmercury. The fact that mercury in vaccines was given by injection only made the exposure levels worse. The study not only showed that those vaccinated with thimerosal-containing DTaP and DTwcp had higher rates of speech disorders, autism and heart arrest overall, but also that the relative risk of each of these disorders correlated with increasing doses of mercury contained in childhood vaccines.

They also commented: “ Because of the similar theoretical and experimental toxicities of ethylmercury and methylmercury, and the immediate build-up of ethylmercury from thimerosal in the tissues of the body, especially the preferential build-up in the brain, there appears to be good biologic

plausibility for the neurodevelopment disorders and heart conditions observed in this study.”

The study was stated to provide strong epidemiologic evidence for a link between increasing mercury from thimerosal-containing childhood vaccines and neurodevelopmental disorders and heart disease.

The study was criticised by the American Academy of Pediatrics because:

- ÿ It relied on VAERS data
- ÿ The authors did not distinguish between methylmercury (found in food) and ethylmercury (found in thimerosal)
- ÿ The authors did not reveal how thimerosal exposure had been calculated
- ÿ Data regarding specific manufacturers of thimerosal (some of whom had incorporated thimerosal as a preservative and some of whom had not), and the age and year of birth of vaccine recipients, were not available in the published study
- ÿ Calculations for incidence rates and relative risk, which required information on age or year of birth) were not shown
- ÿ Using VAERS data meant that one could not be sure whether a child received a thimerosal-containing vaccine at any point before the event for which the VAERS report was created

157. Paper by Blaxill, Redwood and Bernard, *Thimerosal and Autism: A Plausible Hypothesis That Should Not Be Dismissed*, published by Safe Minds (parents' group), Cranford, New Jersey, 2003

This paper was a detailed response to the paper published in Pediatrics in March 2003 by Nelson & Baumann, “Thimerosal and autism?”.

This paper was a response to the review by Nelson & Baumann, which itself was a rebuttal of the Bernard et al paper of 2000. Blaxill et al maintained that Nelson & Baumann’s commentary contained a number of assertions and conclusions that required careful scrutiny, and this latest paper was in turn a refutation of Nelson & Baumann.

Blaxill et al pointed out that Nelson & Baumann’s paper had derived its list of mercurial symptoms largely from relatively high doses of ingested methylmercury in adults. These exposure patterns were not closely comparable to low-dose injected ethylmercury in infants.

Blaxill et al also pointed out that Nelson & Baumann failed to distinguish between the degenerative and the developmental effects of mercury exposure. All Nelson & Baumann's references related to severe exposure in adults leading to death.

Blaxill et al also pointed out that:

\* Nelson & Baumann's suggestion that ethylmercury does not readily cross the blood-brain barrier is contradicted by the 1985 study by Magos et al, which directly compares the brain levels of mercury following comparable doses of methylmercury and ethylmercury. In that study, both methylmercury and ethylmercury entered the brain in significant amounts.

\* Nelson & Baumann had repeated Magos' claim that ethylmercury lacks the active transport mechanism across the blood-brain barrier that others (eg Kerper et al 1992) had found available to methylmercury. But neither Nelson/Baumann or Magos could support this critical claim with evidence, and in fact the available evidence suggests quite the contrary. The potential for transport of ethylmercury across the BBB therefore requires proper study, not dismissal

\* in contradiction of the stance of Nelson & Baumann, other studies (cited by Blaxill et al but not by Nelson & Baumann) show clear evidence in favour of Pukinje cell involvement in mercury poisoning, with increased levels of Pukinje cell loss. Nelson & Baumann's references in this vital respect were inaccurate and incomplete

\* Nelson & Baumann also mention brainstem lesions as being an important neuroanatomical observation in autism, and imply that such lesions were not reported in the mercury literature. Yet brainstem abnormalities are amongst the most common features of prenatal and postnatal mercury exposure

\* Nelson & Baumann had asserted "material differences in the neuroanatomic findings in autism as compared with those in mercury toxicity". But this assertion was based upon a handful of selectively chosen studies of mercury neuropathology in rats and in severely-poisoned adults, and even these only provided meagre support for Nelson & Baumann's assertion. In fact, there was little evidence to support Nelson & Baumann.

In fact, the Verstraeten study had found high levels of exposure to thimerosal-containing vaccines, and the Geiers' studies had linked exposure to thimerosal-containing vaccines with autism. Other evidence (detailed elsewhere in this document) was offered by the work of Holmes et al and by Bradstreet.

In addition, the study by Hoshino et al, in Fukushima prefecture in Japan, produced time trends in autism that were consistent with an etiological role for mercury.

Nelson & Baumann also cite the Faroe and Seychelles mercury studies, by Marsh et al in 1995 and by Grandjean et al in 1997, but the fact that autism was not cited in either study provides little reassurance in relation to thimerosal (in contrast to Nelson & Baumann's assertion).

158. Paper by Bradstreet, Geier, Kartzinel et al, *A Case-Control Study of Mercury Burden In Children With Autistic Spectrum Disorders*, Journal of American Physicians and Surgeons, Vol 8, No. 3, summer 2003

This study was a retrospective analysis of 221 consecutive children with previously-established ASD referred and admitted to the International Child Development Resource Center (ICDRC) Florida.

Among the 221 cases, all had received their scheduled childhood immunisations appropriate for their ages. Among the 18 controls, 10 children had received their full immunisations and 8 had received none, due to religious objections.

ÿ Urinary mercury concentrations were significantly higher in cases than in controls

ÿ Cases had a significantly higher urinary concentration of mercury after DMSA treatment than did controls

ÿ Both groups had similar concentrations of cadmium and lead after DMSA treatment

ÿ Amongst age- and sex-matched healthy (non-ASD) children, 5 vaccinated controls had similar urinary concentrations of mercury, cadmium and lead after DMSA treatment compared with 5 unvaccinated controls

The study paper concluded that these results showed a strong association between increased urinary mercury concentrations following three days of treatment with DMSA and the presence of autistic spectrum disorder.

The authors commented: "Our results are similar to those of the retrospective study by Holmes et al (International Journal of Toxicology 2003). They observed that there was a significant relationship between increasingly severe autism and decreasing mercury levels in first baby haircuts in comparison to normal controls. Our results and those of Holmes probably result from a decreased ability of children with ASD to excrete mercury, resulting in the retention of potentially toxic mercury levels."

**“Moreover, our findings appear to confirm previously published epidemiological evidence showing a direct association between increasing mercury from thimerosal-containing childhood vaccines and neurodevelopmental disorders in children. These studies showed there was a two- to six-fold statistically-significant increased incidence of neurodevelopmental disorders following an additional 75-100mcg dosage of mercury from thimerosal-containing vaccines in comparison to thimerosal-free childhood vaccines.”**

**“The results of our analyses suggest that mercury should be removed immediately from all biologic products.”**

**“Our study is unable to determine whether the statistically significantly higher urinary concentrations of mercury measured in cases in comparison to controls is caused by higher exposure to mercury, reduced ability to excrete mercury or a combination of these explanations.”**

**159. Letter by Geier and Geier in the Journal of American Physicians and Surgeons, Vol 8, No. 3, summer 2003**

**This letter was in response to vociferous but unpublished criticisms of the Spring 2003 article by the Geier and Geier team.**

**Verbatim extracts are:**

**ÿ The VAERS database provides a perspective regarding adverse events following vaccination that is available by no other means of analysis. More than 200,000 adverse event reports are recorded in the VAERS database following more than one billion doses of more than 30 different types of vaccines administered as part of the US national immunisation program.**

**ÿ The appropriate calculation finds that infants were, when thimerosal was present in childhood vaccines, exposed to instantaneous levels of mercury that were many-fold (in some cases more than 100-fold) in excess of the Federal Safety Guidelines for the oral ingestion of methylmercury**

**ÿ We believe that.....CDC studies strongly support a causal relationship between the increasing mercury from thimerosal-containing childhood vaccines and the increase in neurodevelopmental disorders**

**ÿ (The) arbitrary statement that ethylmercury is not like methylmercury in its effects is without basis, is contrary to published data and even ignores the conclusion of the 2001 Institute of Medicine report regarding the biological plausibility of the relationship between ethylmercury from thimerosal in childhood vaccines and neurodevelopmental disorders**

ÿ We believe that there is no doubt that continued immunisations are critical to our safety and welfare, but we need a concerted effort to improve the safety and efficacy of existing vaccines

ÿ Personal assaults on us.....will neither cure the problem nor will it restore confidence in our much needed vaccine program. Rather, we must admit our past mistakes openly and honestly, and then work to improve current and future vaccines. The first step in this process is the immediate removal of thimerosal from all vaccines, which we predict will result in the end of the autism epidemic

160. Study by Baskin, Ngo et al Department of Neurosurgery, Baylor College of Medicine, Houston, Texas and Veterans Affairs Medical Center, Houston, *Thimerosal Induces DNA Breaks, Caspase-3 Activation, Membranes Damage and Cell Death in Cultured Human Neurons and Fibroblasts*, published in *Toxicology Science*, August 2003

This study investigated short-term thimerosal toxicity in cultured human cerebral cortical neurons and in normal human fibroblasts. The study commented that thimerosal (sodium ethylmercury-thiosalicylate) is an antibacterial and antifungal mercurial compound used as a preservative in vaccines.

It noted that:

- in the body, ethylmercury can be converted to inorganic mercury, which then preferentially accumulates in kidneys and the brain (as reported by Blair, 1975)
- Inorganic mercury is known to induce membrane and DNA damage, as reported by Ferrat (2002) and by Ben-Ozer et al (2000)
- Ethylmercury can significantly increase concentration of inorganic mercury in many organs (as reported by Magos et al, 1985)
- After in vivo administration, ethylmercury passes through cellular membranes and concentrates in cells in vital organs including brain, where it releases inorganic mercury, raising its concentrations higher than equimolar doses of its close and highly toxic relative methylmercury (as reported by Magos in 1985)
- Little is known about acute reactions of various types of human cells following short-time exposure to thimerosal in micro- and nanomolar concentrations

The study noted that “our data indicates that thimerosal is toxic to human neurons and fibroblasts if applied in micromolar concentrations (1-250uM)” (my underlining).



**The study report reported:**

- \* Thimerosal toxicity was observed at 2uM based on manual detection of fluorescent attached cells and at 1uM level with the more sensitive GENios Plus Multi-Detection Microplate Reader with Enhanced Fluorescence.**
- \* The lower limit did not change after 24-hour incubation**
- \* cortical neurons demonstrated higher sensitivity to thimerosal compared to fibroblasts**
- \* the first sign of toxicity was an increase in membrane permeability to DAPI (6-diamidino-2-phenylindole dihydrochloride) after 2 hours of incubation with 250uM thimerosal. A 6-hour incubation resulted in failure to exclude DAPI, generation of DNA breaks, caspase-3 activation and development of morphological signs of apoptosis**
- \* the study team demonstrated that thimerosal in micromolar concentrations rapidly induce membrane and DNA damage and initiate caspase-3 dependent apoptosis in human neurons and fibroblasts**

**The study found that:**

- \* concentrations of thimerosal that induced toxic effects in human cortical neurons ranged from 1uM to 250uM**
- \* the cell bodies of neurons treated with higher concentrations of thimerosal (50 to 250uM) were swollen, which is more characteristic for necrotic cell death, whereas cells treated with low concentrations (2 to 10uM) were shrunken, as is typical for apoptosis**
- \* the nuclei of dying neurons treated with 250uM of thimerosal were larger in size, and swollen, in contrast to the shrunken nuclei of cells treated with 2uM of thimerosal. Thus cell death occurring after incubation of neuronal cells with higher concentrations of thimerosal has features of both apoptosis (caspase-3 activation) and necrosis (cell edema and nuclei swelling). The study reported that this could be explained by a direct membrane-damaging effect of thimerosal, which rapidly leads to the loss of membrane integrity and cell swelling**
- \* at lower concentrations of thimerosal, direct membrane-damaging effects were weaker and no swelling was observed**

**The study further noted:**

- \* in the study, the concentrations of thimerosal which induced toxic effects ranged from 1uM (405ug/L) to 250uM (101mg/L), that is equivalent to the levels of inorganic mercury from 201ug/L to 50ug/L
- \* in clinical cases of accidental or intentional usage in high concentrations, thimerosal was administered in doses ranging from 3mg/kg to several hundred mg/kg (as reported by Ball et al, 2001). Such doses had resulted in local necrosis at the application site, and severe central nervous system and kidney injury
- \* much lower concentrations than this are reached during normal vaccination, according to the study, when thimerosal-containing vaccines are used. In the case of a full series of vaccinations containing thimerosal, up to 403ug of thimerosal (equivalent to 200ug of mercury) is received by six months of age (as calculated by Ball et al, 2001)
- \* the lowest toxic concentrations of mercury contained in the thimerosal doses in the study being reported by Baskin et al (201ug/L) is less than four times higher than some of these estimated concentrations
- \* the rapidly developing toxicity of thimerosal in low micromolar concentrations over short time frames is of concern (my underlining), and suggests that additional research is necessary to estimate the effects of prolonged exposure to thimerosal in lower doses

161. Paper by Via, Nguyen, Niculescu et al, University of Maryland School of Medicine, *Low Dose Exposure to Inorganic Mercury Accelerates Disease and Mortality In Acquired Murine Lupus*, published in *Environmental Health Perspectives*, Vol 111, No. 10, August 2003, pp1273-77

This study conducted at the University of Maryland School of Medicine found that:

- ÿ Exposure to low levels of mercury can speed-up and worsen the symptoms of an induced lupus-like disease in mice, even when the exposure occurs before the development of the disease
- ÿ The researchers stated that if this finding was also true for humans, it would redefine the association between mercury exposure and the autoimmune disease lupus
- ÿ Healthy mice that were not genetically susceptible to mercury-induced autoimmune disease were given injections of low-dose inorganic mercury of the course of two weeks. The levels of mercury and length of exposure chosen were much lower than the range commonly used in mouse studies of mercury toxicity

Ÿ Five days later, the mice were given cells from the lupus-inclined mouse strain to induce lupus-like chronic graft-versus-host disease, a well-established mouse model of acquired autoimmunity

Ÿ Antibodies, or markers characteristic of lupus-like autoimmunity, were significantly elevated in the mice that had been pre-treated with mercury

Ÿ The study was the first to connect low-level mercury exposure to the severity of lupus in mice. Previous studies had found that mercury exposure in animals could examine pre-existing autoimmune disease, and even induce autoimmune disease in susceptible animals

Ÿ Co-author Ellen Silbergeld said “These results suggest that we should examine the immune system as a target of mercury toxicity in humans”.

Ÿ Professor Via commented: “Our findings suggest that low-level mercury exposure does not cause lupus.....You have to be a susceptible individual who has the appropriate environmental exposure. But our study clearly shows that mercury can act as a disease modifier for lupus. Exposure to mercury might either lower the threshold of susceptibility or increase the severity of the disease.”

(Lupus is an autoimmune disorder, in which the immune system for unknown reasons attacks connective tissue as though it were foreign.

162. Paper by Sweeten, Bowyer, Posey et al, *Increased Prevalence of Familial Autoimmunity in Probands With Pervasive Developmental Disorders*, Pediatrics, vol 112 No. 5 November 2003 pp e420 (electronic)

Ÿ Previous research has found an increased frequency of autoimmune disorders in families with autistic probands. The authors further investigated this association by determining the frequency of autoimmune disorders in families that have probands with pervasive developmental disorders (PDDs) including autism, compared with two control groups

Ÿ Three study groups, including (1) families that had a child with a PDD, (2) families that had a child with an autoimmune disorder, and (3) families with a healthy control child, constituted the sample. A questionnaire inquiring about which first and second-degree family members had received a diagnosis of having specific autoimmune disorders was completed by 101 families in each group

Ÿ The frequency of autoimmune disorders was significantly higher in families of the PDD probands compared with families of both the autoimmune and healthy control probands

- ÿ Autoimmunity was highest among the parents of PDD probands compared with parents of the healthy control subjects
- ÿ Hypothyroidism/Hashimoto's thyroiditis and rheumatic fever were significantly more common in families with PDD probands than in the healthy control families

The conclusion of this study was that autoimmunity was increased significantly in families with PDD compared with those of healthy and autoimmune control subjects. The preliminary findings warranted additional investigation into immune and autoimmune mechanisms in autism.

163. Paper by Ashwood, Murch et al *Intestinal Lymphocyte Populations in Children With Regressive Autism: Evidence For Extensive Mucosal Immunopathology*, published in the Journal of Clinical Immunology Vol 23 No. 6, Nov 2003 pp 504-517

Detailed analysis of intestinal biopsies in regressive-autism children indicated a novel lymphocytic enterocolitis with autoimmune features, but that links between this finding and cognitive function remained unclear. To characterise these further, the study examined the mucosal infiltrate using flow cytometry.

Duodenal, ileal and colonic biopsies were obtained from 52 affected children, 25 histologically normal and 54 histologically inflamed developmentally-normal controls.

- ÿ At all sites, CD3+ and CD3+CD8+ IEL as well as CD3+ LPL were significantly increased in affected children compared with developmentally normal non-inflamed control groups, reaching levels similar to inflamed controls
- ÿ In addition, two populations - CD3+CD4+ IEL and LPCD19+ B cells - were significantly increased in affected regressive-autism children compared with both non-inflamed and inflamed controls including IBD, at all sites examined.
- ÿ Histologically there was a prominent mucosal eosinophil infiltrate in affected children that was significantly lower in those on a gluten- and casein-free diet, although lymphocyte populations were not influenced by diet.

The study conclusion was that this data provided further evidence of a pan-enteric mucosal immunopathology in children with regressive autism that is apparently distinct from other inflammatory bowel diseases.

164. Study by Ueha-Ishibashi, Oyama, Nakao et al, *Laboratory of Cellular Signalling*, Faculty of Integrated Arts and Sciences, University of

Tokushima, Effect of Thimerosal, A Preservative In Vaccines, On Intracellular Ca(2+) Concentration of Rat Cerebellar Neurons, published in Toxicology, 2004, Jan 15, 195(1), pp77-84

- ÿ The effect of thimerosal on cerebellar neurons dissociated from two-week-old rats was compared with those of methylmercury using a flow cytometer with appropriate fluorescent dyes
- ÿ Thimerosal and methylmercury at concentrations ranging from 0.3 to 10microM increased the intracellular concentration of Ca(2+)((Ca2+)i) in a concentration-dependent manner
- ÿ The potency of 10microM thimerosal to increase the ((Ca(2+)i) was less than that of 10microM methylmercury
- ÿ Their effects on the ((Ca(2+)i) were greatly attenuated but not completely suppressed, under external Ca(2+)-free condition, suggesting a possibility that both agents increase membrane Ca(2+) permeability and release Ca(2+) from intracellular calcium stores.
- ÿ The effect of 10microM thimerosal was not affected by simultaneous application of 30microM L-cysteine whereas that of 10microM methylmercury was significantly suppressed

The study concluded that:

- ÿ The potency of thimerosal was similar to that of methylmercury in the presence of L-cysteine
- ÿ Both agents at 1 microM or more similarly decreased the cellular content of glutathione in a concentration-dependent manner, suggesting an increase in oxidative stress
- ÿ Results indicate that thimerosal exerts some cytotoxic actions on cerebellar granule neurons dissociated from 2-week-old rats, and its potency is almost similar to that of methylmercury

Note: the final point is crucial to the thimerosal/autism argument, and has been repeatedly contested in the past by those seeking to defend the previous use of thimerosal.

165. Paper by Jyonouchi, Geng et al, New Jersey Medical School, Newark, US, Dietary Intervention Therapy for Some With Autism: Mechanisms of Non-IgE-Mediated Adverse Reaction To Common Dietary Proteins In Children With Autism Spectrum Disorders, from the Program & Abstract of Papers Presented During Scientific Sessions of the AAAAI 60<sup>th</sup> Annual Meeting, January 2004

The scientists presenting this paper reported their previous finding, that elevated IFN- $\gamma$ /TNF production by peripheral blood mononuclear cells (PBMCs) against cow's milk protein, soy and gliadin had been found in a substantial number of ASD children. The study had included 11 control children.

The study concluded that dysregulated production of inflammatory and counter-regulatory cytokines may be associated with non-IgE-mediated adverse reactions to common dietary proteins in some ASD children, indicating therapeutic significance of dietary interventions in such children.

166. Paper by Dr. Vijendra Singh, Research Associate Professor of Neuroimmunology at the Department of Biology, Center for Integrated Biosystems, Utah State University, Logan, Utah, US, *Autism, Vaccines and Immune Reactions*, presented at the Institute of Medicine meeting on vaccines and autism, Washington DC, 9th February 2004

Singh and other leading scientists believe that viral infections trigger autoimmune responses and eventually lead to organ-specific autoimmune diseases. In autism, the trigger mechanism is still not known, but viral infections have been suspected. Viruses can enter the brain through nasopharyngeal membranes or can induce an autoimmune response against the brain, thereby impacting upon the development of the central nervous system.

Singh set out his investigative approach, which was to raise two questions:

- Do autistic children harbour abnormal virus serology (antibody levels)?
- Is there a correlation between virus serology and brain antibodies?

The Singh team:

- Studied immune response to viruses by measuring the level of their antibodies
- They measured antibodies to five viruses, measles, mumps, rubella, CMV and human herpes virus 6 (HHV-6). To their surprise, they found that the antibody level of the measles virus alone, and not the other four, was significantly higher in autistic children than in normal children
- The researchers also found an interesting correlation between measles antibody and brain autoimmunity, which was marked by myelin basic protein antibodies

ÿ These two markers correlated in over 90% of the autistic children tested. This suggests a causal link between measles virus and autoimmunity in autism.

ÿ The serology to other viruses and other brain autoantibodies did not show this correlation.

Singh regarded these as very important findings that led the research team to postulate a temporal link of measles virus in the etiology of autism.

Singh also reported that many parents had noted the onset of autistic characteristics shortly after immunisation with MMR or DPT (diphtheria-pertussis-tetanus) vaccines. So, to examine risk factors in autism, the research team had conducted a study of serology (antibody levels) to three vaccines, MMR, DPT and DT (diphtheria-tetanus). Again, they raised the same two questions, (1) do autistic children harbour abnormal vaccine serology (antibody levels)?, and (2) is there a correlation between vaccine serology and brain autoantibodies?

The team found that:

ÿ The level of MMR antibodies was significantly higher in autistic children as compared to normal children or other-disease children

ÿ Autistic children exhibited a very high degree of specificity for MMR antibodies, similar to the team's previous finding for measles antibodies

ÿ The team characterized that this abnormal MMR serology was due to antibodies to the measles sub-unit but not the mumps or rubella sub-unit of the trivalent MMR vaccine

ÿ The same result was also found when the team used monovalent measles vaccine in lieu of the trivalent MMR vaccine, further pointing to there being a problem with the measles sub-unit

ÿ Once again, there was a positive correlation (90% or greater) between MMR antibody and myelin basic protein autoantibody

These findings led Singh to speculate that the measles sub-unit of the MMR vaccine might trigger an autoimmune reaction in a significant number of autistic children.

Singh highlighted what he regards as the important autoimmune factors in autism:

ÿ Autism is commonly associated with microbial infections, in particular viral infections

- ÿ Autistic patients have immune abnormalities, especially those that characterize an autoimmune reaction in a disease
- ÿ Autism shows inappropriate immune responses to vaccines, in particular MMR
- ÿ Autism displays increased frequency for immune response genes (eg HLA, C4B null allele or extended haplotypes) that render susceptibility to autoimmune diseases
- ÿ Autism involves a gender factor, as it affects males about four times more than females
- ÿ Autism has a family history of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and diabetes
- ÿ Autism also involves a hormonal factor, e.g. Secretin and endorphins
- ÿ Autistic patients respond well to immune modulation therapy (IMT)

Singh also reported that in his view, mercury (from vaccine ingredients) was not a risk factor for autoimmunity in autism, but that research was still progressing.

He believed that there were 500,000 cases in the US of autism (not including all ASD cases), and that perhaps 10% were genetic and 90% non-genetic in origin. It was plausible that an atypical measles infection that did not produce a rash but manifested neurological symptoms might be etiologically linked to autoimmunity in autism. The source of the measles virus could be MMR vaccine or a mutant measles strain, but more research was necessary. Singh considered that autistic children had a problem of their immune system, with faulty immune regulation, and hence had an abnormal immune reaction to measles virus and/or MMR.

167. Paper by Dr. Jeff Bradstreet, *Biological Evidence of Significant Vaccine Related Side-Effects Resulting In Neurodevelopmental Disorders*, presented to the Vaccine Safety Committee of the Institute of Medicine, National Academies of Science, US, February 9th 2004

This paper placed an immense amount of information in the public domain. Its release ironically occurred at a time of intense Government and media criticism of Dr. Andrew Wakefield in the UK and around the world. The paper's hypothesis was that:

- ÿ Data supported the unprecedented level of neurodevelopmental and immune disorders within the last two decades



Y There was a hypothesis that a subset of neurodevelopmental and medical disorders including encephalopathy with autistic features, a unique inflammatory bowel disease, and speech, learning and sensorimotor dysfunction, represented the manifestation of injuries related to vaccine components, especially mercury in the form of thimerosal and measles virus from MMR

Y Part of the hypothesis was that there was a specific genetic vulnerability or susceptibility

It was the view of the presenter that epidemiological studies “proving” no MMR/autism link could be challenged on various counts, including (a) inappropriate methodology, (b) lack of statistical power, (c) lack of control groups, (d) indiscriminate diagnostic groupings, (e) non-disclosure of relevant data.

It was also Bradstreet’s view that possible risk factors were beginning to emerge from affected children’s histories, including (a) familial autoimmunity, (b) pre-existing dietary allergies/intolerances, (c) vaccination with MMR when unwell, including current/recent antibiotic administration, (d) receipt of multiple simultaneous vaccine antigens with the associated potential for immunological interference, particularly for mumps upon measles virus.

Bradstreet also pointed out that no-one had published any data which refuted the findings of the Royal Free Hospital group. He also reported that evidence of the “double-hit” phenomena existed, whereby children experience worsening of symptoms with successive exposure to doses of MMR, and reminded the Institute that they had previously accepted that evidence of worsening of symptoms from exposure/re-exposure would indeed constitute strong evidence of a causal MMR/autism association.

He then gave advance details of two further papers that had been submitted for peer-review publication, and these are summarised below.

168. Paper by Bradstreet, International Child Development Resource Center Florida, Dahr, Department of Pediatric Allergy, Tulane University Medical School New Orleans, O’Leary & Sheils, Coombe Women’s Hospital & Trinity College Dublin, Anthony, Department of Histopathology Royal Free Hospital London, and Wakefield, International Child Development Resource Center Florida, *Detection of Measles Virus Genomic RNA In Cerebrospinal Fluid in Children with Regressive Autism by TaqMan RT-PCR: A Report of Three Cases*, summarised at the Institute of Medicine, 9th February 2004

The paper reported that:

- Three children with regressive autism (autistic encephalopathy) underwent cerebrospinal fluid assessment, including studies for

measles virus. All three children had concomitant onset of gastrointestinal symptoms and had already had measles virus genomic RNA detected in biopsies of ileal-lymphoid nodular hyperplasia.

- presence of measles virus fusion gene was examined in samples of cerebrospinal fluid from autistic cases and non-autistic controls
- none of the autistic cases or non-autistic controls had any history of measles exposure, other than MMR
- Serum and cerebrospinal fluid samples were also evaluated for antibodies to measles virus and myelin basic protein
- Measles virus f-gene was present in the CSF from all three autistic cases, but not in non-autistic controls
- Serum anti-MBP autoantibodies were detected in all children with autistic encephalopathy
- Anti-MBP and measles virus antibodies were detected in the CSF of two cases, but the third had neither anti-MBP or measles virus antibodies

The study concluded that the findings are consistent with a measles virus etiology for autistic encephalopathy, and indicate the possibility of a virally-driven cerebral immunopathology in some cases of regressive autism.

169. Paper (precise title not yet obtained) by Bradstreet, International Child Development Resource Center Florida, summarised at the Institute of Medicine, 9th February 2004

This was a further paper, also presented in summarised pre-publication form at the Institute of Medicine.

ÿ A group of 28 autistic children underwent lumbar puncture and examination of cerebrospinal fluid for measles virus genomic RNA. Presence of measles virus fusion gene was examined by TaqMan RT-PCR.

ÿ Samples of cerebrospinal fluid were also obtained from 37 non-autistic children and adults as a control group. This group comprised 20 children in remission from leukemia, three children undergoing shunt insertion for hydrocephalus, seven young adults with multiple sclerosis, and seven with encephalitis other than measles virus-related.

ÿ None of the autistic cases or controls had any history of wild measles infection, and all cases and controls had received MMR.

- ÿ Measles virus f-gene was found to be present in the cerebrospinal fluid of 19 out of 28 (68%) of autism cases, but only in 1 out of 37 (3%) of non-autistic controls.
- ÿ Where the data was available on the CSF (in 5 cases), allelic discrimination assay confirmed that the measles virus haemagglutinin-gene product was consistent with vaccine strain.
- ÿ These findings confirmed a highly-significant statistical association between the presence of measles virus RNA in the cerebrospinal fluid and regression into autism following MMR vaccination.

The paper concluded that these findings “stood atop the base of understanding built by O’Leary, Wakefield, Singh and others, and constituted “formidable evidence” of an association, which was “most likely causal in nature”. There appeared to be a subgroup of children experiencing significant disorders as a result of MMR.

170. Presentation by Geier and Geier, *From Epidemiology, Clinical Medicine, Molecular Biology and Atoms to Politics: A Review of the Relationship Between Thimerosal and Autism*, submitted to the Institute of Medicine, US National Academy of Sciences, January 2004 for the IoM’s meeting of 9th February 2004

This paper summarised the progress to that point with the Geiers’ researches into thimerosal and neurodevelopmental disorders:

- ÿ In their analysis of the VAERS database, the team had evaluated thimerosal-containing DTaP vaccines administered 1992-2000 in comparison with thimerosal-free DTaP vaccines administered 1997-2000
- ÿ They determined that there was a six-fold statistically significant increased incidence rate of autism reported to VAERS following thimerosal-containing DTaP in comparison to thimerosal-free DTaP vaccines
- ÿ The team concluded by suggesting that an association was found between thimerosal-containing childhood vaccines and neurodevelopmental disorders, including autism
- ÿ In their second analysis of VAERS, the team evaluated dose-response curves for the effects of increased doses of mercury from thimerosal-containing childhood vaccines, and evaluated another thimerosal-containing vaccine, whole-cell diphtheria tetanus pertussis vaccine, so as to see if the effects of thimerosal could be observed with a different thimerosal-containing vaccine other than thimerosal-containing DTaP vaccines. They evaluated thimerosal-containing DTaP and whole-cell DTP

vaccines (1992-2000), both in comparison to thimerosal-free DTaP vaccines (1997-2000).

- ÿ The researchers found consistent increasing risk dose-response relationships for autism following both of the thimerosal-containing vaccines in their comparison to their thimerosal-free DTaP vaccines
- ÿ In their third study of the VAERS database, the team combined their dose-response and overall comparison methodologies to evaluate thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. They observed similar results to those in our previous studies by finding an increased risk dose-response curve and overall statistically-significant 2.6-fold increased risk of autism following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines
- ÿ In the team's first evaluation of the US Department of Education data, they evaluated the 2001 US Department of Education report to determine the number of children of various ages that had developed neurodevelopmental disorders including autism and speech disorders. The results of their analysis showed that there was a direct increasing dose-response relationship between the prevalence of autism and additional average mercury doses from thimerosal-containing childhood vaccines
- ÿ In their second analysis of the US Department of Education data, the team once again evaluated the 2001 US Department of Education report using similar methodology, but in this new analysis they established the 1984 birth cohort as a baseline year. They then compared all subsequent birth cohorts against this baseline for the relative prevalence of autism and the average mercury dose from thimerosal-containing childhood vaccines
- ÿ The results of their analysis showed there was a direct increasing risk dose-response for autism following additional doses of mercury from thimerosal-containing childhood vaccines, and the researchers determined that overall there was a statistically significant increased risk for autism in comparison to the 1984 baseline measurement
- ÿ In their third analysis of the US Department of Education data, the Geiers employed similar methods, extending the birth cohorts examined so as to see if this would effect the relationship between the prevalence of autism in comparison to the average mercury dose children received from thimerosal-containing childhood vaccines (birth cohorts 1981-85 and 1990-96) In addition, they evaluated MMR vaccine population coverage estimates to see their potential impact on the population prevalence of autism in comparison to the effects observed from thimerosal-containing childhood vaccines.

