ACCESS to JUSTICE
MMR10 - IN EUROPE

EUROPEAN COURT OF HUMAN RIGHS
STRASBOURG-2006

EDITED by KEITH ROBERTS

Trust for Autism

ACCESS to JUSTICE - the MMR10 in Europe – June 2006

Edited by Keith Roberts and by JHR a Barrister

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Editors Note:

As will be apparent the present piece is a collaboration between a great many people and I would like to take this opportunity to thank them all for their valuable contributions. First of all the 'MMR10', parents of the children whose story this is. In particular I would like to thank Harry's mother, referred to throughout the text for professional reasons, simply as 'J H R'. She is the barrister who has given unstintingly of her time and professional advice and who has been truly and literally the group's friend at court . The case is currently on its way to the European Court of Human Rights in Strasbourg. This story could not have been told without her skill and commitment.

Among many others have been Peter Fletcher MD., Andrew Wakefield MD., F. Edward Yazbak MD**,** without exception people who it has been a huge privilege to have known.

Amongst many others I must mention in particular Jackie Fletcher, the founder of JABS, whose services to all victims of vaccines merits a special mention apart from the excellent briefing notes which she and David Thrower have provided.

What follows is the story of MMR 10's struggle to be heard over the clamour of competing claims both of the profit-driven pharmaceutical companies and government's Byzantine political agenda both here and in the US. Through a combination of fear and money they with other interested parties conspired to condemn more than 500,000 (UK) into the hellish limbo of Autism; the cost of which will eventually be picked up by the parents and by society at large.

Before Legal Aid was suddenly withdrawn from families with autistic children who were mounting a legal action against drug companies, the Judge in the case, Mr. Justice Keith, said that the evidence of Prof O'Leary's discovery of vaccine strain measles in the gut and spinal fluids of some autistic children, was 'pivotal to the claimant's case'. This evidence and that of Dr. Wakefield was rubbished by the defendant drug companies and by government medical officers saying the work could not or had not been replicated.

Well now it has been by a team of scientists in the US led by Dr. Steve Walker at Wake Forest University School of Medicine in North Carolina. Now there is evidence from two separate cohorts of children, and two separate teams of researchers, that the vaccine strain measles virus is present in these children. It remains to be seen if the European Court of Human Rights will accept the expert scientific evidence which daily accumulates.

At the heart of the matter lies the question of *informed consent*. Informed consent is a legal condition whereby a person can be said to have given consent based upon an appreciation and understanding of the facts and implications of any actions. On the one hand the government's medical establishment, say only that vaccination may carry with it the slightest possible risk of headaches and minor temporary inconvenience. On the other hand the pharmaceutical companies anxious to disclaim any liability admit some side-effects may be unavoidable. The World Health Organisation on the other hand acknowledges risks which they say *"since the inception of vaccination it has been recognized that adverse events following immunization will occur".*

Dr. Ley, as we quote (see 07.0), places the responsibility for vaccine damage firmly in the lap of the Government and we earnestly hope that this message will get through and will offer some hope of relief to the children afflicted by this terrible and avoidable condition.

Harry has provided the pictures in this book.

Autism apart from Life _ Autism a part of Life

01.0

The MMR10 Go Forward to Europe.

Procedures in UK and Europe

In October 2005 and in January 2006 the MMR10 presented evidence showing a link between MMR and ASD/IBD to the High Court and Court of Appeal in London,.

Compelling evidence was heard from John Hopkins and New Jersey universities in the USA and from Dr Peter Fletcher (published in the Mail on Sunday in February 2006), as was also the Dan Olmsted evidence of the Amish and other exclusive committees in the USA which do not vaccinate their children. In those communities autism is unknown. This overwhelming and significance evidence is part of the MMR 10 story 'IN HARM'S WAY'.

UK Courts ignored that evidence and relied instead on the contention that the Legal Aid Funding Review Committee was entitled to deny legal aid to the MMR10 children thereby denying them all access to justice. The Trust for Autism places this evidence in their book 'IN HARM'S WAY' for all to see.

Now the MMR10 will go forward to the ECHR. A mother asked at the London Court hearings if legal aid is not for injured and most vulnerable children what is it for ?

The story of the MMR 10 and the world's ASD/IBD children is one of the greatest medical/legal scandals of our time. It will not go away. This book 'ACCESS TO JUSTICE' is to bring that story of the pharmaceutical and government nexus, often meeting in closed session, out into the open.

As described in 'IN HARM'S WAY-The MMR Story' Book I of the series: The

consequence of the withdrawal of legal aid from the MMR 10 and the 1000 or so other cases which were proceeding to a trial of the MMR: Autism/IBD link was catastrophic for the families of the children involved.

£15 million had been spent in legal aid fees up to that point, in preparing the case for trial. Less than £1 million was spent on the 28 expert witnesses who prepared their reports for the claimants. The rest went to the several firms of lawyers involved in representing the children. Not a penny went to the children themselves.

When legal aid was withdrawn from the families the children were left alone to disentangle themselves from the complex legal web which could still prove financially disastrous for some of them in costs.

As Mr. Justice Keith, the judge appointed for the original trial stated the way this was done was hardly a good advertisement for British Justice.

Three of the MMR 10 children's families are seeking to fight to take the case to trial, even though they are at serious risk on costs which might even bankrupt their families.

The rest in including JHR the barrister mother of H, think it is better to take their fight for justice via Judicial Review of the decision to withdraw legal aid to the European Court of Human Rights(ECHR). This is on the basis that since the trial has been denied them in the UK, they should be a compensated for denial of access to justice the ECHR.

To get to that point they have mounted a strong challenge in the High Court and Court of Appeal, including a rehearsal of the expert evidence which they say should have won them their case if it had had gone to trial.

JHR also considers and it is her professional view that the trial cannot

succeed without the evidence of the 28 expert witnesses.

Now there is further evidence from the US backing Dr Wakefield's original findings of 1998 findings in 1992 in the form of the latest Walker/Krigsman report.

However all these witnesses would need to attend court in the cases of the children fighting on alone, M, T and W; and to do so they would require payment for accommodation in London and all their travelling and other expenses and while the trial proceeds. That would prove most expensive as most experts come from across the world, particularly from North America.

Also without legal aid there is no protection for the claimants in costs unless they succeed outright. Despite the merits of their claim they are up against the combined might of the world's most powerful pharmaceutical companies with that their boundless budgets and an army of lawyers. On one day in the High Court at a pre trial hearing JHR was opposed by a cohort of 32 lawyers. Where then is equality of arms?

The MMR 10 and others took their case via the Funding Review Committee, the appeal body of the Legal Services Commission; then to the High Court and the Court of Appeal in the form of a Judicial Review application. There they sought damages for being denied their rights of access to justice under the Human Rights Act 1998 which incorporates the European Convention of Human Rights UK in Law.

They invoked Article 6 of the Convention, i e denial of access to justice (denial of trial of the case as a result of legal aid having been withdrawn. They also claimed breach of article 8, respect for family life, as an the injuries these children have sustained have had catastrophic consequences for each of the family involved.

They also claimed breach of Article 14 which forbids discrimination, as one or two ASD/IBD children were granted legal aid to continue their cases. One of those has withdrawn; the other's solicitors has withdrawn from the case leaving the family in limbo. We shall report further on this in a later book covering the results of the case the European Court of Human Rights, and the updating of the story of the MMR10. This is due to be made into a film in 2006.

The MMR 10 had to go via the UK High Court and Court of Appeal in order to exhaust their remedies before applying to the ECHR, which they are in the process of doing.

There is a time limit for the application to the ECHR of six months from the date of the Court of Appeal decision on 28th February 2006. The case will be submitted to the ECHR in the summer 2006 . The basis of the claim is again that the MMR 10 seek compensation for denial of access to justice (as the trial was denied and did not take place) as a consequence of being denied legal aid. Articles 6, 8, 14 and others are invoked in taking the case to ECHR.

The ECHR is not the EC Court, the European Court of Justice sitting in Luxembourg, which tries matters between EC states, often competition law. The ECHR has jurisdiction over human-rights in accordance with the European Convention and other international laws for the countries of the Council of Europe.

The ECHR sits in Strasbourg. It is and has been since 1950 the court of last resort in matters of human rights for the citizens of Council of Europe nations. These rights are set out in the European Convention of Human Rights itself , and accompanying European and UN Conventions.

The Human Rights Act 1998 has brought the European Convention on Human Rights directly in to UK Law; yet there is still a right to apply from the

UK courts once remedies are exhausted, direct to the ECHR.

The UK courts decided only that the Legal Services Commission(LSC) were entitled to decide as it did in withdrawing Legal Aid from the MMR 10, i.e. that the LSC had the power to do so.

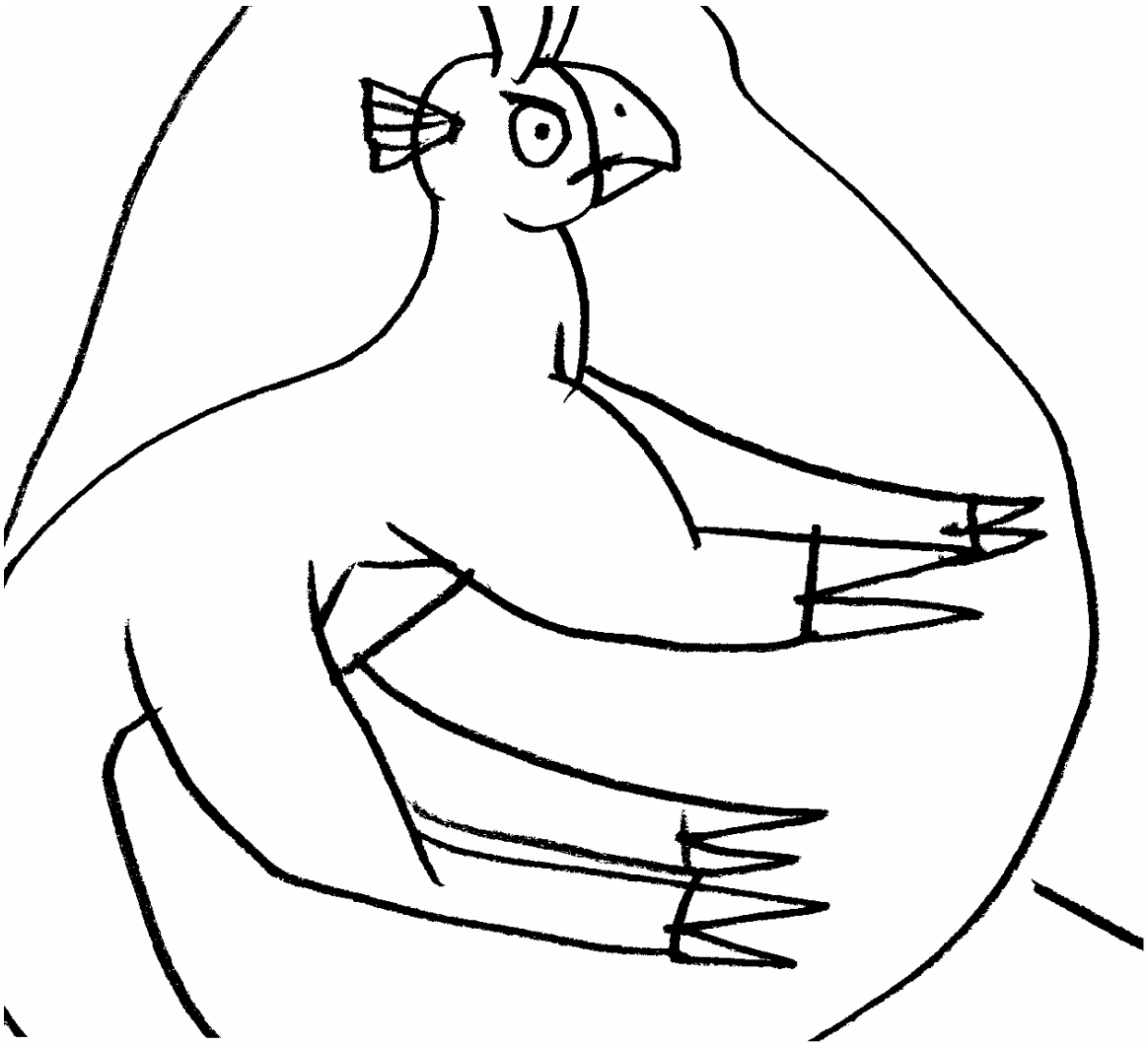
What the MMR 10 is seeking, (and an appraisal of the evidence for trial forcefully presented to the UK courts to show that they had a strong case), is for the proper trial of that evidence.

The MMR 10 say that without such a proper trial of the case, we should have taken place in the UK, they have been denied access to justice. Therefore their children should be a compensated a line with the damages which they were likely to have received if the trial had preceded in the UK.

On the basis of their evidence which was strong, they were most likely to have succeeded in proving, on the balance of probabilities, that the MMR jab caused the children's ASD/IBD.

The MMR 10 case which is now to be filed shortly before the ECHR will receive reference number and acknowledgement once it is submitted. It will then be scrutinised by a Judge rapporteur or will report a committee of three Judges. If it passes that hurdle it will go before a chamber of 7 Judges who will decide whether case meets admissibility criteria for the Court.

Further reports will follow in the forthcoming Book III ‘Judgment at Strasbourg’.



02.0

MMR Vaccine Controversy- JABS Briefing Note (UK) - April 2006

JABS group founded in 1994 as serious vaccine problems were reported:
When the JABS group was founded in January 1994 parents contacted us with their concerns about their children's serious ill health following childhood vaccinations. We asked parents to complete questionnaires on the vaccines given and to describe in detail their children's experience.
We were astounded by the responses. Parents stated the number of days after MMR vaccination when their children had started to become ill and in many cases the number of days quoted were consistent with the incubation period of the vaccine viruses given. Many of the symptoms described were listed in the vaccine manufacturers' own product sheets.
The parents reported that their children had suffered serious consequences after the initial symptoms and had not recovered to the health point they had had before the vaccination was given. The most remarkable aspect of this is that the long term serious health problems that the children now have were also, in the main, listed in the same drug product sheets as the 'rare' events known to be associated with the vaccine.

MMR vaccine introduced into UK vaccination schedule 1988:
Three brands of MMR vaccination were introduced into the UK childhood vaccination programme in October 1988. The vaccines were heralded as a one-off, life-long immunisation against three serious diseases, measles, mumps and rubella. The manufacturers' were SmithKline Beecham, brand name Pluserix , Merieux, brand name Immravax and Merck Sharpe, Dohme, brand name MMRII.
SmithKline Beecham and Merieux used Schwartz strain measles, Wistar RA27/3 strain rubella and Urabe AM9 strain mumps. Merck Sharpe Dohme used Enders' Edmonston strain measles, Wistar RA 27/3 strain rubella and Jeryl Lynn strain mumps.

The UK adverse event surveillance system - 'yellow card':

We asked each family if their child's doctor or consultant had reported the symptoms and change in the child to the UK's Committee on Safety of Medicines, using the adverse events surveillance mechanism known as the 'yellow card' scheme. The vast majority responded that the health professional had declined to use the reporting system as he/she had dismissed the link with the vaccination as 'just a coincidence'. Therefore, the suspected reactions had not been put forward to the central body for detailed investigation.

In theory the system should work to flag up any serious problems with drug products - the guidelines note that all suspected reactions should be reported. In practice the system was largely ineffective because health professionals made their own arbitrary decisions on whether to report the problems.

The Health Protection Agency in its former role as Public Health Laboratory's Service is on record in the Lancet (Vol. 345. March 4, 1995) stating "....there is an urgent need to find more reliable methods of adverse event surveillance." The point being that unless all reactions are put forward to a central body instead of being dismissed as "unrelated" or "just a coincidence" the central database will never hold accurate information on adverse events. How many coincidences are needed before it becomes meaningful enough to warrant scientific, clinical investigation?

Investigations:

Families have urged their medical practitioners who are dealing with their children's problems to investigate the suspected connection with the vaccinations. Some parents have also reported that the doctor/consultant was not interested in finding the reasons for the child's ill health, stating that their role was to treat the problem and, therefore, they did not want to be involved in this aspect.

During the course of the JABS group investigations we have discovered that the UK pre-introductory trials for MMR were inadequate in that they failed to follow up adverse reactions for more than just a few weeks. Serious degenerative conditions are known to take weeks and/or months to develop.

Withdrawn MMR brands:

Proof of inadequacy is in the knowledge that it took the Department of Health four years to identify problems and withdraw two of the three original MMR brands that had been introduced into the UK vaccination programme in 1988. These two brands, Pluserix and Immravax were withdrawn by September 1992 because they contained a mumps strain known as Urabe which had caused mumps meningitis in some children. Many of the badly affected children known to JABS have had these brands of MMR. It is also of concern that this problem must have been known by the UK's Department of Health Chief Medical Officer: The licence for the MMR vaccine containing the Urabe strain in Canada was revoked from May 1990. In Japan it was banned in 1993.

A version of this vaccine made by Chiron was also withdrawn from use in Italy in March 2006.

Drug manufacturers' product sheets:

The drug manufacturers of MMR vaccines have provided the Government's vaccine policy makers with product sheets which list the adverse reactions known to be associated with their vaccines. These lists are virtually identical from each of the drug companies. They state the minor side effects which doctors are happy to describe to parents: namely - rashes, raised temperature etc. These same sheets also state reactions only recently acknowledged in public by the Health Protection Agency e.g. febrile convulsions, blood disorders (ITP). The information sheets also state the severe adverse events: to name but a few - diarrhoea, nerve deafness, arthritis, Guillain-Barre syndrome (a paralysis syndrome), severe vision problems, seizures and encephalitis. Encephalitis (inflammation of the

brain) can lead to a range of disabilities such as epilepsy, loss of speech and communication and acquired autism.

Responsibility for vaccine damage:

Richard Ley, of the Association of British Pharmaceutical Industries said in the Daily Express (May 18 2000): 'The Government implemented the vaccination programme knowing in full detail what the possible side-effects were. They knew what they were taking on, the damage is therefore their responsibility and they should compensate people accordingly.'

The MMR vaccine contains three live attenuated viruses; their major disadvantage is a danger of reversion of the virus strains to more reactive and virulent forms. In plain terms, if the wild virus can cause inflammation in the brain, joints, spine, eyes, ears and bowel then so can the vaccine-virus and to quote an extract from a letter published in the Times (February 9 2002) from Dr David Hall, President of Royal College of Paediatrics and Child Health : 'Some children develop encephalitis (brain swelling) when they catch measles, mumps or rubella viruses and may be left with a variety of handicaps, including physical and mental impairment, deafness, internal organ damage and autism.....'

Raising the issues with UK Government Minister and Health Chiefs:

In October 1997 Dr Andrew Wakefield and Professor Walker-Smith from the Royal Free Hospital, London, JABS and its legal representatives, took part in a meeting with the then Health Minister, Tessa Jowell, also the Chief Medical Officer, Principal Medical Officer and others. During the course of the one hour meeting a full list of children, then affected, was presented. We asked that the Government should instigate a scientific investigation of the children believed to have been damaged which could have been useful on at least two fronts:

i. To answer the question of MMR safety.
ii. If the vaccine was found to be causing harm it may have been possible to identify "at-risk" groups which may have led to a screening programme with the potential to have improved vaccine safety for all children
The Health Minister at the time stated she was willing to look at all scientific evidence but as parents it is very difficult for us to produce this. That is why we believe the current claims by the vaccine policy-makers that there is no scientific evidence to show the MMR vaccine is unsafe will continue to be made. Until the Government instigates a full investigation of the children believed to have been damaged, the "scientific evidence" required by the Department of Health is unlikely to emerge.

Vaccine Damage Payment Act 1979:

The Government is well aware that vaccines can cause severe damage; there is a branch of the Department of Social Security known as the Vaccine Damage Payment Unit. It was set up in 1979 following the Vaccine Damage Payment Act 1979. MMR vaccine damage payments have been awarded for various adverse effects including: epilepsy, Guillain-Barre syndrome (a paralysis condition), SSPE (a brain-wasting condition), neurological problems, profound deafness and death.

US experience:

Any debate on vaccine damage will have Department of Health officials quoting the massive number of doses given to children in the United States. What is never stated by UK officials is that in the US they have a National Vaccine Injury Compensation Programme. In the last 18 years this program has paid out hundreds of millions of dollars in payments to vaccine damaged children of which a 14% share has been paid out for MMR or its components. The drug companies have to contribute to the programme and up to August 1997 they had to pay an excise tax on each dose using a risk-based formula.

The DTP and MMR were taxed at $4.56 and $4.44 respectively, polio vaccines at $0.29 and DT (diphtheria/tetanus) vaccines at $0.06. This must surely give an indication of which vaccines carry the highest risk of a serious adverse reaction.

Japanese experience and compensation:

The MMR vaccine was introduced into the Japanese health programme in April 1989. Shortly after its introduction Japanese parents started to complain to the authorities that their children were suffering severe neurological damage. The Japanese Government failed to act. Many parents started to reject the MMR vaccination for their children and the Japanese Government continued to ignore public concern. Outbreaks of measles then occurred and, unfortunately, it was the most vulnerable group in society, babies under twelve months of age and too young to receive a measles vaccine, that were hit hardest and 69 deaths were recorded.

The Japanese Government banned the MMR vaccine in 1993 and introduced a policy of separate measles and rubella vaccines. (The single Urabe mumps vaccine would not have been accepted as it had been held responsible for the neurological damage when combined in the Japanese MMR vaccine.) The Japanese MMR court cases were heard in March 2003. Over 1,000 children were awarded MMR damages against the Japanese Government and the Research Foundation for Microbial Diseases at Osaka University in Suita, Osaka Prefecture.