ÿ It was determined that there was a close correlation between mercury doses and the prevalence of autism (birth cohorts 1981-85 and 1990-96) from the late 1980s through the mid-1990s

ÿ In contrast, there was a close correlation between the number of primary pediatric measles-containing vaccines administered and the prevalence of autism (birth cohorts 1982, 1985 and 1991-96) during the 1980s

ÿ In addition, it was found that there were statistically significant odds ratios for the development of autism following increasing doses of mercury from thimerosal-containing vaccines (birth cohorts 1985 and 1990-95) in comparison to a baseline measurement (birth cohort 1984)

ÿ The contribution of thimerosal from childhood vaccines (>50% effect) was greater than the potentially small contribution of the MMR vaccine on the population prevalence of autism observed in this study

The Geier team also made the following key observations:

ÿ The lead author of the Verstraeten study into thimerosal, Dr. Thomas Verstraeten, worked for the CDC until he left in 2001-2 to work in Belgium for GlaxoSmithKline, a vaccine manufacturer facing liability over thimerosal-containing vaccines

ÿ In violation of their own standards of conduct, Pediatrics failed to disclose that Verstraeten is employed by GSK and incorrectly identified him as an employee of the CDC

ÿ In the revised version of the Verstraeten study, the authors went outside the Vaccine Safety Database to secure data from a Massachusetts Health Management Organisation, Harvard Pilgrim, in order to counter the association found between thimerosal and speech delays. At that point, Harvard Pilgrim 'was in receivership, its computer records had been in a shambles for years, it had multiple computer systems that could not communicate with one another, and it used a health care coding system totally different from the one used across the VSD database.....The data could be pushed and pulled to get any results

ÿ The final published version of the Verstraeten et al study found a relative risk for autism among the highest exposure group by three months of age of 1.38. The authors concluded that: "no consistent significant associations were found between thimerosal-containing vaccines and neurodevelopmental outcomes.....This demonstrates.....how excessive manipulation of data can lead to absurd results.

**171. Letter by Mark R. Geier, *Parents' Worries About Thimerosal In Vaccines Are Well Founded*, published in Pediatrics journal, 12<sup>th</sup> March 2004**

Geier made the following points (in response to an earlier article by Offit and Jew):

- studies have shown 2- to 6-fold statistically significant increased risks for neurodevelopmental disorders and increasing dose-responsive effects for additional doses of mercury from thimerosal-containing vaccines, in comparison to thimerosal-free vaccines, for children.
- Blaxill has, in an ecological analysis, shown that the prevalence of autism in the US State of California was directly correlated with the doses of mercury that children received from thimerosal-containing childhood vaccines
- Hornig has found that early post-natal administration of thimerosal to mice, using doses and timing that mimic the childhood immunisation schedule, induced mouse strain specific effects that mirrored those of human neurodevelopmental disorders
- It has also been shown by other researchers evaluating the effects of ethylmercury in animal systems that ethylmercury causes distinct-specific damage to the nervous system
- Bernard et al have evaluated mercury and autism and determined that exposure to mercury can cause immune, sensory, neurological, motor and behavioural dysfunctions similar to traits defining or associated with autism
- Evaluation of children with autistic spectrum disorders in comparison to normal-matched controls has shown that autistic children retain abnormally high concentrations of mercury from such sources as thimerosal-containing childhood vaccines, whereas normal vaccinated children retain similar concentrations of mercury as normal unvaccinated children
- Thimerosal has been conceded by authors from the US FDA to cross the blood-brain barrier and placental barrier, resulting in considerable concentrations of mercury in the brain
- It has been reported that children who go on to develop autism have a genetic polymorphism (ie lower numbers of sulphhydryl groups) that causes them to have a decreased ability to excrete mercury, and as a result they build up concentrations of mercury in their brains, resulting in neurotoxicity (Bradstreet, Geier et al, 2003)

- Evaluation of micromolar concentrations of thimerosal on neurons in tissue culture has shown that thimerosal can interfere with the conduction of neurons (Song, Jang et al, 2000), cause neurodegeneration (Brunner, Albertini et al, 1991), and induce DNA breaks, caspase -3 activation, membrane damage and cell death (Baskin, Ngo, 2003)
- Waly et al, 2004, from Johns Hopkins University and elsewhere have published (quote) *“A Recent Analysis of Data from the Vaccine Adverse Events Reporting System.....found a significant correlation between the use of thimerosal-containing formulation (compared with thimerosal-free formulation) of the Diphtheria, Tetanus acellular Pertussis (DtaP) vaccine and autism.....The discovery of the P13-kinase/MAP-kinase/MS pathway, and its potent inhibition by developmental neurotoxins, including vaccine components thimerosal and aluminium, provides a potential molecular explanation for how the increased use of vaccines could promote and increase the incidence of autism”*
- We have found numerous articles that have reported that ethylmercury and methylmercury are similar. Tan and Parkin (2000) have reported that ethylmercury ions and methylmercury ions should display similar complexation and chemical characteristics. Fagan et al (1977) published that although thimerosal is an ethylmercury compound, it has similar toxicological properties to methylmercury, and the long-term neurological sequelae produced by the ingestion of either methyl- or ethylmercury based fungicides are indistinguishable
- Zhang (1984) has reported that ethylmercury compounds have toxicological properties similar to those of methylmercury compounds, and there is evidence that both methyl- and ethylmercury can persist in the body for a long time
- Yonaha et al (1975) have reported that the clinical signs and pathological findings caused by methylmercury compounds in animal experiments are known to be similar to Minemata disease in humans
- Ueha-Ishibashi et al (2004) have conducted studies with thimerosal and methylmercury demonstrating that both had similar in-vitro toxic effects on cerebellar granule neurons dissociated from two-week-old rats
- Even authors from the FDA (Ball et al, 2001) have reported that *“Because higher-dose exposure to ethylmercury from thimerosal results in toxicity comparable to that observed after high-dose exposure to methylmercury, and because of the chemical similarity of the two compounds, it appears reasonable to consider toxicity of low doses of methylmercury and ethylmercury to be similar.”*

- The US CDC conceded to Congressman David Weldon that some of the routinely recommended US childhood vaccines contained the full amount of thimerosal, even as late as 2003, and that many vaccines given to children even today (this was March 2004) contain 25 micrograms of thimerosal, including pediatric Diphtheria Tetanus (DT) vaccine, Tetanus-diphtheria (Td) vaccine), tetanus toxoid vaccine, meningitis vaccine and influenza vaccine. Many of these vaccines have end-2005 expiry dates
- Documents recently obtained from the World Health Organisation state that it is their policy to lobby for maintaining thimerosal in childhood vaccines for the foreseeable future, for use in the developing world, and that if it is banned from US vaccines, then these developing countries may also refuse thimerosal-containing vaccines
- A recent paper by Holmes et al (2003) showed that autism occurred far more in children born to women receiving Rho-immunoglobulin than in comparison with matched controls
- There are literally hundreds of articles in the peer-review literature on the dangers of thimerosal (merthiolate) including case-reports, animal studies, tissues culture studies, genetic studies, toxicology studies and biochemical studies. These papers have been published over many decades by authors from a wide variety of fields of science`

172. Paper by De Water, Ashwood, Hansen et al, *Reduced IgG Response to Common Vaccine Antigens for Patients with Autism Spectrum Disorder*, published by the MIND Institute, University of California at Davis, May 2004

To better define the immune status of children with ASD, the researchers examined by ELISA the serological response of patients and age-matched typically-developing (TD) controls to common vaccine antigens. These included bordetella, diphtheria, tetanus, measles, mumps and rubella.

ÿ All children analysed were vaccinated with DTaP (acellular) and MMR

ÿ Based on vaccination schedules, comparisons were made between patients and controls in three age groups, 2 to 5 years, 5-8 years and 8-14 years.

ÿ The most striking differences were observed in the 2-5 age group. Patients with ASD had a significantly lower IgG response to bordetella, diphtheria and mumps than the normal controls

ÿ There was also a trend for a lower IgG repose against measles and tetanus in the ASD group



- ÿ In the 5-8 group, there were no differences in the response to any of the test antigens
- ÿ In the over-8 age group, while there was a trend towards lower IgG responses to bordetella, tetanus and mumps antigens, only the IgG response to measles was significantly reduced.
- ÿ The response to rubella was equal in groups
- ÿ At no time point did the median of the response of the ASD group exceed that of the typically-developing (normal) controls

The study concluded that all patients with ASD were immunosuppressive for the vaccine antigens tested, and their responses were significantly lower than the typically-developing (normal) controls, suggesting an immune dysregulation in these ASD children.

173. Study, Deth et al, *Activation Of Methionine Synthase By Insulin-like Growth Factor-1 And Dopamine - A Target For Neurodevelopmental Toxins And Thimerosal*, Journal of Molecular Psychiatry, April 2004, 9 (4): 358-370

This study explored the possibility of a link between exposure to certain neurodevelopmental toxins and an increased possibility of developing neurological disorders, including autism and ADHD.

Deth and colleagues found that:

- ÿ Exposure to toxins such as ethanol and heavy metals including lead, aluminium and the ethylmercury-containing preservative thimerosal potently interrupt growth factor signalling, causing adverse effects on methylation reactions (ie the transfer of carbon atoms)
- ÿ Methylation in turn plays a significant role in regulating normal DNA function and gene expression, and is critical to proper neurological developments in infants and children
- ÿ insulin-like growth factor-1 (IGF-1) and the neurotransmitter dopamine both stimulated folate-dependent methylation pathways in neuronal cells.
- ÿ At the same time, they noted that compounds such as thimerosal, ethanol and metals such as lead and mercury effectively inhibited these same biochemical pathways at concentrations that are typically found following vaccination or other sources of exposure.

Deth commented that the recent increase in the incidence of autism led the team to speculate that environmental exposures, including vaccine additives, might contribute to the triggering of the disorder.

He further commented that “during the first years of life, networks of neurons that represent the matrix for learning are being developed in the brain....Methylation and the development of neuronal cells to create these networks are critical during this time. If the process is interrupted, the ability to learn and pay attention would naturally be impaired.”

Deth and his colleagues suggested that exposure to thimerosal, even in doses as low as those contained in one vaccine, has the ability to disrupt methylation. The theory is that certain children are more at risk than others because they lack the normal ability to excrete metals like thimerosal in the urine.

174. Paper by Torrente, Anthony et al, Centre for Paediatric Gastroenterology, Department of Histopathology, Royal Free & University College Medical School, London, *Focal-Enhanced Gastritis in Regressive Autism with Features Distinct from Crohn's and Helicobacter Pylori Gastritis*, published in the American Journal of Gastroenterology, vol 99, issue 4, page 598, April 2004

This paper identified that, following reports of lymphocytic colitis and small bowel enteropathy in children with regressive autism, the gastritis in regressive autism was clearly distinct from that in Crohn's and other conditions, pointing to a distinctive form of gastritis being connected with autism. The paper studied gastric antral biopsies in 25 affected children, in comparison with 10 with Crohn's, 10 with Helicobacter pylori infection and 10 histologically normal controls. The paper found:

- ÿ Distinct patterns of gastritis were seen in the disease states. Diffuse, predominantly CD4+ infiltration in H pylori and focal-enhanced gastritis in Crohn's disease and autism, the latter distinguished by striking dominance of CD8+ cells, together with increased intraepithelial lymphocytes in surface, foveolar and glandular epithelium
- ÿ Proliferation of foveolar epithelium was similarly increased in autism, Crohn's and H pylori compared to controls
- ÿ A striking finding seen only in 20 out of 25 autistic children was colocalised deposition of I gG and C1q on the subepithelial basement membrane and the surface epithelium
- ÿ The study conclusion was that these findings demonstrated a focal CD8-dominated gastritis in autistic children, with novel features

175. Presentation by Professor Boyd Haley, Professor and Chair at the Department of Chemistry, University of Kentucky, *In Vitro Studies Of Pure Thimerosal and Vaccines With and Without Thimerosal Added As A Preservative*, Canada Autism Conference April 2004

Professor Haley reported that:

- ÿ An extensive evaluation of the potential in vitro toxicity of thimerosal and vaccines containing thimerosal as a preservative versus those vaccines not containing thimerosal has been the objective of recent research done in (Haley's) laboratory
- ÿ In these preliminary studies, pure thimerosal has been shown to be more toxic to enzymes of the central nervous system than  $Hg^{2+}$ .
- ÿ Further vaccines with thimerosal added as a preservative consistently demonstrated in vitro enzyme toxicity that was markedly greater than the non-thimerosal or low-thimerosal-containing vaccines
- ÿ We also compared the toxicity of thimerosal to solutions of mercury chloride. The data indicates that thimerosal is usually a more potent toxicant to mammalian enzymes and brain tubulin polymerisation than is  $Hg^{2+}$ .
- ÿ Additionally, the toxicity of thimerosal to pure enzymes is rapid and does not require breakdown of the released ethylmercury into  $Hg^{2+}$
- ÿ Also, the inhibitory profile of thimerosal with enzymes of human brain homogenates is very different from the inhibitory profile of  $Hg^{2+}$
- ÿ This is further proof that the ethylmercury released from thimerosal has its own inhibitory properties, independent of any further breakdown to  $Hg^{2+}$
- ÿ Such data indicate that  $Hg^{2+}$  and ethylmercury could act synergistically to enhance toxicity
- ÿ We have done preliminary studies with tetracycline and ampicillin on the neuron-killing capability of thimerosal. Both antibiotics appeared to enhance the toxicity of thimerosal. This may be due to the interactions of these antibiotics with the heavy metal portion of ethylmercury that may enhance delivery of the toxicant to specific sites in the neurons

Haley further commented:

- ÿ "One fact that has become extremely obvious to me during this past eleven years is that it is impossible to determine the exact toxic level of mercury or mercury-containing compounds that is safe for all humans. There are several reasons why mercury should not be considered safe for humans at the measurable levels currently reported as 'safe' by current government monitoring agencies. First, ethylmercury has its own toxic properties and does not have to break down to  $Hg^{2+}$  to be toxic.

ÿ “Each human would likely have a level of toxicity from other mercury and non-mercury containing sources. These environmental toxicants could work synergistically with ethylmercury, rendering the ethylmercury much more toxic

ÿ “It is impossible to state the toxic effect of an injection of thimerosal unless one knows the toxic exposures of the individual to other heavy metals or other environmental toxicants, or perhaps the properties of the antibiotic given simultaneously

ÿ “ Infants do not make much bile in their early months of life and are unable to remove mercury through biliary transport, the major route for mercury removal. They also do not have a fully developed renal system that would remove other heavy metals.....Therefore, the age factor must always be considered for response to heavy metal exposure as well as spurious microbial infections.

ÿ “Genetic susceptibility is of critical importance.

ÿ “Common sense implies that safety should be proven before use of toxicants in medicine....not after. Nowhere was this lack of common sense more evident than in the exposure of infants to thimerosal”

176. Presentation by Dr. Rashid Buttar, American Board of Clinical Metal Toxicology and Visiting Scientist North Carolina State University, *Autism: The Misdiagnosis of Our Future Generations*, US Congressional Subcommittee on Health and Wellness, May 2004

Dr. Buttar took the view that, despite the debate as to whether or not mercury played a role in autism or other neurodevelopmental disorders, the evidence “is overwhelmingly obvious.”

He noted that as early as July 1991, Eli Lilly (manufacturers of thimerosal) stated that thimerosal was “a product containing a chemical known to the State of Carolina to cause birth defects or other reproductive harm.”

He reported that:

- most individuals exposed to mercury.....have the ability to at least begin the process of eliminating these heavy metals out of their system. But not everyone has this ability, and the extent of variability in the ability of an individual to detoxify their systems will determine the severity of the symptoms of toxicity.
- Patients with impaired detoxification pathways do not show similar results on testing. Their bodies are unable to release the mercury and/or metals, and on testing the mercury does not appear.

- The basis of (Buttar's) treatment protocol for children diagnosed with autism was determined by the clinical observation that certain individuals were unable to detoxify mercury like the vast majority of people
- The autism study undertaken consisted of 31 patients with the diagnoses of autism, autism-like spectrum (ASD) and pervasive developmental delay (PDD). All patients were enrolled sequentially as they presented to the clinic
- All 31 patients were tested for metal toxicity using four different tests, urine metal toxicity and essential minerals, hair metal toxicity and essential minerals, RBC metal toxicity and fecal metal toxicity. The initial tests were repeated at 2, 4, 6, 8, 10 and 12 months, and then every four months afterwards.
- All 31 patients showed little or no level of mercury on the initial baseline test results
- Compared to the baseline, all 31 patients showed significantly higher levels of mercury as treatment continued (eg a 350% increase after 2 months in one patient)
- The improvements in the patients in the study correlated with the increased yield in measured mercury levels upon subsequent testing. As more mercury was eliminated, more clinical improvement was noticed and the more dramatic the change.
- Some patients who had no prior history of speech started to speak at age 6 or 7, sometimes in full sentences
- Patients also exhibited substantially improved behaviour, reduction and eventual cessation of all "stimming" behaviour, return of eye contact and rapid toilet training, the latter sometimes in children aged 5 or 6 who had never been trained
- Additional findings reported by parents included improvement and increase in rate of physical growth, following instructions, becoming affectionate and social, seeking interaction with others, demonstrating appropriate responses and a rapid acceleration of verbal skills

Dr. Buttar concluded: "the underlying common denominator in chronic neurodegenerative disease seems to be either decreasing vascular supply (less blood to the brain) or accumulation of heavy metals, specifically mercury. The inability of an individual to eliminate toxic metals, especially mercury, is directly related to the level of neurodegeneration experienced. In

the young patient population suffering from autism or PDD, the vascular supply is not an issue.”

“Both (autistic and Alzheimers) patient populations suffer from the inability to excrete mercury as a result of a genetic predisposition resulting from the Apo E allele. This allele appears to be associated with the inability to get rid of mercury from the system.....When the mercury is successfully removed from their systems, these individuals begin to significantly improve due to a cessation of the destruction and denudation of the neurofibrils, as evidenced by steady improvement in cognitive function.”

177. Paper by Bradstreet, Dahr, Anthony et al, *Detection of Measles Virus Genomic RNA in Cerebrospinal Fluid of Children with Regressive Autism: A Report Of Three Cases*, published in the *Journal of American Physicians & Surgeons*, Vol 9, No. 2, summer 2004

This paper was the peer-review equivalent of the earlier Institute of Medicine’s meeting’s report of February 2004.

- ÿ Three children underwent cerebrospinal fluid (CSF) assessments, including studies for measles virus (MV). All three children had concomitant onset of gastrointestinal (GI) symptoms and had already had MV genomic RNA detected in biopsies of ileal-lymphoid nodular hyperplasia (ILNH).
- ÿ Measles virus was present in the CSF from all three cases, but not in controls
- ÿ Serum anti-MBP autoantibodies were detected in all children with autistic enterocolitis
- ÿ Anti-MBP and MV antibodies were detected in the CSF of two cases, whilst the third child had neither anti-MBP nor MV antibodies detected in his CSF
- ÿ Findings are consistent with both a measles-virus etiology for the autistic enterocolitis and active viral replication in these children. They further indicate the possibility of a virally-driven cerebral immunopathology in some cases of regressive autism

The authors comment that: vaccinations occurring in close temporal proximity to the encephalopathic regression of these children, when combined with the lack of documented natural measles virus exposure and a very low endemic measles virus rate, make it likely that the persistent measles virus infection originated from the vaccine. The children’s relevant clinical symptoms started soon after MMR vaccination, and were documented as soon as 13 days after exposure in Child Three.”

**“The findings are unexpected in view of the negative epidemiologic data from the US and Europe (but) epidemiologic studies that have examined this relationship have lacked adequate statistical power and have failed to test the correct hypothesis.”**

**“Child Three presents an interesting array of findings.....It is conceivable that multiple mechanisms are active in the children, and that they vary over time, based on other factors including concurrent viruses, toxins and oxidative stressors. Autistic encephalopathy is a complex disorder in which there is clearly more than one potential mechanism for regression. Cofactors including genetic predisposition are likely to influence the presentation and timing of symptom development.”**

**In subsequent correspondence between Dr. Bradstreet, Melanie Johnson MP (the UK Health Minister), Paul Burstow MP (the opposition UK Liberal Democrat Health Spokesman) and myself, Dr. Bradstreet confirmed:**

- **negative findings counter-quoted by Johnson used far less sensitive techniques**
- **the virus genome found in the autistic children in the study was “exclusively consistent with vaccine strain”**
- **the fact that Dr. O’Leary’s findings in relation to the specificity of the assay had been questioned was true, but that this, in itself, could not be taken to negate those findings**
- **the results by O’Leary had been separately confirmed by Kawashima (Dig. Dis. Sci. April 2000) and Professor Finbar Cotter (UK High Court), and so it was untrue, as Johnson had claimed, that they had not already been reproduced for both bowel and circulating monocyte observations. The CSF findings had not been reproduced but were consistent with the finding by Singh (Ped Neurol April 2003)**

**178. Paper by Deth, Professor of Pharmacology, North-Eastern University, Boston, Massachusetts, *Molecular Aspects of Thimerosal-Induced Autism*, paper presented to the Health & Wellness Sub-Committee of the Committee for Government Reform US Congress, 8<sup>th</sup> September 2004**

**The paper reported as follows:**

- **It has been proposed that increased use of vaccines containing the ethylmercury derivative thimerosal is the major contributing factor to the 40-fold increase in autism in the US during the past two decades**
- **Thimerosal is an exceptionally potent inhibitor of biochemical pathways that transfer single carbon atoms between molecules. These methylation pathways are critically involved in several important**

functions, including the regulation of gene expression and the molecular mechanism of attention

- Recent lab studies (by Deth) indicate that thimerosal exerts its toxic effects on methylation by interfering with formation of the active form of vitamin B12, also known as cobalamin
- Dietary B12 must be converted to methylB12 (methylcobalamin) in order to assist the transfer of single-carbon methyl groups from the folic acid pathway by the enzyme known as methionine synthase
- By reducing methylB12 formation, thimerosal inhibits this enzyme and thereby interferes with methylation events
- Autistic children have abnormal plasma levels of methylation-related metabolites and exhibit higher frequencies of genetic mutations that affect this pathway
- These genetic risk factors make them less able to detoxify thimerosal and also increase their sensitivity to its mechanism of toxicity
- Taken together, these facts indicate that increased exposure to thimerosal has combined with genetic risk factors in a sensitive sub-population to cause the recent rise in autism

Deth noted that:

- autism is caused by a combination of predisposing genetic factors and environmental factors that synergise with each other to cause the symptoms that are typical of the disorder
- methylation is the process by which a single carbon atom is transferred from a methyl donor to another molecule, commonly resulting in a change in the function of the recipient molecule. This is vital to the normal developing human
- abnormal methylation could alter the pathway of normal development and could contribute to neurodevelopmental disorders such as autism. Abnormal DNA methylation has previously been implicated as an important causative factor in Rett and Fragile-X
- the major methyl donor in biological reactions is S-adenosylmethionine (SAM), an activated form of the essential sulphur-containing amino-acid methionine. After donating its methyl group, the residual portion of SAM, S-adenosylhomocysteine (SAH) serves as a regulator of methylation by competing with SAM and inhibiting its methyl donation



- the concentration ratio of SAM and SAH therefore reflects the potential for methylation, and any increase in SAH or decrease in SAM will lower methylation
- children with autism have low levels of SAM and elevated levels of SAH, indicating an impaired potential for methylation
- Methylation of neurotransmitters such as dopamine and serotonin terminates their signaling activity, which may also play a role in autism
- Availability of the methyl donor SAM is critical for methylation. SAM is formed by addition of an adenosyl group from the high energy molecules ATP to methionine, as a part of the methionine cycle. After methyl donation, the adenosyl group is removed from SAH, in a reversible reaction yielding homocysteine (HCY) and adenosine
- Any unusual build-ups of adenosine can shift this reaction backwards towards SAH formation, whilst lowering HCY levels. This occurs with many children with autism
- Activity of the vitamin B12 dependent enzyme methionine synthase converts HCY back to methionine, using a methyl group from the folate pathway
- In summary, the four-step methionine cycle involves (1) activation of methionine (MET) by ATP-dependent adenosylation, (2) methyl donation by SAM, (3) reversible dissociation of SAH, and (4) remethylation of homocysteine (HCY) to MET by the vitamin-B12 dependent enzyme methionine synthase, using methylfolate (5-methylTHF) as the methyl donor. HCY can alternatively be converted to cysteine and glutathione

Also:

- the methionine cycle is also involved in the ability of the neurotransmitter dopamine to stimulate methylation of phospholipids in the neuronal membrane
- dopamine-stimulated phospholipids methylation (PLM) appears to be involved in the molecular origins of attention, and genetic variations in the D4 sub-type of dopamine receptor that carries out PLM have been linked to ADHD disorder (work of LaHoste, Swanson et al, 1996), and the ADHD-linked variant form is weak in its ability to carry out methylation. Impaired attention is a symptom of autism, and it is possible that this reflects reduced activity of dopamine-stimulated PLM

- during dopamine-stimulated PLM, a methionine that is an integral part of the D4 receptor protein is converted to SAM, then SAH, then HCY, then back to methionine again. Thus enzymes in the methionine cycle such as methionine synthase, actually have two substrates, one being a small individual amino acid and the other being the large D4 dopamine receptor protein
- methionine synthase is located at the intersection of the single carbon folate pathway and the methionine cycle, and is thus well positioned to regulate methylation. Its activity serves to maintain a low level of HCY, limiting its backward conversion to SAH and thereby promoting methylation
- methionine synthase activity in cultured neuronal cells has been shown (Waly, Olteanu, Deth et al 2004) to be substantially stimulated by both dopamine and insulin-like growth factor-1 (IGF-1). IGF-1 mediates many of the effects of growth hormone and is a key regulator of development, as well as promoting myelinisation
- the mechanism of methionine synthase activation involves an intracellular signaling pathway, the PI3-kinase pathway, commonly activated by many different cellular growth factors including those that promote cellular differentiation and development
- in subsequent investigations, Deth and colleagues found that methionine synthase activity in neuronal cells is absolutely dependent upon the ability of this signaling pathway to promote the formation of the biologically active form of vitamin B12 (ie methylB12 or methylcobalamin). It is a pathway that is inhibited by thimerosal
- methylcobalamin synthesis requires glutathione (GSH) and SAM, and levels of each of these metabolites are reduced in autistic children. Although additional studies are needed to clarify this further, growth factors apparently augment synthesis of the intermediate glutathionylcobalamin, which is subsequently converted to methylcobalamin
- the resultant higher level of methylcobalamin increases methionine synthase activity, lowering HCY and SAH levels and increasing methylation
- in support of this mechanism, Deth et al's studies have shown that IGF-1 and dopamine increases the methylation of both DNA and membrane phospholipids in conjunction with their activation of methionine synthase

- dietary or multivitamin forms of B12 (cobalamin) must be converted to the active methylcobalamin form via a two-step process requiring glutathione (GSH) and SAM.

Deth reported:

- Deth and colleagues investigated the mechanism by which thimerosal inhibits methionine synthase. When enzyme activity was measured in the presence of either hydroxycobalamin or cyanocobalamin, thimerosal caused almost complete inhibition. In the presence of methylcobalamin, thimerosal caused no inhibition. Furthermore, when activity was measured in the presence of glutathionylcobalamin and SAM, thimerosal inhibition was again absent, although when SAM was not added, inhibition was observed
- This pattern indicates that thimerosal inhibits the availability of glutathionylcobalamin, and that this action is responsible for its inhibition of methionine synthase and methylation

Deth and colleagues also examined the ability of different cobalamins to support methionine synthase activity after inhibition of P13-kinase:

- treatment with the selective P13-kinase inhibitor wortmannin caused a pattern of absolute dependence on methylcobalamin or its synthesis (glutathionylcobalamin + SAM), that was identical to the effect of thimerosal
- since thimerosal and wortmannin produce identical effects, this data strongly suggests that thimerosal acts by inhibiting the P13-kinase signaling pathway. This is the likely mechanism by which thimerosal causes autism. It may also be the molecular basis for its effect as a preservative

In further detail, Deth reported:

- As described by James et al (see elsewhere), the concentration of each of the individual metabolites in the methionine cycle and the trans-sulphuration pathway leading to glutathione synthesis, is significantly abnormal in autistic children as compared to normal controls
- Notably, methionine and s-adenosylmethionine (SAM) levels are low, consistent with lower activity of methionine synthase
- Whilst a low homocysteine (HCY) level might not be expected, the elevated levels of both s-adenosylhomocysteine (SAH) and adenosine indicate that HCY is being drawn backwards towards SAH via the reversible activity of the enzyme SAH hydrolase

- Thus an elevated level of adenosine restricts the availability of HCY for both methionine (and SAM) synthesis and for the formation of cysteine and glutathione
- Metabolites in the methionine cycle and transsulphuration pathway are abnormal in autism
- The 20% lower levels of cysteine and 54% lower levels of glutathione in autistic children will adversely affect their ability to detoxify and excrete heavy metals and thimerosal. These two compounds directly bind inorganic and organic mercury and help direct them to the kidneys for excretion
- As a result, these toxic materials will reach a higher free concentration in the bloodstream of autistic children, will have an increased potential for transfer to tissue compartments such as the brain, and will remain in the body for a significantly longer period of time, as compared to their counterparts who have normal levels of cysteine and glutathione
- These differences begin to define the sub-population of children who are more vulnerable to thimerosal and heavy-metal exposure
- Earlier metabolic and genetic studies provide clues as to the cause of the increased adenosine level in autistic children. Page et al found 8- to 10-fold higher activity of the enzyme that makes adenosine (5'-nucleotidase) in a subgroup of children, whilst Stubbs et al found that the enzyme that degrades adenosine (adenosine deaminase) has lower activity in autistic subjects
- Genetic studies have also shown that a polymorphism in the adenosine deaminase that weakens the enzyme is more common among autistic subjects
- Impairment of adenosine deaminase may result from dysfunctional interactions with its binding partner, enzyme dipeptidyl peptidase IV
- These metabolic defects can combine with thimerosal exposure and other genetic risk factors to inhibit methylation and cause autism
- There is recent evidence that polymorphisms in genes for methionine synthase and closely-related enzymes are another source of risk for autism. For example, there are two well-characterised disabling polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene, the enzyme that makes methylfolate available to methionine synthase, and these polymorphisms are more common in autism. MTHFR polymorphisms reduce methylfolate levels, which slows the methylation of Cbl and increase the probability that it will oxidize to

CobII. As a consequence, MTHFR polymorphisms increase methylcobalamin demand for the three-domain form of methionine synthase

- A disabling polymorphism in methionine synthase, in a location that can affect the proportion of three- vs four-domain enzyme forms, is reported to be six-fold more prevalent in autistic children (Bradstreet, Geier)
- Finally, a polymorphism in the enzyme methionine synthase reductase, which assists in the rescue of cobalamin, may also be more frequent in autism
- Whilst other polymorphisms remain to be discovered, these examples serve as instances of genetic risks that characterise autistic children, making them more sensitive to the toxic effects of thimerosal, and more prone to develop autism

179. Paper by Hornig, Chian and Lipkin, *Neurotoxic Effects of Post-Natal Thimerosal are Mouse-Strain Dependent*, Mailman School of Public Health, Columbia University, published in *Molecular Psychiatry* September 2004, Vol 9

This was a very important study, and was noted for receiving no real criticism from the usual sources.

The study found that post-natal exposure to thimerosal could increase the risk of autism-like damage in mice. The study reinforced previous studies showing that a genetic predisposition affect risk in combination with certain environmental triggers.

Y Timing and quantity of thimerosal dose for the mouse model were developed using the US immunisation schedule for children, with doses calculated for mice based upon 10th percentile weight of US boys at age 2, 4, 6 and 12 months

Y The researchers found that the subset of autoimmune disease susceptible mice with thimerosal exposure to express many aspects of the behavioural and neuropathologic features of ASD, including abnormal response to novel environments, behavioural impoverishment, significant abnormalities in brain architecture and increased brain size.

The editor of *Molecular Psychiatry*, Dr. Julio Licinio of University of California at Los Angeles, commented that the study clearly showed that there was a link between vaccines and autism for some groups and not for others. "Showing that genetic background impacts on the outcome of thimerosal exposure is a major breakthrough".

Press reports stated that the researchers had not yet identified the human analog of the mouse gene or genes that conferred susceptibility to the effects of thimerosal, so it was not clear what proportion of children could be at risk from vaccinations containing thimerosal preservative.

What they did know was that the genes involved were involved with the immune system and that they make the mice more vulnerable to autoimmune diseases. Researchers already knew that as many as one-third of families with an autistic child have a history of autoimmune problems.

Author, Associate Professor Dr. Mady Hornig, commented to Medscape: “The same immune responses genes in mice that predict mercury-related immunotoxicity also predict neurodevelopmental damage in our model and are associated with the development of features reminiscent of those observed in autism. These include generalised impoverishment of behavioural responses and abnormal reactions to novel environments, brain enlargement, correlated closely with the observed behavioural abnormalities in exploration and anxiety, increased cell packing in the hippocampus, and disturbances in glutamate receptors and transporters.”

Dr. Hornig also commented that the design of published epidemiologic studies may have been inadequate to appropriately estimate risk. Although MHC and non-MHC genes, age, sex, nutrition, route and frequency of administration and maturity of the metabolic, immune and nervous systems are known to affect mercury toxicokinetics, previous studies have not evaluated such factors.

**180. Letter by Geier and Geier, Genetic Centers of America, Thimerosal Does Not Belong In Vaccines, published in Pediatrics, September 2004**

Geier and Geier commented:

- \* it has become apparent from recently-emerging clinical, animal-model and molecular evidence that thimerosal is responsible for neurodevelopmental disorders in a number of children, regardless of the findings of large population-based epidemiological studies
- \* investigators have shown that children with ASD have significantly higher body burdens of mercury
- \* a genetically susceptible mouse strain has developed autistic features, including growth delay, reduced locomotion, exaggerated response to novelty, increased brain size, decreased numbers of Purkinje cells, significant abnormalities in brain architecture affecting areas sub-serving emotion and cognition, and densely-packed hyperchromic hippocampal neurons with altered glutamate receptors and transporters following administration of thimerosal mimicking the US vaccination schedule

\* molecular studies in vitro have demonstrated that acute thimerosal exposure at extremely low concentrations, that are comparable to the expected body distribution of mercury resulting from thimerosal-containing vaccines, can kill or significantly adversely-affect neuronal growth and development

\* pharmacokinetic studies on infant primates exposed to solutions containing similar concentrations of thimerosal, as thimerosal-containing vaccines, have shown that the half-life of mercury in the brain of the infant primates was approximately 28 days

\* male mice were considerably more sensitive than females to the neurotoxic effects of low-dose alkyl mercury exposure (which of course echoes the dominance of males in ASD)

181. Paper by Ashwood, Anthony, Torrente and Wakefield, *Spontaneous Mucosal Lymphocyte Cytokine Profiles in Children with Autism and Gastrointestinal Symptoms: Mucosal Immune Activation and Reduced Counter-Regulatory Interleukin-10*, published in the Journal of Clinical Immunology, Vol 24, No. 6, November 2004

This paper linked autism to a novel form of intestinal illness, building on earlier work. It identified a novel form of inflammatory intestinal disease in some children who had previously appeared to exhibit normal development but who had then regressed into autism.

It also suggested that the nature of the intestinal disease was viral.

Wakefield and colleagues had studied 86 children in England, including 21 with autism. They found that autistic children had significantly more cells, of a type associated with intestinal inflammation, in their digestive tracts. Eleven of the autistic children were on restricted diets involving dairy products, gluten-containing products, or both. These children had fewer inflammatory chemicals in their intestines than had the children that were not on restricted diets.

The study's key findings were that:

- molecules (cytokines) produced by immune cells in the intestine, that cause or control inflammation, show an abnormal pattern in autistic children compared with children without autism
- this pattern is different from other forms of intestinal inflammation
- the disease resembles a longstanding viral disease of the intestine, not unlike the intestinal inflammation seen on patients with other viral infections such as HIV-associated enteropathy (intestinal disease) that often accompanies infection with HIV

- the level of one potent pro-inflammatory molecule called tumor necrosis factor alpha (TNF $\alpha$ ) was particularly high in the cells from the intestinal lining, providing a potential target for treatment. Drugs that blocked this molecule have been shown to be beneficial in patients with Crohn's disease and rheumatoid arthritis
- in children on a diet that excluded gluten (from wheat and other cereals) and casein (from cow's milk products), that is often used by parents to benefit affected children, levels of pro-inflammatory molecule TNF $\alpha$  were significantly lower than those not on such a diet

182. Paper by James, Slikker et al, Department of Pediatrics, University of Arkansas, Children's Hospital Research Institute, Little Rock, Arkansas and Division of Biochemical Toxicology, National Center for Toxicological Research, Jefferson, Arizona, *Thimerosal Neurotoxicity Is Associated With Glutathione Depletion: Protection With Glutathione Precursors*, published in *Neurotoxicology*, 26 (2005) December 2004

This study, by Dr. Jill James of the University of Arkansas for Medical Sciences, found that autistic children are metabolically different and may not be able to excrete mercury and other heavy metals.

James studied 20 autistic children. She initially had studied only 10, but the results were "very very striking" and so she studied a further 10 as a check; the results of the second 10 endorsed those of the first 10.

James found that the autistic children studied had a severe deficiency in glutathione, the body's most important detoxifier. The autistic children in the study had 133% more "inactive" glutathione than had healthy children, and 68% less "active" glutathione.

James et al commented that considerable concern had been expressed over the cumulative dose of mercury given to children through routine immunizations, and that all forms of mercury were known to be neurotoxic, especially during early brain development. The high affinity binding of mercuric compounds to the thiol (-SH) group of cysteines in essential proteins was thought to be the basis for mercury-induced cytotoxicity. In vivo studies in rodents had demonstrated that ethyl mercury was able to cross the cell membrane and was then converted intracellularly to inorganic mercury, which then accumulates "preferentially" on the brain and kidney.

Intracellular accumulation of inorganic mercury was shown to be higher for ethyl compared with methylmercury, although clearance of ethylmercury was faster. The purpose of the James et al study was to determine whether the mechanism of ethylmercury toxicity was similar to that previously reported for ethylmercury.



Glutathione provided the major intracellular defence against oxidative stress-induced cell damage and apoptosis. Agents or conditions that deplete mitochondrial glutathione would indirectly induce cell death in a variety of cell types. Mercury and other heavy metals were well known to increase oxidative stress and deplete intracellular glutathione.

A major unanswered question was therefore whether mercury-induced depletion of glutathione preceded the increase in reactive oxygen species or whether mercury-induced ROS induces glutathione depletion. Whether mercury-induced depletion of glutathione is the initiating factor for increased oxidative stress and cell death in brain cells has yet to be evaluated.

James commented that these results made sense because glutathione levels are naturally lower in males, and this in turn would explain why 70% of affected children were boys. Estrogen, found more predominantly in females, is an antioxidant like glutathione, so females had more chemical weaponry to fight against metal toxins. The glutathione findings are also consistent with the earlier finding by Wakefield and others that many autistic children have intestinal disorders; glutathione is vital to full functioning of the intestines.

183. Paper by US Environmental Working Group, (Suite 100, 1436 U St NW, Washington DC), *Overloaded - New Science, New Insights, About Mercury and Autism in Susceptible Children*, published in December 2004

This paper noted the report by James that a “signature” metabolic impairment, or biomarker, had been found in autistic children, that strongly suggested that they would be susceptible to the harmful effects of mercury and other toxic chemicals.

The EWG undertook an eighteen-month review of the evidence. It concluded that:

- scientists had identified a signature biomarker in autistic children
- this finding (by James) reversed the Institute of Medicine’s much-criticised 2004 judgment that research into any thimerosal/autism link should be abandoned
- it strengthened the case for additional research
- newly published research by James had uncovered a unique and consistent metabolic imbalance in autistic children. This finding was consistent with the concept that if such children were exposed to a potentially toxic dose of mercury or other compound, then they would be much less likely to mount any effective defence

- reduced antioxidant defence might characterize a group of individuals who were demonstrably more sensitive to the effects of a range of toxic chemical exposures, and sheds light on increasing rates of related learning and behavioural disorders
- such findings raise serious concerns about the studies that have “proved” the safety of mercury in vaccines. Dr. James’ studies significantly strengthen the possibility of a mercury/autism link
- the weight of all evidence to date now “strongly supports” increased research into the relationship between thimerosal and autism

The Environmental Working Group concluded that it strongly supported the vaccination policies recommended by the American Academy of Pediatrics and the Centers for Disease Control, but that there should be the removal of thimerosal and any other mercury-based preservatives from all US vaccines. The weight of the evidence supported a re-examination of the mercury/autism hypothesis.

184. Paper by Blaxill, Redwood and Bernard, Safe Minds, 14 Commerce Drive, PH Cranford, New Jersey 07016 US), *Thimerosal and Autism? - A Plausible Hypothesis that should not be Dismissed*, published in *Medical Hypotheses*, (2004) 62, 788-794

In this paper, the authors provide evidence to refute the Nelson and Bauman critique (detailed elsewhere), and state the evidence for the mercury-autism hypothesis. They conclude:

- \* in the March 2003 issue of Pediatrics, Nelson and Bauman unilaterally dismiss the mercury/autism hypothesis. In that process, they effectively oppose the findings of the Institute of Medicine, which in October 2001 found the connection between thimerosal and neurodevelopmental disorders to be biologically plausible
- \* Nelson and Bauman, whilst offering no new evidence, “consider it improbable” that thimerosal and autism are linked, and support continued use of thimerosal. Their positions violate the precautionary principle, and scientific method
- \* their arguments misinterpret the evidence on early mercury exposure and autism characteristics
- \* the incidence of autism has increased in a decade: such an order of magnitude of increase must have environmental roots
- \* instead of speculative dismissals of the thimerosal-autism link, more proper evidence-based research is needed

**185. Paper by Havarinasab, Haggqvist et al, Department of Molecular and Clinical Medicine, Molecular and Immunological Pathology, Linköping University, Sweden and Department of Analytical Chemistry Umeå University, Umeå, Sweden, and Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, California, *Immunosuppressive and Autoimmune Effects of Thimerosal in Mice*, published in *Toxicology and Applied Pharmacology* 204 (2005), 109-121**

**This paper studied the effects of thimerosal by treating mice, susceptible to induction of autoimmunity by heavy metals.**

**The study noted:**

- **there are notable similarities and differences in the kinetics of mercury following oral administration of methylmercury and injection of thimerosal in vaccines**
- **the absorption rate and initial distribution volume of total Hg appear to be similar between thimerosal and oral methylmercury**
- **there will be approximately equal peak total blood Hg levels following a single exposure to either methylmercury or thimerosal, or following episodic exposures that are apart by longer than four elimination half-life (i.e. greater than 80 days for methylmercury or greater than 28 days for thimerosal)**
- **whilst the initial distribution volume of total Hg is similar for the two groups, a biphasic exponential decline in total blood Hg is observed only following injections of thimerosal. This suggests continual distribution into, and localization in, tissue sites over time.**
- **The kidney-to-blood concentration gradient of total Hg is much higher in the thimerosal infants than in the methylmercury infants, and therefore the second slower phase of washout could also represent the gradual biotransformation of ethylmercury (the presumed principal organic form of mercury after thimerosal administration) into Hg-containing metabolites that have a different tissue distribution or are more slowly eliminated**
- **It appears that the difference in brain Hg exposure between thimerosal and methylmercury is largely driven by their differences in systemic disposition kinetics (i.e. the blood levels). The average brain-to-blood partitioning ratio of total Hg in the thimerosal group was slightly higher than that in the methylmercury group. Thus the brain-to-blood mercury concentration ratio established for methylmercury will underestimate the amount of mercury in the brain after exposure to thimerosal (my emphasis)**

- The large difference in the blood Hg half-life compared to the brain half-life for the thimerosal-exposed infants (6.9 days versus 24 days) indicates that blood Hg may not be a good indicator of risk of adverse effects on the brain, particularly under conditions of rapidly changing blood levels such as those observed following vaccinations
- The blood concentrations of the thimerosal-exposed infants in the current study are within the range of those reported for human infants following vaccination (here, Burbacher et al cite a study by Stajich et al, 2000). Data from the current (Burbacher et al) study predicts that, while little accumulation of Hg in the blood occurs over time with repeated vaccinations, accumulation of Hg in the brains of infants will occur
- Thus, conclusions regarding the safety of thimerosal drawn from blood Hg clearance data in human infants receiving vaccines may not be valid (my emphasis), given the significantly slower half-life of Hg in the brain as observed in the infant macaques (primates)

The study found that:

- the autoimmune response was T-cell dependent
- the maximum added renal concentration of thimerosal and inorganic mercury occurred after 14 days' treatment and was 81ug Hg/g
- EtHg made up 59% and inorganic mercury 41% of the renal mercury

The authors concluded that the organic mercury compound thimerosal (EtHg) has initial immunosuppressive effects similar to those of MeHg. However, in contrast to MeHg, thimerosal treatment leads in genetically susceptible mice to a second phase with strong immunostimulation and autoimmunity, which is T-cell dependent, H-2 linked and may at least partly be due to the inorganic mercury derived from the metabolism of ethylmercury.

The authors commented in their discussion that “since thimerosal once taken up in the body is rapidly metabolized to EtHg, which has similar chemical properties and similar distribution as MeHg, the interaction of MeHg with the immune system is likely to be relevant also for the effects of thimerosal.....Our study clearly indicates that EtHg is similar to MeHg with respect to the immunosuppressive effect on the immune system in vivo.”

186. Press Report by Los Angeles Times (reporter, Myron Levin), February 8<sup>th</sup> 2005

Although this section deals almost exclusively with scientific studies, this press report is sufficiently important to be included here. It is quoted verbatim, in shortened form.

“A memo from the drug giant Merck & Co. shows that nearly a decade before the first public disclosure, senior company executives were concerned that infants were getting an elevated dose of mercury in vaccinations containing a widely used sterilizing agent.”

“The March 1991 memo, obtained by the Times, said that six-month-old children who received their shots on schedule would get a mercury dose up to 87 times higher than health guidelines for the maximum daily consumption of mercury from fish. ‘When viewed this way, the mercury load appears rather large’ said the memo from Dr. Maurice R. Hillerman, an internationally renowned vaccinologist. It was written to the president of Merck’s vaccine division.”

“.....The Merck memo shows that at least one major manufacturer knew of the concern much earlier (than the FDA, which announced it in 1999). Merck officials would not discuss the contents of the memo, citing pending litigation. Separately, the company is trying to fend off a legal onslaught over Vioxx.....”

“The legacy of thimerosal, meanwhile, is causing problems for Merck and other companies. More than 4,200 claims have been filed in a special federal tribunal, the Vaccine Injury Compensation Program, by parents asserting that their children suffered autism or other neurodevelopmental disorders from mercury in vaccines. A handful of similar claims are awaiting trial in civil courts.”

“The seven-page Merck memo was provided to the Times by James A. Moody, a Washington lawyer who works with parents’ groups on vaccine safety issues. He said he obtained it from a whistle-blower whom he would not name. The memo provides ‘the first hard evidence that the companies knew - or at least Merck knew - that the children were getting significantly more mercury’ than the generally accepted dose, Moody said.”

“Hillerman, 85 (and since deceased), director of the Merck Institute for Vaccinology, had officially retired and was a consultant to Merck when he wrote the 1991 memo. He declined to be interviewed.”

187. Study by Associate Professor Raymond F. Palmer and Professor Claudia Miller, into Environmental Mercury/Autism Link, published in Health and Place journal, March 2005

Further corroboration of a possible link between mercury and autism came in Spring 2005 from an entirely different direction, unconnected with vaccines. A study in the journal Health and Place (US) by Professor Claudia

Miller, Health Science Center, University of Texas at San Antonio, found that for every thousand pounds (weight) of environmentally released mercury (from hundreds of US coal-burning power stations), there was a 17% increase in autism rates.

This was the first time that a major study confirmed a link between mercury emissions in power stations and autism, and provides oblique support for the thimerosal/autism connection.

The key features of the study were:

- \* It was the first study to look at total legal amounts of released mercury from different sources of industry, and the relationship between that and developmental disorders
- \* there is a hypothesis that mercury (from thimerosal in vaccines) is associated with autism. This (Texas) study supports that general hypothesis, but it in no way confirms it
- \* the gap between damage allegedly caused by ethylmercury and damage by methylmercury is starting to close, because there are studies starting to show that ethylmercury (in thimerosal) is as toxic (as methylmercury)
- \* (unpublished) data at States level are reporting that States with the highest levels of mercury emissions also have the highest level of developmental disorders, including autism

A further US press report in March 2005 stated that the Harbard Center for Risk Analysis had provided a study on the health benefits of reducing mercury pollution, but that the Environmental Protection Agency of the US Food & Drug Administration had sidestepped the study by publishing new guidelines without reference to the study's findings.

188. Paper by Jyonouchi, Geng et al, Department of Pediatrics, New Jersey Medical School, *Dysregulated Innate Immune Responses in Young Children with Autism Spectrum Disorders - Their Relationship to Gastrointestinal Symptoms and Dietary Intervention*, published in *Neuropsychobiology*, February 2005, 51 (2), 77-85

This paper's importance was that it confirmed the findings of the Wakefield team from the UK, by finding evidence of marked inflammatory and immune abnormalities in children with autism associated with gastrointestinal symptoms.

The study compared the production of inflammatory and intra-inflammatory molecules by immune cells in autistic children on an unrestricted (n = 100) or elimination (n = 77) diets, with developmentally-normal children with

non-allergic food hypersensitivity on unrestricted (n = 14) or elimination (n = 16) diets, and healthy typically-developing children.

In response to challenge with bacterial toxins or dietary proteins from cow's milk, immune cells from autistic children with bowel symptoms showed a strong pro-inflammatory response and a reduced ability to switch off immune system activity compared with other children.

The authors concluded that their findings:

- indicate intrinsic defects of these immune responses in autistic children with intestinal problems
- suggest a possible link between gastrointestinal and behavioural symptoms mediated by immune abnormalities

189. Letter by Balzola, Barbon et al, Department of Gastroenterology, Department of Neuropsychiatry for Children, Department of Pediatric Gastroenterology, and Department of Biomedical Science and Human Oncology, all of the University of Turin, *Panenteric IBD-Like Disease in a Patient with Regressive Autism Shown for the First Time by the Wireless Capsule Enteroscopy - Another Piece in the Jigsaw of this Gut-Brain Syndrome?*, published in the American Journal of Gastroenterology, 100 (4) page 979, April 2005

The letter stated:

- a 28-year-old male came to the authors' attention with regressive autism, with unexplained microcytic anemia requiring intravenous iron supplementation
- severe constipation with bloating and abdomen distension and symptoms of gastroesophageal reflux were reported by parents
- gastroscopy under general anesthesia revealed hemorrhagic gastritis with inflammatory pseudopolyps that reached the pylorum with a pearl-necklace appearance
- the biopsies in the stomach and duodenum confirmed the chronic active inflammation, whereas those in the second part of the duodenum were inconsistent with celiac disease
- the whole colon and the terminal ileum were macroscopically normal at colonoscopy, whereas random biopsies showed a chronic severe active mucosal inflammation (intraepithelial lymphocytes and eosinophyls infiltrations and villous focal atrophy with reactive lymphoid nodular with intraepithelial CD3 and mucosal CD8), compatible with active inflammatory bowel disease

- the wireless enteroscopy capsule revealed areas of patchy erythema, mucosal erosions and ulcers in both jejunum and ileum
- a panenteric IBD-like disease, consistent with previous descriptions of autistic enterocolitis, was finally diagnosed
- the patient then received immunosuppressive agents, with clinical improvement in both gastrointestinal and behavioural symptoms.
- To the authors' knowledge, these were the first images of small intestinal disease in autism, beyond the limits of the duodenum and terminal ileum. They demonstrate the potential for the entire bowel to be implicated in this inflammatory disease.
- The authors think that the published data, together with their findings, are more than a simple coincidence. The response to treatment in this patient had positive effects on his behaviour, suggesting that inflammatory involvement of the entire bowel undoubtedly worsens the quality of life of such patients

190. Paper by Balzola, Daniela, Repici et al, Department of Gastroenterology, Department of Neuropsychiatry for Children, Department of Pediatric Gastroenterology, and Department of Biomedical Science and Human Oncology, all of the University of Turin, *Autistic Enterocolitis - Confirmation of a New Inflammatory Bowel Disease in an Italian Cohort of Patients*, presented to the American Gastroenterological Association, May 2005

This was an important paper as it independently confirmed the findings of the Wakefield team at the Royal Free hospital in the late 1990s.

The paper reported that:

- nine consecutive male patients (mean age 18 years, range 7-30 years) with a diagnosis of autism according to ICD-10 criteria, who showed chronic intestinal symptoms (abdominal pain, bloating, constipation and/or diarrhoea) were enrolled for the study
- after routine blood and stool tests, gastroscopy and colonoscopy with multiple biopsies were performed under sedation
- a wireless enteroscopy capsule was also performed in three adult patients
- anemia and fecal blood positive test was found in 2 patients and 3 patients respectively



- gastroscopy revealed mucosal gastritis in 4 patients, esophgitis in 1 patient, duodenitis in 1 patient
- histological findings showed a chronic inflammation of the stomach and duodenum in 6 patients, but inconsistent with celiac disease
- macroscopic mucosal abnormalities (aphtoid ulcerations and loss of vascular pattern) were found in 1 patient at colonoscopy, and LNH in the terminal ileum in 4 patients
- microscopic colitis with intraepithelial lymphocytes and eosinophils infiltrations, mucosal atrophy and follicular hyperplasia was histologically present in all the patients, whereas a chronic inflammation with iperemia and villous shortening of the terminal ileum was shown in 6 patients
- the wireless capsule revealed areas of bleeding or patchy erythema, mucosal erosions and ulcers in both jejunum and ileum in 1 patient
- a particular chronic jejunum and ileal erosive pattern was evident in the other two

The authors report that these preliminary data are strongly consistent with previous descriptions of autistic enterocolitis and supported a not-coincidental occurrence. Moreover, they showed for the first time a small-intestinal involvement, suggesting a pan-enteric localization of this new inflammatory bowel disease. The treatment to gain clinical remission had still to be tried.

191. Paper by Humphrey, Cole et al, Department of Pharmacology, Joan C. Edwards School of Medicine, Marshall University, Huntington US, and Graduate Center for Toxicology, University of Kentucky, *Mitochondrial Mediated Thimerosal-Induced Apoptosis in a Human Neuroblastoma Cell Line*, published in Neurotoxicology, Vol 26, Issue 3, pp407-416, June 2005,

This study reported that:

- Environmental exposure to mercury continues to be a public health issue due to effects on immune, renal and neurological function
- The safety of thimerosal has been recently questioned
- Mercurials have been reported to cause apoptosis in cultured neurons, though the signalling pathways resulting in cell death have not been well characterized
- The objective of this study was therefore to identify the mode of cell death in an in vitro model of thimerosal-induced neurotoxicity, and to

elucidate signaling pathways which might serve as pharmacological targets

- Within two hours of thimerosal exposure (5  $\mu$ M) to the human neuroblastoma cell line, SK-N-SH, morphological changes including membrane alterations and cell shrinkage were observed
- Cell viability showed a time- and concentration-dependent decrease in cell survival upon thimerosal exposure
- In cells treated for 24hrs with thimerosal, fluorescence microscopy indicated cells undergoing both apoptosis and oncosis/necrosis. To identify the apoptotic pathway associated with thimerosal-mediated cell death, the study evaluated the mitochondrial cascade, as both inorganic and organic mercurials have been reported to accumulate in the organelle. Cytochrome c was shown to leak from the mitochondria, followed by caspase 9 cleavage within 8 hours of treatment. In addition, poly(ADP-ribose) polymerase (PARP) was cleaved to form a 85kDa fragment following maximal caspase 3 activation at 24hrs.

The authors concluded that their findings suggest deleterious effects on the cytoarchitecture by thimerosal, and initiation of mitochondrial-mediated apoptosis.

192. Paper by Burbacher, Shen et al, Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, *Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal*, published in *Environmental Health Perspectives*, National Institutes of Health, Department of Health & Human Services.

This study examined both the amount and the type of mercury reaching the brain. Its findings implied that health officials originally had examined the wrong compound and had failed to test sufficiently rigorously when originally approving thimerosal.

Burbacher concluded that regulators trying to assess the potential for harm from thimerosal had used methylmercury, a compound that had been widely studied. In practice, thimerosal is based upon ethylmercury, a little-studied substance. Using methylmercury as a substitute for ethylmercury was inappropriate.

The study exposed 41 infant crab-eating monkeys (*Macaca fascicularis*) - and please note, my reporting this does not imply that I in any way condone experiments with animals - to thimerosal and methylmercury. The monkeys are regarded as close proxies to human infants. Infant monkeys assigned to the thimerosal group received the typical schedule of injected

vaccines for human infants, whilst infants assigned to a methylmercury group were exposed through a feeding tube.

Burbacher et al found that:

- Absorption and initial distribution of total mercury proved to be similar for both thimerosal and methylmercury
- However, injected thimerosal reacted differently from methylmercury in that it cleared from the infant much more quickly
- The peak blood mercury concentration in the methylmercury group rose to a level three times higher than the thimerosal infants after the fourth dose
- Brain concentrations of total mercury were significantly lower for the thimerosal group compared to the methylmercury group
- These results suggested that ethylmercury is de-alkylated much more extensively than methylmercury (de-alkylation is a detoxification mechanism that helps to protect the central nervous system)
- However, ethylmercury's fast breakdown leaves higher levels of "inorganic" mercury in the brain. Inorganic mercuric lingers in the brain for a year or more, potentially causing cell damage
- previous studies have found such cells (in elevated quantities) in children with autism
- experimenting with primates, Burbacher had found that the brains of thimerosal-exposed infants had twice the level of inorganic mercury as had methylmercury-exposed infants
- the FDA has never required testing of thimerosal's safety or of its safe exposure levels for newborn infants and children

The study concludes (verbatim quote):

**"Recent publications have proposed a direct link between the use of thimerosal-containing vaccines and the significant rise in the number of children being diagnosed with autism.....Results from an initial Institute of Medicine review of the safety of vaccines found that there was not sufficient evidence to render an opinion on the relationship between ethylmercury exposure and developmental disorders in children (IoM 2001)."**

**"The IoM review did, however, note the possibility of such a relationship, and recommended further studies be conducted."**

**“A recently published second IoM review (IoM 2004)(this was the much criticized review of April 2004) appears to have abandoned the earlier recommendation as well as backed away from the American Academy of Pediatrics goal. This approach is difficult to understand, given our current limited knowledge of the toxicokinetics and developmental neurotoxicity of thimerosal, a compound that has been (and will continue to be) injected into millions of newborns and infants.”**

**“The key findings of the current study are the differences in the disposition kinetics and demethylation rates of thimerosal and methylmercury. Consequently, methylmercury is not a suitable reference for risk assessment from exposure to thimerosal-derived mercury.”**

**“Knowledge of the biotransformation of thimerosal, the chemical identity of the Hg-containing species in the blood and brain, and the neurotoxic potential of intact thimerosal and its various biotransformation products, including ethylmercury, are urgently needed to afford a meaningful interpretation of the potential developmental effects of immunization with thimerosal-containing vaccines in newborns and infants. This information is critical if we are to respond to public concerns regarding the safety of childhood immunizations.”**

**Congressman David Weldon, a doctor who supports the US immunization program but who has also championed the cause of the children believe to have become autistic after vaccination, wrote to Secretary Michael Levitt of the US Department of Health & Human Services about the Burbacher et al study, on 19<sup>th</sup> April 2005, as follows (extract, verbatim):**

**“Prior to Burbacher’s study, public health authorities relied extensively upon data that suggested that mercury from thimerosal, ethylmercury, was cleared from the blood more quickly than methylmercury (see Pichichero study, 2002). Based upon this result.....many officials assumed, perhaps incorrectly, that ethylmercury was less toxic to infants than methylmercury. Pichichero concluded, based upon blood mercury level studies, that ‘thimerosal in routine vaccines possesses very little risk to full term infants, but that thimerosal-containing vaccines should not be administered to very low weight premature infants.’”**

**“Yet until Burbacher’s present work, assessments of brain levels of mercury in all its forms after exposure to thimerosal through immunizations had never been done.”**

**“And to date, no one has examined whether low levels of mercury in the brain have toxic neurodevelopmental effects. As recently as 2003, public health officials acknowledged that ‘no data exist on the capacity of low-dose chronic exposure to ethylmercury to harm the developing nervous system’ (Offit & Jew, 2003).”**

“Clearly, prior assumptions about the way thimerosal is handled by the human body must be revisited, and follow-up studies must be undertaken. Were thimerosal to be newly introduced to the market today, the FDA would require these basic animal toxicology studies before approving its use. I strongly urge that the National Institutes for Health continue funding these studies until the basic toxicology profile of thimerosal is fully understood.”

“Now that Burbacher has demonstrated that inorganic mercury accumulates in the brain of monkeys after thimerosal exposure, we must determine the developmental consequences of this accumulation in infants. Non-human primate infants that have been exposed to thimerosal by injection should be assessed by behavioural tests as they develop.....The brain samples (of these) should also be examined directly for evidence of brain damage.”

“With these concerns in mind, I would like you to meet with me soon to discuss the proactive steps you.....will be taking to ensure that funding is provided for research following-up on Burbacher’s work.”

193 Paper by Wakefield, Ashwood et al, *The Significance of Ileo-colonic Lymphoid Nodular Hyperplasia in Children with Autistic Spectrum Disorder*, published in the European Journal of Gastroenterology and Hepatology, 2005, vol 17 no. 8

The aim of this paper was to assess ileocolonic LNH in autistic spectrum disorder and control children, and to test the hypothesis that there is an association between ileo-colonic LNH and ASD in children.

- 148 consecutive children with ASD (median age 6 years, range 2-16), 127 of them male, with gastrointestinal symptoms, were investigated by ileocolonoscopy
- Macroscopic and histological features were scored and compared with 30 developmentally-normal (non-IBD, non-coeliac disease) controls (median age 7 years, range 1-11, 25 of which were male), showing mild non-specific colitis in 16 cases (13 male) and normal colonic histology in 14 cases (12 male)
- 74 ASD children and 23 controls also underwent upper gastrointestinal endoscopy
- The influence on ileal LNH of dietary restriction, age at colonoscopy, and co-existent LNH elsewhere in the intestine, was examined

The results were that:

- the prevalence of LNH was significantly greater in ASD children compared with controls, in the ileum (129/144) vs. 8/27 in controls,

and in the colon (88/148) vs. 7/30 in controls, whether or not controls had co-existent colonic inflammation

- the severity of ileal LNH was significantly greater in ASD children compared with controls, with moderate to severe ileal LNH present in 98/144 ASD children vs. 4/27 controls.
- Severe ileal LNH was associated with co-existent colonic LNH in ASD children
- The presence and severity of ileal LNH was not influenced by either diet or age at colonoscopy
- Isolated ileal LNH without evidence of pathology elsewhere in the intestine was a rare event, occurring in less than 3% of children overall
- On histopathological examination, hyperplastic lymphoid follicles were significantly more prevalent in the ileum of ASD children (84/138) compared with controls (2/23)

The study team concluded that:

- ileocolonic LNH is a characteristic pathological finding in children with ASD and gastrointestinal symptoms, and is associated with mucosal inflammation
- differences in age of colonoscopy and in diet did not account for these changes
- the data supported the hypothesis that LNH is a significant pathological finding in ASD children

193A Paper by Geier and Geier, *Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines*, published in the *Journal of American Physicians and Surgeons*, vol 11, no. 1, Spring 2006

This was an extremely important paper, as it powerfully demonstrated that the increase in use of thimerosal-containing vaccines in California was paralleled by an increase in neurodevelopmental disorders, specifically autism, and then the reduction in the use of thimerosal-containing vaccines in California was followed by a reduction in the rate of newly-diagnosed cases of autism in the State, strongly suggesting that thimerosal and autism numbers were causally linked.

This paper explained that:

- the US Vaccine Adverse Events Reporting System (VAERS) database had been maintained by the CDC since 1990
- the online public-access VAERS database was surveyed for neurodevelopmental disorders (NDs)
- the total new number of adverse event reports for each type of ND received on a reporting-quarter basis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) for 36 consecutive quarters from 1<sup>st</sup> Jan 1994 to Dec 31<sup>st</sup> 2002, and for 14 consecutive quarters 1<sup>st</sup> Jan 2002 to 30<sup>th</sup> Jun 2005 were evaluated in VAERS (the overlap was to ensure capture of the peak numbers in both groups)
- in addition, the California Department of Developmental Services (CDDS) database was examined. The total number of new autism reports received by the CDDS during the 36 quarters from 24<sup>th</sup> Jan 1994 to 6<sup>th</sup> Jan 2003, and the 15 quarters from 3<sup>rd</sup> Jan 2002 to 4<sup>th</sup> October 2005 were analyzed

The results were that:

- there was a significant difference in the trends for new autism cases, from an increasing to a decreasing slope, for autism and for speech disorder
- about 350 fewer cases of autism were reported to the CDDS in the reporting quarter ending 4<sup>th</sup> Oct 2005, than would have been expected from extrapolating the trend line for the first set of 36 reporting quarters
- about 200 fewer new cases of autism were reported to the CDDS in the last reporting quarter of the second set of 15 consecutive quarters, than in the first of that set
- there is a median lag time of three to four years between the time of birth and the diagnosis of an ND. As a result, the first children evaluated, whose reports were entered into the VAERS and CDDS databases in early 1994, were probably born in the late 1980s or early 1990s. These children probably received approx 100 micrograms of mercury from four doses of thimerosal-containing DTP vaccines, starting at two months of age
- subsequently, children entered into the VAERS and CDDS databases from early 1994 through mid to late 2002 were probably born from the late 1980s to early 1990s through the late 1990s. These children received increasing doses of mercury from additional thimerosal-containing vaccines (HIB, Hep B and in some cases influenza), as they

were added to the schedule. Peak exposure to TCVs during the first 18 months of life was 275 micrograms

- children entering into the VAERS and CDDS databases in the last period, beginning in mid-2002, were probably born from the late 1990s through the early 2000s. After July 7<sup>th</sup> 1999, as thimerosal was removed from vaccines (i.e. use of thimerosal-containing vaccines gave way to thimerosal-free vaccines), the total mercury dose children received from TCVs was gradually reduced, and remaining mercury in vaccines was administered to a less rigorous schedule
- overall, it appears that the increasing, and subsequent decreasing, trends in the rates of neurodevelopmental disorders observed in both the VAERS and CDDS databases correlates with temporal periods when the cumulative amount of mercury in the childhood immunisation was expanded, and then later contracted
- the consistency of the effects observed for the spectrum of neurodevelopmental disorders, including autism and speech disorders, and the agreement between the observations from two separate databases, support the conclusion that the effect is real, and not a chance observation. The magnitude in the change of the trend lines is substantial
- the biological plausibility of the present findings is further supported by recently emerging extensive toxicokinetic, molecular and animal studies

## PART J

### OTHER RELEVANT PAPERS

#### 194. 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



ÿ developmentally-affected children were nearly four times as likely to have had adverse reactions to immunisations

195. 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".*

196. Unpublished Paper by Kathryn M. Carbone, Laboratory of Pediatric & Respiratory Viral Diseases, Division of Viral Products, OVR, 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:

- ÿ 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.
- ÿ Administering neurovirulent vaccines to infants also places the child's CNS at increased risk for injury.
- ÿ 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.
- ÿ 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:

- ÿ We have identified vaccine virus related perturbations in CNS gene expression by standard semiquantitative RT-PCR and by differential display techniques, including endogenous immune mediators of the CNS.
- ÿ We have recovered un-characterised gene products from new genes that are altered by virus infection of the brain.