MMR and Autism:

The statement that the health secretary, John Reid, made on GMTV in November 2003: "It is unequivocal that there is no evidence at all that MMR is linked to autism." needs to be challenged. World experts in the field of virology and pathology have replicated results found by Dr Wakefield's team when he

was at the Royal Free Hospital, London and other independent Japanese scientists have also duplicated the findings. (Ref. 1 below)
Children who have developed autism, epilepsy and other neurological conditions were progressing normally before they were vaccinated, had passed all milestones and had acquired skills appropriate to their age.
* They did not simply fail to progress; they actually regressed, losing skills which they had already attained. In many instances this is borne out by videos taken of the children before and after they were vaccinated.
* They showed other physical changes at the time that they became autistic (such as sleep patterns, appetite changes, temperature control etc. in addition to many of them suffering bowel problems).
* The development of autism and other conditions are closely linked in time to the administration of the vaccine. The onset of this condition generally started within about a month of vaccination whenever the vaccination took place. In other words, it would be later for children vaccinated at 18 months than those vaccinated at 12 months. On top of that a substantial proportion of the children had an immediate reaction to the vaccination, and the change which came over them dates directly from that reaction.

For more information on MMR, Thimersoral, Autism connection please refer to the home page of JABS (www.jabs.org.uk <http://www.jabs.org.uk>) and http://www.putchildrenfirst.org/

MMR Legal Cases:

Unfortunately, the UK MMR victims had their legal aid stopped just six months before the cases were to be heard at the High Court in April 2004. In some cases legal aid had been provided for nearly ten years to children with wide ranging health problems including autism, epilepsy, loss of speech and communication skills, chronic arthritis and deafness.
Each family had to personally apply to try and prevent their child's legal aid certificate from being discharged. In the interest of justice, these children

deserve to have the issue of MMR safety resolved in court and for this reason families need the help of legal aid.

* Many parents believe that the withdrawal of legal aid prior to the court cases being heard was another way to delay or prevent access to justice for vaccine damaged children. The families' representatives were able to present to the legal aid appeal committee (the Funding Review Committee) evidence not only that measles virus had been found in cerebro-spinal fluid (CSF) taken from three out of six of the test cases, but also that it had not been found in 19 out of 20 controls. If the measles virus is in the CSF then it must almost certainly be in the brain. Bearing in mind:

* that these children, suffer from a form of brain damage.

* that measles is known to be able to cause brain damage and

* that no other cause of autism has been suggested for the overwhelming majority of the families involved

Adding to the stress of this situation, one of the MMR drug companies had sent some parents a letter offering not to seek costs against the child or them if they signed an undertaking "not to issue any further proceedings arising out of vaccination with MMR against them in this or any other jurisdiction".

The MMR court cases were and still are vital not only to the families involved in the pursuit of justice for their children, but for all parents who are concerned about whether the vaccines they are giving their healthy children are safe. JABS believes the Government can no longer claim that MMR is the "safest way to protect your child" as they have denied the parents an opportunity to have all the information out in the open and heard properly. Until the evidence is formally presented in court the question mark over the issue remains.

At the moment (April 2006) a small number of parents have had MMR legal aid certificates re-instated for their children. Also, ten families who lost their appeal plan to take their children's cases to the European Court of Human Rights.

Single vaccines:

The Government's Chief Medical Officer needs to reconsider the availability of single dose vaccines as a matter of choice. If there is a potential for measles epidemics they must provide a real choice for those parents who have lost confidence in the combined MMR but still want to vaccinate against the separate illnesses. It should not have to be MMR or nothing situation.
It does not require new legislation it just needs the Department of Health to place orders with the drug companies currently supplying the UK market with the MMR vaccines.
When the MMR vaccine was introduced into the childhood vaccination schedule the doctors' Green Book, 'Immunisation against Infectious Disease' clearly stated: 'MMR vaccine will replace measles vaccine in the second year of life, or after this age if appointments have been missed. For children whose parents refuse MMR vaccine, single antigen measles vaccine will be available'. (Page 60, 10.2 Recommendations) Reference to this choice appeared in the 1988, 1992 and 1996 editions of this book. Why has this option been quietly removed without explanation?

Cochrane Review:

A study by the respected Cochrane Library (October 2005) has said, on the basis of 31 pieces of research into the possible side effects of MMR, that it found no association between MMR, autism, Crohn's disease and long-term disability.
The Department of Health is hailing it as another 'final nail' in the MMR controversy but there is another side to this that they have missed.Since the MMR vaccine was introduced in 1988 many parents have complained publicly that they believe their children have been seriously damaged by MMRvaccine. Each time the Dept of Health have cited many reports as being conclusive proof that the vaccine is both safe and effective. It is important to note that the authors of the Cochrane Review have scrutinised 5,000 related studies and in

this context found the majority lacking. Only 31 of the 5,000 studies were thought to "possibly fulfil their inclusion criteria".

The Cochrane Review is a significant piece of work because it actually exposes all the 5,000 related studies as being inadequate in some way, as all fail to find any link with long-term disability for which compensation has been paid or acknowledged by the vaccine manufacturers in their own product sheets.

Of course the MMR vaccine is responsible for long-term disability in some children. All drug products have the potential to cause both minor and serious adverse reactions one has only to read the manufacturers' product information sheets to be aware of this.

Vaccine damage, and in this case, MMRvaccine damage has been recognised by Governments, three examples are:

1. The US Govt has a National Vaccine Injury Compensation Programme and 14% of all claims have been paid out to children damaged by MMR vaccination.
2. The Japanese authorities have paid out substantial compensation to parents of MMR vaccine damaged children after a successful court case in March 2004. (There is an on-going UK case.)
3. The UK Government has a Vaccine Damage Payment Unit which has paid out hundreds of thousands of pounds to children affected by childhood vaccines including MMR vaccine.

Many children who suffer adverse reactions are individually assessed by Government doctors' panels. These panels determine the reported adverse event and association with vaccination (known to the manufacturers) and make recommendation for compensation for the individual. The criteria used is extremely high and compensation awards are not made lightly.

For the medical authorities now to conclude that this review gives the MMR vaccine a clean bill of health does a great injustice to all those children who have been awarded vaccine damage payments by ignoring their

existence.

It will also bolster those that sustain the failed passive vaccine reaction surveillance system which continues to ensure very few reactions are put forward or recorded in medical data. It is this poor data that was used in many of the reports reviewed by Cochrane which they identified as inadequate. Therefore a continued cycle of failure by the medical authorities to identify and reduce vaccine adverse events in children will be assured.

For the Department of Health to continue trying to convince parents, many of whom have family and friends with children believed to have been affected by MMR vaccine, exposes them to being blind to the reality.

Summary:

In our opinion the current Government has failed in its duty of care. At the meeting in 1997 the Health Minister should have instigated a scientific study of the children believed to have been damaged to discover why the children's lives changed so dramatically within such a short time of MMR/MR vaccine being given. Since that meeting the reports of MMR/MR damaged children to JABS has greatly increased.
The issue of safety surrounding the MMR vaccine has not yet been resolved. The Department of Health have relied on epidemiological studies as their basis for stating the vaccine is safe. These studies are not designed to collect data on 'rare' events.
The Department of Health has failed to adopt the precautionary principle. Until the question of MMR safety is resolved the option of single dose vaccines should be made available for parents who have lost confidence in the combined vaccine.
A question that must be asked of the present Health Minister is: if the drug

companies have informed the Department of Health's doctors of the known vaccine problems and parents have informed the doctors that these problems are occurring. Why is the Department of Health denying the problems and ignoring the parents?

It could be argued that the vaccine manufacturers have a duty to provide compensation, as they have to in the United States by contributing to the US National Vaccine Injury Programme. The pharmaceutical industry profits from the supply of vaccines to the UK and also, ironically, from the victims because they produce the anti-convulsants, pain killers and other medical products these children need. At the moment however, in the UK, they do not contribute financially in any way to the vaccine damage payment scheme. The UK Vaccine Damage Payment Act 1979 has gone some way to address the issue. Unfortunately, because the criteria are so strict most families cannot access justice for their children through this Government scheme and therefore it is relatively ineffective. Until a compensation programme similar to the US scheme is implemented in the UK, parents will seek redress through the courts and for this reason families need the support of legal aid to pursue justice. Legal aid should be re-instated.

Critics of the JABS group must think of this: If our members had been anti-vaccine lobbyists our children would not have been taken for vaccines and subsequently damaged. We are parents who put our faith in the UK healthcare system; our children have reacted usually in the time frame known to the manufacturer and, in the main, are living with long term problems also known to the manufacturer. We want the children to be recognised and compensated and clinically investigated to help develop a screening programme to improve vaccine safety.

JABS believes in a safe vaccination programme but the emphasis is on safe and reducing risk wherever possible.

References:

Ref. 1: MMR and Acquired Autism (Autistic Enterocolitis) - A Briefing Note by David Thrower March 2006 http://www.jabs.org.uk/pages/Autism_Review.pdf

Relevant Extracts:

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

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

* Solution phase RT PCR yielded specific MV N gene amplification in affected children (10/10)
* Distinct measles virus genome was identified in FDC reactive follicular centres by in-cell RNA amplification
* None of the normal controls showed any evidence of measles virus genome
* The data highlighted a possible causal link between measles virus infection and ileo-colonic lymphoid nodular hyperplasia in affected children

96. 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,

(1) was measles virus present in gut biopsies of affected children?
(2) where was measles virus located in the gut biopsies of the affected children?
(3) how much virus was present?

* The O'Leary team used in-situ hybridisation (with/without tyramide signal amplification), in-cell PCR, solution-phase PCR, TaqMan quantitative PCR and DNA sequencing to determine the answers to these questions.
* Using TaqMan PCR the team was able to quantify the measles virus copy number per 1,000 mucosal cells using gene dosage correction formulations. The copy number of measles virus in gut biopsies from children with autistic enterocolitis was low, at approx. 30-50 measles virus genomes per 2,000

mucosal cells (inc. Gut, epithelial, lymphoid and dendritic cells).
* Confirmation of the presence of measles virus genomes was achieved using positive and negative strand sequencing of cDNA measles amplicons.
* The results were that 24 out of 25 (96%) of the autistic children were positive for measles virus, including 2 children from the USA who were included in this analysis
* In the controls, only 1 of the 15 children (6.6%) was positive for measles virus.
* The study therefore localised, quantified and sequenced measles virus genomes in gut biopsies of children with autistic enterocolitis. The study team then posed the question, "how did it get there?".

97. Paper by Kawashima, Takayuki et al, Detection and Sequencing of Measles Virus from Peripheral Mononuclear Cells from Patients with Inflammatory Bowel Disease and Autism, Digestive Diseases & Sciences Vol. 45, No. 4, April 2000, pp723-729 Following reports that measles virus might be present in the intestines of children with Crohn's Disease, a new syndrome was reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases after MMR vaccine, was reported (see papers by Wakefield et al). It was not known whether the virus, if confirmed as present in these patients, derived from wild strain or vaccine strain.

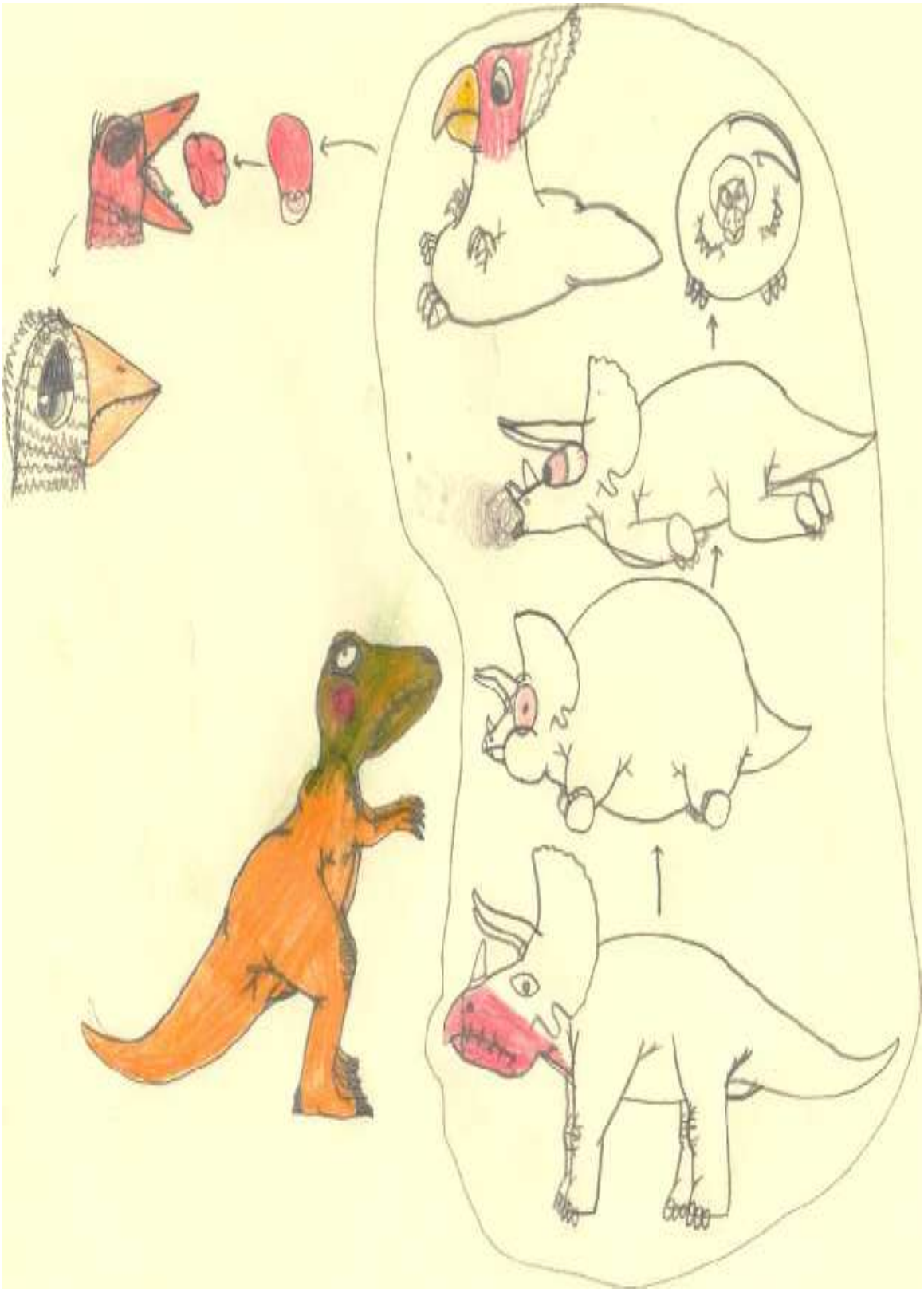
This study carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in 8 patients with CD, 3 patients with UC and 9 patients with autistic enterocolitis. As controls, the study used 8 cases of either healthy children or children with SSPE, SLE or HIV-1. The results were:

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

*These results were consistent with the exposure history of the patient. This study is obviously particularly important because it points to infection with vaccine-strain measles virus.
Detection of Measles Virus Genomic RNA in Cerebrospinal Fluid of Children with Regressive Autism: a Report of Three Children J.J. Bradstreet, M.D., J. El Dahr, MD, A. Anthony M.B., PhD, J.J. Kartzinel, M.D., A.J. Wakefield, M.B.

Ref. 2:

http://www.who.int/vaccine_safety/causality/en/



03.0 **SUBMISSIONS TO ECHR**

II Statement of facts for the European Court of Human Rights

This Application to the European Court of Human Rights is on the basis that the 10 child Applicants, all of whom suffer from ASD/IBD allegedly caused by MMR vaccines, have been denied access to justice. See Schedule of Claimants attached.

They were deprived of a trial by legal aid having been withdrawn by the Legal Services Commission in the summer of 2004. The Funding Review Committee rejected their divers appeals against the withdrawal of funding in October 2004. Subsequently judicial review of that decision was sought in the High Court, and renewed in the Court of Appeal, on both occasions unsuccessfully.

Some £15 million had been spent preparing the case of over 900 ASD/IBD children to go to trial, funding originally having been granted for these cases in the mid-1990s and later.
Generic legal aid was withdrawn in the summer of 2003. The claimants were not involved in that decision or its Judicial Review challenge in any way. JHR ('JHR') was denied the right to appeal the JR decision which was taken on behalf of a lead Claimant who then declined to appeal.
That lead Claimant acted as a sample, not as a representative of the group, as JHR was informed by her child's then Solicitors. These 10 Claimants therefore had no locus standi in, and could not be bound by that decision.
The withdrawal of legal aid meant that the trial could not go ahead, as expert witnesses could not be paid for without legal aid; nor the necessary team of lawyers to ensure a level playing field against powerful pharmaceutical companies. Nor would the Claimant families be protected in costs without legal aid.
Denial of legal aid deprived the children of access to justice in a case of worldwide significance as well as of the utmost importance to these severely

injured children. The decision was disproportionate not only by virtue of the outstanding importance of the trial but also on the basis of relatively small projected further expenditure necessary to bring the case to trial. The then solicitors' estimate was £10 million more to include further research. We claim that the evidence as it stood was enough to prove causality on the balance of probabilities.

Moreover the decision was disproportionate by virtue of other expenditures by the Legal Services Commission-for example some £250 million was spent on non¬ national asylum seekers cases in 2005 alone. This was cited to the Court of Appeal by one of the parents at the hearing.

The present case concerns not only these children, but those of Europe, and the world, as there is now a worldwide epidemic of regressive autism, as to which evidence is included in the papers in this Bundle now before ECHR. It is to be hoped that similar cases will reach the ECHR from other countries within the ECHR jurisdiction. The combined effect of such cases will it is hoped impress on the European Court that it is dealing with one of the greatest medical/legal scandals of all time. Access to justice has been denied to some of Europe's most vulnerable children.

Access to justice is a small request to make, and a basic right. These children have been denied justice by the UK and now seek assessment of damages for denial of their basic right under Article 6 of the Convention; also under Article 8 as the family lives of these children have been devastated as a consequence of their injuries (see the parents witness statements); also Article 14 as some of those granted legal aid were ASD/IBD sufferers, and these Claimants have been unfairly discriminated against.

The Claimant children also seek to challenge the 10 year limitation period of the UK Consumer Protection Act 1987 as was mentioned in the Court of Appeal hearing.

As the European Parliament and the UK Law Commission have argued the limitation period for consumer protection cases should be extended very substantially or related to 'the foreseeable future of the product's use',.

Preferably it should be extended indefinitely in this case. That is the situation for disabled children in negligence cases in the UK, and arguably, and it is so argued, the Consumer Protection Act 1987 should have its limitation period also extended throughout the Claimant children's lifetimes: see Article 6(1) and Article 14 d also protocol 12 and also Article 13 - right to an effective remedy.

III Legal Basis of Application to ECHR

It is submitted that by denying the Applicants legal aid to enable a trial to take place in the UK of the MMR and ASD/IBD link, the UK courts have deprived these children of their right to access to justice.

This is a case of the utmost importance to the world, not only to these children. The decision to deny them a trial of the issue constitutes denial of access to justice, in the circumstances, contrary to Article 6(1) of the European Convention.

Some ASD/IBD claimants (two are known) were granted legal aid to continue their claim, so the LSC/FRC decision was discriminatory against these 10 Applicant children contrary to Article14 of the Convention (see also protocol 12).

The injuries these children have suffered, and consequent devastation of the lives of their families, who struggle to cope, and in relation to which the UK has denied a trial, is also in breach of article 8 of the convention (see the witness statements of the children's parents).

The decisions to deny access to justice by the LSC/FRC, High Court and Court of Appeal, were disproportionate. The Applicants were denied a level playing field (equality of arms) at all stages of the legal proceedings following the abrupt termination of their legal aid in the summer of 2004.

The Applicants were left unrepresented and stranded in the middle of complex litigation. That too marks a breach of their right to access to justice. At no stage has there been a level playing field (equality of arms) in the attempt to continue the litigation against the pharmaceutical companies thereafter.

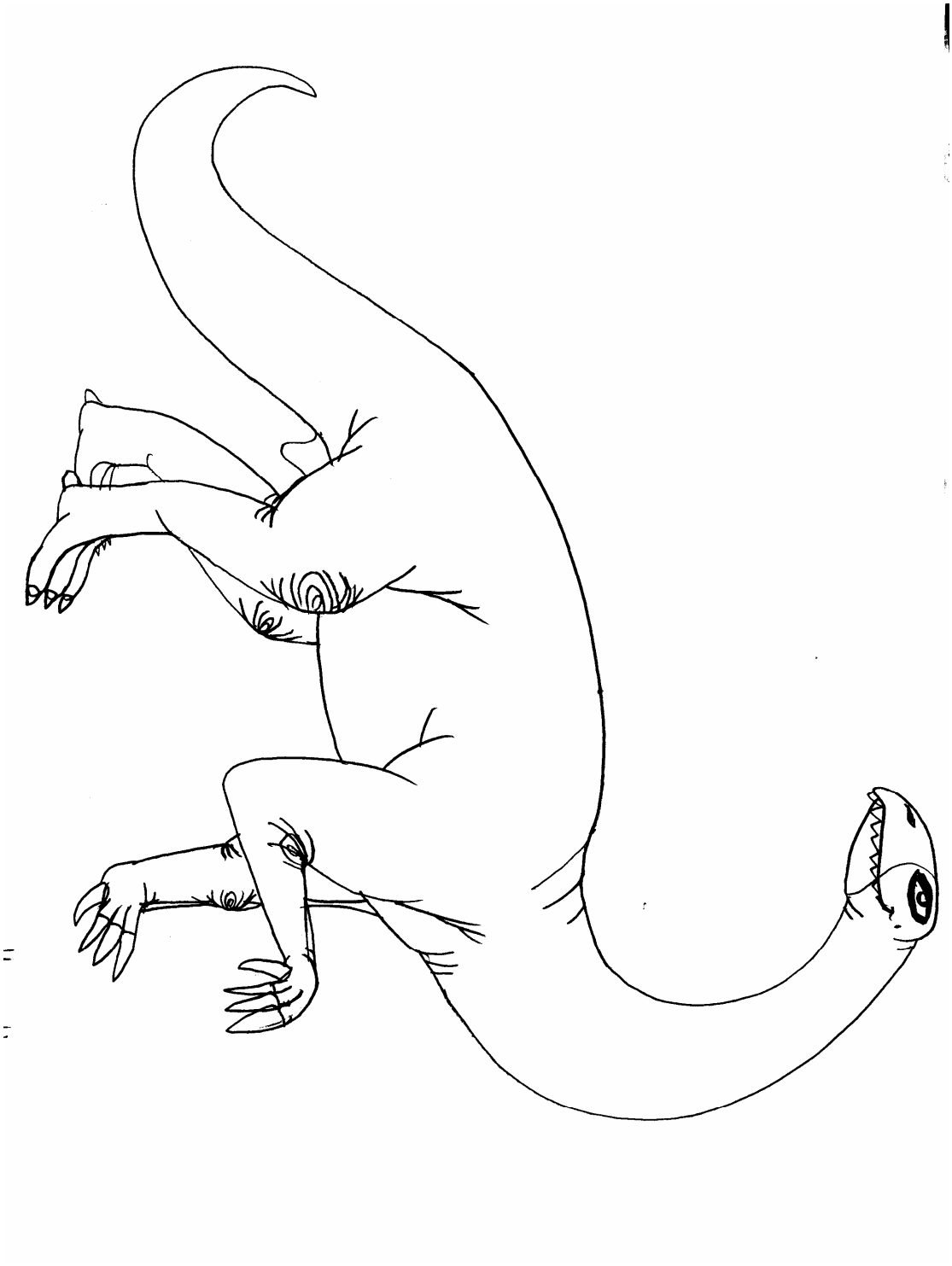
A barrister mother, JHR has taken on the task of furthering this case before the LSC/FRC, in the High Court, Court of Appeal, and before this ECHR without, perforce, the benefit of any assistance from any solicitor. As soon as legal aid was withdrawn the Solicitors previously involved withdrew from and abandoned representation of the Claimants.