ÿ 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:

ÿ 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.

ÿ 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.

ÿ A developmental study of damage to developing brains (e.g. Cerebellum) in virus infected rats was performed, demonstrating anatomical, behavioural and neurological consequences.

197. 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.

ÿ The study used amplification of the mumps virus genome by reverse transcription-polymerase chain reaction (RT-PCR).

ÿ The mumps virus genome was not detected in intestinal specimens or peripheral blood lymphocytes.

ÿ 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)

198. 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:

ÿ (Commenting on safety studies) "*I have not found scientifically sound safety studies*"

- ÿ (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”.*
- ÿ (On single vaccines) *“The intrusion of the authorities in the legitimate freedom of choice of responsible parents by proscribing monovalent products is self evident”*
- ÿ (On evidence for/against a link) *“The data about biological plausibility of an MMR/autism link has gradually become more persuasive.”*
- ÿ (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.”*
- ÿ (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.”*
- ÿ (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”*
- ÿ (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.”*
- ÿ (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.”*

ÿ 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.”

199. 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:

ÿ Vaccine safety was the Cinderella of public health research. Government officials had failed to make it a high priority

ÿ There was some good research, but it was overwhelmed by the bad

ÿ The public had been let down because the proper studies had not been done.

ÿ 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

ÿ 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.”

200. Paper by Russell Blaycock, Clinical Assistant Professor Neurosurgery, University of Mississippi Medical Center, Jackson, Mississippi, *The Central Role of Excitotoxicity in Autism Spectrum Disorders*, published in JANA, vol 6, no. 1, winter 2003

Blaycock made the following points, amongst others, in his paper’s conclusions:

- ÿ While purely genetic disorders can explain a small sub-set of cases, most cases of ASD appear to involve children who are healthy until they receive their vaccination. Several vaccines are suspect, especially MMR, DPT and HepB.
- ÿ Today, US children are being given up to 22 doses of 6 types of vaccine before the age of five years. This represents a tremendous antigenic load for an immature immune system to deal with, especially when given so close together
- ÿ Until recently, children were also exposed to high concentrations of mercury. A US child receiving all of their vaccinations often received as much as 62.5ug of mercury per visit, one hundred times the exposure allowed by the Environmental Protection Agency as safe for an infant.
- ÿ Another problem is the use of live virus vaccines
- ÿ There is serious concern that “stealth viruses” may have infected millions of people, due to contamination of vaccines
- ÿ Attenuated viruses from vaccines may mutate by a process of recombination of genetic material with other viruses, with the possibility of transforming to more virulent forms
- ÿ Increased oxidative stress associated with antioxidant nutrient deficiencies could cause viruses to mutate from a non-virulent form to a highly-virulent form. With the high degree of oxidative stress and low antioxidant defences in the autistic child, the risk of such an event would be greatly enhanced
- ÿ We know that immune activation of the brain, especially when intense and prolonged, can precipitate the release of excitotoxins from astrocytes

and microglia. Excitotoxicity is now known to be a major mechanism of neural destruction in cases of viral infections of the brain

- ÿ Immune activation can trigger the release of the excitotoxins quinolinic acid and glutamate, leading to neurodegeneration
- ÿ Chronic elevations of glutamate during critical brain growth periods can result in the development of faulty neural pathway circuitry, which can have profound effects on complex higher cortical functions as well as hypothalamic functions. Even transient interference during the period of rapid brain growth can result in the apoptotic death of millions of developing neurons and the loss of millions of synaptic connections
- ÿ Destruction of synaptic connections and dendrites can occur in the absence of neuron death itself, which means that it can occur at much lower levels of glutamate and aspartate, especially when antioxidant levels, cellular energy generation and/or magnesium levels are low.
- ÿ Clinical seizures occur in approximately one-third of autistic children. Excitotoxicity is intimately connected to seizures, and explains the neural damage seen when they are prolonged or repeated
- ÿ Seizures in the developing brain result in irreversible changes in neuronal connectivity. A recent study (by Villeneuve, Ben-Ari et al) found that repeated seizures during early life resulted in persistent changes in the CA1 pyramidal neurons in the hippocampus, which is related to observed behavioural changes
- ÿ Mercury exposure is also intimately related to neonatal seizures. A recent study (by Szasz, Bavana et al) found that maternal exposure to mercury during pregnancy significantly increases epileptogenicity in the offspring
- ÿ Of special concern as well is the recent discovery that glutamate, by activating the NMDA receptors on the blood-brain barrier, can disrupt the barrier, leading to free access of blood-brain toxins to the CNS. In addition, free radicals themselves have been shown to open the BBB
- ÿ Seizures can open the BBB
- ÿ Autistic children have a high incidence of reactive hypoglycemia, which increases their risk of seizures and excitotoxicity. There is some evidence that candida infections may also increase the incidence and severity of hypoglycemia in autistic children

201. Paper by Singh and Rivas, *Prevalence of Serum Antibodies to Caudate Nucleus in Autistic Children*, published in *Neuroscience Letters*, vol 355, issues 1-2, January 2004

Singh and Rivas studied regional distribution of antibodies to rat caudate nucleus, cerebral cortex, cerebellum, brain stem and hippocampus. The study included 30 non-autistic and 68 autistic children.

• Autistic children, but not normal children, had antibodies to caudate nucleus (49% positive sera), cerebral cortex (18% positive sera), and cerebellum (9% positive sera)

• Brain stem and hippocampus were negative

• Antibodies to caudate nucleus were directed towards three proteins having 160, 115 and 49 kD molecular weights

Since a significant number of autistic children had antibodies to caudate nucleus, the authors proposed that an autoimmune reaction to this brain region may cause neurological impairments in autistic children, and that the caudate nucleus might be involved in the neurobiology of autism

Testimony of Lyn Redwood, President, Coalition for Safe Minds, to the US Congressional Sub-Committee on Human Rights and Wellness (Committee on Government Reform), US House of Representatives, 8<sup>th</sup> September 2004

This presentation included the following key points:

- even before the 1999 announcement (that mercury content of all products would be assessed), the US FDA had, over the previous decade, received early warnings about thimerosal that they chose to ignore. Between 1990 and 1998, the FDA had received 47 adverse event warnings reported through the US Vaccine Adverse Events Reporting System (VAERS) regarding mercury or thimerosal. From 1998 until July 2000, another 15 reports were received. These warnings were ignored
- pharmacokinetic studies, determining toxicity and maximum safe exposure levels to thimerosal, were not conducted, or have not been made public
- Medline research reveals hundreds of peer review articles which document the toxicity of thimerosal, including severe morbidity from high-level exposure
- Safe Minds has obtained relevant documentation through Freedom of Information that showed by December 1999 the Centers for Disease Control knew thimerosal could be linked to the increased incidence of neurodevelopmental disorders

- Between February 2000 and November 2003, Dr. Verstraeten and his supervisors at the National Immunisation Program produced four separate iterations of an analysis designed to assess the impact of vaccine mercury exposures on neurodevelopmental disorders in children. With each iteration, elevated and statistically-significant risks were reduced and/or eliminated
- Dr. Verstraeten conducted an earlier analysis of these issues in November and December of 1999. He never prepared a formal report on this work, but statistical tables obtained through Freedom of Information have demonstrated large and statistically-significant mercury effects in many cases that exceeded the findings of the later-iteration reports. These initial analyses compared disease risk in the highest-exposure population groups with disease risk in zero-exposure population groups
- The results of these “zero” analyses are striking and more supportive of a causal relationship between vaccine mercury exposure and childhood developmental disorders (especially autism) than any of the results reported later (after subsequent iterations). Relative risks of autism, ADD, sleep disorders and speech/language delay were consistently elevated relative to other disorders, and frequently significant statistically
- Disease risk for the high exposure groups ranged from 1.5 to 2 times at the low end to 11 times the zero-exposure group at the high end
- The strongest effect was for the highest levels of mercury exposure at the earliest time of exposure, consistent with the idea that infant brain development is most sensitive to the earliest exposures
- The elevated risk of autism for the highest exposure levels at one month ranged from 7.6 to 11.4 times the zero exposure level. This significant increased risk level corresponds to the tenfold reported increase in autism rates that have been seen since increased vaccine mercury exposures took place from 1990
- The difference in these more alarming reports in comparison to later reports have exposed a number of methodological choices that may in themselves have been a powerful source of bias in later iterations of the analysis
- Dr. Verstraeten presented his findings to a closed group of Centers for Disease Control and Health & Human Services officials and outside experts, many of whom were academics with close ties to the vaccine manufacturers. The Simpsonwood meeting became a vehicle for making numerous deliberate methodological choices that took finds in a single direction, towards “insignificance”. CDC and National



**Immunisation Program employees demonstrated clear biases against reporting positive results**

- **Rather than take swift and aggressive measures to eliminate all exposure to thimerosal for future infants, the CDC delayed publication of the data for years while conducting its further iterations**
- **Subsequent attempts for independent review of the Vaccine Safety Datalink data have been met with numerous obstacles. HHS and CDC have placed near-impenetrable obstacles and restrictions on access and study of VSD data**

**202. Paper by Richler, Luyster et al, *Is There A Regressive Phenotype of Autism Spectrum Disorder - A Collaborative Programs for Excellence in Autism (CPEA) Study, 2004***

**This was a multi-site study of 351 children with ASD and 31 typically-developing children. These included 163 with regression and 188 without regression. There were no significant differences between regression and non-regression groups in terms of ethnicity, gender, level of maternal education or diagnosis.**

**The findings were that:**

- **A substantial minority (20%-33%) of parents of children with ASD reported that their children seemed to acquire some social and communicative skills that they subsequently lost, typically at between 15 and 24 months of age (findings by Davidovitch, Glick et al, 2000, and Goldberg et al, 2001)**
- **children who had acquired skills that they subsequently lost were described as showing a greater number of skills prior to 24 months of age and fewer of these skills by 36 months of age than other children with ASD**
- **children who had experienced losses of skills also showed poorer outcomes in verbal IQ and social reciprocity, and a greater number of gastrointestinal symptoms than children with ASD without regression**
- **low prevalence rates of GI disorders were found for both the regressive and non-regressive groups**
- **differences found between children with ASD and regression and those without regression provide some evidence for the existence of a sub-group of children with regressive autism who have a later age of onset**

- this sub-group also has a greater tendency towards GI dysfunction and possibly poorer outcomes in verbal IQ and social reciprocity
- there was little evidence to suggest that children with regression had normal pre-loss development. The majority of the children in the regressive group had few or no skills in the typical range prior to loss
- the children who most closely fitted the new phenotype had few normal pre-loss skills

The study recommendations included that further research should include:

- further investigation of the timing of, and nature of, GI symptoms
- studies to investigate a possible link between regression in ASD and aspects of family medical history such as autoimmune disorders and environmental factors such as MMR

## PART K

### STUDIES THAT HAVE BEEN USED TO DENY AN MMR/THIMEROSALAUTISM 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.

These studies, and reviews of studies, are exclusively epidemiological. In other words, they are based upon surveys of information such as patient records.

#### 203. Limitations Of Epidemiology - A Preface

The limitations of epidemiological studies are well-known, and were eloquently expressed recently:

*“The validity of observational research depends on the validity of existing knowledge about the cause of the studied disease. In other words, causal association cannot be established by data from observational research alone. Supportive evidence from experimental research, including basic science and randomised trials, is essential....In observational research, such as cohort study and case-control study, compared groups can differ in many features and are thus not truly comparable. Whether this built-in limitation can be overcome depends on whether all major confounding factors can be identified and appropriately controlled. Recognition and*

*identification of confounding factors, however, require a comprehensive and in-depth understanding about the complex biological mechanism in pathogenesis. If the mechanism of a disease is poorly understood, some unexpected confounders probably remain unidentified and uncontrolled.....Data from observational research just cannot be used as the sole evidence to.....deny a causal link" - letter by Fang and Shau, Department of Internal Medicine, National Taiwan University Hospital, Taipei, published in The Lancet, Vol 360, No. 9328, 20th July 2002*

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

- ÿ 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.
- ÿ 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.
- ÿ The studies are also of random groups of children, but not of the actual children reported by parents as damaged by MMR.
- ÿ Finally, the UK 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 UK Department of Health itself.
- ÿ Similar errors of logic have been committed in the US by the CDC and the Institutes of Health, and by the Institute of Medicine.

204. 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).

- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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)
- ÿ 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

205: 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.

- ÿ 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.

ÿ 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:

ÿ 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

ÿ 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.

ÿ 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.

ÿ 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.

ÿ 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  $2 \times 582$ , or less frequently, this study would not have found it.

The authors did actually acknowledge this, stating:

ÿ *“The study was designed to explore relatively common symptoms and signs occurring after the vaccination”* (they mean, “within 21 days of”), and

ÿ *“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

**206: 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**

**207. 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).

Y 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.

Y 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

Y The study’s case-selection being a few cases out either way would neutralise or completely reverse the findings of the study.

Y 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.**

(Note: in May 2005, Gillberg was on trial in Sweden over the alleged destruction of study-related records, and was found guilty in late 2005, and fined).

**208. 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.

Note: in mid-2005, Professor Gillberg was found guilty by a Swedish Court of “breach of duty” for not releasing research material about Attention-Deficit Hyperactivity Disorder, and fined fifty times his daily income.

209. 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 Maudslay Hospital, London.

- ÿ For ASD, three diagnostic groups were examined, autism, atypical autism including disintegrative disorder, and pervasive developmental disorder
- ÿ Medical disorders were coded for a 25-year period, including Crohn’s and ulcerative colitis, for 8889 patients.
- ÿ 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.
- ÿ 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.



- ÿ He found 174 cases with autism.
- ÿ One child of the 6100 had Crohn's, and one had ulcerative colitis. Neither were autistic
- ÿ 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.

210. 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:

- ÿ Information on the children was extremely variable in quality and completeness
- ÿ 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*")
- ÿ 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?

- ÿ 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.
- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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).
- ÿ 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.

211. 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.

- ÿ 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.
- ÿ Taylor, Miller found a steep increase in autism, (“*There was a steady increase in cases by year of birth*”), but did not explain it.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.

Y 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)

**212. 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:

Y *“Our conclusion, based on the findings of our study, is that there is no evidence of a causal association between MMR and autism”.*

Y *“The case series method has a proven track record with respect to identifying and measuring a risk of adverse events after various vaccines”.*

Y *“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.”*

Y *“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.

**213. 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,

- ÿ 173 potentially serious adverse reactions were claimed to have been caused by MMR, out of almost 3 million doses.
- ÿ There were 77 neurologic reactions, 77 allergic reactions, 22 miscellaneous reactions and one death.
- ÿ Some 45% of these reactions were dismissed by the study as probably caused or contributed by other factors.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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:

- ÿ The study was part-funded by Merck Sharp Dohme (MMR manufacturers).

- ÿ The study barely refers to autism or IBD.
- ÿ 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.

214. 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.

- ÿ 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.
- ÿ 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)
- ÿ 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%.

- ÿ The study concluded that no correlation existed between MMR and autism, and that the explanation for increased autism remained uncertain
- ÿ 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
- ÿ The authors then argue that if MMR was a major cause, then the risk of autism should have stopped rising within a few years.
- ÿ 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.
- ÿ They also acknowledge that time trend analysis is a “*relatively crude method*”.
- ÿ 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.
- ÿ 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.
- ÿ 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
- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ 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.

215. 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 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:

- ÿ “*Diagnosis is not always straightforward*”. This is an extreme understatement.
- ÿ “*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*”
- ÿ “*Observation of parallel trends over time.....generally do not constitute strong evidence for a causal association between the two events*”
- ÿ “*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.
- ÿ “*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.
- ÿ “*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.
- ÿ “*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?
- ÿ 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.

Ÿ 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.

216. Paper by De Wilde, 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:

- Ÿ It may be difficult to place a definite date upon degeneration
- Ÿ Parents may not seek assistance from their GP immediately, or even at all in some cases
- Ÿ Parents may seek advice from health visitors or other health professionals
- Ÿ Parents may see a GP only once, to obtain a referral to a specialist paediatrician
- Ÿ Parents may see their GP for reasons unconnected with autism, confusing the data in some cases
- Ÿ 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).**

**217. 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:**

- ÿ 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?**
- ÿ 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:**

- ÿ the risk of inflammatory bowel disease was the same whether for vaccinated or unvaccinated people**
- ÿ there was an average of 140 months between vaccination and diagnosis for cases.**
- ÿ 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.

**218. 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.

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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:

- ÿ for the 357 cases, the observation periods had a median of 89 months, a maximum of 191 months.
- ÿ The oldest age at diagnosis was 180 months.

- ÿ Some 64 did not receive MMR.
- ÿ Some 43 received MMR after age 2 years, at median age 57 months, maximum 165 months.
- ÿ 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:

- ÿ Regarding the whole period following MMR as being “at risk” is questionable.
- ÿ 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)
- ÿ 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)

It was subsequently pointed out that both Miller and Taylor had received significant funding from vaccine manufacturers, and that this represented a conflict of interest.

219. 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:

ÿ 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.

ÿ 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.

ÿ 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.

Y 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.

Y 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.

Y 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:

- ÿ 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
- ÿ 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.
- ÿ 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)

220. Further 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:

- ÿ Recorded bowel problems lasting at least three months
- ÿ Age of reported regression (where it was a feature)
- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ 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:

- ÿ 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.

- Y 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).
- Y 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.
- Y 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.
- Y 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).

- Y 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.
- Y 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.

- Y 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.
- Y 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
- Y “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.
- Y 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.
- Y 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)

221. 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:

- ÿ no evidence of an MMR/autism link.
- ÿ strong evidence that both MMR and single measles vaccination virtually eliminated risk of measles and measles complication
- ÿ 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:

- ÿ The study was only a review. It offered no fresh evidence.
- ÿ It was not a clinical study. It did not examine any children.
- ÿ 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 a box that is known to be empty, you should not be surprised at finding nothing.
- ÿ 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?*".
- ÿ Absence of evidence is not evidence of absence
- ÿ 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.

222 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.

223. Study by Madsen, Hviid, Vestergaard, Schendel, Wohlfarht, 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.

The vaccine/autism debate has increasingly centred around “studies in Denmark”. There have been several, all in a short space of time and with overlapping authors and funding, and this has encouraged confusion amongst parents and journalists.

In summary, the five recent studies have been:

- one published in 2002 (reviewed below), led by Madsen
- one in 2003 led by Madsen (reviewed later)
- one in 2003 led by Hviid (reviewed later)
- one in 2004 led by Lauritsen (reviewed in the section covering prevalence)
- one in 2005 led by Larsson (reviewed later)

The 2002 Madsen study paper, also not to be confused with the Pediatrics paper previously reviewed above, also 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’s authors included Dr. Diana Schendel of the US CDC - the US agency that promotes vaccination - an obvious conflict of interest. The study was also co-funded by the CDC.

Interestingly, the covering letter for the study, by its authors, stated that “*So far, no study has had sufficient power to address (the MMR/autism connection)*”. So the previously-acclaimed studies (i.e. acclaimed by those seeking to defend MMR), including studies by Dales, Kaye, Peltola, Taylor and many others, were now being dismissed as inconclusive and under-powered by this Danish study, despite their earlier enthusiastic receipt.

The 2002 Madsen et al paper featured:

- ÿ A retrospective cohort study of all children born in Denmark from January 1991 through till December 1998
- ÿ 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
- ÿ 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).
- ÿ 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:

- ÿ 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.
- ÿ The Madsen study only focussed on MMR and not other vaccines implicated in autism
- ÿ The study (as noted elsewhere) failed to distinguish between different types of autism
- ÿ 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.
- The study did not, of course, involve the clinical examination of any children or the analysis of samples.

The study was also questioned in a letter to the New England Journal of Medicine (6/3-06 issue) by Professor Walter Spitzer of McGill University, Montreal, as follows:

Ÿ The study has some methodologic problems. A review of the clinical records for only 40 of the 316 children with autistic disorder is inadequate

Ÿ Without a multidisciplinary review of lifetime records, important errors would have been unavoidable

Ÿ Although it would be difficult, with the use of clinical criteria one could identify subgroups among most of the children, notably subgroups with regression

Ÿ The power of the study was high, but misleading.....(potentially) masking the (MMR) association in a small sub-group

The study was also criticised in the same publication by Dr. Michael Mullins of Washington University School of Medicine, St. Louis:

Ÿ (the study) has multiple flaws that compound the bias toward a finding of no association. First the use of person-years instead of persons magnifies the weight of the early cases (when the prevalence of autism was relatively low) and minimizes the weight of the later cases (when the prevalence was five times that in the early period).

Ÿ Secondly, mean ages at diagnosis were 51 months for autism and 63 months for other autistic-spectrum disorders. A child born early in the study period had a higher likelihood of receiving a diagnosis than a child born later in the study period

Ÿ Thirdly, children in the unvaccinated group underwent a mean of 5.0 years of follow-up (482,360 person-years for 96,648 persons), as compared with 3.7 years in the vaccinated group (1,647,504 person-years for 440,655 persons). This discrepancy also reduced the likelihood that autism would be detected in a vaccinated child as compared with an unvaccinated child.

Ÿ The authors overstate their conclusion in the abstract by saying “this study provides strong evidence against the hypothesis that MMR vaccination causes autism”. Even if the study did not suffer from these flaws, the strongest defensible conclusion would be that the study did not detect an association between MMR and autism.

Madsen responded to these published comments by admitting:

Ÿ We cannot rule out the possibility that at least one child would not have become autistic if he or she had not been vaccinated

Ÿ we can say that MMR vaccination is not the explanation for an increasing incidence in autism

Ÿ we can say that MMR vaccination is not one of the common causes of autism. *But we cannot prove anything.....*

Ÿ We do not claim to have proven that MMR vaccination can never cause autism

Ÿ We cannot rule out the existence of a susceptible subgroup with an increased risk of autism if vaccinated, but such a subgroup must be small

The researchers, in a press comment, admitted that they did find a dramatic increase in the number of diagnosed cases of ASD during the study period. “No one knows why this increase is taking place.....the study was not designed to answer that question.....”

Comment: there are clearly 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.

224. 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.

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:

Ÿ 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

Ÿ 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

Y 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:

- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ The study sample was not drawn at random, but reflected convenience.
- ÿ 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
- ÿ 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.
- ÿ 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.

ÿ 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.

ÿ 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.

ÿ 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:

ÿ It makes improper use of methylmercury safety levels as a marker for ethylmercury risk

ÿ There has never been any full assessment of thiomersal safety. This has been admitted by the US Food & Drug Administration.

ÿ 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.

Pichichero also incidentally commented in January 2003 on the new 5-in-1 vaccine that was just then licensed by the US Food & Drug Administration. Welcoming the Pediarix-DTaP, hep B and inactivated poliovirus vaccine that



was recommended for infants at 2, 4 and 6 months, Pichichero said that its advantage was that it offered “fewer injections for kids”, but, he then continued.....”which would make room for new vaccines that are on the horizon”.

225. Paper by Makela, Nuorti and Peltola, *Neurologic Disorders after Measles-Mumps-Rubella Vaccination*, 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:

ÿ Of the 535,544 children who were vaccinated, 199 were hospitalized for encephalitis, 161 for aseptic meningitis and 352 for autistic disorders.

ÿ 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

ÿ The study detected no clustering of hospitalizations for autism after vaccination

ÿ 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:

Ÿ 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.

Ÿ Peltola stated unequivocally in a BBC interview that his 1996-completed study did not address autism as a possible outcome from MMR vaccination

Ÿ 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.

Ÿ 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.

226. Commentary by Nelson and Baumann, *Thimerosal and Autism*, Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, and the Children's Neurology Service, Harvard Medical School, Boston, Massachusetts, published in *Pediatrics*, Vol 111, No. 3, March 2003, pp674-679

This paper looked at whether then-current evidence indicated that mercury at any known dose, form, duration, age or route of exposure leads to autism.

The paper commented:

Ÿ There has clearly been a broadening of the criteria for autism (note: Yazbak reports that the reverse is the case), better case-finding, increased awareness by clinicians and by families, and an increase in referrals of children for services. Whether the sum of these is sufficient to account for the more frequent diagnosis of autism is a matter of contention....

Ÿ Researchers Aschner and Walker (*Molecular Psychiatry* 2002, 7, S40-41) found no paper published in the peer-review literature that reported an abnormal body burden of mercury, or an excess of mercury in hair, urine or blood

ÿ Findings by other researchers support the observation that the risk of toxicity from ethylmercury is overestimated by comparison with the risk of intoxication from methylmercury

ÿ In both prenatally and postnatally exposed brain. the atrophy associated with neuronal loss and in the infant cases the reduced white matter volume suggest that these brains were likely to be reduced in size.....By contrast, examined at autopsy, brains of autistic persons are commonly enlarged both by weight and volume.....Thus, there seem to be major differences in the neuroanatomic findings in autism as compared with those in mercury toxicity.

ÿ If thimerosal was an important cause of autism, the incidence of autism might soon begin to decline (Note: it did, in 2004, in California).

ÿ Mercury poisoning and autism both affect the central nervous system, but the specific sites of involvement in brain and brain-cell types affected are different in the two disorders, as evidenced clinically and by neuropathology. Mercury also injures the peripheral nervous system and other organs that are not affected in autism. Overall, the clinical picture of mercurism from any known form, dose, duration or age of exposure does not mimic that of autism

ÿ On the basis of current evidence (the authors) consider it improbable that thimerosal and autism are linked

A commentary was provided by Sallie Bernard and Lyn Redwood of the US parents' group Safe Minds:

ÿ Thousands of parents have reported biological and neurodevelopmental changes in their children directly following administration of mercury-containing vaccines. Symptoms, including sudden onset of shyness, GI distress, loss of motor skill functioning, allergies, the inability to speak, tremors and autonomic disturbances, mimic those associated with mercury poisoning

ÿ The Nelson/Bauman paper has a number of inaccuracies that call into question the paper's conclusions. For example, they claim that survivors of acrodynia, a form of mercury poisoning, did not have behavioural disorders, suggestive of autism, but case descriptions clearly show that they did, such as loss of speech, odd behaviours and social withdrawal. Likewise, the authors remark that mercury studies from the Faroe Islands found no cases of autism, but these studies, by design, excluded any children with neurological disease.

ÿ The Pediatrics paper's authors base their argument of thimerosal safety on a purportedly "weak association" between neurodevelopmental disorders and exposures to thimerosal-containing vaccines found by the

CDC in an unpublished study (this refers to the Verstraeten study). The supposedly “weak association” is a mis-characterisation. Safe Minds obtained an earlier version of the CDC study (the suppressed version) that in fact found a 2.5 times increase in the risk of developing autism after exposure to increased thimerosal in vaccines. In a court of law, a relative risk of 2.0 or greater is sufficient to substantiate that a given exposure caused disease.

These serious criticisms suggest that the Nelson & Bauman study remains ambiguous in its implications, and cannot be taken as evidence that thimerosal in vaccines is safe.

227. Study by Madsen, Lauritsen, Pedesen et al, *Thimerosal and the Occurrence of Autism: Negative Ecological Evidence from Danish Population-Based Data*, Pediatrics, 2003 Sept 112(3) 604-606

This was the second in the sequence of “Danish studies”. This study is not to be confused with the Madsen et al study into MMR, referred to earlier and which was published shortly afterwards in the New England Journal of Medicine.

The study examined whether discontinuing the use of thimerosal-containing vaccines in Denmark led to a decrease in the incidence of autism. The study analysed data from the Danish Psychiatric Central Research Register, recording all psychiatric admissions since 1971 and all outpatient contacts in psychiatric departments in Denmark since 1995.

The Madsen, Lauritsen et al study used the argument that, as autism kept rising in Denmark *after* thimerosal’s cessation of mass-usage in Danish vaccines, it therefore meant that thimerosal couldn’t cause autism. This needs to be set against the UK arguments of Dr. Elizabeth Miller over MMR. Dr. Miller has argued that as autism started to rise in the UK *before* MMR’s introduction, then MMR could not possibly cause autism.

Clearly, when these two scenarios are set alongside each other, both fall apart, *because neither acknowledge the obvious possibility that both thimerosal and MMR might cause autism*, and that increases in both countries could be reflecting that situation. In the case of Denmark, autism might have risen because of thimerosal and then kept rising because of MMR’s introduction, despite thimerosal’s withdrawal, and in Britain, autism might have risen before MMR because of thimerosal and then kept rising after MMR’s introduction.

Now to the study by Madsen, Lauritsen, Pedesen et al. The patients included all children between 2 and 10 years old who were diagnosed with autism during the period from 1971-2000.

A total of 956 children, with a male to female ratio of 3.5 to 1, had been diagnosed with autism during the period 1971-2000. There was no reported trend towards an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990. From 1991 until 2000, the incidence increased and continued to rise after the removal of thimerosal from vaccines, including increases amongst children born after the discontinuation of thimerosal (in Denmark).

The study authors concluded that the discontinuation of thimerosal in 1992 was followed by an increase in the incidence of autism, and that the data did not support a correlation between thimerosal-containing vaccines and the incidence of autism.

There are some very serious criticisms of this study. Firstly, if autism was linked to thimerosal (which was reduced) and the intensity of the vaccination schedule (which was increased) during the study period, the two factors could work against each other, masking trends and confounding the study conclusions.

Also, if the take-up of MMR and any consequential effect on autism increased, or the increased effect of another factor, such as antibiotic use, came into play, this too would confuse the study outcomes.

The study also fails to differentiate between different types of autism. The focus of investigation on autism is upon late-onset/degenerative autism. As this study does not address this, it offers no insight into the MMR/thimerosal/autism controversies.

The study did not declare an obvious conflict of interest, that two of the authors were working for the Danish manufacturer of thimerosal vaccines. The journal *Pediatrics* also receives substantial advertising revenues from vaccine manufacturers. The American Academy of Pediatrics was in part responsible for recommending new thimerosal-containing vaccines into the US.

The study was criticised by Dr. Robert Byrd of the MIND Institute, University of California at David, who pointed out that it only used data on hospitalised autistic children up until 1995, then added-in outpatients after that date. This would have confused any assessment of changes in autism rates.

The parents' group Safe Minds alleged that the increase purported to have been demonstrated during the 1990s was not real, and was "falsely created by the authors using three deceptive techniques":

Y Firstly, the authors added outpatient autism cases to their database from 1995 onwards, as noted. These outpatient cases outnumbered existing inpatient cases by 13.5 to 1, and represented 93% of all autism

cases, thus artificially boosting case numbers from 1995. No account of this is taken by the authors.

ÿ Secondly, the authors added cases from a large clinic in Copenhagen, starting in 1992. Previously, records from this centre were excluded. The centre accounted for 20% of the caseload in Denmark. No allowance was made by the authors for this factor.

ÿ Thirdly, in 1994 the Danish psychiatric system changed its classification scheme and began to diagnose autistic patients under the infantile autism criteria (ICD-10) rather than the old psychosis proto-infantilis (ICD-8), a category that has never been used in published autism surveys outside Denmark. The old category would have excluded a proportion of autistic children, relative to the new criteria.

Mark Blaxill of the US group Safe Minds also commented: “The autism trend data are described as an “incidence study”. But the report is in no way a proper incidence study. It relies instead for its definition of the “incidence” of autism on the date when cases were entered into the new registry of outpatients. Many of these children were between 7-9 years old, and most were over 4 years old, when recorded as part of an increasing “incidence” trend. Yet the onset of autism must occur, by definition in the diagnostic criteria, before three years of age. Recording incidence at, say, seven years is clearly incorrect.”

Blaxill also comments: The report also estimates inpatient rates for the pre-1993 psychosis proto-infantilis at well below 1 per 10,000. If these were true rates for autism, these would be amongst the lowest rates measured anywhere in the world at any time period. This low rate would also contradict the single published survey of autism rates from Denmark, which indicated an autism rate of over 4 per 10,000 as far back as the 1950s. Madsen et al fail to mention this study, as they fail to comment on the unusually low autism rates for the earlier years of their study period.”

Blaxill concludes that there in fact only three conclusions that can be drawn from the Madsen study:

ÿ The rates in the 1990s are low compared with the US and UK and possibly stable with respect to trend

ÿ The 1990s Danish autism rates are similar to rates in the 1950s

ÿ There are still no published usable data about Danish autism rates in persons born 1960-1990.

Blaxill concluded: “In summary, the report by Madsen et al appears to be an attempt to present selectively-chosen data that provide support for policy choices in which the authors and their collaborators are involved.”

The study was also strongly criticised in a well-argued paper by Dr. F. Edward Yazbak, *Studies That Count, Studies That Don't*:

- ÿ The present rise in autism in Denmark has clearly started 4 or 5 years after the introduction of the MMR vaccine, and it appears to correspond with the percentage of children who received MMR
- ÿ The mean age at the time of diagnosis in Denmark is probably around 4.7 years. Approximately 25% of autism cases in Denmark are reported in children under the age of 5 with the remaining 75% of affected children being reported when they are 5 to 19 years old
- ÿ Given these percentages, any inferences about disease in the under-5 group, in which the disease has not yet become manifest, are potentially flawed
- ÿ The 2,129,864 person-years reported in the Madsen study divided by the number of children (537,303) indicates that the average age of the children in the study is less than 4 years (range 1 to 7 years). Those children would be 5 to 12 years old in 2003. Because the mean age at diagnosis is 4.7 years in Denmark, the Madsen study could not have detected many of the cases of autism that were subsequently diagnosed when these children were older, thereby missing the temporal connection between MMR and autism
- ÿ The 0 to 4 year old group of children (in the Madsen study data) remains the lowest from 1980 to 1991, because autism was/is rarely diagnosed under the age of 4 in Denmark. The prevalence of autism in that age group starts climbing after 1991, 4 years after the introduction of the MMR vaccine, to become the second-highest by 1993.
- ÿ The 5-9 age group is the earliest cohort that received the MMR vaccine after coverage had improved, and is also old enough to be diagnosed. There are consistently more and more affected children in this age grouping.
- ÿ The 10 to 14 age group (in the data) represents the earlier cohort that first received MMR but at lower coverage rates. Those affected children aged 10-14 in 2003 were aged 1 to 5 in 1994. They reflect the start-up of the autism increase associated with the start-up and progression of the MMR vaccination programme.
- ÿ The 15-19 age group were aged 1 to 5 in 1989; their number (in terms of autism) increases but at a much slower rate than in the younger age groups.

- Ÿ Lastly, argues Yazbak, the 20 to 24 age group shows only a slight increase, starting in 1994, possibly because few if any of this cohort received MMR at a vulnerable age.
- Ÿ Even when one takes into account the classification change that took place in 1993-94 and the addition of outpatients to the database in 1995, it is evident, when five additional years are considered, that the conclusions of the Madsen study are invalidated and that the data appears to support the hypothesis that increases in autism in Denmark may be correlated with increases in percentage coverage and number of children receiving MMR.
- Ÿ It is likely that the 0-4 year group of affected children represents those who were not generally diagnosed earlier, and that the 5-9 age group represents the highest increase that occurred after widespread coverage of MMR, and that the 10-14 age group represents the earlier cohort that first received MMR but at a lower coverage rate (for further details, see the Madsen study, and the Yazbak paper)
- Ÿ Yazbak then argues that the rate of autism would now level-off at the higher rate, since children receiving MMR immunisation have now saturated the age-groups and replaced individuals in the age -groups that were previously unvaccinated
- Ÿ When MMR vaccination coverage improved beyond a certain level, from 1993-2001, there was a steady and increasing trend in autism every year. That gradual rise levelled-out after the entire cohort aged less than 10 years was almost completely vaccinated. It is therefore entirely possible that many of the children in the most-affected 5 to 9 group could have started with symptoms as early as the second year of life
- Ÿ The prevalence rate of autism in Danish children under the age of 14 has increased by 729% from 17.67 per 100,000 population (1 in 5,659) in 1980 to 146.42 in 100,000 (1 in 683) in year 2002.
- Ÿ The prevalence of autism in children and teenagers under the age of 14 in Denmark, which was 131.42 per 100,000 (1 in 761) in the seven years before MMR vaccine, increased by 542% to 843.73 per 100,000 (1 in 119) in the most recent seven years.
- Ÿ Two doses of MMR are administered in Denmark, one at age 15 months and one at age 12 years. The Madsen data suggests that the main concern is the vaccination given at age 15 months.
- Ÿ The prevalence of autism in Denmark in the 0 to 14 year-olds levelled-off in the latest three years, when toddler MMR coverage reached the 95%-98% level. The reason why this did not similarly take place in the US in the 1990s was probably because pediatric vaccines in the US



contained thimerosal, further underpinning the argument that the Madsen study was fundamentally flawed in principle because countries with strikingly-differing vaccination practices cannot and should not be compared.

Dr. Yazbak concludes that autism has increased in Denmark after the introduction of the MMR vaccine, as evidenced by the fact that the rate ratio (ie the incidence of autism after versus before MMR introduction) is 8.8, among 5-9 year old Danish children. The Madsen study did not reveal this statistically-significant increase.

228. Hviid, Stellfeld et al , *Association Between Thimerosal-Containing Vaccine and Autism*, Journal of the American Medical Association, Oct 1st 2003 vol 290, no.3, pp1763-66.

The objective of this third Danish study was to determine whether vaccination with a thimerosal-containing vaccine is associated with development of autism.

The study was a population-based cohort study of all children born in Denmark from Jan 1st 1990 until Dec 31st 1996 (467,450), comparing children vaccinated with a thimerosal-containing vaccine with children vaccinated with a thimerosal-free formulation of the same vaccine.

The study results were:

- During 2,986,654 person-years, the study identified 440 autism cases and 787 cases of other ASD
- The risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with thimerosal-containing vaccine and children vaccinated with thimerosal-free vaccine
- There was a relative risk 0.85 for autism
- There was a relative risk of 1.12 for other ASD
- The study found no evidence of a dose-responsive association for autism and other ASD

The study concluded that its results did not support a causal relationship between childhood thimerosal-containing vaccines and the development of autistic-spectrum disorders.

This study was heavily criticised. Rep. David Weldon, US Congress, commented:

- ÿ Hviid works for the Danish Epidemiology Science Center, which is housed in the Staten Serum Institute, the government-owned Danish vaccine manufacturer
- ÿ All of his co-authors work with him at the Center or are employed by the SSI
- ÿ Staten Serum makes a considerable profit from the sale of vaccines and vaccine components
- ÿ If Hviid were to find an association between thimerosal and autism, the SSI.....would face significant lawsuits
- ÿ Danish children received 75mcg of mercury by 9 weeks and another 50mcg at 10 months. By comparison, children in the US received 187.5mcg of mercury by age 6 months - nearly two and a half times as much mercury as Danish children in just the first 6 months of life.....Comparing the exposures in the US to those in other countries is like comparing apples and cows
- ÿ Hviid states that the rate of autism went up after they began removing thimerosal from vaccines in 1992. The numbers in the Hviid study are skewed in that they added outpatient autism diagnosis to the number after 1992.....Like the Verstraeten study, Hviid would not be able to pick up a group of children who were genetically susceptible to mercury toxicity.
- ÿ Danish autism rate is about 6 in 10,000 (1 in 1,666), vs 30 in 10,000 (1 in 333) in the US.....Indeed, I believe it can legitimately be argued that the lower rate of autism in Denmark is attributable to the lower exposure to mercury in their population

The Danish studies attracted a great deal of media attention, almost all of it unanalytical and unquestioning.

However, the parents group Safe Minds issued a critical commentary, "Something Is Rotten In The State of Denmark", in May 2004. This alleged that:

- \* the then-recent series of articles on mercury and inautism in Denmark were in fact conducted and sponsored by a single "network" of associated authors. The studies gave the impression of each having been independent, and endorsing the findings of all the others, but they had in fact all come from the same camp
- \* the authors were tied, either directly or indirectly as employees, to a not-for-profit vaccine manufacturer, the State Serum Institute, which itself had a direct financial interest in the outcome of their analyses.

\* the investigators therefore had a clear conflict of interest, which was not openly declared

\* the Statens Serum Institut relies heavily on its own vaccine products for its revenue, its profitability and for its future growth. The growth and profitability of exported vaccine products has enabled the SSI to build strong international ties with UK and US public health bodies and individuals, and the SSI therefore cannot be said to be wholly and independently objective. The SSI's position is thus fundamentally compromised.

229. Study by Miller, Taylor et al, *Bacterial Infections, Immune Overload and MMR Vaccine*, published in *Archives of Diseases in Childhood*, 2003; 88; 222-223

This was a further paper by Dr. Elizabeth Miller and Professor Brent Taylor and co-researchers. The hypothesis tested was that, if MMR does induce clinically significant immunosuppression, susceptibility to infection should be increased during the post-vaccination period.

ÿ The authors tested this hypothesis using cases of invasive bacterial infection and pneumonia in children aged 12-23 months admitted to hospital between 4/91 and 3/95.

ÿ The study conclusion was that MMR vaccine did not increase the risk of hospitalisation.

The study was part-funded by GlaxoSmithKline, the manufacturers of MMR.

Congressman Rep. David Weldon commented:

ÿ The Miller study examines the population of children in the UK. This study is still unpublished (Note: in terms of raw data), which limits a critical and public evaluation of its findings

ÿ Dr. Miller has actively campaigned against those who have raised questions about vaccine safety. She and her Department (the UK Public Health Laboratory Service, now part of the Medicines and Healthcare Regulatory Agency) receive funding from (the) vaccine manufacturers who are being sued

ÿ This study, like the Verstraeten study, is a dose response study, which is limited in that it does not compare children who receive thimerosal to those who did not

Comment: this study did not examine how children who became autistic were healthy before MMR and degenerated into autism in the period (often longer than three months) following vaccination. It did not clinically examine

children. It offers no convincing evidence against the alleged link between MMR and autism. It is puzzling, if child health datasets are so readily available, as to why these researchers did not compare rates of autism between large cohorts of children who (a) had received MMR, (b) had received single vaccines and (c) were unvaccinated altogether (with measles-containing vaccine, although a fourth cohort could include children who had not had either DTP or MMR. Surely, studies of such groups could readily expose different rates of autism, were they to exist, provided the groups were large enough?

230. Further study by Taylor, Miller et al, Archive of Diseases In Childhood, 2003, 88, 666-670

This study looked at a cohort of 567 children in five districts in NE London who were born between 1979 and 1998 and who had been given a diagnosis of ASD.

Y The study showed that the condition reached a plateau between 1992 and 1996, of 2.6 cases per 1000 live births (1 in 385). This followed an apparent rise from 1979 until 1992

Y the study argued that if autism was associated with MMR, the number of cases should have increased throughout the early 1990s, as MMR was introduced in the UK in 1988. Taylor argued that the rise occurred before MMR

Y the latest figures in the study showed “only” 45 to 50 cases (this in these districts, not across the UK) being diagnosed each year between 1992 and 1996

Y the study noted that MMR was cited as the trigger in two out of 46 cases before August 1997, but this proportion increased to six out of 30 cases (20%) after 1997, due to the publicity surrounding the February 1998 Wakefield paper

The researchers commented that the apparent plateau in cases, plus the drop in age at diagnosis, “suggests that the earlier recorded rise in prevalence was not a real increase but was likely to be due to factors such as increased recognition, a greater willingness on the part of educationalists and families to accept the diagnostic label, and better recording systems”.

Professor Taylor was quoted as stating: “The claims that MMR vaccine is involved in the initiation of autism, and/or with regression, and/or with bowel problems associated with autism, are not associated with any credible scientific evidence, while there is compelling and increasing evidence showing no association.”

**Comment: as usual, this study took a simplistic line of inquiry, treating data on increases in autism as though it should behave in a direct linear relationship with MMR's coverage, finding that it did not, and concluding that the two could not possibly be connected.**

**The study was based upon data that was less than trustworthy in nature. Autism diagnosis is not always given to children with autism, in any formal way, and even if given, is often delayed.**

**The study treats all autism as being the same, failing to differentiate those cases where a child developed normally and then regressed inexplicably - the focus of the MMR/autism debate. This was a crucial failure. No-one is suggesting that all autism is caused by MMR, and it is vital to distinguish between children who were progressing satisfactorily pre-MMR and those who were not.**

**No children were clinically examined in this study.**

**The study is also far too willing to "explain" its findings ("Likely due to factors such as increased recognition") without providing scientific evidence to support these conclusions. The finding that increases were due to better recognition does not accord with the much more detailed study by Byrd et al in California, which reported in late 2002 (before this London study was published), which found that increases were real.**

**The study also does not allow for the possibility of two potential causes being at work, increased take-up of MMR and increased intake of thimerosal. This, of course, would invalidate the study findings.**

**Overall comment: this study fails to provide any convincing contribution to the MMR/autism and thimerosal/autism debate.**

**231. Article by Verstraeten, Davis, DeStefano et al, *Safety of Thimerosal-Containing Vaccines - A Two-Phased Study Of Computerized Health Maintenance Organisation Databases*, published in *Pediatrics*, vol 112, no. 5, November 2003**

**(note: Verstraeten, the lead author, was accredited in this paper as being part of "the Vaccine Safety Datalink Team at the time of the study". In fact, at the point of publication, he had been working for several years for GlaxoSmithKline - manufacturers of thimerosal-containing vaccines, who were potentially-facing a large number of legal cases)**

**The study objective was to assess the possible toxicity of thimerosal-containing vaccines (TCVs) among infants**

**Y A two-phased retrospective cohort study was conducted, using computerised health maintenance organisation (HMO) databases**

- ÿ Phase one screened for association between neurodevelopmental disorders and thimerosal exposure amongst 124,170 infants who were born during 1992 to 1999 at two HMOs (“A” and “B”)
- ÿ Phase two was that the most common disorders associated with exposure in phase one were re-evaluated among 16,717 children who were born during 1991-97 in another HMO (HMO “C”)
- ÿ Relative risks for neurodevelopmental disorders were calculated per increase of 12.5ug of estimated cumulative mercury exposure from TCVs in the first, third and seventh months of life
- ÿ In phase one at HMO A, cumulative exposure at three months resulted in a significant positive association with tics (relative risk 1.89). At HMO B, increased risks of language delay were found for cumulative exposure at 3 months rr 1.13) and 7 months (rr 1.07)
- ÿ In phase two, at HMO C, no significant associations were found.
- ÿ In no analyses were significant increased risks found for autism or attention-deficit disorder (but see later section in this Briefing Note, covering evidence for an association, for further details on these claims and on this study’s re-working of its statistics)

The study conclusions were:

- ÿ No consistent significant associations were found between TCVs and neurodevelopmental outcomes
- ÿ Conflicting results were found at different HMOs for certain outcomes
- ÿ For resolving the conflicting findings, studies with uniform neurodevelopmental assessments of children with a range of cumulative thimerosal exposures are needed

Congressman David Weldon MD offered the following comment on this study:

“Most recently, the CDC produced an article by Dr. Verstraeten, published on November 3rd.....Dr. Verstraeten is a former CDC employee. Since 2001 he has worked for GlaxoSmithKline, a vaccine manufacturer. While working for the CDC in 2000, the first version of Dr. Verstraeten’s unpublished study found an association between higher thimerosal exposures and neurodevelopmental disorders, including autism. Between 2000 and 2003, Dr. Verstraeten and co-authors manipulated and stratified the data so much that each of these associations magically disappeared. I don’t know if it was deliberate, but that is nonetheless what happened. This (latest published)

study has done nothing in my mind to put those concerns to rest, but only serves to raise suspicions.”

“In a recent article (Expert Review of Vaccines), Dr. Verstraeten et al state that ‘Any pharmacoepidemiologist working on a (large linked database) will soon be tempted to construct models with multiple strata and covariants in an effort to adjust for every possible confounder available. The large number of variables and multiple strata make it virtually impossible to understand how the results from the crude data differ from the final analyses, which have therefore been referred to as ‘Black Box Analyses’.” This over-stratification appears to be the exact method employed in the final version of the published Pediatrics study.”

This study was also heavily criticised by Geier and Geier. They pointed out:

ÿ The head author, Verstraeten, had worked for the previous several years for GlaxoSmithKline, a company that had manufactured millions of thimerosal-containing vaccines and which faced many lawsuits over thimerosal’s links with autism

ÿ This was the same basic study that had been the subject of the 2000 Simpsonwood meeting, where it had been revealed that the initial study had found statistically-significant dose-response effects between increasing doses of mercury from thimerosal-containing vaccines and various neurodevelopmental disorders

ÿ that meeting had expressed the desire for the data to be “handled”. Even Verstraeten himself had expressed surprise in a subsequent email that the data was to be manipulated, stating that one’s desire to disprove an unpleasant theory should not interfere with sound scientific methods to evaluate the relationship between thimerosal and neurodevelopmental disorders

ÿ There were also significant issues about the methods used to determine the mercury dose that children received from vaccines. Calculations indicate that Verstraeten et al did not take thimerosal-free DTaP vaccine into account in their study, or if they did, then their paper as it stands is replete with inaccurate information

232. Paper by Stehr-Green, Tull, Stellfeld et al, *Autism and Thimerosal-Containing Vaccines; Lack of Consistent Evidence for an Association*, published in the American Journal of Preventative Medicine, 25 (2003), pp101-106

The study’s methods were as follows. Between the mid-1980s and through the late 1990s, the team compared the prevalence/incidence of autism in California, Sweden and Denmark with average exposures to thimerosal-containing vaccines

Graphic ecologic analyses were used to examine population-based data from:

• the United states (national immunisation coverage surveys and counts of children diagnosed with autism-like disorders seeking special educational services in California

• Sweden (national inpatient data on autism cases, national vaccination coverage levels, and information on use of all vaccines and vaccine-specific amounts of thimerosal

• Denmark (national registry of inpatient/outpatient-diagnosed autism cases, national vaccination coverage levels, and information on use of all vaccines and vaccine-specific amounts of thimerosal

The results were:

• In all three countries, the incidence and prevalence of autism-like conditions began to rise in the 1985-89 period, and the rate of increase accelerated in the early 1990s

• However, in contrast to the situation in the US, where the average thimerosal dose from vaccines increased throughout the 1990s, thimerosal exposures from vaccines in both Sweden and Denmark - already low throughout the 1970s and 1980s - began to decrease in the late 1980s and were eliminated in the early 1990s

The conclusions were that the body of existing data, including the ecologic data presented therein, is not consistent with the hypothesis that increased exposure to thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.

The study was once again very strongly criticised. Mark Blaxill of Safe Minds commented:

\* the authors minimized the severity of the California situation, where high and rising autism rates pointed to a public health emergency, and merited accurate measurement and precise classification

\* The study's autism cases accounted for only a fraction of the real autism population. The large majority of autism cases were to be found in outpatient populations. Yet the study's analyses in Sweden (exclusively) and Denmark (for two-thirds of the study period) relied on inpatient population data.



- \* one recent Danish study (Madsen) revealed that 93% of autistic records were for outpatients. Clearly, the small remaining group of inpatient registrations would have little value in trend assessment
- \* the rate and exposure assessments in the study contained multiple errors. Despite these flaws, the study team claimed that the choice of Swedish and Danish sources was based on 'high quality records'.
- \* the study authors' interpretation of the autism-mercury hypothesis is incorrect. Based on flawed trend assumptions, the authors use the shift in Sweden and Denmark to thimerosal-free vaccines in an attempt to falsely-interpret the autism-mercury hypothesis
- \* reductions in comparatively-low thimerosal exposures need not produce decreasing autism rates in stable low-prevalence populations for the autism-mercury hypothesis to hold
- \* the authors' attempts at trend analysis demonstrate the dangers of misinterpreting ecologic analyses, especially when relying on shifting data sources and incomplete time-series

Stehr-Green et al responded to Blaxill's criticisms in the American Journal of Preventative Medicine, Vol 26, No 1, but were unable to substantively refute his points. They also acknowledged that "no single study - including ours - is likely to provide definitive irrefutable evidence with regard to this issue".

233. Paper, *Age At First MMR Vaccination In Children With Autism and School-Matched Control Subjects: A Population-Based Study In Metropolitan Atlanta*, DeStefano, Bhasin, Thompson, Yeargin-Allsopp and Boyle, Pediatrics, 2004; 113: 259-266

(note: several of the participants, including DeStefano, Yeargin-Allsopp and Boyle, have a high-profile involvement in the MMR controversy, and their work can be found elsewhere in this Briefing Note. DeStefano has co-authored papers with the UK's Dr. Elizabeth Miller, and also was a critical peer-reviewer of the Wakefield team's 1998 Lancet paper)

The objective of this paper, curiously, was to compare ages at first MMR vaccination between children with autism and children who did not have autism, in the total population and in selected subgroups, including children with regression in development.

A case-control study was conducted in metropolitan Atlanta, comparing 624 autistic cases with 1,824 controls. Vaccination data was abstracted from immunisation forms required (in the US) for school entry. Records of children born in Georgia were linked to birth certificates for information on maternal and birth factors.

The results were:

- ÿ The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children
- ÿ Most case (70.5%) and control (67.5%) children were vaccinated between 12 and 17 months. Similar proportions of cases and controls had been vaccinated before 18 months or before 24 months.
- ÿ No significant associations for either of these age cut-offs were found for specific subgroups, including those with evidence of developmental regression

Comment - this study, which compares age of exposure to first MMR between cases of autism and controls without autism, has been very heavily criticised on numerous fundamental aspects:

- ÿ The hypothesis is a very strange one to test. It has never (as far as is known) been previously proposed. It is not appropriate to draw such a hypothesis from the 1998 Lancet paper by Wakefield et al, as the authors seem to do.
- ÿ Ironically, the study does show a positive association between age at first MMR and a risk of autism. DeStefano and colleagues' data actually confirms a striking positive trend towards (a) exposure to MMR before 36 months, and (b) autism. This is particularly so with the younger cohorts.
- ÿ The attempt to ascertain regression status from a retrospective analysis of patient records is wholly flawed and pointless. This is because (a) the process of regression, or alternatively the absence of regression as a feature of the child's condition, does not normally form part of the diagnostic process of autism. Secondly, (b) the very concept of regression is not recognised by many paediatricians, because the common view is that the child was "always" autistic but that the parents failed to notice it. The very detailed review of cases carried out by UK lawyers confirmed these facts. Patient record data is therefore meaningless for this study's purpose.
- ÿ Detailed data provided by Dr. Bernard Rimland of the US Autism Research Institute has exposed how unrepresentative DeStefano and colleagues' data is in the context of regression status.
- ÿ Without providing any justification, DeStefano et al seek to explain-away the MMR/autism observation by saying that it is likely to reflect the vaccine entry requirements for special education. If that was truly the case, then the MMR/autism link should also have been seen in the other

autistic groups who had earlier mental retardation (as well as in those who did not, and only later regressed) - but it is not.

Y The study is also mis-designed, because it underestimates numbers of children who will ultimately receive a diagnosis of autism. This is because the mean age of diagnosis is five years, but the study control group includes many children under five.

Y Worse still, the children that are most likely to be underrepresented - non-autistic controls, who then later receive an autism diagnosis - are the late-onset regressive children with an earlier normal IQ, in other words, the very children we are most concerned about

To summarize, the “explanations” offered by the DeStefano study are invalid. The DeStefano et al study should therefore be a cause for actual deep official concern, not reassurance.

In addition to these epidemiological criticisms, this study of course was just that - an epidemiological study, of records that would reveal little of relevance. No children were clinically examined.

Conclusion: this study offers no evidence of MMR’s safety, and cannot in any way be taken as a proven contradiction of other clinical studies that point to an MMR/measles virus/gut/autism link.

234. Paper, A Voxel-Based Investigation of Brain Structure In Male Adolescents With Autistic Spectrum Disorder, Waiter, Williams et al, University of Aberdeen, Royal Cornhill Hospital Aberdeen and University of St. Andrews, Scotland, published in Neuroimage, Vol 22, Issue 2, June 2004, pp619-625

This study reported a voxel-based morphometric whole brain analysis using a group-specific template on 16 individuals of normal intelligence with ASD and a group of 16 age- sex and IQ-matched controls.

Y Total grey matter volume was increased in the ASD group relative to the control group, with local volume increases in the right fusiform gyrus, the right temporo-occipital region and the left frontal pole extending to the medial frontal cortex

Y A local decrease in grey matter volume was found in the right thalamus. The increase in grey matter volume in ASD subjects was greatest in those areas recognised for their role in social cognition, particularly face recognition (right fusiform gyrus), mental state attribution, “theory of mind” (anterior cingulate and superior temporal sulcus) and perception of eye gaze (superior temporal gyrus).

The study authors concluded that the picture may reflect an abnormally functioning social cognitive neural network, and that it suggested that increased grey matter volume may play a pivotal role in the aetiology of ASD.

The press commentary that accompanied this article was high in its claims. Dr. Justin Williams (co-author) claimed that the findings demonstrated unequivocally that the MMR vaccine could not be responsible for causing autism: “This study indicates that autism is the result of normal development processes not taking place.....The bottom line is that autism is not the product of brain damage”.

Dr. Robert Minns (not a co-author) stated that the study “.....proved beyond doubt that autism could not be linked with MMR”.

However, the autism expert Dr. Ken Aitken commented: “This appears to be a further study showing that there are differences in grey-white matter distribution in autism. It does not seem to add anything further to the various recent studies.”

“The conclusion drawn should clearly be that there are likely to be various different.....possible causes of autism.”

Another researcher commented: “Excess grey matter in children with autism would be entirely consistent with the effects of exogenous opioid peptides which interfere with the normal process of programmed neuronal death (apoptosis). These findings support such a mechanism, and provide indirect evidence for gastrointestinal-related disease induced by MMR.”

Conclusion: this study does not disprove an MMR/autism link in cases of regressive autism. The study incidentally does not differentiate between regressive autism and other forms of ASD - a crucial failure.

235. Paper by Smeeth, Cook, Fombonne et al, *MMR Vaccination and Pervasive Developmental Disorders - A Case-Control Study*, published in *The Lancet*, Vol 364, September 2004

This was an important paper in that it claimed to have looked at a very large number of child health records, giving it considerable claimed authority. The study had been set up in the UK in the light of strong public concern (and probably a degree of internal UK Government unease) over the safety of MMR vaccination.

Data were abstracted from the UK General Practitioner Research Database. The study found that:

- MMR vaccination was not associated with an increased risk of subsequent PDD diagnosis. The study found “no convincing evidence”

that MMR vaccination increased the risk of autism or other pervasive developmental disorders

- The “odds ratio” associated with MMR vaccination varied according to the age at which a person joined the GPRD. In particular, the odds ratio associated with MMR vaccination was higher among children who joined the GPRD at birth or before their first birthday. This was dismissed as possible selection bias or a “chance result”
- Research into the cause(s) of autism was urgently needed

The study included over 1,000 cases with a diagnosis of PDD. Despite its size, the study had a number of drawbacks, some of which the study authors admitted:

- some recording of previous vaccination history, where children came onto a GPRD after date of vaccination, was acknowledged to be possibly incomplete
- the study admitted that it was not able to separately identify the subgroup of cases with regressive symptoms, so as to be able to investigate the hypothesis that only some children were vulnerable to MMR-induced disease and that this was always regressive. This was a crucial failing, as this hypothesis lies at the very heart of the allegations of parents and the views of researchers such as Dr. Andrew Wakefield. On page 967, the authors stated that “we were not able to separately identify the sub-group of cases with regressive symptoms (so as) to investigate the hypothesis that only some children are vulnerable to MMR-induced disease and that this is always (in those cases) regressive”. The authors thereby are admitting that they have not, in fact, conducted an investigation of “the Wakefield hypothesis”
- The study claimed that its results were similar to a Danish cohort study (the Madsen et al study). However, the use of thimerosal-containing vaccines in Denmark has not matched that in the UK, and so comparing the two countries’ experiences may be inappropriate

The study also had to declare one serious conflict of interest, specifically that “E. Fombonne has provided advice on the epidemiology and clinical aspects of autism to scientists advising parents, to vaccine manufacturers (for a fee), and to several Government committees.”

In plainer language, Fombonne had been a paid adviser to the manufacturers of MMR in the then-impending 1,500-strong class action High Court case in the UK that alleged that MMR had precipitated children’s degeneration into autism. The wisdom of using a paid witness to the

manufacturers, as defendants, in a central authorship role in a supposedly-independent research paper, might be questioned by many.

This study was heavily criticised:

- the study is only epidemiological, not clinical. No children were examined
- the UK GP Research Database, the basis for this study, was not designed to be used for a study such as this
- there may have been some misclassification of cases (the authors admitted this flaw). In fact, it is understood that no fewer than 73 “controls” were discovered during the course of the study to be “cases”, illustrating the difficulty of relying on the GPRD database
- insufficient controls were used. Although the study, which used 1,294 cases and 4,469 controls, had initially indicated that there would be ten controls per autism case, 594 cases had fewer than three controls, 72 cases had only one control and 25 had none at all. It was not explained why the study’s original protocols had been apparently disregarded
- only 62% of the children had received MMR before 18 months. Yet the focus of concern needed to be on infants younger than this, 15 months or less. This makes the study less relevant to the core area of concern
- methodological flaws in the study were pointed out to the study team at early stages of the study, but do not seem to have been taken into account
- the study deliberately excluded children who did not have a record of seeing their GP in the 12 months prior to the “index date”, which was the date at which the children received a diagnosis of PDD. This could have increased the risk of excluding children who had undergone definite regression after MMR

**Comment:** this study cannot be taken as offering reliable evidence to deny an MMR/autism link, despite the claims made at the time. It is worth reminding readers as to the original “Wakefield hypothesis”, as published in the Israeli Medical Association Journal, 1999, Volume I, pp1-5:

*“There exists a subset of children who are vulnerable to developing a particular form of regressive autism following previously normal development, in combination with a novel form of inflammatory bowel disease. Onset may occur over weeks or sometimes months, and is triggered by exposure to a measles-containing vaccine, predominantly the measles mumps rubella*

*vaccine (MMR) that is in use in much of the world today. This exposure leads to long term infection with measles virus within key sites, including the intestine where it causes inflammation.”*

**236. Paper by Heron, Golding et al, Unit of Pediatric and Perinatal Epidemiology, Department of Community-Based Medical Sciences, University of Bristol, UK, *Thimerosal Exposure in Infants and Developmental Disorders - A Prospective Cohort Study in the United Kingdom Does Not Support A Causal Association*, published in *Pediatrics*, Vol 114, No. 3, September 2004**

The purpose of this study was to test whether there was any evidence to justify concern over a thimerosal (in vaccines) link with autism.

The study used population data from an existing longitudinal study on childhood health and development, that was monitoring the health of 14,000 children from the former Avon County Council area (around Bristol). These children were born in 1991-92.

The ages at which thimerosal-containing vaccines had been administered was recorded. Measures of mercury exposure were calculated for ages 3 months, 4 months and 6 months. This was compared with a number of measures of childhood cognitive and behavioural development covering 6 months to 7 years 7 months (91 months) age.

The results were that:

- exposure at 3 months was inversely associated with hyperactivity and conduct problems at 47 months
- it was also inversely associated with motor development at 6 months and 30 months
- it was also inversely associated with difficulties with sounds at 81 months and speech therapy, special needs designation and “statementing” (the UK system of identifying special educational needs) at 91 months

In detail:

- of 13,617, dates of immunization were available for all 3 doses for 12,810 children. In fact, details were eventually available for 12,956.
- None had received influenza or Hep B vaccines (which contained thimerosal)

Eight results therefore were claimed to support a beneficial effect from thimerosal. (Comment: it is remarkable to note this claim that injecting a

neurotoxic substance into an infant should produce a beneficial effect. If it were true, then it would suggest that most infants will benefit from a small dose of mercury in infancy, during their early and childhood development).

After adjustment for birth weight, gestation, gender, maternal education, parity, housing tenure, maternal smoking, breast-feeding and ethnic origins, the study found one result (out of 69) to be in support of the direction of the thimerosal/damage hypothesis. This was that poor pro-social behaviour at 47 months was associated with exposure by 3 months of age with thimerosal-containing vaccines. This finding was shrugged-off with the comment that: “a single finding is to be expected, given the 69 statistical tests performed”. But it did not explain-away the finding.

The study concluded: “We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcomes.”

Comment: this study is remarkable for concluding that thimerosal is beneficial to infants. If this is so, however, then it does at least establish a connection between thimerosal and the neurodevelopmental status of children, something that has been routinely denied by the US and UK Governments. If thimerosal is linked positively to mental condition, then clearly it is relevant to it, and important to undertake comprehensive safety testing. As is widely acknowledged, such testing has never been done.

The study also did report one adverse finding - the link between exposure at 3 months and poor pro-social behaviour at 47 months. That finding is of clear concern, and importance to the vaccine/autism debate. The finding was wholly-unconvincingly dismissed. And it has received no subsequent attention - publicly - from the US or UK Governments, and this suggests that governments are only interested in findings that support their stance.

The study also, crucially, yet again failed to examine regressive cases of autism. The study did not apparently seek to identify such cases. Although, on the face of it, this study looks convincing in its size, it is not addressing the core issue - “is vaccination associated with a subset of (possibly rare) regressive autism disorder?”

Concluding comment - the study cannot be said to offer any convincing evidence of there not being any vaccine/regressive autism link, as it does not address the central hypothesis. It also found a link between an adverse outcome and thimerosal, and dismissed it unconvincingly. It also claims to establish a link - even if supposedly beneficial - between thimerosal and child development. The study was also only a “desk study” of child records and questionnaires. No children were clinically examined, and the role of gut pathology - as identified by a number of researchers - could not be assessed within the study.



237 Paper, (precise title not known) Dr. William Barbarisi and co-authors, Mayo Clinic, published in Archives of Pediatrics and Adolescent Medicine, January 2005

This study reviewed data from the Rochester Epidemiology Project, a database of all in-patient and outpatient records in Olmsted County, Minnesota. It concluded that there was no link between autism and immunizations. It also suggested that apparent increases were due to improved awareness and to changes in diagnostic criteria.

The study was heavily criticized in a letter by Dr. F. Edward Yazbak, published in the online British Medical Journal in January 2005. Yazbak commented that:

- according to the US Individuals with Disabilities Education Act database (IDEA), the number of children with autism ages 6-21 attending Minnesota schools increased from 296 in 1992-93 to 4,116 in 2002-03, a 1,300% increase in ten years.
- The number increased further, to 5,076, in 2003-04, a 23% increase in a single year.
- In contrast, the authors had identified 124 children under 21 years of age with autism, had reviewed their histories, and had concluded that “most had not been diagnosed as having autism, but rather as having developmental delay, delayed speech and language development, attention deficit or hyperactivity disorder, and mental retardation”. These children were in Olmsted County. The population of Olmsted County was 84,104 in 1970 and 124,277 in year 2000.
- In 2003, it was estimated that 0.1 children aged 6-21 in Minnesota, and 0.5% in California, had autism. This should be seen as alarming.