This case marks a great scandal in UK legal history for which the Applicants now seek redress under Articles 6, 8, 14 (and Protocol 12) and Article 13 of the Convention, before the European Court.

The limitation period which is 10 years under the UK Consumer Protection Act 1987 is discriminatory, and denies these Applicant children access to justice at any later stage of their lives, if circumstances were to allow, which is also contrary to Articles 6, 14 (Protocol 12) and 13.

The limitation period should be extended indefinitely throughout the children's lifetimes; as is the case with clinical negligence for disabled children in the UK. See also the UK in Law Commission Report 'Limitation of Actions 2001 LC 270'.

It is therefore also submitted that the limitation period of the UK Consumer Protection Act should be declared unlawful by this Court; and a greatly extended limitation period be recommended to replace it.



04.0

Vaccine Update-JABS Briefing -JUNE 2006

JABS CALLS FOR THE SUSPENSION OF THE CONTROVERSIAL MMR VACCINE AS A NEW STUDY CONFIRMS MMR MEASLES VIRUS IN BOWELS OF AUTISTIC CHILDREN

A study due to be presented June 1-3 at the International Meeting for Autism Research (IMFAR) in Montreal, Canada, has confirmed the finding of a link between MMR vaccine and childhood autism. The study has confirmed the previous UK/Irish findings of measles virus in the inflamed intestinal tissues of children with autism. The study also confirms that the MMR vaccine was in each case the source of the measles virus.

The study has involved collaboration between:

Dr. Arthur Krigsman MD, a pediatric gastroenterologist specialising in bowel disease in children with developmental disorders such as autism, and formerly of New York University Medical School.
Dr. Steve Walker, a scientist and an expert in molecular biology at Wake Forest University School of Medicine.
Dr. Karin Hepner, a molecular biologist from California and J. Segal.

Medical and clinical data have been collected for over 275 patients who fitted the study inclusion criteria. For each patient, medical histories, vaccination records, histopathology reports and ileocolonoscopic biopsy tissue were available for evaluation.

PCR analysis on terminal ileum biopsy tissue from an initial 82 patients has shown that 70 (85%) are positive for the measles virus f-gene amplicon and14 patients have so far been verified by DNA sequence. An additional 56 are

being sequenced currently. Further work is being undertaken on the remaining specimens and relevant control tissue samples.

The findings of this study should be a cause of the greatest concern, since they are not consistent with the officially-accepted view as to how children are thought to respond to measles vaccine virus. The vaccine strain of measles virus is not expected to remain in the body after vaccination. Previous thinking by vaccine experts is that it should be cleared from the body within 30 days of vaccination. The continued presence of measles vaccine virus in the diseased intestinal tissue of sick children cannot be considered as unimportant or innocuous, given the consistent parental stories of how children regressed into autism following their MMR vaccination.

There is now sufficient evidence for a link between ileal lymphoid nodular hyperplasia and regressive autism, for a link between measles virus and ileal lymphoid nodular hyperplasia, and between MMR and persistent measles virus in the guts of regressive autistic children to warrant urgent clinical investigation of UK children.

VITAL CONSIDERATIONS:
Parental-accounts consistently suggest some children are suffering neurological and gastrointestinal problems following MMR vaccination.

The existing published evidence for an abnormal immune response to measles virus in autistic children, compared with developmentally-normal children.

The consistency of these findings in independent and geographically-distinct populations of children.

Parents are not given all of the information before starting their children’s vaccination programme. They are not, therefore, in a position to give informed

consent. The Department of Health only provides information that describes the minor reactions in relation to MMR; slight temperatures, rashes etc. The Joint Committee on Vaccinations and Immunisations has published MMR reactions, including deaths, for the years 2001, 2002, 2003. (http://www.dh.gov.uk/assetRoot/04/12/01/96/04120196.pdf) The reactions considered as serious numbered 160 in a three year period and "consisted largely of recognized reactions". The final sentence stated: "Overall, the pattern and type of reactions reported does not appear to have changed and no significant safety issues have been identified." JABS is concerned that serious reactions are considered routine by the Department of Health but parents are only informed of the potential for minor reactions.
The Department of Health has failed in its duty of care. It is estimated that only 10 per cent of adverse drug reactions are reported by doctors using the 'yellow card' passive surveillance system. The Government's Health Minister should now instigate a clinical study of the children claimed by parents to have been damaged. Measles virus has been found in the areas of damage in children. Gut biopsies, spinal fluid tests and brain biopsies have revealed measles vaccine virus in children with severe neurological conditions which include epilepsy and autism.

The Department of Health has relied on epidemiological studies (studies of data e.g. GP records, hospital notes) as its basis for stating the vaccine is safe. These studies are not designed to collect data on 'rare' events.

The Department of Health should re-examine the current vaccination programme for children. The MMR should be suspended and single jabs reinstated immediately. We cannot continue to take `risks with our children.

Background Information

This background briefing takes the reader through the clinical evidence for each stage of the autism/MMR issue. The references are listed at the end of the briefing.

A significant number of researchers, in a number of countries around the world, have now also produced corroborative findings that are contributing to the understanding of an extremely complex process.

When the controversial Lancet paper by Wakefield et al appeared in February 1998, almost all of the evidence referenced below did not exist.

The most important aspect is that the evidence listed below, pointing towards an MMR-gut-autism linkage, entirely comprises clinical evidence based directly upon detailed examination of damaged children.

In contrast, the evidence against any MMR-autism link, referenced at the end of these pages, is only epidemiological evidence - desk studies - based upon health records and other data that are often totally inadequate and near-meaningless in the context of a novel and unrecorded disease.

Autism and Autism Increases

Autism is a complex disorder of learning and behaviour, usually starting early in childhood. The number of children diagnosed with autism and related disorders on the autistic spectrum has increased dramatically in many countries during the past fifteen years

Many parents have reported the onset of regressive autism following immunisation , for example during a 2001 US study (2)

A number of independent researchers have reported large recent increases in autism, for example Blaxill in 2001 (3).

A May 2006 statement (4) by the US Centers for Disease Control and Prevention admitted that 1 in 175 US children was autistic, and that some 300,000 children across the US within the 4-17 years age-range now have a diagnosis of autism. The US House of Representatives member David Weldon has commented that “For eight years, I’ve had parents and clinicians coming to me saying we have an epidemic of autism, and may people in Government are reluctant to accept that……..the CDC has really, finally, admitted that we have an epidemic.” (5)

On a proportionate basis, using the US CDC figure, the UK could have an estimated quarter of this number, perhaps 75,000. The Scottish Schools Census (6) has recorded a 325% increase in pupils with a primary diagnosis of autism in seven years, from 820 in 1998 to 3,484 in 2005. If reflected across the UK, on a crude pro-rata basis, this would give a figure amongst school-age children of 38,000, to which would need to be added children under school age and children awaiting diagnosis. The UK total might therefore be in the 45,000-75,000 range for children under 19. Official UK Government data is still at an early stage.

Independent study has confirmed that the observed major US increases are real. A 2002 study (7) by the MIND Institute at the University of California at Davis stated that “the unprecedented increase in autism in California is real and cannot be explained away by artificial factors such as misclassification and criteria changes”, nor by in-migration. The study confirmed firm evidence of a major rise.

A 2003 study by Yeargin-Allsopp, Rice et al (8) and funded by the US Centers for Disease Control found that autism was running at a rate of 1 in 294 amongst children ages 3-10 in metropolitan Atlanta, US, in 1996 (the accepted preponderance of autism amongst males rather than females would mean a significantly higher rate than this would have existed amongst males). The study concluded that the rate of autism was higher than rates found in US studies during the 1980s and early 1990s, but was consistent with more recent studies.

A 2003 study by Gurney, Fritz et al (9) found that, examining special educational disability data from the Minnesota Department of Children, Families & Learning, from 1981-82 through to 2001-02, prevalence rates of autism rose substantially over time within single-age groups, and increased from year to year within birth cohorts, and that ASD prevalence amongst children ages 6-11 years rose from 1 in 3,333 in 1991-92 to 1 in 192 in 2001-02. The same study found that the trend showed no sign of abatement, nor any corresponding decrease in any special educational disability to suggest any diagnostic substitution (re-classification) as an explanation for the trend. It also did not ascribe increases to criteria changes.

A 2003 paper by Yazbak (10) reported that autism had greatly increased across the US. For example, DSM-IV (i.e. profound) autism had increased in California by 97% in the four years up until it being reported by the State Department of Developmental Services in early 2003, compared with increases of only 29% for mental retardation and only 16% for cerebral palsy. Autism across the US as identified by Individuals with Disabilities Education Act data had risen from 12,000 in 1992-93 to 119,000 in 2001-02 (it has since risen to 166,000).

A 2004 review by Blaxill (11) reported that autism in the US increased from less than 1 in 3,333 (3 per 10,000) in the 1970s to greater than 1 in 333 (30 per 10,000) in the late 1990s, a tenfold increase. In the UK, autism rose from less than 1 in 1000 (10 per 10,000) in the 1980s to roughly 1 in 333 (30 per 10,000) in the 1990s. Reported rates for the full spectrum of autistic spectrum disorder rose from the 5-10 per 10,000 range to the 50-80 per 10,000 range in the two countries during this period.

A 2005 study by Newschaffer, Falb et al (12) reported further confirmation of increases, that increase were real and not a case of past misdiagnosis, and were not due to greater awareness or diagnostic switching. Clear cohort differences were apparent, with the greatest increases for birth cohorts born between 1987-92. Diagnostic substitution (re-classification) did not explain these increases. The authors concluded that “the drastic increase in the prevalence of autism classification presents a major challenge”.

The above evidence offers confirmation that autism, a historically relatively rare condition, is now found at a greatly-increased rate amongst US and UK children, and that there has been a real increase. Increased numbers are not down to greater awareness, re-classification, altered criteria, past misdiagnosis or better recognition.

The Link Between Autism and a Novel Form of Inflammatory Bowel Disease

There is now ample evidence, confirmed by independent groups of researchers, of a link between regressive autism and a novel form of inflammatory bowel disease.

The possible association between MMR vaccine, regressive autism and intestinal symptoms was first reported by parents to Dr. Andrew Wakefield, a UK gastroenterologist at the Royal Free Hospital, London, in 1995. The first group of children presenting in this way to Dr. Wakefield and colleagues at the Royal Free were reported in The Lancet as a clinical case series in February 1998 (13). Although the interpretation put on this paper at the time was the subject of intense controversy - particularly in the absence of corroborative clinical research by other researchers at that time - the strong evidence of a hitherto-unreported link between autism and a novel intestinal disease, ileal-lymphoid nodular hyperplasia, has not been disputed, and stands as an important initial clue as to the causes of regressive autism.

A group of researchers led by Horvath (14) subsequently independently reported in 1999 upon patients with autism who had gastrointestinal symptoms, including a study of 36 children with autism that found grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15 (42%) and chronic duodenitis in 24 (67%).

Further research published in September 2000 (15) by Wakefield, Anthony et al confirmed that ileal-lymphoid nodular hyperplasia (ILNH) was found in 54 out of 58 (93%) children with autism or other disorders (50 with autism, 5 Aspergers, 2 disintegrative disorder, one ADHD, one schizophrenia, one dyslexia), but only 5 out of 35 (14.3%) normal controls, pointing to a very strong ILNH-autism link.

Research published in 2001 by Furlano, Anthony et al (16) reported on ileocolonoscopy performed on 21 consecutively-evaluated children with

autistic spectrum disorders and bowel symptoms, and made “blinded” comparisons with 8 children who had a histologically normal ileum and colon, plus 10 developmentally-normal children with ILNH, 15 with Crohn’s Disease, and 14 with ulcerative colitis. The study confirmed a distinct lymphocytic colitis in the children with ASD, in which the epithelium appeared particularly affected, offering further corroboration for gut epithelial dysfunction in autism.

Research reported in 2001 by Buie (17) reported that, as a result of over 400 gastrointestinal endoscopies with biopsies and evaluation of digestive enzyme function, on children with autism, he had found the presence of chronic inflammation of the intestinal tract, although the incidence was less frequent than in the Royal Free Hospital group of patients reported by Wakefield et al, and that biopsy results indicated the presence of chronic inflammation of the digestive tracts, including esophagitis, gastritis and enterocolitis. Ileal lymphoid nodular hyperplasia, as first found by the Royal Free study, had been found in 15 of 89 children examined for it.

A review published in September 2002 by Wakefield, Anthony, Montgomery et al (18) noted that as early as 1986, a researcher named Soddy had noted that recurrent gastrointestinal upsets were a constant feature of autistic children, and that in a systematic analysis of an unselected population of 385 children on the autistic spectrum, clinically-significant gastrointestinal symptoms occurred in 46%, compared with 10% of 97 developmentally-normal controls, strongly suggesting a gastrointestinal-autism link. Mucosal lesions in the small and large intestine were consistent with an autoimmune pathology, and suggested the possibility of an autoimmune response leading to cerebral damage.

A June 2002 presentation (19) by Krigsman to the US Congressional Committee on Government Reform reported that a large percentage of his autistic patients suffered from chronic unexplained gastrointestinal symptoms. Of 43 patients, the majority had a clear history of developmental regression, after previous normal development, suffering gradual or precipitous decline between age 12 months and 18 months. Most regressive children also exhibited poor growth. Patients had undergone colonoscopy. Findings were that the lymphoid nodules of the terminal ileum were markedly enlarged, thus confirming the early work of the Royal Free team. Evaluation of biopsy specimens confirmed that 65% had colitis, 51% had active colitis, 40% had chronic colitis, 7% had eosinophilic colitis, 90% had lymphoid nodular hyperplasia of the terminal ileum, and 35% had neither active nor chronic nor eosinophilic colitis. Patterns of inflammation were patchy and unpredictable, but findings were similar and consistent from patient to patient within affected sub-groups.

A November 2003 paper published by Ashwood, Murch et al (20) reported on the examination of 52 affected autistic children, compared with 25 histologically-normal developmentally-normal controls and a further 54 histologically-inflamed but developmentally-normal controls. Analysis of intestinal biopsies in regressive-autistic children indicated a novel lymphocytic enterocolitis with autoimmune features, though the precise linkage between the finding and cognitive functions still remained unclear. The study concluded that it provided further evidence of a pan-enteric mucosal immunopathology in children with regressive autism, that is distinct from other previously-known inflammatory bowel diseases.

An April 2004 paper by Torrente, Anthony et al (21) identified, following earlier reports of lymphocytic colitis and small bowel enteropathy in children with regressive autism, that the gastritis in regressive autism was clearly distinct

from that in Crohn's and other conditions, pointing to a distinctive form of gastritis being linked with regressive autism.

A November 2004 paper by Ashwood, Anthony et al (22) found that molecules (cytokines) produced by immune cells in the intestine, that cause or control inflammation, showed an abnormal pattern in autistic children compared with non-autistic children. The pattern was different to other forms of intestinal inflammation, and the disease resembled a longstanding viral disease of the intestine, not unlike the intestinal inflammation seen on patients with other viral infections such as HIV-associated enteropathy (intestinal disease) that often accompanies infection with HIV.

A February 2005 paper by Jyonouchi, Geng et al (23) further confirmed the original ileal-lymphoid nodular hyperplasia/regressive autism link first reported by the Wakefield team in 1998. The study again found evidence of marked inflammatory and immune abnormalities in children with autism associated with gastrointestinal symptoms.

An April 2005 letter (24), Pan-Enteric IBD-Like Disease in a Patient with Regressive Autism Shown for the First Time by the Wireless Capsule Enteroscopy - Another Piece in the Jigsaw of this Gut/Brain Syndrome?, reported that a 28-year-old male with regressive autism, severe constipation, bloating, abdomen distension and symptoms of gastroesophageal reflux was examined. Gastroscopy under general anaesthesia revealed hemorrhagic gastritis with inflammatory pseudopolypsthat had reached the pylorum, with a pearl-necklace appearance, and a panenteric IBD-like disease consistent with previously-published descriptions of autistic enterocolitis was finally diagnosed. The wireless capsule images were the first to be obtained beyond

the limits of the duodenum and terminal ileum, and demonstrated the potential for the entire bowel to be implicated in this inflammatory disease.

A May 2005 study (25) by Balzola, Daniela et al reported on 9 consecutive patients (range 7-30 years) with autism and chronic intestinal symptoms (abdominal pain, bloating, constipation and/or diahorrea). Routine blood and stool tests and gastroscopy and colonoscopy with multiple biopsies were performed under sedation, and wireless enteroscopy capsules were used in three of the adult patients. Gastroscopy revealed mucosal gastritis in 4 patients, esophagitis in 1 patient and duodenitis in 1 patient, and histological findings showed chronic inflammation of the stomach and duodenum in 6 patients, inconsistent with celiac disease. The authors reported that preliminary findings were strongly consistent with previous descriptions of autistic enterocolitis, and supported a not-coincidental occurrence. They showed for the first time a small-intestinal involvement, suggesting a pan-enteric localization of this new inflammatory bowel disease.

Also in 2005, a further paper by Wakefield, Ashwood et al (26) was published, assessing ileocolonic lymphoid nodular hyperplasia in ASD and normal control children. Some 148 consecutive children with ASD, with gastrointestinal symptoms, were investigated by ileocolonoscopy, with 74 ASD children and 23 normal controls undergoing upper gastrointestinal endoscopy. The presence of lymphoid nodular hyperplasia was significantly greater in ASD children compared with controls, in the ileum (129 out of 144, compared with 8 out of 27 controls), and in the colon (88 out of 148, compared with 7 out of 30 controls). Comparative percentages were 90% vs 30% and 59% vs 23%. This was whether or not controls had co-existent colonic inflammation. The severity of ILNH was significantly greater in ASD children compared with controls, with moderate-to-severe ILNH present in 98 out of 144 ASD children compared with 4 out of 27 controls; percentages

were 68% and 15%. On histopathological examination, hyperplasic lymphoid follicles were significantly more prevalent in the ileum of ASD children (84 out of 138, or 61%) compared with normal controls (2 out of 23, or 9%). The data thus further corroborated the finding that ileal lymphoid nodular hyperplasia is a significant pathological finding in autistic children.

Additionally in 2005, a study (27) was published by Gonzalez, Lopez et al, seeking evidence of immunological alterations in 68 autistic children ages 22 months to 11 years and presenting with digestive systems, and examining biopsies from their digestive tracts. Endoscopies and colosopies were undertaken, with biopsies of the esophagus, stomach, duodenum and colon, with verification of presence of inflammation, eosiophil infiltration, lymphoid nodular hyperplasia and CD-4 and CD-8 cells. The results were that lymphoid nodular hyperplasia was discovered in 2/68 esophagus, 6/68 stomachs, 8/68 duodenums and 36/68 (53%) of colons. Eosiophil infiltration with more than 20 eosiphils per field were found in 3/68 eosphagus, 1/68 stomach, 8/68 duodenum and 24/68 (35%) colons. Inflammatory reactions were found in 56/68 (82%) esophogitis, 64/68 (94%) gastritis, and all (100%) presented with duodenitis and colitis. CD-4/CD-8 relationship existed of >3 in 42/68 (62%) and <1 in 16/68. The authors concluded that the children presented immunological and immunohistochemical alterations of the biopsies of their digestive tracts, and that there was a significant finding of lymphoid nodular hyperplasia, eosiophilinfiltration, and that prevalence of greater CD-4 than CD-8 cells in the inflammation of the intestinal wall demonstrated in favour of a Th2 type allergic reaction.

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

The Link Between Inflammatory Bowel Disease and Measles Virus

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

A study (28) published by Uhlmann, Sheils et al found that measles virus nucleoprotein (N antigen) was detected in association with follicular dendritic cells in patients.

A paper (29) presented in 2000 by Singh to the US House of Representatives Committee on Government Reform reported a hyperimmune response to the measles virus, with an association between measles virus antibody levels and incidence of brain autoantibody.