238. Paper by Dr. Hideo Honda and Professor Michael Rutter, Yokohama Rehabilitation Centre and the Institute of Psychiatry, London, *No Effect of MMR Withdrawal On The Incidence of autism - A Total Population Study*, published in Journal of Child Psychology & Psychiatry, 2005

This was a study of autism rates that examined the records of 31,426 children born in Yokohama, Japan, between 1988 and 1996. Its significance was that it was a study undertaken in a country where MMR was first introduced and then withdrawn (in April 1993).

The researchers found that the number of children diagnosed as autistic by the age of seven years continued to multiply, even after the withdrawal of MMR. This, of course, assumed that MMR was the cause, or even the sole cause, of autism. The study did not address the thimerosal issue.

The researchers stated that they had addressed five potential criticisms:

- they found no change in the incidence of ASD with regression, between the periods before and after the withdrawal of MMR
- if MMR was sufficient to cause a detectable rise in ASD, then the cessation of MMR use should create a detectable fall
- the study deliberately focused in birth cohorts age up to seven years, to give adequate follow up period after MMR
- it was extremely unlikely that they missed many cases
- the proportion out-migrating from the study area was very small, and only a very large out-migration would account for a false finding

The researchers concluded that MMR “cannot have caused autism in the many children with autism-spectrum disorder in Japan who were born and who grew up in the era when MMR was not available (in Japan)”.

A critique of the Honda study included the following observations:

- the safety studies of MMR were demonstrably inadequate
- there was clear evidence from the early field trials of MMR of viral interference between the component viruses
- children who had experienced concurrent natural measles (or a single measles vaccine) and natural mumps infection within the same year were at known greater risk of inflammatory bowel disease
- the Honda study does not explain anything about the incidence of ASD prior to 1988. Following the introduction of MMR, there was a rise in the annual incidence of ASDs from less than 25 per 10,000 before MMR to 85.9 per 10,000 born in 1990. The incidence subsequently declined to 55.8 per 10,000 for children born in 1991. The incidence then rose sharply again to 161 per 10,000 in 1994. ASD incidence is not as accurately measured beyond 1994
- although MMR was discontinued in this infant population beyond 1993, children vaccinated according to the recommended schedule were still receiving M+M+R at age one year. The administration of the separate vaccines in close time proximity amounts biologically to overlapping exposure
- the Japanese data are therefore entirely consistent with what is known about the behaviours of these three viruses. The authors

make the basic error of examining MMR as an isolated exposure without giving any consideration to other arguments

- in the light of this, the data could be interpreted as indicating a major influence of the pattern of exposure to vaccine viruses upon ASD incidence
- it also suggests a re-challenge effect
- the conclusion by some commentators that the Honda study offers the last word on the MMR/autism link is misleading
- there is a major methodological flaw in the study. The authors define regression as demonstrable loss of skills after 18 months. Therefore children who have developed normally for their first year, then received MMR at 12 months, and who then regress over the next 6 months, will be misclassified as non-regressive. The study's regression data is thus unusable

Criticisms of the study by parents of affected children around the world were that:

- the selected cut-off point of 1996 meant that many children would not have been diagnosed until after that period
- the statement by Honda that MMR was withdrawn in Japan after there were cases of aseptic meningitis linked to the Urabe strain of the mumps element of the vaccine was not strictly correct, as other types of MMR had been tried and there had been side effects from these too
- data based upon only seven years of observations by psychiatrists was not sufficiently robust to be reliable
- the study does not take into account the administration of other vaccines, which could potentially constitute a confounding factor, and changes in the overall immunization schedule
- yet again, critics asked why the study - if it had access to such data, in a country where there was a substantial cohort of children who did not receive MMR, alongside the cohort of children of the same ages who had received MMR, did not simply compare the rates of autism amongst the two age-matched groups - or compare an MMR group with a totally-unvaccinated group
- the study was also criticized for (yet again) being purely epidemiological (i.e. a desk study) without any immunological tests being carried out on any affected/unaffected children

- the study by Takahashi et al (2003) had pointed to monovalent measles vaccination being a risk factor for autism
- continued increases in ASD after MMR's withdrawal could be linked to other unspecified agents, and insufficient allowance appeared to have been made in the study for altered criteria of ASD diagnosis, improved diagnostic procedures and greater awareness and recognition
- there was a serious failure (as mentioned earlier) to address the thimerosal issue. The study period between 1988 and 1996 included children born between 1988 and 1992 who may have received MMR and up to 150ug of mercury in scheduled DTP (three doses of 25ug in their first year of life), and Japanese encephalitis (JE) vaccine (three doses of 25ug between three and four years of age). In contrast, those born between 1993 and 1996 would be likely to have received monovalent vaccines and no MMR (banned in Japan in April 1993), and would not have attained the age for JE vaccine before the study end date of 1996
- there was also considerable parental concern over MMR before its final withdrawal, with uptake falling between 1988 and 1992, and this creates a further confounding factor
- no account appears to have been taken by the study of differing risk factors associated with the different types of MMR. Kimura et al (1996) demonstrated that Standard MMR was associated with 16.6 cases of aseptic meningitis per 10,000 recipients, compared with Biken MMR which had 0/10,000 cases, Takeda MMR which had 11.6 per 10,000 cases, and Kitasato MMR which was associated with 3.2 cases per 10,000 recipients
- the study's conclusion that there was an uninterrupted increase in the incidence of ASD between 1988 and 1996 was also criticized as not standing up to close scrutiny, as the incidence varied considerably during the eight years covered by the study. Incidence of ASD was 85.9 per 10,000 in 1990, then 55.8 in 1991, then 63.3 in 1992, then 96.7 in 1993, then 161.3 in 1994, then 115.3 in 1995, then 117.2 in 1996. These variations appear to have been ignored by the study

**Conclusion:** the Honda & Rutter study does not enable any conclusion to be drawn about MMR and autism.

**239. Study by V. Seagroatt, Unit of Healthcare Epidemiology, Department of Public Health, University of Oxford, *MMR Vaccine and Crohn's Disease, Ecological Study of Hospital admissions In England, 1991 to 2002*, published in the British Medical Journal, 2005, 1120-1121, 14<sup>th</sup> May**

This study reviewed counts of emergency admissions to hospital for patients aged  $\leq$  (less than or equal to) 18 years with a main diagnosis of Crohn's disease, in the years April 1991-March 2003.

Temporal trends in age-specific rates of MMR take-up were plotted, differentiating between the rates for those born before and after MMR in the UK. Data for those born in 1987-88 (MMR was introduced in the UK in October 1988) were excluded from the analysis. The MMR programme was then modeled as a variable with two levels (vaccination rates of  $\geq$  than 84% and of  $\leq$  than 7%).

The study found that although age specific rates of Crohn's disease increased over the study period (there were 4,463 admissions for Crohn's during the study period, 923 of which occurred in those born in 1988-89 or later), "no obvious changes occurred that coincided with the introduction of MMR vaccine".

The study concluded:

- the introduction of MMR vaccine, replacing the single measles vaccine, was not associated with an increase in Crohn's disease. The study claimed that "all but a small risk would have been detected"
- could this negative finding be due to confounding? (extraneous influences). If so, some factor would have to be negatively associated with Crohn's disease, be introduced over the same three year period and be targeted at the same population of infants as MMR vaccine to mask a true association. "This seems highly unlikely".
- The study provided "strong evidence" against the hypothesis that MMR vaccine increases the risk of Crohn's disease

Comment:

This study:

- was a desk study. It clinically examined no children
- did not examine the link between regressive autism and vaccination. It did not even look at autism
- it only looked at a possible link between Crohn's and MMR - and even for this, it only examined emergency admissions. It also found that these rose during the study period
- the study could not rule out a "small risk"
- it also looked at MMR records and Crohn's records in isolation, in other words without examining other possible relevant factors.

Comment: this study is of little or no value to the regressive autism issue. It does not address the relevant hypothesis. Specifically, it seems unaware to any degree of detail of the thimerosal/MMR/autism debate. The study fails completely to address the possibility that Crohn's and/or autism is linked in a small subset of cases to MMR and/or thimerosal. Such a hypothesis might be complicated to test epidemiologically, but is well within the bounds of possibility in terms of biological plausibility. Epidemiology seems incapable, as practiced, of being applied to even relatively simple biological scenarios.

This study therefore is of only very limited value in the Crohn's/vaccination debate, and of no value at all in the debate about a vaccine/regressive autism link, as it does not address the autism issue, let alone regressive autism, in any way.

## PART L

### REVIEWS CONCLUDING THERE IS NO EVIDENCE OF A VACCINE/AUTISM LINK

(again, it is important to point out that all these reviews were only desk studies. No actual damaged children were examined)

#### 240. 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

- Y that there was no current evidence linking bowel disease or autism with MMR
- Y 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.

#### 241. 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:

- ÿ 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".
- ÿ Dr. Miller had demonstrated that MMR has enabled "excellent" control of measles, but that is not the point at issue.
- ÿ 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.
- ÿ 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.
- ÿ 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.
- ÿ 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.

- ÿ 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”.
- ÿ The claim that “*there is no evidence*” (for a link) is factually incorrect (see elsewhere).
- ÿ 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 disturbing, 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 long since been overtaken by subsequent events.

242. 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.

- ÿ The group was to develop a strategy for further research, monitor and steer future MRC support, and report at least annually.
- ÿ The subgroup recognised that the level of MRC support, particularly for IBD (but why not autism?) was “*relatively weak*”.
- ÿ 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 self-comforting claim.*

- ÿ 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:

- ÿ 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)
- ÿ Development of tests to investigate gastrointestinal involvement in autism (no progress on this has since been reported)
- ÿ 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).

#### 243. 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:

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

- ÿ Studies may not have sufficient precision to detect very rare occurrences at a population level

- ÿ 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
- ÿ 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
- ÿ 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:

- ÿ Its conclusion did not exclude the possibility that MMR vaccine could contribute to autism in a small number of children
- ÿ The epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR leading to autism
- ÿ 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:

- ÿ 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)
- ÿ the IoM report actually supports, not refutes, what the parents contend.
- ÿ 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.
- ÿ 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)

244. 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:**

- ÿ It was not comprehensive enough at the time of publication, particularly in respect of published and unpublished evidence supporting a link
- ÿ 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)
- ÿ 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
- ÿ The review relies almost entirely upon epidemiology and epidemiological sources. No children were clinically examined
- ÿ 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)
- ÿ 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.**

**245. Paper by Dr. David Elliman, Dr. Helen Bedford & Dr. Elizabeth 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:

- ÿ Children are more at risk from separate measles, mumps and rubella injections than from the combined MMR

ÿ 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.

246. 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:

- ÿ 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)
- ÿ The prevalence of autism is higher than had been thought (a rate of 1/166 was quoted)
- ÿ 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.

- ÿ 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
- ÿ Autism was found to result from several causes, with a genetic component. The interplay between genetic and environmental factors “was not yet known”.
- ÿ 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.
- ÿ 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.

- ÿ 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.
- ÿ 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.

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

**This found that:**

- ÿ **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”**
- ÿ **Epidemiological studies to date favoured rejection of a causal relationship between multiple immunisations and increased risk for infections and for type 1 diabetes**
- ÿ **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:**

- ÿ *“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”*
- ÿ *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.**

**248. 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)

Y The Expert Group took the view that the current scientific evidence does not support the hypothesised link between MMR and autism.

Y On adverse event reporting, the Group was only descriptive rather than critical.

Y 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.).

Y 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:

Y Improve the monitoring of vaccine safety issues

Y Vaccination records of patients should include details of the name and batch number of the vaccine administered

Y The Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation (JCVI) should keep vaccine contraindications under review

Y 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.

249. Review by Wilson, Mills et al, *Association of Autistic Spectrum Disorder and the Measles Mumps and Rubella Vaccine - A Systematic Review of Current Epidemiological Evidence*, published in *Archives of Pediatric and Adolescent Medicine*, Vol 157, July 2003

The objective of this review was to consider the evidence for and against the existence of an association between ASD and MMR

The authors conducted a “systematic” review of the medical literature to identify all controlled epidemiological articles examining for an association.

Twelve articles met the inclusion criteria. One study found no difference in the rate of ASD and the MMR vaccine in children who were vaccinated and those who were not. Six studies examined for evidence of an increase in ASD associated with an increase in MMR coverage, none of which showed evidence of an association

Four studies examined if a variant form of ASD was associated with MMR, none of which showed evidence of an association

Eight studies attempted to determine if there was a temporal association between developing ASD and receiving the MMR vaccine. Of these, one study identified an increase in parental concern in the six-month period following vaccination with MMR in one of its analyses. The results of all other studies showed no association between ASD and MMR.

The study concluded that the current literature does not suggest an association. However, the authors qualified this carefully: “limited epidemiological evidence exists to rule out a link between a rare variant form of ASD and the MMR vaccine”.

Comment: this was yet another review of published evidence that missed-out most of the uncomfortable evidence, due to the latter not being epidemiological. It did not examine any child histories, nor did it examine any children clinically. In effect, all it did was to echo the findings of the very

poorly-designed and weak epidemiological studies, and thus (as these all tested the wrong hypotheses) did not advance the debate.

250. Review by the US Institute of Medicine, Washington, US, February 9th 2004

This review was possibly the most controversial event to date in the US vaccine/autism debate. The review only lasted one day, with just one hour being devoted to the MMR aspect, with only two witnesses being called on this latter topic.

The review stated that:

- ÿ Based on a thorough review of clinical and epidemiological studies, neither the mercury-based vaccine preservative thimerosal nor MMR are associated with autism
- ÿ The hypotheses regarding how the MMR vaccine and thimerosal could trigger autism lack supporting evidence and are theoretical only. Further research to find the cause of autism should be directed toward other lines of inquiry (Note: this latter outcome caused intense anger)
- ÿ The review committee chair, Professor Marie McCormick, of Harvard School of Public Health, Boston, stated: The overwhelming evidence from several well-designed studies indicates that childhood vaccines are not associated with autism.....Resources would be used most effectively if they were directed toward those avenues of inquiry that offer the greatest promise for answers. Without supporting evidence, the vaccine hypothesis does not hold such promise.” (Note: when later asked what these other “avenues” were, Prof. McCormick was unable to suggest any).

The review updated two previous Institute of Medicine reviews, published in 2001. At that time, the IoM determined that the evidence did not show an association between MMR and autism, but that there was not enough evidence to determine whether thimerosal was associated with neurodevelopmental disorders such as autism.

For its 2004 review, the committee placed most weight upon epidemiological studies. Five epidemiological studies conducted in the US, the UK, Denmark and Sweden since 2001 “consistently provided evidence that there is no association between thimerosal-containing vaccines and autism>”

“Similarly, 14 large epidemiological studies consistently showed no association between MMR and autism”

“The committee also reviewed five studies that reported links between thimerosal and autism, and two that indicated a connection between the MMR vaccine and the disorder.” It also alleged: “However, limitations in how

these studies were conducted and how the data were analysed led the committee to conclude that they did not provide evidence supporting an association between vaccines and autism.”

“The committee also reviewed evidence related to possible biological mechanisms by which immunisations might trigger autism. For example, it has been hypothesised that the measles virus in the MMR vaccine might lodge in the intestines and trigger the release of toxins that lead to autism. Another hypothesis suggests that the MMR vaccine might stimulate the release of immune factors that damage the central nervous system, resulting in autism. It has also been suggested that thimerosal may interfere with biochemical systems in the brain, leading to the disorder.”

“However, no evidence has yet been found that the immune system or its activation play a direct role in causing autism....The studies exploring these hypotheses raise interesting questions, (but) they do not address the specifics of how autism could result. Therefore, evidence for any biological mechanism linking vaccines with autism can only be considered theoretical.”

Inexplicably, and reprehensibly, the IoM Review allowed just one hour on MMR/autism, 9.30am until 10.30am, and allowed just two speakers, one from Toronto General Research Institute and one from the National Immunisation Program, Centers for Disease Control, US.

The IoM review was fiercely criticised. The US Congressman, Rep. Dave Weldon, a physician as well as a politician, stated:

- ÿ Half of Dr. Wakefield’s theory has been proven correct and accepted in the medical community
- ÿ In 2001 (the IoM) concluded that “exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders”
- ÿ Deth provides a plausible mechanism to explain why some children are more susceptible
- ÿ Bradstreet found that with chelation, children with autism excrete more mercury than controls
- ÿ Holmes found less mercury in first baby haircuts for autistic children versus controls
- ÿ Geier found in VSD an association between higher mercury exposure levels and autism
- ÿ Verstraeten.....found an association between higher exposures to thimerosal and neurodevelopmental disorders in some HMO populations

- ÿ There is very little science to back up claims of no harm. In fact, a review of the medical literature appears to show just how harmful thimerosal is
- ÿ As with thimerosal, my concerns about MMR have not subsided
- ÿ Vaccine-strain measles virus has been identified in the inflamed GI tract of children with regressive autism
- ÿ Measles virus antibodies have been found in the cerebrospinal fluid of children with regressive autism
- ÿ Re-challenge (ie double-hit) cases of children with regressive autism have been observed and documented
- ÿ The medical community has largely accepted a new form of bowel disease in children with regressive autism
- ÿ A significant shortcoming of (the IoM's) meeting was that Dr. Wakefield was not invited.....The lack of an invitation is puzzling
- ÿ The CDC has a built-in conflict of interest that is likely to bias any reviews. CDC is tasked with promoting vaccination, ensuring high vaccination rates and monitoring the safety of vaccines. They serve as their own watchdog - neither common nor desirable when seeking unbiased research. This has been a recipe for disaster with other agencies.
- ÿ Unfavorable safety reports lead to lower vaccination rates. An association between vaccines and autism would also force CDC officials to admit that their policies irreparably damaged thousands of children
- ÿ The relationship between the CDC and vaccine manufacturers has become extremely close
- ÿ The CDC has erected excessive barriers (to the US Vaccine Safety Database and has imposed severe limits on access to the data
- ÿ Researchers are not provided with data collected beyond December 2000, seriously limiting the ability to provide for independent research to observe the effects of the removal of thimerosal
- ÿ CDC places strict limits on what data is available to researchers, access to the complete database is virtually impossible, and the data is made available on an inadequate PC

ÿ Raw datasets used by the CDC to conduct their studies are not made available to independent researchers.....Thus the CDC's work cannot be evaluated by outside researchers

*"I am concerned that the agenda set forth in the (IoM) meeting is inadequate and incomplete. With respect to the MMR/autism concerns, the IoM is dedicating one hour. Two witnesses are woefully inadequate to update the committee on the research to date.....To the outside observer, (the meeting) does not appear t be a serious effort to examine these critical issues. Any conclusions drawn from this meeting.....will be viewed as suspect given the very limited time dedicated to examining very incomplete information". - Congressman David Weldon, writing to Dr. Gerberding ahead of the Institute of Medicine's meeting of 9th February 2004*

In his subsequent press release, he further stated:

ÿ "Today's report is premature, perhaps perilously reliant on epidemiology, based on preliminary incomplete information, and may ultimately be repudiated. It will only drag the IoM under the cloud of controversy that has currently engulfed the (US) Centers for Disease Control"

ÿ "In 2001, the IoM stated that it is "unclear whether ethylmercury (from vaccines) passes readily through the blood-brain barrier....." The IoM recommended several biological and clinical studies to answer this question and whether this mercury could cause developmental problems. These studies were in a large part never done"

ÿ "The IoM's scope of investigation was severely narrowed for this review. This raises suspicions that this IoM exercise might be more about drawing pre-designed conclusions aimed at restoring public confidence in vaccines rather than conducting a complete and thorough inquiry into whether or not thimerosal might cause developmental disorders"

ÿ "Dr. Thomas Verstraeten.....recently stated in an April 2004 letter to Pediatrics: "The bottom line is and has always been the same - an association between thimerosal and neurological outcomes could neither be confirmed nor refuted, and therefore more study is required". It was after this study was published that the IoM scope was narrowed"

ÿ "Many of the authors have conflicts of interest, including funding from vaccine manufacturers, employment by manufacturers, or conflicts in that they implemented vaccine policies that are now being investigated. Furthermore, the studies were designed to examine entire populations and would miss subgroups of genetically susceptible populations.....The epidemiological studies reviewed by the IoM in drawing today's findings could easily have missed a link between thimerosal and

neurodevelopmental disorders.....Relying on these studies is shaky ground”

ÿ “With regard to the MMR vaccine, the IoM review of this matter is totally premature; that NIH (National Institute for Health, US) is only now attempting to duplicate the work of Dr. Andrew Wakefield. Half of Dr. Wakefield’s work (the autism/gut link) has been demonstrated to be correct. Attempting to draw conclusions at this time is counterproductive. Statistical studies of this matter are of little benefit, only a clinical pathological study will lay this issue to rest”

ÿ “I am troubled by the lack of liability or accountability by these decision-makers should they be proved wrong. I want more than just a “sorry” from them, should their conclusions be found erroneous a few years down the road.”

Previously, in giving evidence to the IoM committee, Weldon had commented:

ÿ Many (researchers) have described encountering apathy from government officials charged with investigating these matters, difficulty in getting their papers published, and the loss of other research grants. Others report overt discouragement, intimidation and threats, and have abandoned this field of research

ÿ Some have had their clinical privileges revoked, and others have been hounded out of their institutions.....A clinician (this was Dr. Krigsman) in New York was poised to repeat Wakefield’s work two years ago, but he ultimately was refused by his Internal Review Board, and then subsequently had his clinical privileges withdrawn”.

ÿ A significant shortcoming of (the review) is that Dr. Wakefield was not invited. In 2001, you found that cases of MMR “rechallenge” (Note: this is where children degenerate after MMR then degenerate a second time after a booster dose) would provide evidence in favour of causality. It is my understanding that Dr. Wakefield has developed such a case series. The lack of an invitation is puzzling.

ÿ The Centers for Disease Control has a built-in conflict of interest that is likely to bias any reviews. The CDC is tasked with promoting vaccination, ensuring high vaccination rates, and monitoring the safety of vaccines. They serve as their own watchdog - neither common nor desirable when seeking unbiased research. Unfavourable safety reports lead to lower vaccination rates. An association between vaccines and autism would force CDC officials to admit that their policies irreparably damaged thousands of children

ÿ The relationship between the CDC and vaccine manufacturers has become extremely close

In a further speech, to the Autism One conference in Chicago on May 29th 2004, Rep. Weldon stated:

ÿ “In my ten years of service in the US Congress, I have never seen a report so badly miss the mark.....It is plagued with serious flaws

ÿ “On January 15th (2004) I wrote to Dr. Julie Gerberding, the Director of the CDC (asking) her to postpone the February 9th IoM meeting.....In a follow-up telephone conversation to me on February 3rd 2004, Dr. Gerberding assured me that the IoM’s February was “not an attempt to draw conclusions” but merely to “update on the science” of where we are at this point in time. However, it clearly draws conclusions and in what is perhaps the greatest outrage it goes further, to call for a halt to all further research

ÿ “The IoM (review) relies almost exclusively on five epidemiology studies. The principal authors of all five studies have serious conflicts of interest

ÿ “(The) IoM was instructed to give biological evidence little consideration, and was prohibited from allowing biological evidence to lend evidence towards causality

ÿ “The IoM process became little more than an attempt to validate the CDC’s claims that vaccines have caused no harm, while quashing research to better-understand whether or not, and how, the MMR or thimerosal might contribute to the epidemic of neurodevelopmental disorders, including autism

ÿ “Most importantly, (the Verstraeten) study did not compare children who got thimerosal to those who did not. Instead, its CDC-employed authors focused primarily on a dose-response gradient

ÿ “Five months after the (Verstraeten) article was published, and largely after the IoM report had been written, (Verstraeten) broke his silence in a letter to Pediatrics, stating: “The bottom line is and has always been the same: an association between thimerosal and neurological outcomes could neither be confirmed nor refuted, and therefore more study is required.”

ÿ “Dr. Verstraeten, the lead author of the study, says that an association between thimerosal-containing vaccines and neurodevelopmental disorders cannot be refuted based on his study, yet the IoM in their assessment of the same study state that it is a basis for

concluding that 'there is no association between thimerosal-containing vaccines and autism'. (Note: my underlining)

ÿ It is also critical to note that the Verstraeten study cannot be validated. The earlier datasets have been destroyed.....The raw unaltered data is not available.”

Weldon commented that the IoM “was on very shaky ground in drawing the conclusions they did”, and that they based their decision on five epidemiological studies (Verstraeten, Madsen, Hviid, Stehr-Green and Miller):

- \* Three of them examined the genetically-homogenous population of Denmark
- \* At least one employee of the Staten Serum Institute serves as a co-author of at least three of the studies
- \* only one study examined US children, and that study did not compare those with no mercury exposure to those with exposures
- \* four of (the studies were) with populations receiving less than half the mercury exposure that children in the US received
- \* none of (the studies included) any ascertainment of prenatal or postnatal background mercury exposures
- \* none of (the studies) considered pre-natal exposures which may have given children (a mercury dose)
- \* none of (the studies are) able to detect a susceptible subgroup that may have had a susceptibility to mercury toxicity
- \* three of (the studies) failed to address how the addition of outpatient cases of autism in Denmark might have perilously skewed the results
- \* four of (the studies) examined populations with autism rates considerably below that in the US
- \* one of the studies has not been published and been subject to public review

Weldon further commented:

- \* “The Institute of Medicine recommended that the following studies be done, but the US Centers for Disease Control and National Institutes for Health failed to dedicate the resources to fund these studies:



- \* Identify primary sources and levels of prenatal and postnatal background exposures to thimerosal, including Rho (D) immune globulin in pregnant women and other forms of mercury (fish) in infants, children and pregnant women - not done
- \* compare the incidence and prevalence of NDDs before and after removal of thimerosal from vaccines - not done, and the CDC (confirms) they will not begin such studies until 2006
- \* research how children, including those with neurodevelopmental disorders, metabolize and excrete metals, particularly mercury - not done
- \* conduct research on theoretical modelling of ethyl mercury exposures, including the incremental burden of thimerosal with background mercury exposures from other sources - not done
- \* Conduct careful rigorous and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism - not done
- \* Conduct comparative animal studies of the toxicity of ethyl mercury and methyl mercury to better-understand the neurodevelopmental effects of thimerosal - only partly done, (and) with very little Federal support
- \* In 2001, the IoM stated that it is 'unclear whether ethyl mercury (from vaccines) passes readily through the blood-brain barrier'. The IoM recommended several biological and clinical studies to answer this question, and whether this mercury could cause developmental problems. - these studies were in a large part never done.

On the MMR/autism issue, Weldon commented:

- \* They (the IoM) devoted only one hour of discussion to this topic at the February meeting and failed to invite those who were most intimately involved in this research to be present
- \* As with thimerosal, the IoM relied almost exclusively on epidemiology
- \* the IoM still cannot answer the question as to why measles is in the intestines of some autistic children. Why is it there? What is it doing? How did it get there? Is it contributing to autism? The IoM attempts to explain this away by saying it's likely that the presence of measles could just be a co-morbidity to autism
- \* the National Institutes for Health is only now attempting to duplicate the work of Dr. Andrew Wakefield

Professor Boyd Haley, Chair, Department of Chemistry, University of Kentucky, commented:

Y I am at a loss to understand how the IoM can suggest that the apparent increase in autism in the USA and England is due to a recent change in what considerations are given to warrant a diagnosis as autistic

Y The observations of mercury level differences in birth hair of autistics versus normals.....was replicated using a different approach by Massachusetts Institute of Technology researchers. It was also confirmed retrospectively by Dr. Bill Walsh. Why did the IoM totally ignore this in their report and call the thimerosal hypothesis “theoretical only”?

Y The existence of this biochemical data does not totally prove thimerosal is causal for autism, but it certainly should have prevented the IoM from saying they “conclusively” proved thimerosal was not involved. To state researchers should not continue investigating thimerosal as being involved in autism is blatantly out of line and represents very poor analysis of the literature, the published literature and scientific logic”.

Y It is my opinion that the most ignorant statement in the IoM report is the charge to “stop looking at vaccines and thimerosal as being involved in autistic spectrum disorders”.

The parents’ group Safe Minds commented:

Y They placed too much weight upon flawed epidemiological analysis and paid little attention to scientific research that demonstrated clear links between mercury-related exposures and autism”

Y The IoM chose to completely ignore pervasive conflicts of interest in the authors’ groups involved in dismissing connections between mercury and neurodevelopmental disorders including autism, in groups directly linked to vaccine manufacturers or the public health agencies that promoted the expansion in the exact vaccine exposures under question.

Y This committee and its report clearly chose to ignore groundbreaking scientific research on the mercury/autism link, and instead the IoM has issued a flawed, incomplete report that continues to put....children at risk”.

251. Review by Demicheli, Jefferson et al, *Vaccine For Measles, Mumps and Rubella in Children (Review)*, The Cochrane Collaboration, published by Wiley & Sons, UK, from The Cochrane Library, 2005, Issue 4, art. No. CD004407

The Cochrane Collaboration is a very highly respected international team of epidemiologists, and their review was very widely reported in October 2005. The review stated:

- The study team carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR
- The team searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, MEDLINE 1966 to December 2004, EMBASE 1974 to December 2004, Biological Abstracts (1985 to December 2004), and Science Citation Index (from 1980 to December 2004). Other manual searches for relevant papers were done
- Eligible studies were comparative, prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing, or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. These studies were carried out by 2004
- The review identified 139 articles possibly satisfying the inclusion criteria, and included 31 in the review (i.e. they discarded 108 as not relevant)
- MMR was associated with a lower incidence of upper respiratory tract infection, a higher incidence of irritability, and similar incidence of other adverse effects compared to placebo. The vaccine was likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints, febrile convulsions within two weeks of vaccination, and aseptic meningitis (mumps)(Urabe strain-containing MMR)
- Exposure to MMR was unlikely to be (my emphasis) associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps)(Jeryl-Lynn strain containing MMR)
- The review could not identify studies assessing the effectiveness of MMR that fulfilled their inclusion criteria, even though the impact of mass immunisation on the elimination of the disease has been largely demonstrated

The review concluded:

- the design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate (a remarkable statement)

- the evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target disease
- measles, mumps and rubella are three very dangerous infectious diseases which cause a heavy disease, disability and death burden in the developing world
- researchers from the Cochrane Vaccine Field reviewed 139 studies conducted to assess the effects of the live attenuated combined vaccine to prevent measles, mumps and rubella in children. MMR protects children against infections of the upper airways but very rarely may cause a benign form of bleeding under the skin and milder forms of measles, mumps and rubella
- no credible evidence of an involvement of MMR with either autism or Crohn's disease was found
- no field studies of the vaccine's effectiveness were found, but the impact of mass immunisation on the elimination of the diseases has been demonstrated worldwide

Comment - first, some immediate comments on the above.

- it is very interesting that Cochrane acknowledge that the design and reporting of MMR's safety outcomes in studies is (quote) "largely inadequate". This is almost the first admission that studies have been wanting in design and reporting. This finding went virtually completely unreported by the media at the time of release of the study
- the statement that the evidence of adverse events cannot be separated from the role of preventing diseases is a curious one to include. One does not (for instance) preface the report of an inquiry into aircraft safety by playing tribute to the role of air travel in promoting tourism. It is very far from clear why any investigation of possible adverse events has to be couched in these terms. The issue at stake here is specific adverse events occurring to specific named children, not to debate the wider value of immunisation programmes as a whole. Inclusion of references to the value of immunisation would appear to constitute a degree of subtle moral blackmail, even if technically justified in any wider debate that might more appropriately be held elsewhere
- the Cochrane study claims to be "systematic" in its literature search. However, a comparison of its references with the list of studies and presentations at the start of this review document shows that, by searching only for peer-review papers through Medline etc., much useful information has been effectively screened-out from the Cochrane study. Because the vaccination/autism debate is relatively

new and is highly controversial with the medical establishment, a search solely based upon peer-review status is going to miss a great deal, and thus assist a “we found no evidence” outcome.

- Furthermore, the Cochrane review sought “eligible” studies that “were comparative, prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing or a combination of measles, mumps and rubella antigens on healthy individuals”. In contrast, many of the papers and presentations that have been included in this alternative review, by the parent of an affected child, inevitably do not fit this description. The Cochrane study has thus artificially eliminated some important evidence from its purview. Because of the way the study has trawled the evidence, a significant element of selectivity, and thus bias, has resulted
- It is incidentally interesting that Cochrane comments that “(it) could not identify studies assessing the effectiveness of MMR that fulfilled (their) inclusion criteria”. This is an interesting admission, in itself. Again, this comment was missed by most of the media at the time of publication. However, effectiveness, as already remarked upon, is not the issue at stake
- The Cochrane review sought out studies that included “systemic adverse events including fever, rash, vomiting, diarrhoea and more generalized and severe signs including.....autism” (and others such as joint and limb symptoms, Crohn’s disease and ulcerative colitis). However, as far as is known, no large scale studies with long-term (one-year-plus) follow-up have been undertaken that compare the incidence of autism in a large cohort (5,000-plus) of MMR recipients with an equally-large cohort of recipients of single measles, mumps and rubella vaccines, and compared further with 5,000 children who have not received any of either multiple or single measles vaccines, or with 5,000 children who have not received any thimerosal-containing vaccines (such as DTP) whatever. When such a study is put forward, the response is usually that it would cost far too much to undertake. But it remains the obvious study to do, and (as at 2006) it remains wholly undone. The studies that Cochrane have looked at do not, individually or in combination, provide an adequate alternative to sufficiently-rigorously test the vaccine/autism hypothesis

Cochrane did not look at clinical studies. It looked at the following studies: Beck 1989, Benjamin 1992, Black 1997, Black 2003, Bloom 1975, Ceyhan 2001, Davis 2001, De Stefano 2002, De Stefano 2004, Dourado 2000, Dunlop 1989, Edees 1991, Fombonne 2001, Freeman 1993, Jonville-Bera 1996, Lerman 1981, Madsen 2002, Makela 2002, Makino 1990, Miller 1989, Park 2004, Peltola 1986, Robertson 1988, Schwarz 1975, Smeeth 2004, Stokes 1971, Swartz 1974, Taylor 1999, Vestergaard 2004, Weibel 1980, and da Cunha 2002 (a total of 31 studies).

The nature of each, with my own commentary alongside, is set out below:

<i>(study and year of publication)</i>	<i>(method and numbers involved)</i>	<i>(adverse outcomes reported by study)</i>	<i>My comment (in context of autism)</i>
<b>Beck 1989</b>	<b>MMR vs. placebo, 196 children involved</b>	<b>Some reactions, but did not look at autism</b>	<b>Follow-up was only 30 days. Study did not look at autism. Study not relevant</b>
<b>Benjamin 1992</b>	<b>MMR vs. “non-vaccinated” (not clear if this meant non-MMR or no vaccines whatever). 5,017 children involved</b>	<b>Reported some joint complaints within 6 weeks of MMR, plus other effects</b>	<b>Follow-up was only 6 weeks. Study did not look at autism. Study could thus be argued to be irrelevant</b>
<b>Black 1997</b>	<b>Looked at 59 children with aseptic meningitis, compared with 188 controls</b>	<b>Found risk of aseptic meningitis</b>	<b>Follow-up was only 30 days. Study did not look at autism. Study therefore of questionable relevance</b>
<b>Black 2003</b>	<b>Looked at 23 children with idiopathic thrombocytopaenic purpura, with matched controls</b>	<b>(See next column)</b>	<b>No apparent relevance to autism. Some details unclear.</b>
<b>Bloom 1975</b>	<b>Study compared three different types of MMR with placebo, total 282 children involved</b>	<b>Various reactions</b>	<b>Study follow-up limited to 7-21 days. No apparent relevance to autism</b>
<b>Ceyhan 2001</b>	<b>Study looked at MMR given to 1,000 children</b>	<b>Reactions included diarrhea</b>	<b>Time of observations of adverse events not specified. No apparent relevance to autism</b>

<b>Davis 2001</b>	<b>Study looked at 142 children exposed to MMR or other measles vaccines plus 432 controls</b>	<b>Not known</b>	<b>No details of vaccine type. (This study is criticized elsewhere in my document).</b>
<b>De Stefano 2002</b>	<b>Study looked at Vaccine Safety Datalink data (167,240 children).</b>	<b>Asthma</b>	<b>No relevance to autism</b>
<b>De Stefano 2004</b>	<b>Study looked at Metropolitan Atlanta records (development Disabilities Surveillance Program), 624 children, plus 1,824 controls.</b>	<b>(unclear) Focus was on autism.</b>	<b>Not defined more precisely than “exposure to MMR”. Probable bias in enrollment, and cases may not be representative.</b>
<b>Dourado</b>	<b>Before/after study of aseptic meningitis, looked at 452,344 children</b>	<b>Aseptic meningitis</b>	<b>No relevance to autism</b>
<b>Dunlop 1989</b>	<b>Looked at 355 healthy children</b>	<b>Various adverse outcomes, including diarrhoea</b>	<b>Little apparent relevance to autism</b>
<b>Edees 1991</b>	<b>Study of 420 healthy children</b>	<b>Looked at various outcomes including convulsions</b>	<b>Three week follow up by parents, with further three weeks observation; not sufficient, and study did not focus on autism</b>
<b>Fombonne 2001</b>	<b>283 children with PDD</b>	<b>Looked for exposure to MMR/PDD link.</b>	<b>This study is criticized elsewhere in my review. Cochrane noted that “interpretation of the results is impossible”.</b>
<b>Freeman</b>	<b>Unknown number of</b>	<b>Adverse outcomes</b>	<b>No apparent</b>

1993	children	did not include autism	relevance to autism debate
Jonville-Bera 1996	Study of children re MMR/thrombocytopenic purpura	Looked only at thrombocytopenic purpura	No apparent relevance to autism
Lerman 1981	Looked at 502 healthy children	Various outcomes, but not autism	Follow-up only 6 weeks. No obvious relevance to autism.
Madsen 2002	Retrospective cohort study of 537,303 children receiving MMR	Looked at autism, ASD.	Cochrane notes that unlikely that those born later would have diagnosis. This study heavily criticized elsewhere in my review.
Makela 2002	Looked at 561,089 children	Autism included in outcomes	This study is heavily criticized elsewhere in this review.
Makino 1990	Looked at 1,638 healthy children	Various adverse outcomes. Autism not included.	No relevance to autism debate.
Miller 1989	Study of 12,023 healthy children	Autism not included	No relevance
Park 2004	Numbers not known. Study was of aseptic meningitis	Aseptic meningitis	Only looked at 6 weeks after MMR. Study not relevant to autism. Various deficiencies, and 27% of hospital records missing. Selection bias likely.
Peltola 1986	6,086 pairs of twins	Various adverse outcomes, but did not look at autism	No direct relevance to autism debate



<b>Robertson 1988</b>	<b>Looked at 319 children</b>	<b>Looked at large number of adverse outcomes, including diarrhoea, but not autism</b>	<b>No relevance to autism debate</b>
<b>Schwarz 1975</b>	<b>Looked at 1,481 healthy children</b>	<b>Outcomes excluded autism</b>	<b>Age restriction not enforced. Patients missing. No relevance.</b>
<b>Smeeth 2004</b>	<b>UK GP Research Database study</b>	<b>Looked at PDD diagnosis</b>	<b>This study is criticized elsewhere in my review.</b>
<b>Stokes 1971</b>	<b>334 children in US, 632 in Costa Rica</b>	<b>Outcomes studied included gastroenteritis, but not autism</b>	<b>Study muddled two groups. Only 28-day follow-up. No relevance to current debate</b>
<b>Swartz 1974</b>	<b>59 children studied</b>	<b>Autism not included as adverse outcome.</b>	<b>Follow-up 7-15 days, complaints up to 60 days. No relevance.</b>
<b>Taylor 1999</b>	<b>498 children studied (the North London study, UK)</b>	<b>Adverse outcomes included autism (typical and atypical) and Aspergers</b>	<b>Follow-up only 7-15 days. Study is therefore flawed, and has been widely criticized. Cochrane criticism was "absence of unvaccinated controls".</b>
<b>Vestergaard 2004</b>	<b>Looked at 537,171 Danish children</b>	<b>Various – see next column.</b>	<b>This study is heavily criticised elsewhere in my review</b>
<b>Weibel 1980</b>	<b>Looked at 135 children</b>	<b>Various</b>	<b>Follow-up only six weeks. Insufficient</b>

			<b>information. Not useful for MMR/autism debate.</b>
<b>Da Cunha 2002</b>	<b>Study looking at aseptic meningitis, 845,000 children</b>	<b>Aseptic meningitis</b>	<b>Follow-up ten weeks. No relevance to autism debate.</b>

**In the context of the MMR/autism debate,, the above set of studies are a sorry collection, and make for little reliable or conclusive evidence.**

**Other commentators have severely criticised the Cochrane review of 2005 as flawed.**

**In November 2005, the UK lawyer Clifford J. Miller stated in the BMJ (on-line edition):**

- that, although Cochrane was claimed as the “final word” on MMR, by some observers, such a “final word” would need to be something along the lines of “conclusive evidence was found that there is no causal connection between MMR and autism”, or equivalent. And yet no such phrase appeared in the Cochrane conclusions, nor in the discussion, nor anywhere in the text**
- instead, the press release and summary of Cochrane stated “no credible evidence of an involvement of MMR with either autism or Crohn’s disease was found”. This, of course, is not a conclusion in the sense of being an investigative end-point**
- The latter statement, inexplicably, again did not appear in the main body of the review text, or in the discussion, or in the study conclusions. As a “conclusion”, it almost appears to have been added onto the study by a third party**
- The Cochrane review ignored challenge/re-challenge evidence**
- Cochrane seems to have based its outcome upon just a handful of studies, these being DeStefano 2004, Madsen 2002, Makela 2002 and Taylor 1999 (in relation to autism) and Smeeth 2004 (in relation to persistent developmental delay/disorder**
- In the case of Smeeth, the original study stated “We were not able to separately identify the sub-group of cases with regressive symptoms, to investigate the hypothesis that only some children are vulnerable to MMR-induced disease and that this is always regressive”. And yet**

these must surely be the very sub-group of children that is supposed to be being investigated

- Smeeth's paper is demonstrably inconclusive, therefore (see review elsewhere). Smeeth then looks for support to papers by Fombonne and by Taylor, and yet both of these, too, can be demonstrated to be inconclusive or flawed (see appropriate reviews for each). This demonstrates how weak papers are forced to lean upon each other for support. But each can be dismissed (see reviews), and even Cochrane dismisses Fombonne's 2001 paper (again, see review) as impossible to interpret

Also writing in BMJcom in November 2005, UK commentator John Heptonstall commented:

- despite its supposedly evidence-based approach, Cochrane makes a number of wholly unsubstantiated statements, including "the impact of mass immunisation on the elimination of the diseases has been demonstrated worldwide", and "the safety record of MMR is possibly best attested by its almost universal use", and "given the existence of documented elimination of targeted diseases in large populations by means of mass immunisation campaigns.....we have no reason to doubt the effectiveness of MMR". (Nowhere in the actual study text are these sweeping statements backed up)
- of the 31 papers that Cochrane considered worthy of detailed scrutiny, and which met Cochrane's criteria, 39% failed to report the vaccine strain involved
- 10% reported the strain for only one component of MMR
- 84% failed to give complete information on schedule, on doses or on route of administration
- 58% failed to report definitions for all possible outcomes
- 19% had no definitions for safety outcome measurements beyond a description of temperature range measurements, and only 13% had one outcome with a description, and only 16% had more than one outcome with a description
- 48% of those studies monitoring temperatures gave no further description of either numerical range or base reading
- 19% of the 31 studies reported no participants missing for adverse reaction monitoring, but 55% had clearly-missing unintended-event data. Of these, 18% of the 31 studies had under 10% of participants missing, 24% of the studies had between 11% and 20% missing, 47%

had between 20% and 60% missing, and in 12% of the 31 studies, the number of participants missing could not even be determined at all. And yet these 31 studies were all ones that met Cochrane's supposedly-stringent criteria for inclusion

- 26% of the 31 studies had inadequate explanations for their missing data, and for a further 12%, no explanations at all were offered
- 32% of the 31 included studies had insufficient information on study populations and enrolment
- 23% of the studies used by Cochrane had population descriptions that raised doubts as to the generalisability of their conclusions to other settings
- For two of the UK GP Research Database studies, the precise nature of the controlled unexposed subjects (to MMR) was impossible to determine

The UK parents' group JABS further commented:

- Cochrane is critical of the methodology used in many of the (earlier) main studies that are always upheld.....to disprove any implications of the MMR vaccine and (links with) serious reactions
- The US has a National Vaccine Injury Compensation Program, and 14% of claims that have been paid out relate to MMR
- Japanese authorities have paid substantial compensation to MMR-damaged children, following the Court ruling in March 2004
- The UK has a Vaccine Damage Payment Scheme, and some of its payments to victims have involved MMR

These strong critiques therefore highlight a remarkable series of shortcomings in the Cochrane review, and the skewed interpretation put upon its findings by the UK Department of Health and others.

In retrospect, it is the mis-match between the Cochrane press release "Cochrane Library publishes the most thorough survey of MMR vaccination data, which strongly supports its use.....Public health decisions need to be based upon sound evidence.....If this principle had been applied in the case of (the MMR/autism controversy), we would have avoided all the fuss.", and the actual detailed contents of the study text, that is inexplicable.

## **PART M**

## **FLAWED UK REGULATORY AND MONITORING SYSTEMS**

### **252. Fighting Measles, Missing Autism, Overlooking Damage?**

The UK Department of Health 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:

- ÿ The UK Medicines and Healthcare Regulatory Agency has failed to properly monitor adverse reactions to all vaccines, including MMR
- ÿ The UK Department of Health (and its US equivalent, the National Institutes for Health and the Centers for Disease Control) repeatedly demonstrate an entrenched bias in favour of maintaining public confidence in the vaccination programme, and against investigating the causes of autism, or indeed of vaccine damage generally
- ÿ The DoH and other bodies such as the CDC repeatedly demonstrate dual standards of robustness of evidence for/against an MMR/autism link, and repeatedly show this in their embracing of studies and findings that suit their case
- ÿ The studies that the DoH and CDC quote (Taylor, Miller, the Committee on Safety of Medicines study, Gillberg, Peltola, Madsen) are, when critically examined, inconclusive or largely or completely irrelevant in terms of disproving any MMR/autism link.
- ÿ 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
- ÿ 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 and the US CDC to understanding that slow descent into autism takes place - it is not an acute adverse reaction, like other alleged adverse drug reactions. The UK DoH in particular 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 becomes the suggestion is that the DoH actually 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.

### 253. Has The UK Medicines & Healthcare Regulatory Agency Missed The Syndrome?

The (then) Medicines Division, predecessor of the Medicines Control Agency, itself now part of the Medicines & Healthcare Regulatory Agency, 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).

- ÿ It had no effective method of finding files
- ÿ It had severe staff shortages in key areas
- ÿ 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 routinely, with minimal technical investigation - or none at all.
- ÿ The UK Medicines and Healthcare Regulatory 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. Some possible reforms are currently out to consultation as at July 2004.
- ÿ 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)

- ÿ 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, and even if they do, very unlikely to want to submit on that basis, in the face of official Department of Health advice.
- ÿ 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 obviously there will be no data in the database.
- ÿ Yellow Card is voluntary for health professionals, but compulsory for pharmaceuticals manufacturers. But this depends on adverse reactions being reported to manufacturers - again, extremely unlikely, probably never occurring.
- ÿ 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
- ÿ 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).
- ÿ 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.
- ÿ 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)
- ÿ 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.
- ÿ 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)

ÿ 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.

#### 254. Further Statement by Dr. Thomas Jefferson, Cochrane Collaboration

The Cochrane Collaboration is an organisation of scientists that aims to make information about the effects of medicinal products available worldwide, and which promotes high standards in research. Quoted in the UK Sunday Telegraph in March 2004, Dr. Cochrane stated:

ÿ (vaccine safety studies) were the Cinderella of public health research, and Government officials have failed to make it a high priority

ÿ There is some good research, but it is overwhelmed by the bad

ÿ The public has been let down because the proper (safety) studies have not been done

ÿ We need a (Europe-wide electronic register of children’s vaccine exposure that would allow scientists to investigate the risks and benefits.....using data on thousands of participants)....We need such a system urgently...Governments are reluctant to accept this, but in my view they owe it to future generations to back this idea.

ÿ We have a responsibility to these children, they are our future. It is no use having a situation where someone suggests a possible harm and everyone runs around frantically trying to find bits of evidence. What is required is good-quality information that has been systematically collated and assessed

#### 255. Has The UK Committee On Medicines Modified The MMR Vaccine?

Alterations to vaccine formulation, and reports of problems with vaccines, are treated as highly confidential. In fact, all aspects of vaccination safety are regarded as secret. There are seventeen indices of openness of Government in use in the UK at present, and the UK Joint Committee on Vaccination and Immunisation fulfils just one of these, publishing (obscurely) a register of its members’ declared personal and non-personal interests. The UK Committee on Safety of Medicines is slightly less secretive, fulfilling just six of the seventeen criteria.



It would therefore be impossible to find out if the CSM or JCVI has taken any precautionary regulatory action with respect to MMR or thimerosal. But at its meeting of 10th December 2003, the CSM (which publishes the barest minutes) recorded, under the heading "Variation":

*"The Committee considered and advised on an application to change the potency specification of the finished product in respect of one of the components of a combined vaccine."*

Was this a reference to MMR, and perhaps to the weakening (attenuating) of the measles element, as a precautionary measure?

Or it may have absolutely nothing to do with MMR and autism. In the secretive world of vaccine safety, we do not know.

#### 256. 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:

- Y announcing any investigation into the affected children
- Y 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 platform party at the re-launch included Dr. Elizabeth Miller. Dr. Miller has repeatedly featured as a being a lead researcher in many papers detailed elsewhere in this Briefing Note. These papers invariably report no MMR/autism link. She has also been centrally involved in papers researching the safety or otherwise of thimerosal, and has energetically countered the work of Dr. Wakefield, repeatedly appearing before the US Congressional Committee on Government Reform. She also made a presentation to the recent (and heavily-criticised) Institute of Medicine review into vaccine/autism links in Washington in February 2004. Her multiple involvements make her a central figure in the vaccine/autism controversy. She appears to be both a key source of what is required to be independent (of Government) technical investigate research into MMR's safety, and also a part of the Government Health Department's official promotion of MMR.

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.

- Ÿ 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*”.
- Ÿ 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*”.
- Ÿ 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:

- Ÿ North Cheshire Health Authority launched a major advertising campaign
- Ÿ 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.
- Ÿ 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.

Ÿ 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"*.

Ÿ 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"*.

257 Interview with Dr. Peter Fletcher, former Chief Scientific Officer at the UK Department of Health, in the Mail on Sunday, 5<sup>th</sup> February 2006

Although space has precluded reviewing most media statements in this document, this interview is sufficiently important to merit a summary:

Dr. Fletcher, who in the late 1970s had served as Chief Scientific Officer at the Department of Health and Medical assessor to the Committee on Safety of Medicines, stated in his interview:

- \* "the refusal by Governments to evaluate the risks (of MMR) properly will make this one of the greatest scandals of all time"
- \* he had seen "a steady accumulation of evidence" from scientists worldwide that MMR was causing brain damage in certain children
- \* the rising tide of autism cases and growing scientific understanding of autism-related bowel disease have convinced him that the MMR vaccine may be to blame. Fletcher stated: "Clinical and scientific data is steadily accumulating that the live measles virus in MMR can cause brain, gut and immune-system damage in a subset of vulnerable children"
- \* "It is the steady accumulation of evidence, from a number of respected universities, teaching hospitals and laboratories around the world, that matters.....There's far too much to ignore. Yet Government health authorities, it seems, are more than happy to do so.....(Their) official complacency (is) utterly inexplicable."
- \* "There has been a tenfold increase in autism and related forms of brain damage over the past 15 years, roughly coinciding with MMR's introduction, and an extremely worrying increase in childhood inflammatory bowel diseases and immune disorders such as diabetes, and no-one in authority will even admit it's happening, let alone try to investigate the causes".
- \* "(There is) no way the tenfold leap in autistic children could be the result of better recognition and definitional changes, as claimed by health authorities. It is highly likely that at least part of this increase is a vaccine-related problem."

\* He stated that the risks of brain and gut damage from MMR injections seem to be much higher in children where a brother or sister has diabetes, an immune disorder. “That is a very strong clinical signal that some children are immunologically at risk from MMR.....It is entirely possible that the immune systems of a small minority simply cannot cope with the challenge of the three live viruses in the MMR jab, and the ever-increasing vaccine load in general.”

\* Fletcher also condemned the quality of MMR’s safety trials in the UK in the mid-1980s, describing them as “hopeless - an absolute mess”.

#### 258. The Search For Alternatives To MMR

In March 2004, the Sunday Herald, Scotland, included a report that the Irish Government has given Professor Greg Atkins, head virologist at Moyne Institute of Preventative Medicine, Trinity College Dublin, a grant of £482,000 (about \$800,000) to develop a safer alternative to the MMR vaccine.

Professor Atkins was quoted as admitting that the possibility that the existing MMR was the cause of bowel disease and autism in a small number of cases could not be ruled out, and that the present vaccine was known to result in other rare side-effects, such as meningitis and encephalitis. “We think the jury is still out on autism” he acknowledged.

The new vaccine will be made from recombinant (synthetic) RNA (ribonucleic acid) which will express proteins from measles, mumps and rubella viruses. It will stimulate immunity, but will not consist of infectious viruses, unlike the present MMR.

Atkins added that: “The fact that this vaccine does not contain live viruses should make it safer. Because this vaccine will not contain live viruses, it cannot replicate in the body causing persistent measles and other diseases which affect the gut or the brain.”

What is obviously interesting about this development, and this statement, is that the research is being commissioned to overcome the very problem that Wakefield had uncovered.

#### 259. Full Removal of Thimerosal From All Child Vaccines

This process has had a painful and controversial career.

As noted earlier, a memo from Merck dated March 1991, expressing concern that infants who received their full schedule of vaccines were receiving up to 87 times the amount of mercury permitted in fish, was leaked to the Los

Angeles Times. In March 2005, the Los Angeles Times carried a further story headed “Merck Misled On Vaccines, Some say”. This stated that:

- “Drug makers Merck continued to supply infant vaccine containing a mercury-based preservative (thimerosal) for two years after declaring that it had eliminated the chemical.”
- In September 1999, amid rising concern about the risks of mercury in childhood vaccines, Merck announced that the FDA had approved a preservative-free (thimerosal-free) version of its hepatitis-B vaccine. ‘Now Merck’s infant vaccine line is free of all preservatives’ stated a company press release.”
- “But Merck continued to distribute vaccine containing the chemical known as thimerosal, along with the new (thimerosal-free) product until October 2001, according to an FDA letter sent in response to a Congressional inquiry. The thimerosal-containing supplies had expiration dates in 2002.”
- “Merck executives confirmed the details in the FDA letter”
- “Last month, the Times disclosed a leaked Merck memo from 1991 showing that the company was aware at that time of concerns about thimerosal. In the memo, a former Merck scientist calculated that six-month-old children who received their shots on schedule could receive a mercury dose up to 87 times higher than the guideline for the maximum daily consumption of mercury from fish.”
- “Hilleman (the scientist) and Merck executives have declined to discuss the memo.”
- “Rep David Weldon.....said that with the old product continuing to flow into the market, he was fairly confident that newborns continued to get mercury-containing vaccines.”

## PART N

### UK AND US POLITICAL INITIATIVES

#### 260. House of Commons Health Committee, Westminster

ÿ 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.

- Y 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.
- Y The former Health Committee Chairman, David Hinchliffe MP, said 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.

At the time of writing, July 2004, the Committee had just announced an Inquiry into the influence of the pharmaceuticals industry, to take place during late 2004.

#### 261. UK All Party Parliamentary Group On Autism (APPGA), Westminster

- Y An All Party Parliamentary Group on Autism has been formed at Westminster. It is currently looking at diagnosis, education, care and causation issues. The first Chair was Dr. Stephen Ladyman MP (Labour, Thanet South), who later became the Health Minister with responsibility for autism, although he has now moved to Transport.
- Y Current Vice-Chairs are (or were) 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.
- Y 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. The APPGA has been careful to avoid topics of controversy, and tends to focus upon services for those with autism, rather than possible causes..
- Y No real progress has yet been made in collecting health data in any coherent nationwide manner by the UK Government as at August 2004. Some parents regard this neglect as quite deliberate. Data is now about to be collected on a voluntary basis through a "good practice" guide. This is unlikely to achieve results..

#### 262. Scottish Parliament Inquiry, Edinburgh

- ÿ 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.
  
- ÿ In February 2002, the Scottish Chief Medical Officer stated that calls to research the link between MMR and autism would be “resisted”.
  
- ÿ 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.
  
- ÿ 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.
  
- ÿ 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.
  
- ÿ In January 2003, the Scottish Liberal Democrats, the Scottish Conservatives and the Scottish National Party also all called for the immediate withdrawal of thiomersal-containing vaccines due to their suspected link with autism. They were opposed by the Scottish Labour Health Minister, Malcolm Chisholm, who insisted that there was no risk, and, although agreeing to thiomersal being phased out, intended to continue to use up existing stocks in children. The vaccine at issue was DTP. A new thiomersal-free DTP vaccine, Infanrix, was already available but was more expensive. Parents could have this if they chose, but no effort was made to inform them of this choice.

### 263. UK Liberal Democrats

- ÿ In February 2001, Nick Harvey MP, then the 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”.*

- ÿ 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.
- ÿ On December 22nd 2002, the current Liberal Democrat health spokesperson, 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.”

#### 264. UK Conservatives

- ÿ The former Conservative health spokesman, Dr. Liam Fox, a GP, 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.
- ÿ A Conservative MP, Ms. Julie Kirkbride, has vigorously but unsuccessfully 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.

#### 265. 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)

- ÿ Members of these committees, including chairmen, were found to own stocks/shares in the companies that make the vaccines.
- ÿ Individuals held patents for vaccines under consideration



- ÿ The CDC granted conflict-of-interest waivers, a year at a time, to its committee members
- ÿ 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”*.

- ÿ 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.
- ÿ 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).
- ÿ 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.
- ÿ 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
- ÿ 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
- ÿ 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.
- ÿ 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).

- ÿ 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.
- ÿ 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:

- ÿ 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
- ÿ High quality clinical and laboratory research was needed now, not five or ten years from now
- ÿ Independent analysis of previous epidemiological and case control studies was needed as well
- ÿ 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.
- ÿ 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 a new sub-committee of the Government Reform Committee are planned.

Other relevant points are:

- ÿ 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.

- ÿ 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.
- ÿ 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.
- ÿ 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:

- ÿ In 1990, Indiana schools had 116 requests for services for autistic children. By 2001, the number had risen to nearly 3,800.
- ÿ Despite the claims of safety by the US and UK authorities, it had not been demonstrated that thimerosal was safe. The US Institute of Medicine had concluded that a thimerosal/autism link was biologically plausible, and that existing evidence was inadequate to either accept or reject a causal association.
- ÿ The US Food & Drug Administration had in fact ordered the removal of thimerosal from over-the-counter ointments as long ago as 1985, on the grounds of safety and the risk of cell damage.
- ÿ In September 1998, almost a full year before the FDA took action over thimerosal 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”
- ÿ In October 1998, the FDA official responsible for reviewing all scientific literature on the safety of thimerosal in vaccines observed “I disagree with the conclusion regarding no basis for removal of thiomersal”.

Y 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.

Since 2003, a Sub-Committee on Health and Wellness has been established to continue the specific work of the Government Reform Committee on this topic.

266. Commentary, “Are Autism, Vaccines and Mercury Related?”, by US Congressman Rep. David Weldon, February 2005

(note that Weldon is also a GP, and supports the principle of vaccination. Weldon is also a member of the Appropriations Labor, Health and Human Services and Education Sub-Committee of Congress)

“In January 2004, the nation’s pediatricians received an autism ALARM (an acronym for an American Academy of Pediatrics communication) stating that ASD (autism spectrum disorders) were affecting 1 in 166 children, 90% of them boys. This far exceeds the 1 in 3,000 rate of the early 1980s”.

“So far, the Centers for Disease Control and Prevention, the National Institutes of Health and other health officials have been unable to tell us the cause of this dramatic increase. Part of the reason may be that CDC officials have been spending most of their time trying to tell us what hasn’t caused it.”

“National Immunisation Program leaders have attempted to allay public concern about mercury by commissioning an Institute of Medicine report. This report received much press attention when its results seemed to conclude that there was no link between mercury and autism.”

“However, careful review of this report shows that it is based almost exclusively upon European data, where children were exposed to substantially lower levels of mercury, raising serious questions about its validity.”

“Other parents have suggested that their child’s autism followed shortly after their MMR vaccinations.....Several investigators have found measles present in the inflamed intestines of children with autism. Others have discovered evidence of measles particles in the spinal fluid of these children.

Why is it there? What effect is it having on the children. Is it there because the children have autism, or is it contributing to autism? We simply don't know, but we must investigate."

"It's time for a new day of aggressive research to make vaccines safer for everyone, and to understand fully what effects small amounts of mercury may have on infants and to develop better measures to screen out children at risk of an adverse vaccine reaction. The NIH and CDC have been slow to respond to this crisis, and it is time for Congress to act more assertively."

## **PART P**

### **LITIGATION**

#### **267. UK Families' Legal Action**

This Briefing Note is primarily about evidence rather than litigation, but some information on the latter is included for information. The following sections may be considerably out of date, due to lack of time to update them.

One comment about litigation (at least in the UK). If the child wins damages, then the pharmaceuticals industry will have to pay damages which in turn will be used to fund much, or all, of the child's lifelong care. If the child loses, or cannot bring their case to Court, then the taxpayer funds the care. Whatever happens, the child doesn't fund their own care, nor do the parents. So criticisms of families going to Court that they are "out for the money" for themselves or their child, are wide of the mark. What is at stake is, should the manufacturers pay, or should the taxpayers pay? And, whatever the cause(s) of autism, the costs are real, and the children already exist. The bill for care is already there, waiting to be paid.

In the recent UK class action:

- ÿ Almost 2,000 families whose children became autistic or had other serious adverse events after MMR attempted 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.
- ÿ The trial date was originally fixed for October 2003 in the High Court of Justice in London, and then delayed until early 2004. However, in autumn 2003, the UK Legal Services Commission, under the management of a newly-appointed Chief Executive, suddenly withdrew funding from the cases, claiming that there was little chance of success and that it was not the role of the LSC to fund research. This was after

£15m had been spent, and the estimate was that a further £10m would be necessary.

- Ÿ An appeal by the plaintiffs against this decision was unsuccessful. The parents' lawyers then obtained leave for a judicial review of the LSC's decision. This was held in February 2004. The judge upheld the LSC's original decision. The UK legal action has thus stalled due to lack of funding.
- Ÿ Leading UK legal firms involved were Alexander Harris, Freeth Cartwright Hunt, and Hodge Jones & Allen. The action was being brought under the European Union's Product Liability Directive, the Consumer Protection Act. This unfortunately had a ten-year limit, and there was some uncertainty as to exactly how this applied (whether it was from the date of the vaccine's manufacture, its supply or its administration to the child). This ten-year limit forced lawyers to bring the cases at too early a stage in the science.
- Ÿ Cases included 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. A similar vaccine containing the Urabe strain of mumps virus was withdrawn in Canada, following reports of meningitis, fully six months before it was introduced in the UK. Other brands involved in the UK High Court action were MMR II and Priorix.
- Ÿ 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 seriously mentally or physically disabled.

The UK High Court action may not now be able to proceed further, due to lack of legal aid and the ten-year limit imposed by the Consumer Protection Act. However, a number of parents are still pursuing their cases. And future legal action may be contemplated by UK parents via other means.

If the children had reached the UK High Court, and had won substantial damages, this would have funded their care costs during their lifetime. The failure to reach the High Court means that these immense costs will now largely be borne by the UK taxpayer instead, as discussed in a later section. Whatever, it is the case that the children exist, that they will need lifelong care, that they are incapable of funding such care, and that their parents are under no legal or moral duty to fund it.

In December 2004, about 100 families who believed that their children had been damaged by MMR had their legal aid re-instated. These cases do not include autism cases.

A number of other cases, where autism is the main form of damage, are fighting on without legal aid.

#### 268. 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 1978 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:

Y Increasing the £40,000 (formerly £30,000) statutory payment to £100,000. This was effected from July 2000

ÿ Increasing the absolute six-year time limit for claims to any time up until a claimant's 21st birthday

ÿ Lowering the disability threshold (level of damage) from 80% to 60%

However, the scheme remains deeply adversarial, and extremely 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 was as follows (1978-2000):

ÿ Over the 21 years, 4,111 claims were submitted

ÿ 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%

ÿ 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%

ÿ Even with Section 4 awards (subsequent to a review of the medical reasons by an independent tribunal) and awards subsequent to an appeal to the Secretary of State, the award rates remained very low.

ÿ 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 extraordinarily low, only a handful of Section 4 awards succeeding. And only one award following an appeal to the Secretary of State had 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.

The latest figures available for the scheme show just how adversarial it is, and how very few claimants are successful:

<i>Year</i>	<i>Claims Rec'd By UK Vaccine Damage</i>	<i>Nos of initial awards</i>	<i>Nos of awards following a s3A reversal</i>	<i>Nos of awards following appeal</i>	<i>Total</i>
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	<i>Payment Unit</i>				
1990	37	0	0	7	7
1991	42	2	0	3	5
1992	43	4	0	2	6
1993	19	1	0	1	2
1994	78	3	0	7	10
1995	69	0	0	2	2
1996	72	0	0	0	0
1997	152	1	0	1	2
1998	177	0	1	0	1
1999	82	1	1	0	2
2000	171	0	0	1	1
2001	176	1	0	1	2
2002	406	5	0	0	5
2003	68	0	0	0	0
<i>Total</i>	1,592	18	2	25	45

The above therefore means that only 45 out of 1,592 applications (just 2.8%) were successful, surely an extraordinarily low rate.

(note - the scheme applies to damage from all vaccines, not just MMR. It is not known how many of the above cases relate to MMR, thimerosal or autism).

No children suffering from autism have ever won a claim.