An April 2000 paper (30) presented by O'Leary to the Committee on Government Reform reported the investigation whether measles virus was present n the gut biopsies of autistic children, and if so, where and how much. The paper reported that the biopsies of 24 out of 25 (96%) of the autistic children examined were positive for measles virus, and that amongst normal (non-autistic) controls, only 1 out of 15 children (6.6%) were positive, strongly suggesting a connection between measles virus and autism.

A February 2002 paper (31) by Uhlmann, Wakefield, O'Leary et al investigated the presence of persistent measles virus in the intestinal tissue of 91 autistic patients with new-variant inflammatory bowel disease (ileal-lymphoid nodular hyperplasia, or ILNH). Patient samples were provided by the Royal Free Hospital, London. The patients were ages 3-14, and 77 out of 91

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

A February 2004 paper (32) presented by Singh to the US Institute of Medicine, Washington DC, measured antibodies in autistic children to five viruses, measles, mumps, rubella, CMV and human herpes virus 6. Researchers found that the antibody level of the measles virus alone, and not the other four, was significantly higher in autistic children than in normal children. The research also found a correlation between measles antibody and brain autoimmunity, which was marked by myelin basic protein antibodies. The two markers correlated in over 90% of the autistic children tested for them, suggesting a causal link between measles virus and autoimmunity in autism. The serology to other viruses and other brain autoantibodies did not show this correlation. This suggested a temporal link of measles virus in the etiology of autism.

Taken with the present study by Walker, Hepner et al, this provides significant evidence for a link between measles virus and ileal lymphoid nodular hyperplasia, with the latter's already-demonstrated onward link with regressive autism.

The Link Between Measles Virus and Vaccination with MMR

A July 2002 paper (33) presented by O'Leary reported that the strain of measles virus used in MMR had been detected in the gut tissue of 12 autistic children. Medical histories had indicated that each of the children had developed autism after the date of receipt of MMR, and none had exhibited outward signs of measles infection before becoming autistic
An April 2000 study (34) by Kawashima, Takayuki et al confirmed that, amongst 8 patients with Crohn's Disease, 3 patients with ulcerative colitis and 9 patients with autistic enterocolitis, and 8 children who were either healthy or who had SSPE, SLE or HIV-1, 1 out of 8 patients with CD, 1 out of 3 patients with UC and 3 out of 9 patients with autism were positive for measles virus. Controls were all negative. The sequences from patients with CD shared the characteristics of wild-strain measles virus. The sequences from patients with UC and from patients with autism were consistent with vaccine strain measles virus. These results were consistent with patients' medical histories, and point to a connection between autism and vaccine-strain measles virus.

A May 2002 paper (35) by Singh, Nelson, Jensen and Bradstreet found that a significant percentage of autistic children examined had antibodies to myelin basic protein (up to 88% positive) and to MMR (up to 65% positive). Normal children did not exhibit these antibodies. The analysis of paired samples

(serum and cerebral spinal fluid from 7 autistic children also revealed a high degree of serological association between MMR and myelin basic protein. Some 50% of CSF had MMR antibodies, 86% of CSF had MBP antibodies, 75% of sera had MMR antibodies and 100% of sera had MBP antibodies. Therefore there was a strong correlation between MMR antibodies and myelin basic protein antibodies. By using monoclonal antibodies, the authors characterized that the MMR antibodies were due to the measles sub-unit, but not to the mumps or rubella sub-units, of MMR. In the light of this, the authors suggested that in some cases of autism, MMR might cause autoimmunity, and it might be doing so by bringing on an atypical measles infection that manifests neurological symptoms.

An earlier 1999 paper (36) by Bitnun has previously and independently confirmed the presence of measles virus in the brain tissue of a previously-healthy child following exposure to MMR, when the child had no history of wild measles infection.

A February 2004 paper (37) by Bradstreet, O'Leary, Sheils et al to the US Institute of Medicine, and subsequently published later that year, reported that three children with regressive autism had undergone cerebrospinal fluid assessment, including for measles virus. All three had had concomitant onset of gastrointestinal symptoms and had already had measles virus genomic RNA detected in biopsies of ileal-lymphoid nodular hyperplasia. None of the cases nor non-autistic controls had any history of measles exposure other than possibly via MMR. Serum and cerebrospinal fluid samples were also evaluated for antibodies to measles virus and myelin basic protein. The result was that measles virus f-gene was present in the cerebrospinal fluid of all three autistic cases but not in non-autistic controls. Further, serum anti-myelin basic protein autoantibodies were detected in all children with autistic encephalopathy. Anti-MBP and measles virus antibodies were detected in the CSF of two cases, but the third had neither. The study concluded that the findings were consistent with a measles-virus etiology for autistic

encephalopathy, indicating the possibility of a virally-driven cerebral immunopathology in some cases of regressive autism. The virus genome found in the autistic children was “exclusively consistent with vaccine strain”.

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

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

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

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

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

Wider Safety Concerns over the MMR Vaccine:
It is clearly relevant to examine the original, and any subsequent, safety studies of MMR.

An authoritative independent review (38) of the safety studies of MMR vaccine by the Cochrane Collaboration concluded that "the design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate". It further confirmed that neither before nor after the introduction of the MMR vaccine were proper safety trials carried out.

A more recent review (39) from the same organization identified that safety studies for the single measles vaccine were better than those conducted for MMR: "We found only limited evidence of safety of MMR compared to the single component vaccines, that had a low risk of bias". The authors of the Cochrane reviews were highly critical of the safety studies of MMR, which they stated "need to be improved". Cochrane mentioned a specific concern that safety studies followed up the children involved for no more than three weeks, except for one study that lasted just six weeks.

Concern over MMR's safety has been expressed (40) by a key former scientific adviser to the UK licensing authorities. Dr Peter Fletcher, former Principal Medical Officer in the (then) UK Medicines Division, who was medical assessor to the Committee on Safety of Medicines, commented: "Evidence on safety was very thin", and "Too few children were followed for a sufficient time…….Big numbers were necessary, and computerised databases were already in place to permit this, but it was not done"……Caution should have ruled the day"…….There should have been strong encouragement to conduct a 12-month observational study on 10,000-

15,000 children" (this was not done)…….The granting of a product licence was premature"

A year-2000 review (41) by Wakefield & Montgomery examined early safety studies of MMR, by Buynak et al 1969, Stokes et al 1971, Minekawa et al 1974, Schwartz et al 1975, Crawford and Gremillion 1981, and Miller et al 1987. The Buynak study identified viral "interference", but the follow-up period was only 12 days. The Stokes study revealed persistent gastrointestinal problems in the US trial children, but the follow-up was only 28 days. Stokes compared 228 MMR children with 106 unvaccinated controls. Data, from Philadelphia and Costa Rica and San Salvador, was merged - a major methodological error. Gastroenteritis was found to be significantly more common in the Philadelphia vaccinees (24%) compared with the unvaccinated Philadelphia controls (5.6%). No significant difference was found between the vaccinated and the unvaccinated in Costa Rica and San Salvador because of high ambient levels of gastroenteritis anyway (50% in vaccinees, 44% in controls). Combining all the data masked these instructive differences. There was also significant "unrelated" illness in 39% of Philadelphia vaccinees (otitis, allergy, viral infection, abdominal pain), compared with 12.2% in controls. The potential relevance of this was not seen at time. The Minekawa study confirmed viral interference. The follow-up period was only 15 days. The Schwartz study also merged its data, so provided insufficient insight, and again follow-up was only 21 days. The study looked at two different populations, 282 children in Ohio and 926 children in Santo Domingo, Dominican Republic. Again, the merging of data from different countries was a serious error. No data was provided to permit analysis of adverse events. Crawford and Gremillion's study of USAF recruits confirmed viral interference, but the follow-up period was only 19 days. Some 512 vaccinees were compared with 835 unvaccinated controls. The study noted increased fever and diarrhoea in those that received measles and rubella vaccines simultaneously. But the potential effect of trivalent vaccine was only seen as additive instead of potentially synergistic - a key point. The Eddes study (a

small UK study) in 1991 compared reactions to MMR with monovalent measles vaccine. High rates of gastrointestinal disorders (41.9% and 37.8%) were found, but the authors dismissed these as normal background illness. The Dr. Elizabeth Miller study noted that diarrhoea was common (26% of vaccinees), but the follow-up again was only 21 days. This was a major missed opportunity to follow up a large cohort. The Stokes, Schwartz, Miller and Eddes studies were therefore all too small or too superficial to pick up uncommon adverse events. The Plesner et al study of gait disturbance following MMR (Acta Paediatrica, 2000, 89, 58-63) confirmed an association, and indicated that more severe cerebellar ataxias following MMR may be associated with residual cognitive deficits.

We believe that this lack of any long-term safety studies has led directly to the controversy now surrounding MMR's safety. MMR's safety testing has reversed the precautionary principle. Cochrane (39) was forced to conclude that "the safety record of MMR is probably best attested by its almost universal use." Or to put it another way, "the best evidence of MMR's safety we can find is that fact that it's being widely used" - hardly a scientific test of a product's actual safety, particularly when the evidence of problems is through a hitherto-unsuspected link between MMR and autism, that would not have been monitored prior to 1998.

Implications: what we urge should happen next

Those responsible for vaccination policy in the UK, US and elsewhere should prudently re-adopt the precautionary principle, that a product must be adequately safety-tested - safety-testing that, in the context of MMR and regressive autism, has never been properly done to date.

In the light of our findings, and as Dr. Wakefield first controversially suggested in 1998, parents should be once again be given the choice of having single vaccines administered to their children. MMR was originally introduced for

economy and convenience. The slightly greater cost, and the slightly greater inconvenience, of single vaccines will be more than offset by improved safety for children needing to be protected against diseases. If MMR causes regressive autism, the financial costs (not to mention the human costs) would be immense compared with the modest cost of re-adopting single vaccines. We recognise the deep reluctance of the authorities to do this. However, a former UK Minister for Health once said, in the context of another medical intervention, “If there is even a hypothetical risk (of harm), and a safer alternative exists, we should use it”. For MMR, autism and intestinal inflammation, strong suspicion now exists, in the light of this study’s findings, and in the absence of evidence of MMR’s safety, and so this principle should again be similarly applied.

Further research into the possible role of measles-containing vaccines - now firmly a prime suspect in the search for the cause of regressive autism - should be undertaken as a matter of the greatest urgency.

Future studies should start by focussing specifically on the relevant groups of children affected by this devastating disorder

What about the other widely publicised evidence that has hitherto been taken to prove that there is no link between MMR and autism?

Despite the significant number of epidemiological (desk) studies (42-72) that have been claimed to offer evidence that there is no link between MMR and autism, what is most important is that all of these studies that claim to exonerate MMR have only been epidemiological studies. They have been desk studies, of child health records and other information. They have not been clinical studies. No actual children have been clinically examined. They have thus been inappropriate to the investigation of a novel pathology, and have mostly failed to use the best available technology, or suitably trained researchers.

In each case, it has been a case of a link not being found, rather than a link being disproved. Despite this, an impression has been allowed to be given that they have offered conclusive proof of the absence of any MMR/autism link. That has not been the case.

Many of these have been subsequently found to be inconclusive, or can be seen with hindsight as being flawed in design or execution. Many studies have asked the wrong questions. Some have only been reviews (65-72) of the evidence that existed at the time, and have now been completely overtaken by subsequent events, or been contradicted by more recent clinical research.

References for Background Information

(on autism)
(2) Jyonouchi, Sun and Le, Department of Pediatrics, University of Minnesota, Pro-inflammatory 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
(3) Blaxill, The Rising Incidence of Autism, Associations with Thimerosal, presented to the US Institute of Medicine, July 2001
(4) Statement by Dr. Jose Cordero on behalf of the US Centers for Disease Control and Prevention, based on CDC data on 24,673 children, 4th May 2006, source Reuters
(5) Interview with ABC News, 4th May
(6) Source: The Scottish Executive, Edinburgh.
(7) Study by Byrd et al, MIND Institute, University of California at Davis, The Epidemiology of Autism in California, October 2002
(8) Yeargin-Allsopp, Rice et al, Prevalence of Autism in a US Metropolitan Area, Journal of the American Medical Association, 2003, Jan 1st, 289: (1): pp49-55.

(9) Gurney, Fritz et al, Analysis of Prevalence Trends of Autism Spectrum Disorder in Minnesota, Archives of Pediatric Adolescent Medicine, 2003, 157: pp622-627
(10) Yazbak, Autism in the United States – A Perspective, Journal of American Physicians and Surgeons, Vol 8, No. 4, Winter 2003
(11) Blaxill, What's Going On? – The Question of Time Trends in Autism, Public Health Reports, Nov-Dec 2004, Vol 119, pp536-551
(12) Newschaffer, Falb et al, Center for Autism and Developmental Disabilities, Johns Hopkins Bloomberg School of Public Health, Baltimore, and Divisions of Epidemiology and Clinical Research, University of Minnesota, Minneapolis, National Autism Prevalence Trends from United States Special Education Data, Pediatrics, Vol 115 No. 3 March 2005 pp277-282

(on the link between autism and a novel form of inflammatory bowel disease)

(13) Wakefield et al, Inflammatory Bowel Disease Study Group, Royal Free Hospital London, Ileal Lymphoid Nodular Hyperplasia, Non Specific Colitis and Pervasive Development Disorder in Children, Lancet, 28th February 1998
(14) Horvath, Papadimitiou et al, Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Gastrointestinal Abnormalities in Children With Autistic Disorder, Journal of Pediatrics, 1999 November, Vol 135 (5), pp559-563
(15) Wakefield, Anthony et al, Enterocolitis in Children with Developmental Disorders, American Journal of Gastroenterology, Sept 2000, Vol 95, No. 9, pp2285-2295
(16) Furlano, Anthony et al, Colonic CD8 and T-Cell Infiltration With Epithelial Damage in Children with Autism, Journal of Pediatrics, 2001; 138; No. 3, 366-372
(17) Paper by Dr. Timothy Buie, Harvard Massachusetts General Hospital, presented to the Oasis 2001 Conference for Autism, Portland, Oregon, November 2001.

(18) Wakefield, Anthony, Montgomery et al, Inflammatory Bowel disease Study Group, Royal Free Hospital, University College Medical School, London, and Coombe Women's Hospital and Trinity College Dublin, The Concept of Enterocolonic Encepalopathy, Autism and Opioid Receptor Ligands, Aliment Pharmacological 16: pp663-674.
(19) Presentation by Krigsman to the US Congressional Committee on Government Reform's June 2002 hearing, The Status of Research into Vaccine Safety and Autism, held in Washington DC.
(20) Ashwood, Murch et al, Royal Free Hospital, London, Intestinal Lymphocyte Populations in Children with Regressive Autism: Evidence for Extensive Mucosal Immunopathology, Journal of Clinical Immunology, Vol 23 No. 6 Nov 2003 pp504-517.
(21) Torrente, Anthony et al, Centre for Pediatric Gastroenterology, Royal Free Hospital and University College Medical School, London, Focal-Enhanced Gastritis in Regressive Autism, With Features Distinct from Crohn's and Helicobacter Pylori Gastritis, American Journal of Gastroenterology, Vol 99, Issue 4, p598, April 2004
(22) Ashwood, Anthony et al, Spontaneous Mucosal Lymphocyte Cytokine Profiles in Children with Autism and Gastrointestinal Symptoms: Mucosal Immune Activation and Reduced Counter-Regulatory Interleukin-10, Journal of Clinical Immunology, Vol 24, No. 6, November 2004.
(23) Jyonouchi, Geng et al, Department of Pediatrics, New Jersey Medical School, Dysregulated Innate Immune Responses in Young Children with Autistic Spectrum Disorders - Their Relationship in Gastrointestinal Symptoms and Dietary Intervention, Neuropsychobiology, February 2005, 51 (2) pp77-85.
(24) Letter by Balzola, Barbon et al, Department of Gastroenterology, Department of Neuropsychiatry for Children, Department of Pediatric Gastroenterology and Department of Biomedical Sciences and Human Oncology, University of Turin, Pan-Enteric 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?, American Journal of Gastroenterology, 2005; 100 (4) p979
(25) Balzola, Daniela et al, Department of Gastroenterology, Department of Neuropsychiatry for Children, Department of Pediatric Gastroenterology and Department of Biomedical Science and Human Oncology, University of Turin, Autistic Enterocolitis - Autistic Enterocolitis: Confirmation of a New Inflammatory Bowel Disease in an Italian Cohort of Patients, paper presented to the American Gastroenterological Association, May 2005 and published in Gastroenterology 2005: 128 Suppl 2, A-303.
(26) Wakefield, Ashwood et al, The Significance of Ileo-Colonic Lymphoid Nodular Hyperplasia in Children with Autistic Spectrum Disorder, European Journal of Gastroenterology and Hepatology, 2005, Vol 17 No. 8.
(27) Gonzalez, Lopez et al, Endoscopic and Histological Characteristics of the Digestive Mucosa in Autistic Children with Gastrointestinal Symptoms: Preliminary Report, G.E.N. Suplemento Especial de Pediatria, no. 1, 2005; pp41-47

(on the link between inflammatory bowel disease and measles virus)

(28) Uhlmann, Sheils et al, Department of Pathology, Coombe Women's Hospital Dublin, Trinity College Dublin and Royal Free Hospital London, Measles Virus in Reactive Lympho-Nodular Hyperplasia and Ileo-colitis of Children .
(29) Paper presented by Dr. Vijendra Singh, University of Michigan College of Pharmacy, to the US House of Representatives Committee on Government Reform, Washington DC, 2000
(30) Paper presented by Professor John O'Leary, Dublin Women's Hospital, to the US House of Representatives Committee on Government Reform Washington DC, April 2000
(31) 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

(32) Paper by Singh, Department of Biology Center for Integrated Biosystems, Utah State University, Logan, Autism, Vaccines and Immune Reactions, presented to the Institute of Medicine, Washington DC, February 2004

(on the link between measles virus and vaccination with MMR)

(33) Paper presented by O'Leary, Coombe Women's Hospital and Trinity College Dublin to the Pathological Society of Great Britain and Ireland, July 2002

(34) Kawashima, Takayuki et al, Detection and Sequencing of Measles Virus from Peripheral Mononuclear Cells from Patients with Inflammatory Bowel Disease and Autism, Digestive Diseases & Science, Vol. 45, No. 4, April 2000, pp723-729

(35) Singh, Nelson, Jensen and Bradstreet, Abnormal Measles Serology and Autoimmunity in Autistic Children, Journal of Allergy and Clinical Immunology 109 (1) S232, January 2002, and also presented to the 102nd General Meeting of the American Society for Microbiology, Salt Lake City, Utah, May 2002

(36) Bitnun et al, Measles Inclusion-Body Encephalitis Caused by the Vaccine Strain of Measles Virus, Clinical Infectious Diseases Journal, 1999, 29 855-61 (October)

(37) Bradstreet, O'Leary, Sheils et al, Detection of Measles Virus Genomic RNA in Cerebrospinal Fluid in Children with Regressive Autism by TaqMan RT-PCR: A Report of Three Cases, summarized at the Institute of Medicine, February 2004 and subsequently published as Bradstreet, Dahr et al, Detection of Measles Virus Genomic RNA in Cerebrospinal Fluid of Children with Regressive Autism: A Report of Three Cases, Journal of American Physicians and Surgeons, Vol. 9, No. 2 Summer 2004.

Again, taken with the latest study by Walker, Hepner et al, this now provides evidence that it is highly likely that MMR vaccine is the source of the measles virus that is in turn linked via significant evidence with ileal lymphoid nodular

hyperplasia, which in turn is strongly and convincingly linked with regressive autism.

A May 2006 study (38) by Wakefield, Stott and Limb investigated the hypothesis as to whether a dose-response effect of measles-containing vaccine on intestinal pathology existed. If it did exist, this would constitute evidence of a causal association. In the study, children with normal early development and autistic-like developmental regression were divided into two groups. Children were divided into two groups: some 23 re-exposed children, i.e. those who had received more than one dose of a measles-containing vaccine (MCV), and 23 children who had received only one dose of MCV. The groups were matched for sex, age and time that had elapsed from first exposure to time of endoscopy. Comparisons made included secondary gastrointestinal (GI) and related physical symptoms,, and "observer-blinded" scores of endoscopic and histological disease. The results were that re-exposed children scored significantly higher than only-once-exposed for secondary physical symptoms, including incontinence, presence of severe ileal-lymphoid nodular hyperplasia, the number of biopsies with epithelial damage, and number of children with acute inflammation. Markers of acute inflammation include number of children affected, and proportion of biopsies affect. The conclusion of the study was that the data confirmed a re-challenge effect (i.e. a double-hit effect) of measles-containing vaccines on symptoms, and also confirmed a biological gradient effect upon intestinal pathology. These findings thus link exposure to measles-containing vaccines to autistic-like regression and enterocolitis. (Note: it was stated in April 2001 by the Vaccine Safety Committee of the US Institute of Medicine that in the context of MMR and autism "challenge re-challenge would constitute strong evidence of an association".

(On wider safety concerns over MMR vaccine)

(38) Wakefield, Stott and Limb, Gastrointestinal Comorbidity, Autistic Regression and Measles-Containing Vaccines; Positive Re-challenge and Biological Gradient, Medical Veritas 3 (2006) 796-802
(39) Jefferson, Price et al, Unintended Events Following Immunisation with MMR; A Systematic Review, Vaccine, 2003; 21: pp3954-3960
(40) Demicheli, Jefferson et al, Vaccine For Measles, Mumps and Rubella in Children (Review), The Cochrane Collaboration, published Wiley & Sons, UK, from The Cochrane Library, 2005, Issue 4, art. No. CD004407
(41) Commentary by Dr. Peter Fletcher, Journal of Adverse Drug Reactions & Toxicology, 2001, 20 (1), 47 63 Oxford University
(42) Wakefield & Montgomery Through A Glass Darkly (A Look Back At MMR's Safety Trials), Journal of Adverse Drug Reactions, 2000 19(4), 265-283)

(On the other widely publicised evidence that have hitherto been taken to prove that there was no link between MMR and autism)
(note: all of these are only epidemiological (= desk) studies: not one of these have involved the clinical examination of actual patients)

(43) Stokes et al Paper, Trivalent Combined Measles Mumps Rubella Vaccine, Journal of the American Medical Association, 4th October 1971
(44) 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
(45) Miller, Miller, Rowe et al, Surveillance of Symptoms Following MMR Vaccine in Children, The Practitioner, Vol 233, 8th January 1989
(46) Gillberg Study, Sweden, Is Autism More Common Than Ten Years Ago?, British Journal of Psychiatry, 1991, 158; 403-409
(47) Gillberg and Heijbel, Commentaries, Autism, Vol 2 (4) 423-430, 1998
(48) UK Committee On Safety of Medicines Study, Report of the Working Party on MMR Vaccine, Committee on Safety of Medicines, June 1999

(49) Taylor, Miller, Farrington et al, Autism and Measles Mumps Rubella Vaccine: No Evidence for a Causal Association, Lancet 1999, 353, 2026-9
(50) 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
(51) 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)
(52) 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
(53) 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
(54) De Wilde, Carey, Richards et al, Do Children Who Become Autistic Consult More Often After MMR Vaccination, British Journal of General Practice, March 2001
(55) 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
(56) Farrington, Miller and Taylor, MMR and Autism: Further Evidence Against a Causal Association, Vaccine, 19 (2001) 3632-3635
(57) Fombonne & Chakrabarti, No Evidence for a New Variant of Measles-Mumps-Rubella-Induced Autism, Pediatrics, Vol. 108 No. 4 October 2001
(58) 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
(59) 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.

(60) 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.
(61) Taylor, Miller et al, Bacterial Infections, Immune Overload and MMR Vaccine, published in Archives of Diseases in Childhood, 2003; 88; 222-223
(62) Taylor, Miller et al, Prevalence of Autism and Parentally-Reported Triggers in a North East London Population, Archive of Diseases In Childhood, 2003, 88, 666-670
(63) DeStefano, Bhasin, Thompson, Yeargin-Allsopp and Boyle, Age At First MMR Vaccination In Children With Autism and School-Matched Control Subjects: A Population-Based Study In Metropolitan Atlanta, Pediatrics, 2004; 113: 259-266
(64) Smeeth, Cook, Fombonne et al, MMR Vaccination and Pervasive Developmental Disorders - A Case-Control Study, published in The Lancet, Vol 364, September 2004
(65) Honda and 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
(66) Study by 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, 14th May
(67) UK 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)
(68) UK Medical Research Council's Report, Report of the Strategy Development Group Sub-Group on Research into Inflammatory Bowel Disorders and Autism, March 2000.

(69) US Institute of Medicine Review, 2001 (the review included a number of reservations that have proved to be significant in the light of subsequent events - (a) studies may not have sufficient precision to detect very rare occurrences at a population level (b) 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 (c) its conclusion did not exclude the possibility that MMR vaccine could contribute to autism in a small number of children (d) the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR leading to autism (e) the proposed biological models linking MMR vaccine to autism, although far from established, are nevertheless not disproved).

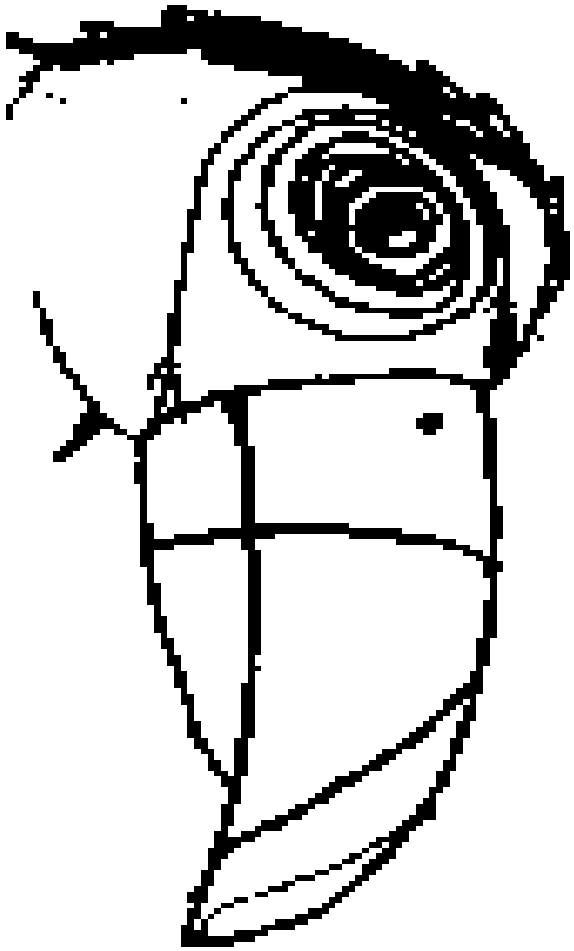
(70) Review By UK Medical Research Council, Review of Autism Research - Epidemiology and Causes, July-December 2001 (What was most notable in the this review's report was just how few studies for/against an MMR/autism link were covered, seven at most against a link and only two in favour).

(71) Further Review By the US National Academy of Sciences Institute of Medicine on Child Vaccinations and Autoimmune Dysfunction, February 2002 (On vaccine-induced neuroimmune dysfunction, the IoM Committee stated: "The Committee was unable to address the concern that repeated exposure of a susceptible child to multiple immunizations over the developmental period may also produce atypical or non-specific immune or nervous system injury that could lead to severe disability or death. There are no epidemiological studies that address this. Thus the Committee recognises with some discomfort that this report addresses only part of the overall set of concerns of some of those most wary about the safety of childhood immunizations".)

(72) 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

(73) Review by the US Institute of Medicine, Washington, US, February 9th 2004. (This review, covering both MMR and the vaccine preservative

thimerosal, was highly controversial. The review only lasted one day, with just one hour being devoted to the MMR aspect, and with only two witnesses being called on this latter topic. Congressman David Weldon commented: “In my ten years of service in the US Congress, I have never seen a report so badly miss the mark”. Dr. Marie McCormick, chairman of the IoM Committee, and Dr. Kathleen Stratton, Study Director of the Committee held the following e-mail exchange three years in advance of the Committee’s review: (Dr. McCormick) “(Centers for Disease Control) wants us to declare, well, these things (i.e. vaccines) are pretty safe on a population basis”. (Dr. Stratton) “The point of no return, the line we will not cross in public policy, is pull the vaccine, change the (immunization) schedule. We could say ‘it’s time to re-visit this’ but we would never recommend that level. Even recommending research (implies) recommendations for policy. We wouldn’t compensate, we wouldn’t say ‘pull the vaccine’, we wouldn’t say ‘stop the program’. (Dr. McCormick) “We are not ever going to come down that (autism) is a true side effect.” (source: pages 74-97, IoM Committee Meeting Closed-Door Transcript, 1/12/2001).



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ANDREW WAKEFIELD, MB, BS, FRCS, FRCPath.

Dr. Andrew Wakefield is an academic gastroenterologist. He graduated in Medicine from St. Mary's Hospital, part of the University of London, in 1981, and pursued a career in gastrointestinal surgery with a specific interest in inflammatory bowel disease. He qualified as Fellow of the Royal College of Surgeons in 1985, and in 1996 he was awarded a Welcome Trust Travelling Fellowship to study small intestinal transplantation in Toronto, Canada.

Discoveries made during his time in Canada led him to pursue the scientific investigation of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. In 1998, he and his colleagues at the Royal Free Hospital reported a novel inflammatory bowel disease in children with developmental disorders such as autism; the condition later became known as autistic enterocolitis. No stranger to controversy, Dr. Wakefield resisted pressure to stop his research on the possible links between childhood immunizations, intestinal inflammation, and autism, and left the Royal Free School of Medicine in 2001. He is involved in much scientific collaboration in the U.S and Europe. The main focus of Dr. Wakefield's research is an investigation of the immunologic, metabolic, and pathologic changes occurring in inflammatory bowel diseases such as autistic enterocolitis, links between intestinal disease and neurologic injury in children, and the potential relationship of these conditions to environmental causes, such as childhood vaccines.

During the course of his work on childhood developmental disorders, Dr. Wakefield became increasingly convinced of the need for a research-oriented, integrated biomedical and educational approach to these disorders in order to translate clinical benefits for affected children into measurable developmental progress; this is the driving aim of Thoughtful House. Dr. Wakefield has published 132 original scientific articles, book chapters, and invited scientific

commentaries, and was awarded the Fellowship of the Royal College of Pathologists in 2001. He is medical advisor to the United Kingdom charity, Visceral, and sits on the board of the U.S. charity, Medical Interventions for Autism.

Summary:

A new medical model of autism and related developmental disorders is emerging, based upon the recognition that many affected children have an underlying intestinal inflammation.

Symptoms of inflammation: children suffer abdominal discomfort, cramping, diarrhoea, constipation (often alternating constipation and diarrhoea), and malodorous stools containing undigested food. Abdominal pain can often manifest as night time waking, distress, self-injury, and irritability.

Nature of the inflammation: the inflammation in the intestine is novel (unlike other diseases such as Crohn's disease and ulcerative colitis). It has features of a chronic viral infection.

Silent GI disease: it is evident that, from our knowledge of occult celiac disease (allergic sensitivity to wheat gluten) and inflammatory bowel diseases such as Crohn's and ulcerative colitis, the absence of obvious GI symptoms does not mean absence of GI disease. Many patients with celiac disease have no GI symptoms. It is likely that the GI inflammation in children with autism affects many more children than is clinically evident from their symptoms.

Secondary activation of the immune system in the brain: a recent study has demonstrated activation of immune cells resident in the brain of affected individuals with autism. This activation appears to be a secondary response to inflammation arising outside the brain, potentially in the intestine.

The innate and adaptive immune systems: the inflammatory response in the intestine and that in the brain of affected individuals is different. The brain shows activation of the innate immune response with lymphocyte proliferation, lymphocyte inflammation, and deposition of antibody in the inflamed tissue.

The gut-brain axis: the emerging picture is of primary inflammation in the intestine and secondary inflammation and tissue damage in the brain.
Treatment possibilities: It stands to reason that treatment of the intestinal inflammation and its local consequences may have a beneficial impact upon the behavioral and developmental aspects of the disease.
Conference Presentation:
Thoughtful House is focused upon recovering children with developmental disorders through this combination of medical care, education, and research. With a disease which is as complex as autism (today we are using autism as a model because we've learned a great deal from autism, but the same might apply to many childhood developmental disorders), so many things have gone wrong by the time the child comes to the clinic. Where do you actually begin? As parents, as physicians, where do you start? It's a very complex problem--where do you begin to unravel this mystery?

The starting point

It is a fundamental rule of medicine that you listen to the patient or, in this case, the patient's parents. You go back to the clinical history and use that as your starting point. Taking a full clinical history and physical examination of the child is, for autism, almost unheard of nowadays. It is important to then focus on investigations that derive firstly from the clues present in the clinical history, as told to you by the parent, and secondly from what you find upon examination of the child. I am a gastroenterologist, so I'm going to give you my perspective on this problem from the gastroenterological point of view. The clinical history that I first started hearing in 1995, at the Royal Free Hospital in London, was of children who had developed normally--acquired skills, social interaction, language--and had then regressed into autism. I knew absolutely nothing about autism. It was so rare when I was in medical school that it wasn't even talked about. At the same time that these children regressed into autism, they had an onset of neurological and gastrointestinal symptoms. In terms of neurological symptoms, for example, a child might have been able to eat with a utensil, and then he could no longer do that.

Some started bumping into things. They became unsteady, clumsy (ataxia). They used to walk, but now they wanted to sit down. They didn't want to climb up the stairs anymore. So something--some hard neurological problem--was occurring in association with their developmental regression. They had also developed gastrointestinal symptoms. When the parents described these gastrointestinal symptoms--diarrhoea 12 times a day, abdominal bloating, pain or posturing, exacerbation of their behavioural symptoms when it came time to go the bathroom--they were told that their child was autistic, and that they were bound, therefore, to have bowel problems. That made absolutely no sense to me whatsoever. In these autistic children there also seemed to be a propensity for recurrent infection. If the rest of the family got an infection, the child with autism got it worse and it lasted longer. The children generally took multiple courses of antibiotics, which may have been a proxy for an immune system that was not working properly, or indeed, antibiotics in some way may have been instrumental in the initiation of the disease process. But certainly we saw and continue to see a lot of upper respiratory tract and ear infections in this population.

So if in doubt, examine the patient. This is as true today as it ever was. The patient in this slide was a little boy with autism. He was a happy, healthy one-year-old, and a delightful little guy. This is him now at the age of six. And the change is extraordinary. This is the sort of image that you might expect to see in a child in West Africa. This child has no muscle mass at all. His ribs are poking through. He has a grossly distended abdomen. He may have early rickets. This child is sick. This child has an underlying gastrointestinal disease. The pediatric gastroenterologist, to whom this child was referred, refused to see him on the basis that this was too controversial. There is absolutely nothing controversial about this child. Bowel disease is bowel disease. The mother of this family was put under investigation by Social Services, for starving her child. But this picture belies that interpretation. There is his sister behind him, and she is perfectly well-nourished. This is the dilemma that medicine has created for itself. You can see how it inspires in

parents an extraordinary loss of trust in the medical profession. This child is sick.

Symptoms reflect inflammatory intestinal disease

We saw that it was necessary to disregard the behavioural disorder and to take the bowel symptoms at face value. We asked simply, do these symptoms reflect an underlying disease of the intestine? Then we performed ileo-colonoscopy (examination of the lower intestine), and here is what we found in the ileum. (Slide titled "Ileo-colonoscopy"). This is marked ileal lymphoid nodular hyperplasia. It is analogous to swelling of lymph glands in the neck when you get a sore throat, but it happens to be in the last part of the small intestine. It would readily cause pain, and change in bowel habit.

Here you see ulcerations (aphthous ulcers) similar to the ulcers you get in your mouth. What is happening is the breakdown of the lining of the intestine. At first we interpreted this as early Crohn's disease-- in fact, it wasn't. This is a new disease. When I left the Royal Free Hospital, we had already investigated approximately 200 children with autism and found this to be a remarkably consistent pattern of intestinal pathology.

I had not seen anything quite like this before, despite many years in gastroenterology. There is an irrefutable disease process in the intestine of these children, based upon hypothesis testing, peer-reviewed and published science. This [paper], the second in a succession of studies, describes the first 60 children in the American Journal of Gastroenterology. What have these various studies shown? The inflammation can be extensive, throughout the intestines, the stomach, the small bowel, the duodenum, the terminal ileum, and the colon and rectum. This is what we call a pan-enteric disease. It's rather like Crohn's in its distribution, although it is not Crohn's disease.

Until recently we've been hampered in our ability to see the entire GI tract. Upper GI endoscopy and colonoscopy provide a limited view of the intestine.

In adults there are up to 21 feet of small intestine that we have been unable to visualize. Now we have the technique of capsule endoscopy. You swallow a small single-use capsule and it is able to take pictures throughout the entire GI tract. These pictures come from a post-doctoral former student of mine, Federico Balzola, who has found the same disease in a cohort of Italian children. ("Autistic Enterocolitis: Confirmation of a New Inflammatory Bowel Disease in an Italian Cohort of Patients." Digestive Diseases Week, Chicago, May 2005 and "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." Balzola F, et al. American Journal of Gastroenterology, April, 2005). So the detection of autistic enterocolitis has been reproduced in American, English, and Italian children.

Functional abnormalities accompany inflammation of the intestine, including digestive enzyme deficiencies and dysmotility. What we see commonly in these children is reflux esophagitis. Food and acid come back up into the esophagus from the stomach, particularly at night when they may wake, very fractious, very upset. At the other end the children may become constipated with fecal impaction. So you have this odd constellation of inflammation, which is usually associated with diarrhoea, impaired GI motility, and constipation. Defective digestive enzyme is evidenced by the presence of undigested food in the stool. And dysbiosis--the overgrowth of bad bugs, bugs that shouldn't normally be there in appreciable amounts but proliferate because of the favourable environment created by the underlying gut disorder. Again, this is something we see in inflammatory bowel disease such as Crohn's disease. Just to illustrate the digestive enzyme function, this [illustration] is the small intestine where food is digested and absorbed under normal circumstances. This is the normal villi surface. Here is a single one of these finger-like structures, a villus, at high power. The enzyme systems line and work along the folded surface of these structures. Normally the enzymes will take complex molecules and break them down into molecules that can

then be absorbed. But when the intestine becomes inflamed or damaged, for example with rotavirus infection, these enzyme systems are impaired, and digestion does not proceed normally. Karoly Horvath was the first gastroenterologist to report this from the University of Maryland School of Medicine, in "Gastrointestinal Abnormalities in Children with Autistic Disorder" (Journal of Pediatrics 1999;135:559-63). In the early days we were focused on looking at the bottom end and he was focused looking at the top end. Dr. Tim Buie, a pediatric gastroenterologist at Harvard, has since provided independent confirmation of these findings.

This intestinal disorder in children with autism appears to be relevant to other developmental disorders. Here we have a paper -- a fascinating paper -- "The Gut-CNS Connection: a New Domain for the Clinician. Gastrointestinal and Behavioural Dysfunction in Children with Non-IgE-mediated Food Allergy, Ileal-Nodular-Lymphoid Hyperplasia (ILNH), and Low Th1 Function: A New Clinical-Immunologic Constellation." (Sabra A et al.). This comes from the clinical studies of Dr Joe Bellanti, head of pediatric immunology and allergy at Georgetown University. While some of the children in this study have autism, the majority have ADHD or anorexia nervosa. It appears that while children may be affected by a spectrum of developmental disorders including severe autism through to ADHD, there is a common denominator. That common denominator is somewhere in the immune system of the gastrointestinal tract.

The nature of the immune disorder

Concerning the nature of the inflammation, I want to discuss the structure of the human immune system in very simple terms. The human immune system is divided into two parts: the innate immune system and the adaptive immune system. This is an overly simplistic interpretation, but it's an important starting point. The innate immune system is the early-warning rapid response system. It is primitive in evolutionary terms and acts as one of the first lines of defense of the host against invading organisms. It is nonspecific and activation may be associated with collateral damage to host tissues. Its lack of specificity is

reflected in the fact that it will respond the same way to the same agent every time that it sees it. It has no capacity for immunological memory. If it's set up in the wrong way in the first place, in utero or in the first few months to years of life, then this can lead to inappropriate immune responses to otherwise benign environmental encounters such as food proteins. It is crucial that the immune system is properly set up in children from very early on. This early education of the innate immune system has a major impact on the way in which the adaptive immune system is set up also.

The adaptive immune system is the laser-guided missile of the immune system. It has memory and specificity. If it has seen an infection before, it retains memory for that infection so that when it sees it again, it can respond rapidly and it can magnify the secondary response greatly. Specific immune cells will respond to one antigen, one agent. Diseases associated with disorders of the adaptive immune system are characterized by infiltration of target tissues by lymphocytes (B and T cells) and the deposition of antibody from the host in tissues of the target organ in the form of immune complexes, as the immune system mounts a response against itself.

What then do we see in the intestinal lesion in children with regressive autism? In this paper published by Dr. Furlano, working with Dr Simon Murch's group in collaboration with my group at the Royal Free Hospital, we demonstrated that there was certainly activation of the innate immune system in the gut, with the infiltration of the epithelium by gamma delta T-cells ("Colonic CD8+ and gamma delta T-cell infiltration with epithelial damage in children with autism" J Pediatr. 2001 Mar;138(3):366-72). This is part of the innate immune system repertoire. The image at the bottom is an illustration of a technique called immunohistochemistry. For this, we took a thin slice of intestinal biopsy tissue and stained it with an antibody that is specific to these particular immune cells. In addition, in the intestinal lesion there is also activation of the adaptive immune system, not just that primitive early warning system of the innate immune system but of the specific-antigen-driven

adaptive immune system also. There is a specific mucosal inflammation associated with an excess of CD8+ lymphocytes in the intestines of these children, providing evidence of an adaptive immune response. In addition, this picture shows the deposition of IgG antibodies from the blood of affected children, in the tissues of what is referred to as the baso-lateral membrane of the epithelial lining cells (in this case in the villi of the small intestine). The IgG antibody deposited in the tissues co-localizes with a protein C1Q which is part of the inflammatory response repertoire of the body. These two things, deposited together as an immune complex, may be associated with cell and tissue injury and is 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 one is looking for something specific such as a virus, one now has a clue as to where to look. It is in the swollen lymph glands--the lymphoid nodular hyperplasia (LNH) in the intestine--that we expect to find evidence of whatever is driving this immune response. We can say this based upon historical experience. Here, for example, is a patient with AIDS. The patient has gastrointestinal disease associated with inflammation and LNH. This tissue from the lymph glands has been stained with an antibody specific for HIV. You see the distribution of the protein in the center of those lymph glands. This is another example. This is New Variant Jakob-Creutzfeldt disease ("mad cow disease"). Here, in the center of the swollen lymph gland, you see the prion protein of New Variant Jakob-Creutzfeldt disease. And in the children with autism we find a different agent, in this case, a virus.

So, what are the immune cells actually doing? They appear to be activated and causing damage. Dr. Paul Ashwood will discuss this work in more detail. Cytokines are communication systems between cells that influence inflammation and immunity. They communicate signals that stimulate or inhibit the immune response. In this paper published by Dr. Ashwood and our group ("Spontaneous Mucosal Lymphocyte Cytokine Profiles in Children with Autism

and Gastrointestinal Symptoms: Mucosal Immune Activation and Reduced Counter Regulatory Interleukin 10" J Clin Immunol 2004;24(6):664-673), we showed that the immune cells in the bowel of these children are switched on and have a rather unique pattern of cytokine expression. In this chart you see the interesting observation that among 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, this Interleukin 10 (IL-10), which is 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, what we have is a novel intestinal disease. The entire intestine may be involved, and there is a characteristic pattern with swollen lymph glands and inflammation (characteristic lymphoproliferative response , i.e. LNH, and immune cell infiltrate). In addition, there is IgG antibody and complement (immune complex) deposition suggesting activation of both the innate and adaptive immune systems.