However, awards for damage from MMR have been made. In March 2005, for example, it was reported in the UK press that a mother named Carol Buxton received an £85,000 award after it had been confirmed that the brain damage suffered by her daughter Hannah, who subsequently died, was linked to MMR. Hannah had subsequently suffered up to 40 fits per day following vaccination in 1988, and had died three days short of her third birthday. The initial claim to the VDPS was turned down, but an appeal was successful. The decision was not contested by the Secretary of State. The VDPS letter stated that "Hannah Buxton was disabled as a result of a vaccination to which the claim relates, and acknowledged that the reaction to the vaccination had caused Hannah's development to deteriorate.

A further press report by the Evening Standard on 16<sup>th</sup> March 2005, based upon data obtained under the UK's then-new Freedom of Information Act, confirmed that:

\* since the scheme's introduction, about 30,000 families had submitted applications to the UK VDPS

\* only "a handful" had been successful

- \* since 1997, some £3.5m had been paid out to 35 families
- \* a total of just 917 payments had been made since 1979
- \* in 2004, the latest year for which data was available, just 1 in 33 applications succeeded

No data was released to confirm how many applications, or awards, related to specific vaccines. Clearly such data exists, even where more than one vaccine is involved, and the refusal to discuss the matter is secretive and unhelpful to any open debate about relative risks of specific vaccines.

#### 269. US Vaccine Injury Compensation Program (VICP)

US families with complaints about children believed to have been damaged by vaccine additives are first required to pursue remedies through the federal Vaccine Injury Compensation Program (VICP).

Y The VICP Act (1986) requires that complaints must first be filed with the VICP, which offers (if the claim is agreed) to pay unlimited medical expenses, “reasonable” legal fees and up to \$250,000 for pain and suffering, if the claim is legitimate.

Y But the system has become highly adversarial. A report by Newsday on 24th November 2002 stated that the Federal government was fighting claims made to the VICP with unexpected vigour, rejecting 68% of the 5,566 claims reviewed to date.

There is a complication in that one provision of the 1986 Act exempts illness, injury or death “associated with an adulterant or contaminant” in vaccines from the VICP procedure. Personal injury lawyers in the US consequently began to claim in 2001-2 that mercury-containing preservative was an adulterant or contaminant, and that it had caused the damage or death. By December 2002, individual or class-action lawsuits on this basis had reached nearly two hundred.

In fact, the US Vaccine Injury Compensation Program has been facing a potential wave of new claims. Officials from the US Department of Justice warned the Department of Health and Human Services Advisory Commission on Childhood Vaccinations as early as December 2002 that the program might not be able to cope. According to a report by Reuters, thanks largely to the thiomersal controversy, the number of claims filed during 2002 had grown more than fourfold.

Even if the thimerosal/autism link was never established, the wall of claims could force the adoption of out-of-court settlements, although the scheme is nearly two billion dollars in credit.

Some lawyers have argued that the Vaccine Injury Compensation Program is stacked against the autistic children.

Y First, parents have to file a claim within three years of the first symptoms. Autism is not typically diagnosed until 18 months - or more - after the first symptoms, and lawyers for the children estimate that two-thirds of his clients have missed this deadline already.

Y Secondly, the burden of proof is harder to meet under the NVIC, which requires plaintiffs to show that a majority of scientists agree with them, as opposed to State courts, where families' lawyers only need to find a number of supporting expert witnesses.

Y Thirdly, the limit of \$250,000 (the UK limit was £100,000, or about \$150,000) is considerably lower than the typical award for autism in State courts. The lifetime care costs of an autistic child had been estimated at \$2m, although a UK study has put them at £2.9m, or about \$4.4m.

Y The NVIC route also means even more delay than the court route, typically taking about four to five years. The delay acts against lawyers taking a case, as there is no fee until they win. It has been calculated that it costs \$200,000 in out-of-pocket expenses plus \$1m in time to bring a single autism vaccine damage case to trial. Lawyers could even go bankrupt before reaching a conclusion. In contrast, the pharmaceuticals industry effectively has a bottomless purse for hiring lawyers.

By early 2003, the US vaccine damage fund stood at nearly \$2 billion.

Initially, the fund had been set up with three goals: to protect vaccine manufacturers from lawsuits, to stabilise the nation's vaccine supply, and to provide generous compensation to families without tying them up in court for years. But two of these three goals were on behalf of the injuring party, not the injured, and campaigners are convinced that a no-fault compensation scheme has been lumbering the community with the costs of damage whilst letting the manufacturers, as defendants, off the hook.

There is also strong criticism of gagging orders. Families have said that in order to receive compensation, they have been forced into signing agreements that would keep information about their case from being published.

Since the US VICP fund has been established, less than a third of the 6,000 cases filed have resulted in compensation. However, despite this, by 2005 the scheme had paid out \$58m to claimants.

A summary of the awards paid out under the VICP is as follows:

(fiscal year)	Number of awards made to petitioners, including fees and costs	Amount US \$, millions
1988-95 (combined)	140 (combined)	96.3m
1996	53	29.8m
1997	57	46.3m
1998	58	52.7m
1999	36	48.5m
2000	72	58.1m
2001	73	74.9m
2002	76	57.6m
2003	60	73.6m
2004	55	62.1m
2005	64	56.4m
2006	5 (to date)	1.1m (to date)
total	749	657.5m

The autism/thimerosal issue has become more important within the VICP scheme, coming to represent a quite significant proportion of total claims. However, all claims are being dismissed:

(fiscal year)	Number of autism/thimerosal claims compensated	Number of claims dismissed
1988-95	0	0
1996	0	0
1997	0	0
1998	0	0
1999	0	0
2000	0	0
2001	0	0
2002	0	4
2003	0	21
2004	0	113
2005	0	38
2006	0	0
total	0	176

#### 270. Families Taking Legal Action in the US over Thimerosal 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 thimerosal, the 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

thimerosal may be interlinked biologically. (The thimerosal issue has been considered in detail elsewhere in this Briefing Note).

- Y The initial US lawsuit was filed by Walters & Kraus (Dallas, Texas, contact C. Andrew Waters).
- Y Other law firms taking action are Anderson & Krieger (Temecula, California), Wallace & Graham (Salisbury, North Carolina), Hendler (Austin, Texas), Thomasson Gilbert Cook & Maguire (Cape Girardeau, Missouri), O'Connell & O'Sullivan (Elgin, Illinois), Dogan & Wilson ((Pascagoula, Mississippi), Ferraro & Associates (Miami, Florida), 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), Nance Cacciatore & Hamilton (Melbourne, Florida), Cantor Arkema & Evans (Richmond, Virginia) and Wise & Julian (Alton, Illinois). The above list is not exhaustive, and more firms are also expected to become involved.
- Y 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.
- Y 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).
- Y 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 thimerosal, and against the vaccine manufacturers that use or used thiomersal in manufacturing or distributing childhood vaccines

- ÿ 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 thimerosal.
- ÿ 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 thimerosal
- ÿ 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.
- ÿ 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.
- ÿ In May 2002 it had also been 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 thimerosal. 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.”*

By April 2005, over 4,200 claims had been filed in the special US Federal tribunal, the Vaccine Injury Compensation Program, by parents asserting that their child suffered autism or other neurodevelopmental disorders from mercury in vaccines. A small number of cases were also awaiting trial in the civil courts..

By June 27<sup>th</sup> 2005, the United States Court of Federal Claims reported that:

- \* approximately 4,800 petitions in autism cases had been filed
- \* about 4,500 remained pending, having been stayed at the petitioners’ request, until the conclusion of the Omnibus Autism Proceeding (many of the cases that were no longer pending were voluntarily dismissed or withdrawn by the petitioners; in most of those cases, the dismissal was due to the fact that, inadvertently, a second petition had been filed pertaining to the same child. A number of other cases were dismissed because they were not filed in time
- \* petitioners have made two extensive discovery requests for materials from Government files, and many thousands of pages of information have been copied to petitioners. Nearly all requests have been resolved. The total pages of information supplied is about 200,000
- \* efforts to obtain information relating to vaccine license applications have proceeded slowly

Information supplied by the US Food & Drug Administration in connection with this action has related to the following vaccines -

- Lederle DTP

- Lederle tetanus
- GlaxoSK hepatitis B
- Aventis DT
- Wyeth tetanus
- Lederle DT
- Merck MMR
- Merck mumps
- Merck rubella
- Merck measles
- Merck hep B
- North American Healthcare DtaP
- Aventis HIB conjugate
- Aventis DTP
- Wyeth-Lederle DtaP
- Wyeth-Praxis DPT
- Wyeth-Praxis DT
- Lederle HIB conjugate
- Lederle DPT/HIB

Files on other vaccines were also being subject to discovery process.

The petitioners' Steering Committee has asserted that a number of studies relevant to the general autism causation issue are still under way, and has stated that it wishes to defer the filing of the Committee's Expert Witness Reports concerning causation until those studies have been completed. The Committee wishes to wait until at least late 2006, and possibly later, before filing the expert reports.

At the end of September 2005, a further update on the cases in the United States Court of Federal Claims was published. The most significant element was a ruling by Special Master George L. Hastings Jnr. in relation to the filing of expert reports. A request for the deadline for these to move to late 2006 was submitted, and opposed by the pharmaceuticals companies. The Special Master ruled that the date be deferred indefinitely - thus giving time for further scientific work. However, petitioners had to designate experts and submit statements from experts justifying delays.

#### 271. US Government Attempts To Block The Thimerosal/Autism Litigation

The progression of the US litigation over vaccines and autism was made very much more uncertain during 2002-2003 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 company denied any knowledge of how these clauses had ended up in the Bill, but needless to say welcomed their inclusion.



The vaccine industry regarded the four clauses as closing what they saw as a loophole. The controversial Vaccine Injury Compensation Program had been set up, effectively at public expense (by being funded by a toll on state-mandated vaccines) to keep the parents of vaccine-damaged children away from the Courts.

The clauses that had been tagged-onto the tail end of the Homeland Security Bill had started life by being drafted by Senator Bill Frist of Tennessee. Frist's Bill was intended to raise the limit on damages that could be paid out by the Vaccine Injury Compensation Program, to extend the statute of limitations on filing claims. But it was also to protect the pharmaceuticals industry.

The inclusion of these clauses was immediately strongly criticised by a range of US politicians, including Rep. Dan Burton (R-Indiana), Sen. Debbie Stabenow (Democrat, Michigan), and Sen. Patrick Leahy (Democrat, Vermont). In fact, the clauses had only been noticed by a handful of Congressmen, and at the last minute.

Burton was furious with his own party's actions. *"These provisions don't belong in this bill. This is not a homeland security issue, this is a fairness issue.....More and more parents believe that the autism affecting their children is related to a vaccine, or a mercury preservative used in numerous vaccines given to their children.....Instead of passing legislation to take away the rights of families with vaccine-injured children, we should be passing legislation to try to help them."* Sections 1714-1717 of the Homeland Security Bill would take away the only remaining recourse to legal action for their children's damage for many families.

Burton urged his fellow-legislators to strip Sections 1714-1717 from the Homeland Security Act. *"Let's not be stampeded into cutting off the legal rights of these children without hearings and a full public debate."* In an excoriating address to Congress on 22nd November, he blasted his own administration: *"Last week, the legislative process was hijacked and we ended up with a fiasco of extreme proportions.....The Centers for Disease Control told us they plan to spend \$11.3m on autism this year and \$10.2m next year.....(but) the CDC is spending over \$932m on the AIDS epidemic this fiscal year (and) will spend \$62m on diabetes. The autism epidemic.....is no less deserving."*

A group of senators, led by Sen. Olympia Snowe (R-Maine) and Sen. Susan Collins (R-Maine), plus Sen. Lincoln Chafee (R-Rhode Island) had threatened Dick Cheney, president of the Senate, and Minority Leader Trent Lott, that they would go against their party and to block the Homeland Security Bill unless there was an undertaking that the clauses relating to Eli Lilly were revisited.

Lott agreed to work up a deal to an early reversal of the autism/thimerosal clauses. Not satisfied, the rebels obtained the same assurances from House Speaker Dennis Hastert, who had been in a plane on the way to Turkey. In a dramatic scene, as time for voting ran out, the phone calls were returned and the assurances obtained.

The politicians who had voted for the Homeland Security Bill but with deep unhappiness about the autism paragraphs tried to justify themselves. *"I am very distressed to see (the sections) on the Bill, with no hearings and no chance for consideration"*, lamented Republican Senator Arlen Specter of Pennsylvania. *"This is really a case where it is a matter of take it or leave it."* Specter concluded that the Bill was "legislative blackmail" which put him "in a very difficult position." On the Democrat side, Senator Daschle and Rep. Pelosi vowed to repeal the offending clauses.

One Republican rebelled. Sen. John McCain, the highly-independently-minded Republican senator from Arizona, voted with the Democrats and backed-up the parents. He said he didn't believe the Republican leadership's promises. *"The fix is in"*, McCain told reporters.

There was also intense suspicion at the influence that Eli Lilly and other vaccine manufacturers had upon US politics. According to a story by reporter Maureen Groppe in the IndyStar on 29th November 2002, the pharmaceuticals industry had given \$19.1m to candidates during the 2002 elections, with 73% of that money going to the Republicans who now controlled Congress.

Within the industry, the largest donor had been Eli Lilly, giving \$1.6m, according to the Center for Responsive Politics. The Center was quoted as saying that Eli Lilly gave more money to Republican congressional candidates than did any other pharmaceutical company. The pharmaceuticals sector had spent even more lobbying Congress. Eli Lilly alone had spent \$6.5m on federal lobbyists during 2001.

Something of a media 'whodunnit' also developed, as the press tried hard to trace exactly how the offending four paragraphs had got into the Homeland Security Bill in the first place. The timing was traced to the 2002 Veterans Day weekend. One Congressional aide named Diamond was quoted in the New York Times as saying that the clauses had even appeared in the House of Representatives' version of the Bill in entirely different typeface, as though it had been cut-and-pasted from elsewhere. No-one would say who was responsible.

According to the Washington Post of 28th November 2002, two sources had stated that an official at the Department of Health and Human Services had given the final approval to include the clauses and shut-out the parents from taking legal action. The Department denied this. But the Post also confirmed that as recently as September 2002, lobbyists for Eli Lilly were on

Capitol Hill trying to get a vaccine-defending bill inserted into the Homeland Security Bill. The lobbyists had then said that they were “as surprised as anyone” when it was finally included.

The “surprise” was echoed within Eli Lilly. *“We don’t know how it became part of the House Bill”,* said Rob Smith, an Eli Lilly spokesman. *“We didn’t know it was part of the Bill, and it was a surprise to us”.* The company’s lobbyists *“made absolutely no contact with Mitch (Daniels) or anyone in his office about this.....(and Sidney Taurel) “did not at any time ask” for any favours. “It’s a mystery to us how it got in there”.*

It wasn’t only the autism families who were affected. In a radio interview broadcast just after the Senate vote, Dr. Len Horowitz, a leading campaigner for increased public scrutiny of the pharmaceuticals sector, warned: *“This legislation not only impacts on the victims of mercury poisoning, but equally guarantees that other ongoing class-action lawsuits, such as those waged on behalf of polio vaccine recipients who developed cancer from monkey-virus contaminations, will have no legal recourse. Nor will those affected by Gulf War Syndrome as a result of drug and vaccine side-effects.”*

The Democrat, Rep. Henry Waxman, who was also the ranking Democrat on Dan Burton’s Government Reform Committee but who had criticised Burton’s ruthless determination to investigate autism, then turned on the Republicans. Waxman sent a letter to Secretary Tommy Thompson, Director of Health and Human Services, and White House budget Director, demanding information on the Bush administration’s involvement in the amendment.

The White House’s director of the Office of Management and Budget, Mitchell Daniels Jr., who also sat on the Homeland Security and National Security Councils, was also a former Eli Lilly executive. He had become senior vice-president of corporate strategy and policy in 1997. But he denied any role in the Homeland Security/Eli Lilly fix. Other press reports said that the Republican leadership must have approved the addition to the Bill.

Mitch Daniels wasn’t the only link between Eli Lilly and the Republican leadership. Eli Lilly’s Chairman, President and Chief Executive, Sidney Taurel, from Indiana, had sat on the Presidential Homeland Security Council since June 2002. He had originally joined Eli Lilly International back in 1971, after holding positions in Brazil, France and London, becoming president of Eli Lilly International in 1986, then executive vice-president of the pharmaceuticals division in 1991.

And George Bush Snr., the former US President, sat on Eli Lilly’s board of directors from 1977, and the current US President, of course, was Bush’s son. Secretary of Defense Donald H> Rumsfeld, who had also been Secretary of Defense under President Ford in the post-Nixon era, had formerly headed

Searle Pharmaceuticals, and was considered by critics to be part of the “drug company axis” within the Bush Jnr. Administration. Other senior Bush aides were known to be lobbyists for the pharmaceuticals industry.

An on-line public interest journal, TomPaine.com, even went as far as offering a \$10,000 reward to uncover the secret, “Who Is The Eli Lilly Bandit?” Who had got the company its big break? On December 18th, the editor, John Moyers, took out an advertisement in the New York Times, offering the reward, to find out. Interviewed on National Public radio on 19th December, Moyers said that, for suspects, *“Top of the list has to be Senator Frist.....Representative (Dick) Arme y has claimed credit (but) he’s most likely just providing cover for somebody else who’s sticking around after Arme y leaves.”*

NPR’s health reporter, Julie Rovner, commented: *“Dick Arme y’s office takes credit and/or blame for this, and they call it credit.....At one point, they said that the White House had asked them to do it, and then a week later, they said that the White House had not asked them to do it.”* Morning Edition host Alex Chadwick quipped: *“And Eli Lilly says that it didn’t ask for any favors, which leaves the mystery unsolved and that \$10,000 reward sweating on the table. Hello, Woodward? Bernstein? Philip Marlowe?”*

The thimerosal move was part of a wider picture of vaccine manufacturers extracting promises of lawsuit immunity. By executive order after the September 11th 2001 terrorist attacks on New York and Washington, President Bush had declared that makers of smallpox vaccines would be protected from any liability if they were sued by damaged patients. By late 2002, Wyeth and Aventis Pasteur were enjoying this indemnity, and as third company was awaiting approval.

This highlighted the peculiar role of the vaccine companies. Vaccination was seen as a public benefit, provided by private companies but under a publicly-promoted and funded programme of immunisation. The public/private partnership worked well if the vaccines were safe, but became a unique barrier to would-be claimants in the event of damage, neither side accepting their responsibilities for redress.

The public, both in the US and the UK, are regularly told that vaccination is good for them. When it isn’t, and it goes wrong, no-one wants to know.

In the four days that led up to the vote on the Homeland Security Bill, opposition to the four clauses exempting Eli Lilly mounted dramatically. Those who followed the Bill’s progress saw the influence of the pharmaceuticals sector in action, as the Lieberman-Daschle-Byrd amendment to strike out the offending four clauses was voted down 47 to 52. The same night, the Senate approved the Bill unamended, by 90 votes to 9.

In fact, the blocking of the US autism legal cases was only part of a far wider picture. On November 21st 2002, the New York Times had run a story, "Election Gives Drug Industry New Influence". Reporting that the industry's political hand seemed stronger than at any time in recent years, it detailed how the major drug and vaccine manufacturers had met the previous week at the Westfield International Conference Center, near Dulles International Airport, Northern Virginia, to plan how "to turn influence into legislative victories". The executives that had met included Sidney Taurel, chairman of Eli Lilly and Raymond V. Gilmartin, chairman of Merck.

According to the New York Times, "they (the companies) discussed specific ways to leverage their investment in this year's elections to advance their agenda b Capitol Hill. An unnamed lobbyist described the meeting as having "a pervasive theme (of) how to block proposals that could erode profits." And the Times commented: "Already, industry executives have been encouraged by a recent move to insert a provision in the Homeland Security Bill limiting the legal liability of vaccine manufacturers like Eli Lilly".

The same report detailed that, according to the group Public Citizen that had been founded by Ralph Nader, the pharmaceuticals industry had recently spent a total of about \$500m on lobbying, including a force of 600 lobbyists that included about two dozen former members of Congress. Democrat strategists said that the drug and vaccine industry had also spent at least \$15m on television advertisements supporting Republican House of Representatives candidates.

The industry had targeted resources at lawmakers from both parties. The Democrat chairman of the Senate Finance Committee, Max Baucus of Montana, had received \$114,000 from the pharmaceuticals industry, and, according to the Center for Responsive Politics, senior Republican Charles E. Grassley of Iowa, the incoming chairman, received about \$100,000. The largest single recipient had been Nancy L. Johnson, chairwoman of the Ways and Means Subcommittee on Health, who had received \$200,000 from the pharmaceuticals and health products industry.

According to US campaigners, most money during the 2002 elections went to the Republicans, probably as much on the basis that they were likely to be the winning side as on any basis of inherent political bias. Examples included the Pharmaceuticals Research and Manufacturers of America, who gave 95% of their \$2.8m donation to the Republican Party, Eli Lilly, who had given 75% of their \$1.4m donation, Glaxo SmithKline, who had passed over 81% of the \$1.1m involved, and Aventis, who had given 78% of their \$0.9m donation to the Republican cause. Merck had given 78% of \$0.6m, Pfizer had given 79% of \$1.6m, Schering had given 79% of \$1m and Wyeth had donated 83% of \$1m.

Campaigning parents of damaged children describe the US Government as "the best that money can buy."

One lawyer, Charles S. Siegal of Dallas, commented dryly: *“I guess my four year old client represents a threat to homeland security.”* According to a report in the St. Petersburg Times of November 16th, Siegal was quoted as saying that Lilly executives had told White House officials that their company would not participate in the administration’s program to produce smallpox vaccine unless it received immunity from any lawsuits filed by those who suffered side-effects.

Whilst the controversy over the Bill raged in the US press and in Congress, there was a further development. A move to seal all thiomersal-related documents was also made at the end of November 2002. The Department had the right to make this request, but if the court granted it, parents would be prevented from gaining access to vital evidence that might potentially prove their claims.

Department of Justice lawyers asked a Special Master, George Hastings, in the US Court of Federal Claims to seal the documents because, according to a Reuters report on 26th November 2002, allowing their automatic disclosure “would take away the right of federal agencies to decide when and how the material should be released.” Justice Department attorney Vincent Matanoski argued that to let plaintiffs use the evidence in a later civil court lawsuit would confer an advantage on plaintiffs who had chosen to forgo federal compensation. Hastings promised a prompt decision.

The ploy was of course also immediately attacked by Rep. Dan Burton, who wrote at the beginning of December 2002 to Attorney General John Ashcroft asking him to withdraw the motion. Burton had also written formally on 21st November 2002 to the President, George Bush, urging that he host a conference on autism. He asked Bush to “galvanize a national effort to determine why autism has reached epidemic proportions”, and “to determine what is causing this outbreak, and how it can be stopped.”

The attempted sealing was then suddenly withdrawn in December 2002, by the US Department of Justice.

The inclusion of the thimerosal clauses led to immediate demonstrations and to meetings between angry parents and their Congress representatives. Reversal of the offending clauses was rapidly promised.

Meanwhile, the media had a field day. *“Thank God our leaders in Congress were wide awake and working day and night, fingers to the bone, to protect us from the scourge of terrorism by trying to prevent parents of autistic children from suing a drug manufacturer”* wrote Mike Argento in the York Daily Record of 23rd November. *“Thank God our leaders in Congress tried to act decisively to keep us safe from the parents of autistic children. Whew! That was a close one. It’s vitally important to national security that parents of*

*autistic children not be allowed to sue a huge pharmaceutical company because.....because.....well, just because."*

In January 2003, a Bill was introduced in Congress which focused solely upon the reversal of clauses 1714-17 of the Homeland Security Bill, the clauses that protected Eli Lilly from lawsuits. This new 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). The Bill passed.

If there is no connection between thimerosal and autism, why was it necessary for the four clauses to be introduced so hurriedly, and so clumsily, in the first place?

After several further attempts at getting product liability exemption through Congress, Senator Bill Frist finally succeeded at the start of 2006, attaching exemption clauses to an unrelated defence spending Bill. The Bill grants unprecedented immunity to the pharmaceuticals manufacturers, with wide powers for the Secretary of Health and Human Services to activate immunity from lawsuits.

The terminology is so broad that it allows a declaration of "emergency" under virtually any circumstances, to be followed by exemption. There is no right of appeal through the Courts. All local State laws are pre-empted. Laws making drug companies liable would be suspended in the event of a "disease threat". Drug companies are even exempt from liability for reckless conduct or gross negligence.

There have been other initiatives to block parents' legal endeavours. On July 25<sup>th</sup> 2004, the New York Times reported that "Bush Moves To Block Medical Suits". The article stated:

\* "The Bush administration has been going to Court to block lawsuits by consumers who say they have been injured by prescription drugs and medical devices

\* The administration contends that consumers cannot recover damages for such injuries if the products have been approved by the Food & Drug Administration. In Court papers, the Justice Department acknowledges that this position @reflects a change in Government policy', and it has persuaded some judges to accept its arguments, most recently (this in 2004) scoring a victory in the Federal Appeals Court in Philadelphia

\* Allowing consumers to sue manufacturers would ‘undermine public health’ and interfere with federal regulation of drugs and devices, by encouraging ‘lay judges and juries to second-guess’ experts at the FDA, the Government said.....If such lawsuits succeeded, some good products may be removed from the market, depriving patients of beneficial treatments.” (source New York Times)

(this appears to be rather like arguing that, if your spouse is negligently killed in an air crash, you can’t sue the airline, because it might prevent other people from traveling by air at some point in the future, and air travel is a “good thing”. It also suggests that juries can’t be trusted, only “experts”.)

#### 272. MMR Litigation In Ireland

At the end of April 2004, the Sunday Times (of Ireland) reported that 150 families there are to sue the manufacturers of MMR after their children developed autism following vaccination. The class action is being handled by Dublin law firm Lavelle Coleman. Legal notice has been given to GlaxoSmithKline, Merck Sharp Dohme and Aventis Pasteur MSD.

#### 273. MMR Litigation in Japan

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

- ÿ MMR was introduced in Japan in the late 1980s. Shortly afterwards, there were reports from parents of severe neurological damage. Many other parents then rejected MMR for their children, and a number of deaths, mostly from infants, resulted from consequent measles outbreaks.
- ÿ The Japanese Government then withdrew MMR altogether in 1993 and introduced separate measles and rubella vaccines. It did not introduce mumps vaccine, as the Urabe mumps strain was held responsible for the neurological damage from MMR.
- ÿ Vaccination against mumps still does not form part of today’s Japanese immunisation schedule. Single mumps vaccine (“otafuku kaze”) is only available privately, for children over one year of age, for parents seeking it.
- ÿ As recently as 1999, Japan reconsidered its decision to discontinue MMR, but re-affirmed its previous stance not to offer it due to safety concerns



- ÿ 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.
- ÿ The group used 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
- ÿ 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".
- ÿ 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.
- ÿ In a paper, *Aseptic Meningitis As A Complication of Mumps Vaccine*, by Sugiara and Yamada, published in *Pediatric Infectious Disease Journal* 1991 Mar 10 (3) pp209-13), the authors state: "Among 630,157 recipients of MMR vaccine containing the Urabe Am9 mumps vaccine, there were at least 311 meningitis cases suspected to be vaccine-related. In 96 of these 311 cases, mumps virus related to the vaccine was isolated from cerebrospinal fluid".
- ÿ The adverse event data reported in the Japanese press 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.
- ÿ The Japanese court cases were held in March 2003. Some 1,065 children were awarded damages over MMR, against the Japanese Government and the Research Foundation for Microbial Diseases, Osaka University, for side-effects, meningitis and death.

#### 274. Litigation Elsewhere

Litigation is also known to be under way in Canada and in Sweden, but no details are yet to hand. Litigation has also been brought in Germany, and further details are being sought.

In April 2005, the Danish Supreme Court upheld a previous 2003 ruling by a lower court that a fifteen-year-old girl's autism was not developed as a result of MMR. The parents of the child had previously gone to court in response to a ruling against them by the Danish Medico-Legal Council.

## PART Q

### SOME BROAD CONCLUSIONS AND QUESTIONS

#### 275. Some Broad Conclusions

The above document puts “under one roof” a considerable amount of information on the MMR/autism and the thimerosal/autism issues (which are likely in at least some cases 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:

- ÿ 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 that really has been a very sharp rise, and only in the past decade or so. Diagnostic criteria have actually become more restrictive, so that cannot explain the ongoing dramatic increases being reported around the world.
- ÿ 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.
- ÿ 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

- ÿ 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
- ÿ There is now very strong evidence to link thimerosal in vaccines with autism
- ÿ The inclusion in the US Homeland Security Bill of December 2002 of clauses debarring parents from initiating litigation against Eli Lilly over thimerosal 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
- ÿ 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, including thimerosal-containing 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 thimerosal, or both, is also supported by the consistent accounts of the parents of the actual children.

#### 276. Some Unanswered Questions

Some outstanding questions, which readers and the media may find useful to bear in mind, are offered here...

- ÿ Does the UK Department of Health and US Centers for Disease Control even accept in principle that vaccines can cause brain damage?
- ÿ Do these bodies accept that parents' reports of children's descent into autism after vaccination are to a consistent pattern?
- ÿ Why was regressive (late-onset) autism rare a couple of decades ago but now relatively common?
- ÿ Why do UK and US Health Ministers still continue to claim in debates that the apparent rise can be explained through "greater awareness" or "better diagnosis", when detailed studies from the US point to the increases being real, and not explainable through these factors?
- ÿ 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 apparently routinely disregarded?
- ÿ Why do reviews such as the 2001 review by the UK Medical Research Council - which found extremely high rates of autism - stretch out so hard to reach the comforting explanation that increased numbers are

mainly a matter of better recognition and improved diagnosis, when they have no robust scientific justification or hard data to justify doing so?

- ÿ 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, perhaps? At what point does the apparent increase register as a real increase?
- ÿ Why were most autism cases prior to the late 1980s (the time of introduction of MMR in the UK) of children who failed to develop from very early infancy, whereas the majority of cases nowadays - paradoxically, when there is now much better recognition of the condition (and when it is therefore much less likely to have been missed in early infancy) are now of late-onset or "acquired" autism, after a normal infancy?
- ÿ Does the UK DoH, US CDC etc accept that the alleged new syndrome sometimes involves slow degeneration over many weeks/many months/several years, rather than always an automatic acute event within a few days, or at most three or four weeks, of MMR vaccination?
- ÿ Does the UK DoH, US CDC etc accept that many autistic children also have acquired extreme multiple food allergies, and that the onset of these approximately coincided with the onset of their autism?
- ÿ Ditto question for bowel conditions.
- ÿ Related question: does the UK DoH, US CDC, etc accept that simultaneous or sequential onset of gut/bowel/autism problems could be interlinked causationally? (the UK Department of Health has speculated publicly that the gut/bowel conditions could be caused by the autism, which is clearly far-fetched, and far less likely than the other way around ).
- ÿ Does the UK DoH etc accept the principles of "challenge/re-challenge", with children suffering a "double-hit", regressing after both 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).
- ÿ Is the DoH monitoring England/Wales autism numbers centrally? (they are not, although the Departments of Education and of Health were supposedly encouraging some form of "good practice" assessment of the scale of special educational needs children from 2004. The US already has central monitoring of education data.)

- ÿ Are UK regional health authorities/Boards monitoring autism locally, to a consistent degree? (it is known that they are still not)
- ÿ Why, when the UK DoH is aware of the well-documented huge increase in autistic pupils in the US, 1994-2004, up from 22,780 in 1994 to 166,302 in 2004? (and this only includes ages 6-21, the under-6s are additional to these), does it not monitor autism numbers.
- ÿ 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?
- ÿ What research has the UK Department of Health etc commissioned into possible causes (as opposed to the genetic susceptibility aspect) of autism.
- ÿ What is the £ value of such research, over how many years? How does this compare with US expenditure?
- ÿ 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, which was awarded a further £300,000 at the start of 2003, plus the Lipkin study in the US). And why is the UK study using researchers who were also being paid by the manufacturers as expert witnesses in the recently-stalled UK High Court cases?
- ÿ Has the Treasury (or anyone in the UK or US Governments?) 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)?
- ÿ 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?
- ÿ Did the UK Medicines Division (predecessor of the Committee on Safety of Medicines and the Medicines & Healthcare Regulatory Agency) license MMR on the basis that it was apparently only the amalgamation of three existing licensed vaccines (i.e. "1+1+1 = 3), without considering that their combination could have a synergistic effect?
- ÿ 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? (this is a very important question, and should cause the authorities some difficulty in answering)

- ÿ Are UK doctors (or US doctors) now specifically advised by the DoH (or US CDC) to look out for degeneration as a *potential* adverse consequence of immunisation? (Lord Hunt recently confirmed in a UK Parliamentary Written Answer to Lord Clement-Jones that they are not).
- ÿ Why has the UK Medicines Control Agency not instructed health authorities to replace existing stocks of thimerosal-containing vaccines with non-thimerosal containing vaccines, when there is serious concern over adverse reactions to thimerosal, and when the manufacturers have been operating a free-exchange scheme in the US, and when US litigation is under way?
- ÿ How will the Department of Health/CDC/relevant national body rebuild confidence in the immunisation programme if it finally emerges that the parents were correct all along, and that their children became autistic after MMR or thimerosal-containing vaccination?

Finally, an appeal. If any reader has further published or unpublished scientific evidence - not just personal anecdotes - to suggest that either vaccines/autism are not linked or that they are linked, I would be pleased to receive it.

I would also be particularly interested to learn of any documented cases of completely unvaccinated children who have later dramatically and inexplicably regressed into autism after a normal infancy. To date, no such case has ever been identified to me.

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