Dr. Jyonouchi from the University of New Jersey Medical School, recently published a study ("Dysregulated Innate Immune Responses in Young Children with Autism Spectrum Disorders: Their Relationship to Gastrointestinal Symptoms and Dietary Intervention" Neuropsychobiology. 2005;51(2):77-85). This study compared innate and adaptive immune responses of blood lymphocytes, rather than intestinal lymphocytes, in children with autism, and developmentally normal controls. What's interesting about this population is that in the autistic children there was an excess risk of immunization reactions and atopic disease. There was something about their immune systems that made them overly responsive, for example developing adverse reactions to vaccines (prolonged fever, febrile seizure, lethargy, extreme irritability, loss of speech within one week, or systematic urticaria/angiodema), and 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 children. Furthermore, she observed excessive innate immune responses in a high proportion of ASD children, particularly in TNF-alpha production.

She demonstrates that in the blood of affected children there is disordered innate immunity with excessive pro-inflammatory response (TNF-alpha) and inadequate counter-regulatory response (IL-10) to dietary proteins and bacterial toxins. This cytokine response was particularly evident in children with gastrointestinal symptoms, but it is also notable that with dietary intervention (a gluten- and casein-free diet) there was not only resolution of the GI symptoms but a dampening of the cytokine response. So she suggests, and I agree with her, that there is a fundamental defect in innate immune responses in this population.

Is there a link between the inflammation in the intestine and brain injury or encephalopathy? By analogy, if your liver fails, then you fail to detoxify the bacterial products and toxins that come from the intestine and get through to the blood stream under normal circumstances. In these circumstances, the patient becomes encephalopathic. There is nothing new about gut-brain interactions. The question is, "Are they relevant to some children with autism and if so, what is the mechanism?" Potential mechanisms include toxicity, immune consequences of intestinal inflammation, or direct infection of the brain from a primary source in the intestine or somewhere outside the brain.

Now it gets really interesting. In this paper from Johns Hopkins, "Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism," (Vargas, et al; Annals of Neurology; Published Online: November 15, 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 brain from autism cases 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 (CSF) cytokine profiles using protein arrays. The bottom line is that 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 Purkinjie 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 adaptive 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 CSF they found inflammatory cytokines of lymphocyte origin. Lymphocytes were not present in the brain, and they were not present in the CSF. So where are 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 secondary injury in the brain? This is a very interesting possibility. In summary, albeit that the findings have been made in distinct populations of autistic patients, we have evidence of a primary immune system activation in the gut and secondary immune system activation with no obvious source in the blood and the brain.

Have we seen this somewhere before? Is this biologically plausible? We've seen it in celiac disease, an allergic sensitivity to wheat gluten, 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 on population screening. So, while in prospective studies it is apparent that GI symptoms are common in 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.

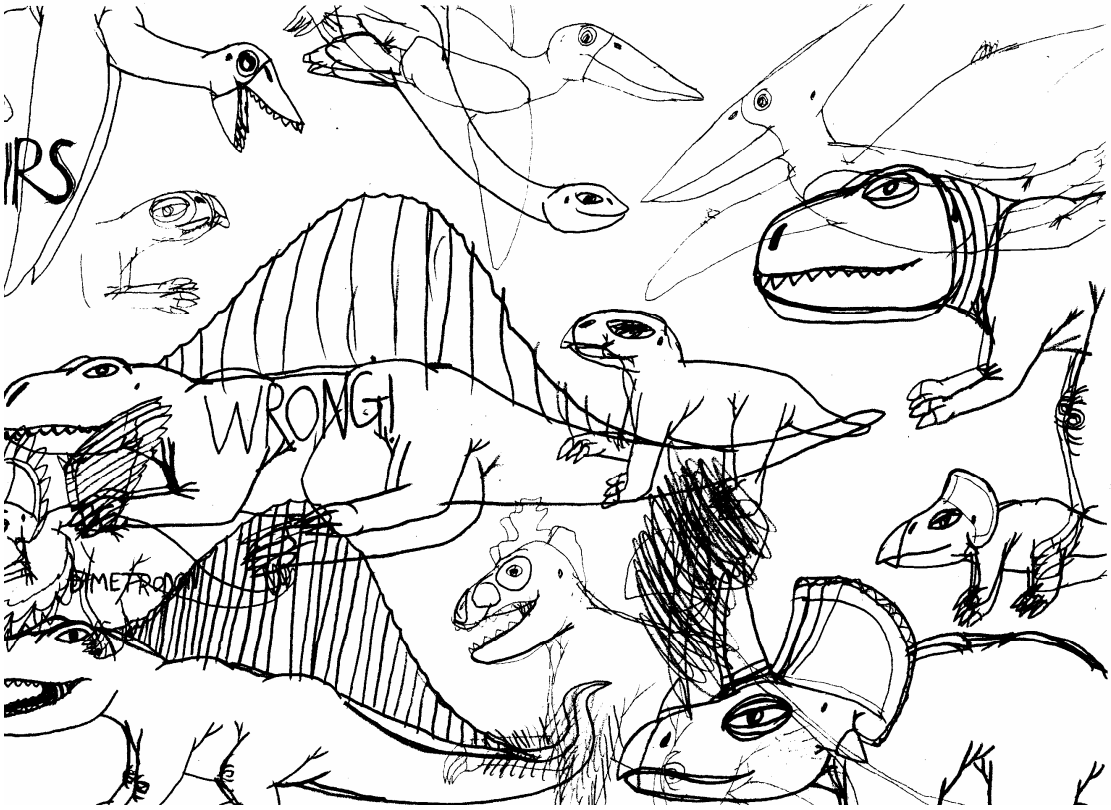
In the face of an epidemic disease, with unambiguous implications for a major environmental influence in causation, what is disrupting the innate immune system in children such that they can then not respond appropriately to other, perhaps, ordinarily benign environmental exposures? How do we define that risk at the biochemical level? I'm not going to talk about this in depth; I'm going to refer you to the elements of the presentations that follow. We need a starting point. There is no better starting point than (i) the clinical history and (ii) a knowledge of known causes of autistic spectrum disorders including viral exposures in utero or in the perinatal period, including rubella and measles. My belief is that the answer will come from examining the determinants of the innate immune system function that operate early in life.

How is an increased risk determined at the biochemical level? We will be looking today at the genetic and environmental influences upon detoxification reactions and the body's principal mechanism for dealing with 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, subjects that will be covered in detail by subsequent speakers.

In summary, many children with developmental disorders have an underlying and potentially primary inflammatory bowel disease. This disease is novel and similar in different behavioral subsets including autism, ADD, and 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, and 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 CNS function. I think much of the answer to the autism puzzle will come from understanding the influences on the education and functioning of the innate immune system.

Ultimately the question for today is, "How do we use the knowledge that has been gained to recover children?" How do we take the elements of the history, the physical examination, and pathologic findings, and put these together in order to unravel the health problems in these children? And how do we prevent disease?



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Dr.Andrew J. Wakefield : Gastrointestinal comorbidity, Autistic Regression and Measles-containing Vaccines: positive re-challenge and biological gradient:

Abstract

Background: A temporal association between exposure to measles-containing vaccine (MCV) and autistic-like developmental regression in a sub-set of children with enterocolitis has been reported. Measles virus (MV) was detected in ileal biopsies from these children at higher prevalence than in developmentally normal paediatric controls.

This study tested the hypothesis of a dose-response effect of MCV exposure on intestinal pathology, as evidence of a causal association.

Methodology/Principle Findings: Children with normal early development and autistic-like developmental regression were divided into two groups: re-exposed children (n=23), who had received more than one dose of a measles-containing vaccine (MCV), and once-exposed children (n=23), who had received only one dose of MCV. The groups were matched for sex, age, and time-elapsed from first exposure to endoscopy. Comparisons included: secondary (2o) gastrointestinal (GI) and related physical symptoms and observer-blinded scores of endoscopic and histological disease. Re-exposed children scored significantly higher than once-exposed for 2o physical symptoms including incontinence, presence of severe ileal lymphoid hyperplasia, number of biopsies with epithelial damage and number of children with acute inflammation. Markers of acute inflammation included number of children affected and proportion of biopsies affected

Conclusion/Significance: The data identify a re-challenge effect on symptoms and a biological gradient effect on intestinal pathology, which links MCV exposure to autistic-like developmental regression and enterocolitis.

1. Introduction

Autism spectrum disorders (ASDs) are a complex set of developmental disorders of childhood, characterized by pervasive impairments in social interaction, deficits in verbal and non-verbal communication and stereotyped, repetitive patterns of behavior and interests. Manifestations frequently begin within the first three years of life. The prevalence of ASD diagnoses has increased substantially over the last decade in developed countries [1,2].
There is a growing awareness of gastrointestinal (GI) and immunological co-morbidity in some ASD children [3-6] that, for those with GI symptoms, may be associated with later onset of behavioral deterioration [7].
An ASD phenotype has recently been described that is associated with developmental/behavioral regression, enterocolitis, and immune abnormalities [3-6,8,9]. Parental reports from the U.K., the U.S., and elsewhere frequently cite exposure to the measles-mumps-rubella (MMR) vaccine as the trigger for their child's physical and behavioral deterioration. The characteristic intestinal pathology in the affected children – ileocolonic lym-phoid nodular hyperplasia (LNH) and mucosal inflammation – and the systemic immunologic abnormalities are consistent with a viral etiology [10].
Flow cytometric and immuno-histochemical analysis of mucosal lymphocyte populations in ASD children have demonstrated qualitatively consistent abnormalities at different anatomic sites, indicating a relatively homogenous mucosal lymphocyte infiltrate of predominantly CD8+ phenotype [8,9,11]. The cytokine profile of this lymphocyte infiltrate includes a significant increase in the proportion of CD3+TNFα+ cells and a significant decrease in the proportion of CD3+IL-10+ cells com-pared with non-diseased pediatric controls [12]. This constellation of pathology is reminiscent of HIV enteropathy [13,14].
Recent reports have implicated MV as one possible etiological agent, and indicate the presence of MV antigen [10] and genomic RNA [15] in foci of hyperplastic gut mucosal lymphoid tissue. Singh et al. have reported an atypical humoral immune response to MV in ASD children that correlates with abnormal serum antibody titers to myelin basic protein [16,17]. These findings

are consistent with, but not proof of, a causal relationship between MV in some form and ASD in a subset of affected children.
Challenge re-challenge refers to a situation where re-exposure of an individual to an agent (e.g., a drug or a toxin) elicits a similar adverse reaction to that seen following the initial exposure. The secondary reaction associated with re-challenge may either reproduce the features associated with the primary challenge, or may lead to worsening of the condition that was provoked or induced by the initial exposure. Alternatively, the risk of an adverse outcome may increase with in-creasing exposure.
During the course of our clinical investigations, we have observed that some children who received a second dose of MMR or boosting with the combined measles rubella (MR) vaccine experienced further deterioration in their physical and/or behavioral symptoms following re-exposure. It was stated in April 2001 by the Vaccine Safety Committee of the U.S. Institute of Medicine (IOM) that, in the context of MMR vaccine as a possible cause of autism "challenge re-challenge would constitute strong evidence of an association" [18]. doi: 10.1588/medver.2006.03.00100
A.J. Wakefield, C. Stott, K. Limb/Medical Veritas 3 (2006) 796–802 797
This study tested the hypothesis that GI features, including symptoms and mucosal pathology, may exhibit a different pat-tern and degree of severity in ASD children who received more than one dose of MMR/MR compared with ASD children who received only one dose.

2. Patients and Methods

From the cohort of 179 children with developmental disorders and GI symptoms (ASD children) referred for a gastroenterological opinion to the Royal Free Hampstead NHS Trust, all children were identified, from hospital record review, who had received more than one dose of a measles-containing vaccine (MCV) (monovalent measles, MMR or MR). These constituted the "re-exposed" group. Developmental diagnoses had been made by appropriate specialists prior to referral for GI opinion.

A child was further eligible for inclusion if there was no documented evidence of abnormal development from clinical records for at least the first 12 months of life. All but three children had received a diagnosis of an ASD. The exceptions were one girl who was under review with a provisional diagnosis of a complex learning disorder, one boy who had a diagnosis of attention deficit hyperactivity disorder (ADHD) with autistic features and a complex learning disorder, and one girl who was considered to have a variant of Rett's syndrome. The last child was included since, in common with other affected children, she had ileal LNH and enterocolitis and was positive for MV RNA in intestinal lymphoid tissue and blood. In addition, while the predisposing genetic lesion for Rett's is known, infectious, enteritic and vaccine exposures are reported to be triggers for the development of this syndrome [19,20].
An important consideration in those elements of this study that rely upon reporting of historical symptoms is recall bias: once a possible association between exposure and outcome has been made, subsequent responses may be biased in favor of this association. In addition, it is possible that physical deterioration, with apparently long-term residual effects, is part of the natural history of some ASDs. In an attempt to address these possibilities in the design of this study, a comparison sample was included. For each case, a child was identified who had no evidence of abnormal development in clinical records during at least the first 12 months of life and a formal diagnosis of developmental disorder (all ASD), as described above, but who had received only one MCV ("once-exposed"). Re-exposed and once-exposed ASD children were matched as closely as possible for sex, age, and time elapsed from first MCV exposure to GI endoscopy.
In order to minimize potential selection bias, the once-exposed group was selected consecutively from the list of those ASD children investigated in the paediatric GI clinic.

3. Clinical History

Efforts were made to obtain all routine clinical, developmental and educational records on each child. These included re-cords from general practitioners

(including vaccination re-cords), health visitors, outpatient and inpatient attendances and parents. Medical history and age of symptom onset were deter-mined on the basis of the available information. The focus of this study is GI aspects of the children's medical history. An analysis of the developmental history of these children is be-yond its scope.
The term "primary physical symptoms" (1o symptoms) refers to the onset of novel GI, or other potentially related physical symptoms (e.g., failure to thrive) after the first MCV (MCV1). The term "secondary physical symptoms" (2 o symptoms) refers to the chronic exacerbation of 1o symptoms, or acquisition of new GI and related symptoms, which must, by definition, have followed 1o symptoms. Symptoms were ascertained from the medical records and are based upon the parental history given to the pediatric gastroenterologist at the patient's initial presentation. Data were cross-checked in the follow-up interview with the parents, which was possible for more than 90% of children.

4. Ileocolonoscopy and Histopathology

All children had undergone ileocolonoscopy. Symptomatic indications for ileocolonoscopy included diarrhoea (sometimes spurious, in association with faecal impaction), abdominal pain and bloating, and failure to thrive (see below). No children were receiving anti-inflammatory or gastrointestinal medications. All endoscopic and histological data were gathered prospectively as described previously [4], without awareness of the vaccination status of the child. The assessed features included presence and grade of ileal LNH: absent (0), mild (1), moderate (2), and severe (3). The qualitative and quantitative evaluation of ileal LNH in these children has been described previously [4,8]. In addition, the mucosal features of: colonic LNH, red halo sign [21], loss of vascular pattern, granularity, erythema, and ulceration, were scored as present (1) or absent (0), as described previously [4]. Colonic biopsies were obtained from the cecum; the rectum; and the ascending, transverse, and descending/sigmoid colon. All ileal and colonic biopsies were scored on a standard pro-forma as described and validated previously [4]. The same pathologist scored all the biopsies from re-exposed and once-

exposed children. All scoring was conducted prospectively, without any knowledge of the vaccination status or specific developmental history of the child. Biopsies were scored for the presence and grade of acute (neutrophilic) and chronic (lymphocytic) inflammation, epithelial and crypt pathology, lymphoid reaction, and eosinophil infiltration. Presence of acute mucosal inflammation, characterized by neutrophil infiltration of the lamina propria, cryptitis, and crypt abscess formation, reflects more severe, active disease. All children were screened for celiac disease by anti-endomyseal antibody testing. Routine stool culture and microscopy, and serological analyses were performed to screen for common pathogens.

5. Statistical Analysis

Data analysis was carried out using SPSS for Windows v11. Analysis comprised cross-tabulation with p values reported on the chi-square statistic. Where the expected count in any cell was less than 5, Fisher's Exact Test was used. The relative risk statistic (RR) is presented as an estimate of the differential risk associated with re-challenge. 95% Confidence Intervals (CIs) provide information about the degree of certainty around the point estimate with an indication of 5% statistical significance.

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A CI which includes the value of 1 indicates a p value of >0.5. Owing to differences in site and number of biopsies per child, and frequency of ileal examination during endoscopy, data were analyzed using unpaired analysis. The Mann-Whitney test was used to compare time elapsed between (i) those with and with-out acute mucosal inflammation, and (ii) those with grade III (severe) and grade I (mild) ileal LNH. Statistical significance for all relevant analyses was accepted to be $p<0.05$.

6. Ethics Approval

Ileocolonoscopy and histopathology were performed accord-ing to clinical need with informed parental consent. Record review was undertaken as part of studies already approved by the Ethical Practices Committee of the Royal

Free Hampstead NHS Trust. In order to minimize the potential for reporting and recall bias parents were not made aware of the specific aims of the study, although they were aware of the potential association between exposure to MCV and onset of an ASD.

7. Results

After exclusion of children for whom satisfactory documentation or corroborative evidence was not available, adequate clinical records on 23 re-exposed and 23 once-exposed ASD children were available for comparison. Table 1 provides a summary of the relevant details for each child in the following format: Column 1 provides the number (by row) of each re-exposed child (left panels) and once-exposed child (right panels). The sex and age of individual children are shown in column 2. Time elapsed from MVC1 to GI endoscopy is provided in column 3. Column 4 identifies the measles-containing vac-cine exposure of children and the age in months at which these vaccines were given. The right-hand side of the table provides the identical information as above, for once-exposed children. There was no evidence of celiac disease in any child. Giardia cysts were identified in one once-exposed child (No. 8, Table 1).

Onset of 1o physical symptoms followed MCV1 in 22 of 23 (96%) once-exposed children and 16 of 22 (73%) re-exposed children. Re-exposed child no. 23 (Table 1) was excluded from this analysis because he received a first MMR at 4 months of age. This was so early and at such variance with all other children that a valid assessment of physical symptoms was deemed impractical. The 1o physical symptoms included frank diarrhea (4 re-exposed, 7 once-exposed), constipation (2 re-exposed, 5 once-exposed), alternating constipation and diarrhea (4 re-exposed, 3 once-exposed), abdominal pain, often associated with bloating (5 re-exposed, 8 once-exposed), blood per rectum (2 re-exposed, 1 once-exposed), and recurrent mouth ulceration (2 re-exposed). Non-GI symptoms included onset of seizures (1 re-exposed, 1 once-exposed) and gait disturbance with loss of motor skills (6 re-exposed, 7 once-exposed). These neurological features are reported here for interest,

given their documented association with GI inflammation [22]. Of the 6 re-exposed children who developed 1o physical symptoms after MCV2, 5 children suffered onset of 1o chronic GI problems as described above. One child stopped growing for 18 months; his growth re-commenced only after the introduction of a gluten-free, casein-free (GFCF) diet.

Onset of secondary (2o) GI symptoms after the second MCV (MCV2) was evident in 11 of 22 (50%) of the re-exposed group; i.e. 11 of the 16 (69%) children who had experienced 1o GI symptoms following MCV1. Because none of the once-exposed children developed 2o physical symptoms it was not possible to calculate a quantitative relative risk estimate. How-ever the difference between re-exposed and once-exposed children for occurrence of 2o GI symptoms is statistically significant (RR ∞ (infinity) $p<0.0001$). The difference between re-exposed and once-exposed children for occurrence of 2o fecal and/or urinary incontinence (having previously been continent, i.e., toilet trained) is also statistically significant (RR 2.44; 95% CI, 1.68-3.55).

The 2o physical symptoms involved chronic exacerbation of pre-existing GI problems and development of novel chronic GI symptoms including: severe constipation (4), diarrhea (3), alternating constipation and diarrhea (2), blood and mucus per rectum (2), recurrent mouth ulceration (3), failure to thrive (2), and fecal incontinence (6). Some children had more than one symptom. Accompanying these GI symptoms were loss of co-ordination with gait disturbance (3), erythema nodosum (1) and joint pains (1). The latter was diagnosed as anti-nuclear anti-body-positive juvenile arthritis. One re-exposed child became clumsy with non-epileptiform falling episodes after his initial MMR at 15 months; following his booster MMR at 96 months he was unable to stand at all for 2 weeks, a situation that gradually resolved over several months.

8. Ileo-colonoscopy

The ileum was evaluated in 23 re-exposed and 22 once-exposed children. Ileal LNH was present in 22 of 23 (96%) re-exposed and 21 of 22 (95%) once-exposed children (NS). Severe (grade III) ileal LNH was present in 14 of 23

(61%) re-exposed children and 3 of 22 (14%) once-exposed children (RR 4.46; 1.48-13.43). Of the remaining children, both groups exhibited similar proportions of grades 0-2. The entire colon was visualized in all children. Colonic LNH was seen in 12 of 23 (52%) exposed children and 10 of 23 (43%) once-exposed children (NS). There was no predilection for LNH in any particular part of the colon. Features indicative of colonic mucosal inflammation, including erythema, loss of vascular pattern, and mucosal granularity were seen in 12 (52%) re-exposed children, and 14 (61%) once-exposed children (NS). Aphthoid ulceration was seen in two (9%) re-exposed and one (5%) once-exposed child (NS).

9. Histopathology

Details of surgical pathology are provided in Table 2. Pathological changes were patchy and distributed throughout the colon as described previously [4]. Acute inflammation of the colonic mucosa was present in 14 of 23 (61%) re-exposed children and 3 of 23 (13%) once-exposed children (RR 4.67; 1.55 - 14.09) (Table 2). For large bowel biopsies, the proportion with acute inflammation is significantly greater in re-exposed children: than in once-exposed children (RR 4.93; 2.15-11.35) (Table 2).

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A.J. Wakefield, C. Stott, K. Limb/Medical Veritas 3 (2006) 796–802 799

In order to make a valid comparison of the severity of acute inflammation between groups, grades of inflammation were expressed as a proportion of biopsies showing acute inflammation in each group, i.e., where acute inflammation was present, how did its severity compare between groups? Moderate and severe grades were combined for the purposes of statistical analysis since there were no once-exposed children with severe inflammation. The severity of acute inflammation although, greater in re-exposed children than in once-exposed children (RR 4.35; 0.72-26.37) (Table 2), was limited in power by the fact that so few biopsies from once-exposed children had even mild acute inflammation.

There is no significant difference between re-exposed children and once-exposed children for the presence of chronic inflammation

The number of children showing epithelial damage, including disruption of the epithelial basement membrane, crypt architectural changes, and goblet cell depletion, is not significantly different between re-exposed and once-exposed children (RR 1.36; 0.81-2.30) (Table 2). However, the number of biopsies showing epithelial damage is significantly greater in re-exposed children than in once-exposed (RR 1.49; 1.09-2.03) (Table 2).

10. Time-elapsed from MCV1 to endoscopy

Re-exposed and once-exposed groups were matched as closely as possible for time elapsed from MCV1 to endoscopy in order to take into account any progression of disease over time. There is no significant difference between re-exposed and once-exposed children for time elapsed (mean +/- standard deviation: 89 ± 28 months in re-exposed children versus 78 ± 27 months in once-exposed children). However, a mean difference of approximately 11 months may be biologically significant in terms of the disease's natural history.

In order to determine whether time elapsed was independently associated with mucosal pathology, re-exposed and once-exposed groups were merged and then segregated into those (i) with and without acute inflammation, and (ii) those with mild or severe ileal LNH. There is no significant difference in time elapsed between those groups with and without acute inflammation or between those with mild and severe ileal LNH.

11. Discussion

This study tested an a priori hypothesis and the results pro-vide evidence of a re-challenge effect associated with polyvalent measles-containing vaccines, specifically MMR and MR vaccines. The data build upon the growing clinical and basic scientific evidence of an association between autistic-like developmental regression, mucosal immunopathology and MV exposure [3,10,15-17].

Clearly it would be of interest to examine ASD children who do not have GI symptoms, and ASD children who had received only monovalent measles-containing vaccine in a similar manner. However, in the former case, the

ethical constraint against performing invasive procedures on asymptomatic children means that this comparison is not feasible. In the latter case, the fact that all countries with comparable demographics and diagnostic facilities have used MCV over the same period makes this comparison impossible at this time.

A potential shortcoming of this study is that not all expert developmental diagnoses were re-evaluated in our unit. Re-evaluation has been performed in previous studies [3,4,8], and we have no reason, based upon these prior observations, to doubt the accuracy of the original diagnoses. All children studied remain under review by local developmental pediatricians, and we are unaware of any case in which the diagnosis has been revised. Vaccination histories were verified in the study children. It is possible, however, that without access to complete records on all 179 children, because of available resources, some re-exposed children may not have been identified for inclusion in the study.

All children in this study were identified from the same source population, that is, children with a pervasive develop-mental disorder referred for investigation of GI symptoms. Inclusion of a once-exposed group was considered essential in order to minimize selection and recall biases. One potential problem with this kind of study is that because the conditions of interest (neurodevelopmental and physical symptoms) are often insidious in onset and diagnosis considerably delayed [23], there is rarely a specific acute event to be documented. Physicians may also be reluctant to ascribe a novel event to an ad-verse vaccine reaction. In addition, documentation was generally of a relatively poor standard. In light of previous experience [24], it was considered that these factors would tend to bias towards the null hypothesis, i.e., no association.

The natural history of the mucosal lesion is not known. We are not yet in a position to say whether the excess of acute inflammation in the re-exposed group is permanent, or whether, as with classical inflammatory bowel disease, it reflects episodic reactivation. We can only say that acute inflammation was more common and had a tendency to greater severity in the re-exposed

group. The proportion of biopsies with acute inflammation was also greater in re-exposed children, although this particular statistical analysis assumed that all observations derived from independent cases. This will function to underestimate the observed standard error and leads to the possibility of a Type I error in which the null hypothesis is incorrectly rejected. It is possible that inflammation either progresses or remits over time. However, time-elapsed was not an independent risk factor for pathology, including acute inflammation and LNH, when those children with and without these features were compared.

In order to examine further the relationship of these out-comes, acute inflammation and presence and severity of LNH were independently linked to age at endoscopy in a study of the first 148 ASD children in the source population [25]. There is no significant association between age and any of these mucosal features. It might be anticipated that symptoms and disease severity would be greater in the once-exposed group; these children were not re-vaccinated since, for the majority, parents had made an association between symptoms and MCV1 expo-sure and therefore, did not have their children re-vaccinated with MCV. This possibility is supported by the observation that 1o physical symptoms were reported in all once-exposed children following MCV1, whereas they were reported only after MCV2 in 6 re-exposed children. This suggests that, if anything, the initial disease ran a milder course in re-exposed children and that, if there were no causal association with MCV, the mucosal pathology should be less severe. This was not the case.

Several aspects of this study strengthen the possibility of a causal association between MCV and the syndrome of autistic-like developmental regression and enterocolitis. First is a challenge re-challenge effect on physical symptoms. Second, is a “biological gradient” [24] seen particularly in the severity of mucosal inflammation. Severe ileal LNH and acute “active” inflammation were more common in re-exposed children. In addition, the risk of an event such as onset of physical symptoms increased with higher frequency of exposure, with primary symptoms starting only after MCV2 in some children. The

idiosyncratic nature of the mucosal lesion that, as detailed pathological studies have indicated, is distinct from classical inflammatory bowel disease (Crohn's disease or ulcerative colitis) [8,9,11,12,26], supports a specific etiological process.

The importance placed upon re-challenge in determining causation is evidenced by reports from the IOM's Vaccine Safety Committee, where judgment favouring acceptance of a causal relationship has been based solely on the evidence of one or more convincing case reports. For example, Coulter and Fisher [27] reported one case of haemolytic anaemia in a 2-year-old boy, which occurred six days following a fourth dose of DPT vaccine. The boy returned to health until 6 days after his fifth DPT vaccine, when he was re-hospitalized with the identical symptoms that accompanied his initial reaction plus loss of consciousness.

Autistic regression with loss of faecal and urinary continence is consistent with descriptions of childhood disintegrative disorder (CDD) [28]. Although the majority of children had never achieved full continence by the time of their 1o regression, in those re-exposed children who did achieve continence after MCV1, loss of continence and faecal soiling frequently followed MCV2. There are a number of possible reasons for this; a relatively common finding in these children is acquired megarectum, with faecal impaction and overflow or "spurious" diarrhoea. This may lead to loss of normal rectal sensation, and faecal in-continence that might operate either independently of, or in concert with, developmental regression. Disturbances in maturation may also follow impaction of the rectum.

Reports of clumsiness, gait disturbance, and ataxia were present in a proportion of these children. Symptoms appeared to be prominent during the earlier phases of regression. This may be relevant to reports of loss of coordination in CDD [28], and gait disturbance and ataxia following MMR as reported by Plesner et al. [29,30]. In Denmark this association had not been detected with any other vaccine administered to children of the same age prior to the introduction of MMR in 1987, indicating that a novel adverse event might be associated with the combined MMR vaccine, rather than the

monovalent component vaccines. In a recent follow up of Denmark's mandatory passive reporting system, Plesner confirmed this association and indicated that more severe ataxias following MMR may be associated with residual cognitive deficits in some children [30]. It would be of value to establish the nature of these residual deficits.

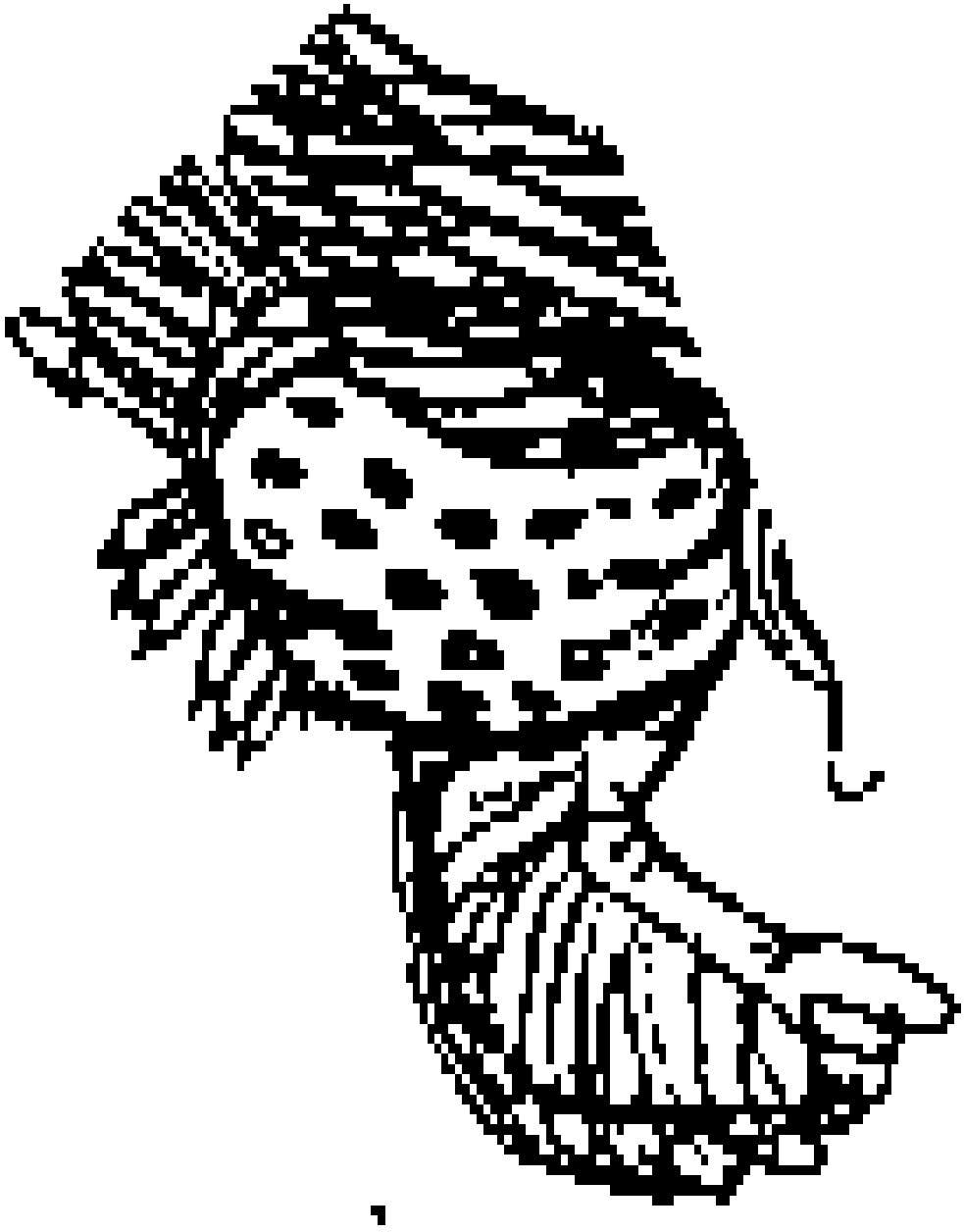
Epidemiological studies that have examined the possible MMR-autism association have concluded that the data provide no evidence in support of this hypothesis [31-35]. These studies have been challenged on a number of counts including inappropriate methodology [36], lack of statistical power and lack of a control group [37,38], indiscriminate diagnostic groupings, [39] and non-disclosure of relevant data [40]. Reanalysis of the data of Dales et al. [34] and Madsen et al. [41] has, in fact, identified a positive association for some children [42,43].

Clearly, meaningful epidemiological studies should test a priori hypotheses that derive from all clues evident in the clinical histories of affected children. Thus far, this has not happened.

A crucial question relates to what makes a child susceptible to a possible adverse event to a MCV. Potential risk factors are beginning to emerge in the histories of affected children including: familial autoimmunity, pre-existing dietary allergy/intolerance, vaccination with MCV while unwell (including current or recent antibiotic administration), and receipt of multiple simultaneous vaccine antigens, with the associated potential for immunological interference [43-45], particularly for mumps upon measles virus [44].

The growing burden of infant vaccines may increasingly skew the immune response away from optimal antiviral immunity towards a dominant T-helper cell type 2 repertoire [46]. The rapid increase in numbers of children with dietary allergy—itself associated with reduced CD8 cell numbers, pro-longed viral infections, and familial autoimmunity [47] with increasing infant exposure to heavy metal toxicity and antibiotic use over the last 10-15 years—suggests that the number of children who may be at risk of aberrant responses to atypical infectious challenges will have risen in the last decades. A likely

autoimmune component to the pathogenesis of regressive autism [9,25] suggests that any causal association with MCV would lead to a continuing upward trend in incidence after vac-cine introduction, in developed-world but not developing-world populations, in parallel with other autoimmune lesions. In summary, this study confirms that there is a challenge re-challenge effect of MMR/MR upon GI symptoms and ileocolonic pathology in these children with pervasive developmental disorder, principally autism. In accordance with previous findings of the IOM, this constitutes evidence suggestive of causality.



05.1

Dr.Steve Walker:

PERSISTENT ILEAL MEASLES VIRUS IN A LARGE COHORT OF REGRESSIVE AUTISTIC CHILDREN WITH ILEOCOLITIS AND LYMPHONODULAR HYPERPLASIA:

Steve Walker, Karin Hepner, Jeffrey Segal, Arthur Krigsman, Wake Forest University School of Medicine

Background: Autistic enterocolitis, consisting of a nonspecific ileocolitis coupled with ileocolonic lymphonodular hyperplasia (LNH), was first introduced as a new, potentially virus-induced disease entity eight years ago in a group of ASD children with developmental regression.

Objectives: The primary objective of this study was to examine ileal biopsy tissue in a large cohort of pediatric patients who carry a diagnosis of regressive autism and whose chronic gastrointestinal symptoms warranted diagnostic endoscopic evaluation, for evidence of measles virus RNA.

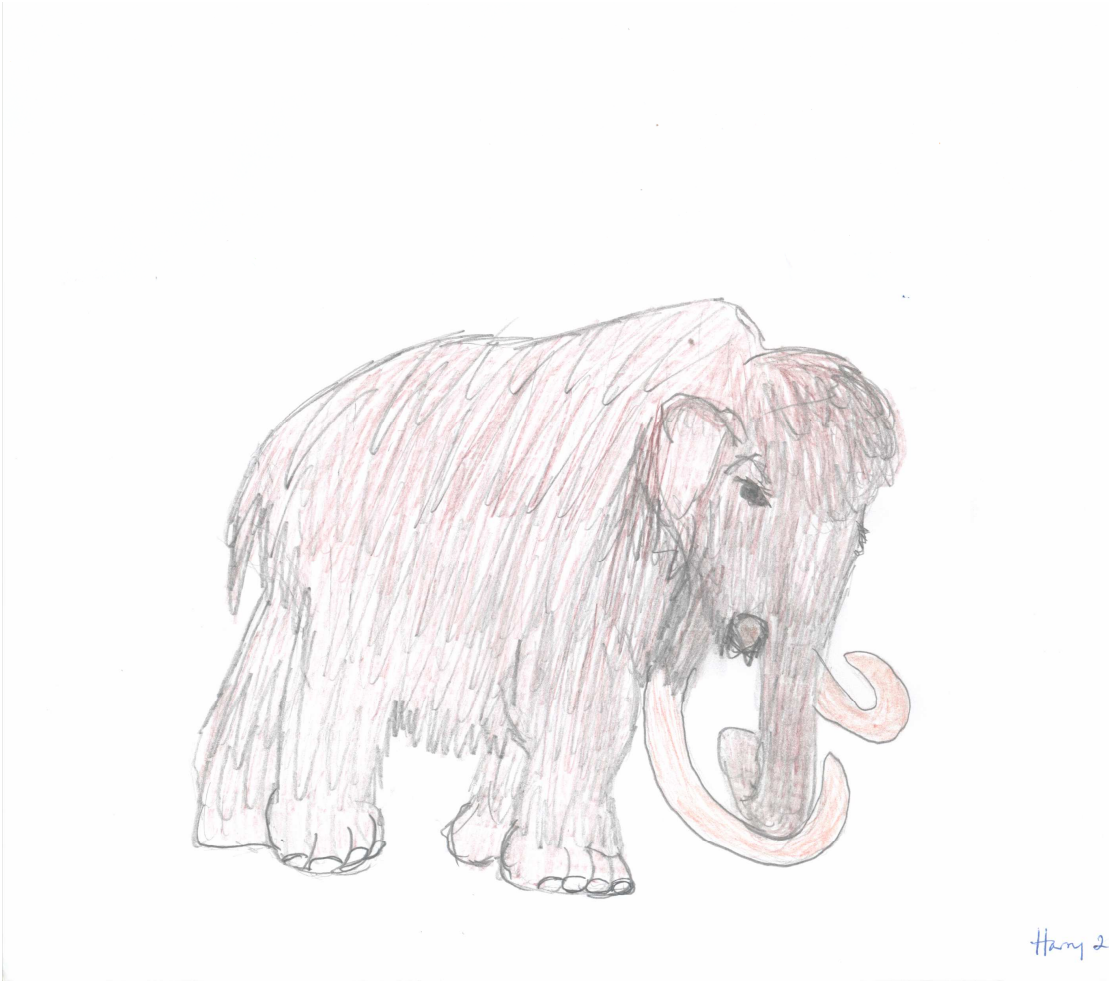
Methods: Patients who had been diagnosed with autism and who were referred to a pediatric gastroenterologist for evaluation of chronic GI symptoms were eligible to participate in this IRB approved study. For each patient, medical histories, vaccination records, histopathology reports, and ileocolonoscopic biopsy tissue were available for evaluation. Terminal ileum (TI) biopsy tissue was assayed by RT-PCR for the presence of measles virus RNA and PCR-positive samples were sequenced.

Results: Medical and clinical data have been collected for >275 patients who fit the study inclusion criteria. PCR analysis on TI biopsy tissue from an initial 82 patients showed that 70 (85%) were positive for the F gene amplicon. Fourteen have been verified by DNA sequence and an additional 56

amplicons are being sequenced now. Work is ongoing to assay the remaining specimens (~200) and to identify and assay relevant control tissue samples.

Conclusions: Preliminary results from this large cohort of paediatric autistic patients with chronic GI symptoms confirm earlier findings of measles virus RNA in the terminal ileum and support an association between measles virus and ileocolitis /LNH. Sponsors: ARI; NAA; individual donations

(The F gene amplicon is not unique to vaccine strain measles, but the is unlikely to be otherwise as the wild measles strains with the same signature are not endemic and do not appear in Europe or North America - KA).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06.0

Less is More

One-size-fits-all vaccination policies do not work. There is biodiversity among humans and to suggest that every human being will respond the same way to vaccination - or any medical intervention - is illogical given the different genetic factors inherent in biodiversity.

Until vaccine policies acknowledge the real risks and needs of the individual rather than dismissing individuals as expendable in service to the community, to many humans will become tragic casualties of the one-size-fits-all approach.

It appears that vets are more willing to consider the individual risks and needs of pets than pediatricians and public health officials are willing to consider the individual risks and needs of children when it comes to vaccination.

Most people are vaccinated for everything, even though the trend in medicine has been to tailor vaccine programs to lifestyle and risk.

The clarion call among doctors in recent years has been a movement away from reflexive annual "shots" and toward a more individualized approach: In its 2002 vaccine report, the American Medical Association rejected the idea of "one-size-fits-all" protocols, suggested that unnecessary over stimulation of the immune system might incur health risks, and divided vaccines into "core" and "non-core"categories.

A year later, the American Hospital Association went a step further: In its Vaccination Guidelines, it added a third category -not recommended at all - and gave suggested intervals of vaccination for each vaccine. Earlier this year, the association published an update of the guidelines, adding some new information about specific vaccines and the vaccination needs of very young children.

The original 2003 guidelines were "largely driven by the medical profession ‘s understanding that the way we have always done things may not be the way they will continue to be done," The fact that the 2003 protocols did not result in any obvious disease outbreaks reinforces the guidelines' message that "less is better".

Guidelines vs. habits. While some doctors have kept up with changing times, old habits die hard. "We have a lot of work yet to change the attitudes of most doctors in practice. We are trying to get them away from the annual thing and get them to understand that immunity doesn't stop on the precise day that the vaccine expires”.

Some doctors resist this nuanced approach to vaccination because of habit and economics. Urging a client to come in for annual shots is more compelling than a postcard cheerily announcing that it's "wellness exam" time.

Labels aren't guidelines. Another problem is Byzantine labelling and clever marketing on the part of vaccine manufacturers. "The label means nothing". Vaccines licensed for one year and three years are often the same product. "The label has an arbitrary and capricious annual revaccination requirement, and it takes an act of Congress to take it off" - literally. The Department of Agriculture has applied to remove the language, a legislative process that is estimated will take seven years.

Too much, too soon. Immunologist Jean Dodds of Santa Monica, Calif., a lecturer on vaccines, stresses that over vaccination can overwhelm the immune system. The new born child entering a new environment is at greater risk here, as its relatively immature immune system can be temporarily or more permanently harmed. Consequences may be the increased susceptibility to chronic debilitating diseases and or brain damage.

Vaccine labels themselves state that vaccines should only be given to the healthy. Carers who worry about their children's' immunity are recommended titers, or blood tests that can measure antibody levels.

Titers: What do they tell us? Many people who are trying to reduce vaccination are interested in using "titers" as a test to measure whether or not their child is still immune to a disease. They often speak of titers as showing "high" or "low" immunity, or of "having to" re-vaccinate when a titer is low. While there is not a tremendous amount of research on titers in children, I think it's fair to say there is quite a bit of misunderstanding on the part of carers, and even many doctors, as to what a titer test does or does not tell us.
A "titer" is a measurement of how much antibody to a certain virus (or other antigen) is circulating in the blood at that moment. Titers are usually expressed in a ratio, which is how many times they could dilute the blood until they couldn't find antibodies anymore. So let's say they could dilute it two times only and then they didn't find anymore, that would be a titer of 1:2. If they could dilute it a thousand times before they couldn't find any antibody, then that would be a titer of 1:1000.
A titer test does not and cannot measure immunity, because immunity to specific viruses is reliant not on antibodies, but on memory cells, which we have no way to measure. Memory cells are what prompt the immune system to create antibodies and dispatch them to an infection caused by the virus it "remembers." Memory cells don't need "reminders" in the form of re-vaccination to keep producing antibodies. (Science, 1999; "Immune system's memory does not need reminders.")
We should think about vaccines as a double-edged sword: necessary medical procedures that also have their risks and downsides. "Vaccination is an elective medical procedure that's going to be individual for each child instead of a knee-jerk sort of thing. Becoming informed yourself is very important. "

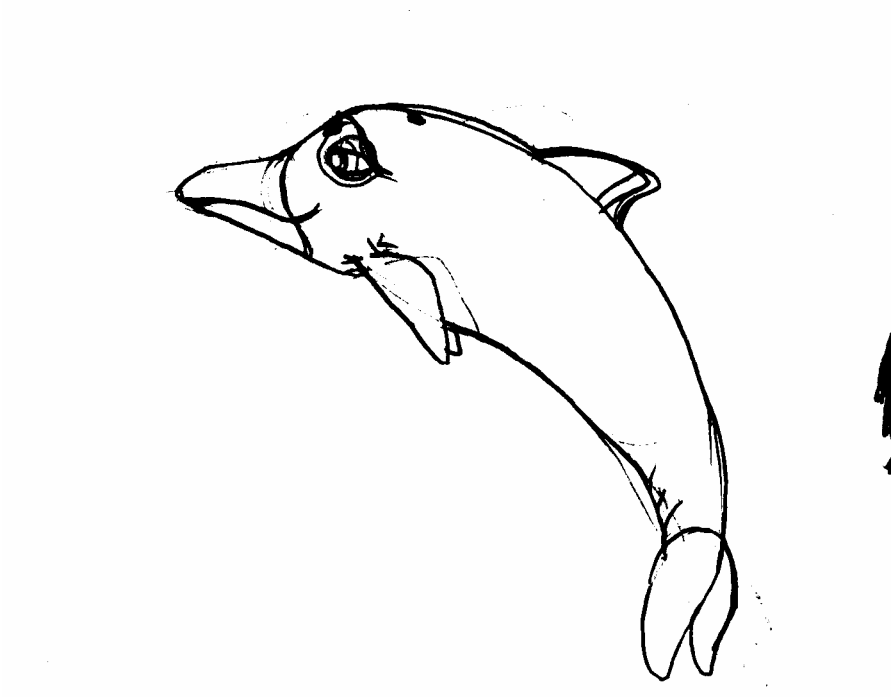
To that end, we encourages carers to discuss vaccination with their doctor - and if their doctor is unresponsive to their questions, to find someone

who does respond. "The key is using the right vaccines absolutely only as often as the child needs." We conclude. "Most assuredly, less is more."

07.0

Responsibility for vaccine damage:

Dr. Richard Ley, of the Association of British Pharmaceutical Industries said in the Daily Express (May 18 2000): 'The Government implemented the vaccination programme knowing in full detail what the possible side-effects were. They knew what they were taking on, the damage is therefore their responsibility and they should compensate people accordingly.'



08.0

World Health Organisation (WHO) - Causality of Adverse Events:

"Since the inception of vaccination, it has been recognized that adverse events following immunization (AEFIs) will occur." (Ref. 2 below)
The WHO gives criteria to be considered when an adverse event is reported:

1**. Consistency.** The association of a purported adverse event with the administration of a vaccine should be consistent, i.e. the findings should be replicable in different localities, by different investigators not unduly influencing one another, and by different methods of investigation, all leading to the same conclusion(s).
As already mentioned problems following MMR vaccination have been reported and accepted in Japan and the United States. A report from Finland described the immunization of 1.8 million individuals and gave rise to 173 potentially serious reactions claimed to have been caused by MMR vaccination. In all, 77 neurologic, 73 allergic and 22 miscellaneous reactions and 1 death were reported. (Ref. 3) Furthermore most of these cases were not followed up for more than a few weeks. And this Finnish study "did not examine the relationship of MMR and autistic spectrum disorders.....and does not therefore provide useful evidence on this point." Medical Research Council December 2001.

2. Strength of the association. The association should be strong in the magnitude of the association (in an epidemiological sense), and in the dose-response relationship of the vaccine with the adverse effect. JABS has been contacted by thousands of families who believe their children have suffered severe damage or have died following the MMR/MR vaccination. In the main, doctors cannot give any other medical explanation for the child's deterioration or death. It must be remembered that many of the children have been given the now withdrawn Urabe containing MMR vaccines which were known to

cause inflammation of the brain. Furthermore, many of JABS children shared the same batches of MMR vaccine and subsequently suffered the same long term effects.

3. Specificity.
The association should be distinctive and the adverse event should be linked uniquely or specifically with the vaccine concerned, rather than its occurring frequently, spontaneously or commonly in association with other external stimuli or conditions.

The three viruses, measles, mumps and rubella, are known to be linked with the children's conditions in their wild state. The vaccines contain the live viruses.

4. Temporal relation. There should be a clear temporal relationship between the vaccine and the adverse event, in that receipt of the vaccine should precede the earliest manifestation of the event or a clear exacerbation of an ongoing condition. For example, an anaphylactic reaction seconds or minutes following
immunization would be strongly suggestive of causality; such a reaction several weeks after vaccination would be less plausible evidence of a causal relation. A substantial proportion of the children had an immediate reaction to the vaccination, and the change which came over them dates directly from that reaction.

5. Biological plausibility. The association should be coherent; that is, plausible and explicable biologically according to known facts in the natural history and
biology of the disease. The viruses are known to be linked with the health problems when caught as the wild diseases. The vaccine manufacturers' acknowledge this by recording these problems as the 'rare' adverse events associated with their products. Many of the children have had a variety of

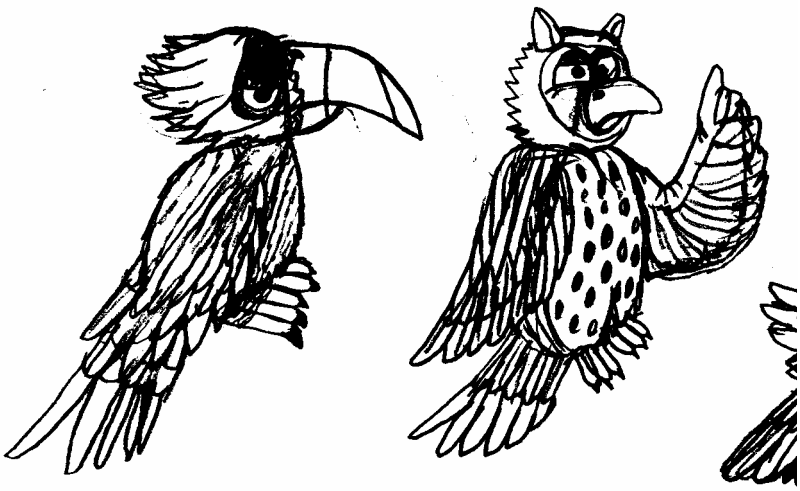
medical tests and examinations to rule out other causes. The WHO continues with:

a. The requirement for biological plausibility should not unduly influence negatively a consideration of causality. Biological plausibility is a less robust criterion than the others described. If an adverse event does not fit into known facts and the preconceived understanding of the adverse event or the vaccine under consideration, it clearly does not necessarily follow that new or hitherto unexpected events are improbable. Biological plausibility is most helpful when it is positive; it is less so when negative. This is an important statement as it makes it quite clear that just because something has not been recognized as linked with the vaccine in the past doesn't mean it isn't linked. This supports our concern that with the failure of the post-vaccination adverse event surveillance system to collect data on unexpected reactions and therefore a failure to investigate them could be allowing a serious problem to go undetected. This could lead to a catch 22 system; because the problem hasn't been linked with MMR vaccine before, further reports of the same problem are not put forward because they are not known to be linked with the MMR vaccine.

b. Consideration of whether the vaccine is serving as a trigger (trigger in this context is an agent that causes an event to happen which would have happened some time later anyway). When acting as a trigger, the vaccine may expose an underlying or pre-existing condition or illness. An example of the latter would be an auto-immune condition triggered non-specifically by the immune stimulus of the vaccine. This is an interesting point. Many of the parents report that their child's health problems are not known in the family's medical history but they have been told by their medical practitioner that the vaccine acted as a trigger
to reveal the underlying condition. What is particularly worrying is that the child usually has more than one, supposedly, rare condition that started at the same time e.g. autism and bowel problems, epilepsy and loss of speech and

communication and a failure to move on mentally from the point of vaccination. Some children developed health problems when vaccinated at four years of age or ten years of age or sixteen years of age after many years of good health and development progress.

c. In the case of live attenuated vaccines, if the adverse event may be attributable to the pathogenicity of the attenuated vaccine microorganism and thus not be distinguishable (except, perhaps, in severity) from the disease against which the vaccine is being administered, a causal connection is more plausible. Identification of the vaccine organism in diseased tissue and/or in the body fluids of the patient in such a situation would add weight to causality. There are exceptions to both these above points. Measles virus has been found in the spinal fluid - and therefore the brain - in three of the six children at the centre of the huge UK high court battle over the safety of the vaccine. It has also been found in 18 children in the United States who developed autism after receiving MMR.



09.0

Financial Cost of Vaccine Damage.

David Thrower (Letter to the Lancet, Spring 2004)
'Sir, As one of the parents who, through enforced circumstance, has become involved in the controversy surrounding the causes and consequences of autism, I wish to respond to your commentary.
(1) As you imply, the 2002 UK autism research funding of $2.75m was lamentably inadequate, and should be set against the very considerable economic costs of autism. It has previously been estimated that just one severe case of autism will cost the community up to £3m over that person's lifetime. The degree of severity and consequent precise costings could be debated at length. Costs include special needs education, home-to-school taxiing, escorts, daily respite care, overnight respite breaks, transport, health care, attendance and disability allowances, carer's allowance, and loss of tax revenues from the parent who has to cease work to become the child's carer. From age 16, you can add-on independent living fund payments and incapacity benefit. From age 19, schooling costs cease, but most of the other costs continue for life, and you also have to add in the lost tax revenue from the autistic person. In these circumstances, the estimate of £3m for the costs of a severe case of autism may well be an underestimate. But let us stay with £3m, for the sake of simplicity. So the 2002 autism research grant, for the UK, was actually less than the lifetime cost of just one severe case of autism.
And then you can try to estimate the numbers of UK cases. The recent unsuccessful UK High Court action alone involved 1,300 families. There have been many attempts at trying to gauge the numbers of UK autism cases. But hard State-collected data from the US Individuals With Disabilities Education Act database points to there being 120,000 children and young people ages 6-21 in full time education in the US with a primary diagnosis of autism, so a pro-rata application of those figures to the UK would give around 35,000 cases in the UK within that age-band. Obviously, not all cases

are severe, but a reasonable estimate would be that an assumed 35,000 cases would cost the taxpayer somewhere between £35 billion and £100 billion over the next seven decades, or between £500m and £1.4 billion per annum. This, of course, excludes any future cases that enter the autistic population over that time, plus the present existing small numbers of autistic adults. If autistic children continue to emerge at the rate now being recorded across the US, then the UK taxpayer could be facing an immense autism bill of several billion pounds per annum, within a couple of decades.
On those terms, even your sought-after £12.5m for autism research therefore seems grossly inadequate to research a condition that is clearly already creating an economic burden, and one that seems set to increase. And these future autism costs will apply wholly irrespective of the current controversy about autism's actual detailed causes. The children already exist now, today, for whatever reason. The economic stakes over seeking autism's causes are therefore extremely high.

I would also strongly support the efforts of Dr. Tom Jefferson in bringing adverse event surveillance out of the nineteenth century and into the twenty-first (2). But I would ask, how genuinely keen is our Department of Health, and government departments in other countries, to actively seek out every potential case of vaccine damage, and to analyse the data proactively? There seems to have been a marked lack of enthusiasm to date. The Medicines & Healthcare Products Regulatory Agency's existing Yellow Card system has been admitted by its predecessor, the Medicines Control Agency, to record only 10%-15% of even serious adverse events, yet the Agency seems quite content to live with that. In other areas of life, it is very difficult to imagine (say) the Vehicle Inspectorate being content with such a poor system for vehicle inspections, so why is medicine's Yellow Card scheme's inadequacy tolerated so readily? Perhaps the Agency lacks the determination that parents of damaged children have to investigate adverse outcomes.
Finally, as you rightly point out, "the discovery of a possible link between bowel disease and autism is a serious scientific idea.....and one that

deserves further investigation." The original Royal Free team paper was in February 1998. It is now Spring 2004. It is the continued abject failure to fund clinical research in this area, based upon the detailed examination of regressive-autism cases, that is the least acceptable aspect of the autism controversy, and I would welcome some candid explanation from the relevant authority, the Medical Research Council, as to what it has - or has not - been doing over the past six years.

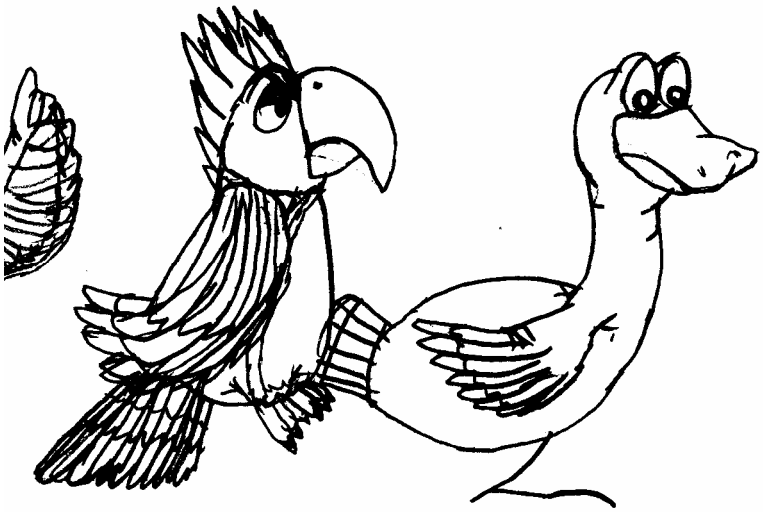
Yours faithfully,

David Thrower

References

(1) Commentary, The Lessons of MMR, Lancet, 2004, 363

(2) Jefferson T, Price D, Demicheli V et al. Unintended events following immunisation with MMR: a systematic review. Vaccine 2003; 21: 3954-60



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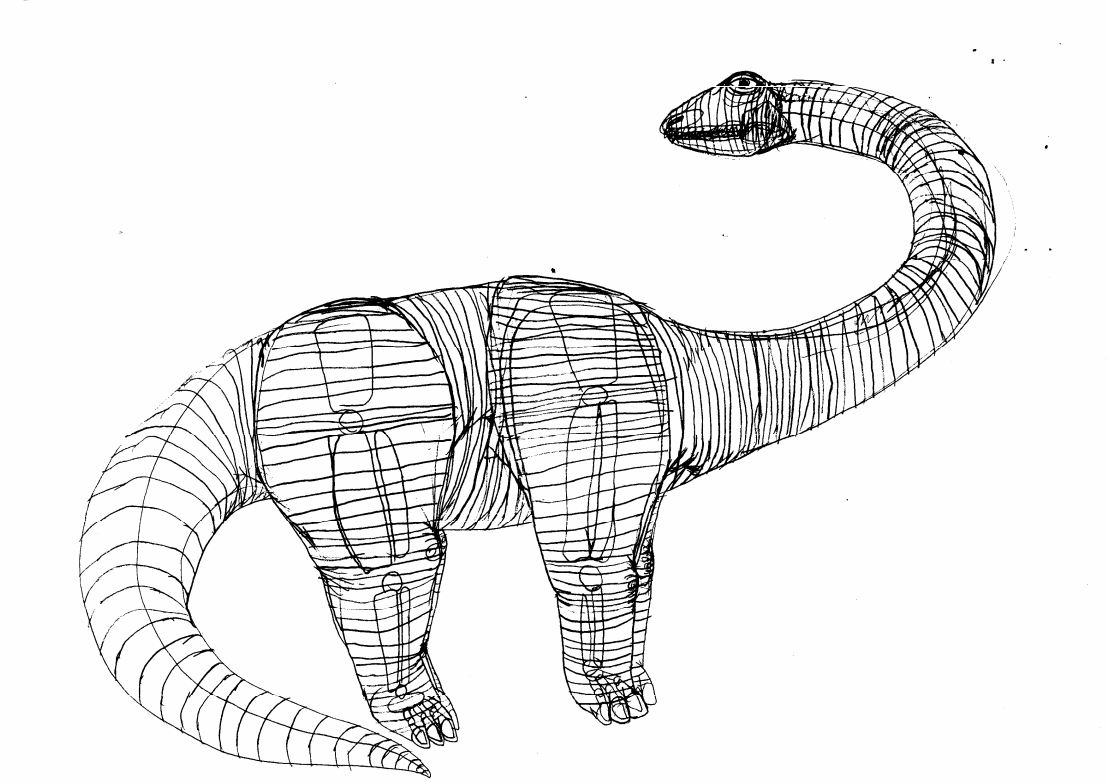
EVIDENCE OF HARM : Mercury in Vaccines and the Autism Epidemic - A Medical Controversy by David Kirby

Autism, rare in the past, is exploding in the United States , where it is now found in one in 166 children. Attention-deficit disorder also has skyrocketed. And 1 in 6 children today has a learning disability. David Kirby investigated whether one of the causes of these childhood afflictions is thimerosal, a vaccine preservative that contains mercury, a well-documented neurotoxin. In the 1990s, the mercury-containing additive was injected into children far in excess of federal safety levels.

Kirby told the story of stonewalling, denial and cover-up by federal regulators, medical groups and the pharmaceutical industry. And he documents covert efforts by some of those same powerful forces - along with the U.S. Congress - to grant blanket immunity for drug companies that put mercury in vaccines. Like so many scientific controversies involving complex science and big business, the topic is controversial. Kirby's careful and meticulous reporting is exemplary in its balance, accuracy and documentation.



11.0.

Dr. Mark Geier.

Mark R. Geier, MD, PhD, (b. 1948, Washington, D.C.) is a medical doctor based in Silver Spring, Maryland, who also holds a doctorate in genetics and is board-certified in medical genetics and forensic medicine. He was a researcher at the National Institutes of Health (NIH) for ten years, and previously was a professor at Johns Hopkins University. He has studied vaccines for more than 30 years and has published over 50 peer-reviewed papers on vaccine safety, efficacy, contamination and policy. He has authored over 90 publications and has made several presentations to the Institute of Medicine (IOM) on the adverse effects of vaccinations. He was an early critic of the whole-cell pertussis vaccine and is an expert on the biological effects of vaccine-induced infant death. He has published papers in over 30 different peer-reviewed journals including Annals of Internal Medicine and Rheumatology, on safety issues concerning hepatitis-B, Rubella, pertussis, Lyme disease, rotavirus, anthrax, and smallpox vaccines.
He and his son, David Geier, are the only independent researchers ever to have been permitted to study the Vaccine Safety Datalink (VSD) database of the Centers for Disease Control (CDC).

Controversial studies link vaccines with autism.

Geier and his son have published seven studies on the possible link between autistic spectrum disorders and Thimerosal-Containing Vaccines (TCVs). In their first study, they compared the number of complaints associated with TCVs, administered between 1992 and 2000, to the number of complaints resulting from a thimerosal-free vaccine administered between 1997 and 2000. The children who received greater amounts of ethylmercury from TCVs were more likely to have a complaint filed with the Vaccine Adverse Event Reporting System (VAERS). Further studies by the Geiers yielded similar results. In 2006, the Geiers published an article , "Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines", which contends that recent data confirms a reduction in autism

diagnoses corresponds directly with the removal of TCVs from childhood vaccination schedules.

US health agencies have uniformly rejected the conclusions of the Geiers' studies, and one of the Geiers' articles was the subject of heavy criticism by the American Academy of Paediatrics. Geier says public health officials are "just trying to cover it up." On the other hand, "Mercury in Medicine Taking Unnecessary Risks", a report prepared by the staff of the Subcommittee on Human Rights and Wellness, House Committee on Government Reform, Chaired by Dan Burton, was published in the Congressional Record in May, 2003, stated:

"However, the Committee upon a thorough review of the scientific literature and internal documents from government and industry did find evidence that thimerosal did pose a risk. *Thimerosal used as a preservative in vaccines is likely related to the autism epidemic*. This epidemic in all probability may have been prevented or curtailed had the FDA not been asleep at the switch regarding the lack of safety data regarding injected thimerosal and the sharp rise of infant exposure to this known neurotoxin. Our public health agencies' failure to act is indicative of institutional malfeasance for self-protection and misplaced protectionism of the pharmaceutical industry."[1].

Geier wrote the article, "The True Story of Pertussis Vaccination: A Sordid Legacy?" which won the first annual Stanley W. Jackson award for the best paper published in the Journal of the History of Medicine and Allied Sciences during the period of 2000 to 2002.

Geier has testified before the US House of Representatives Committee on Government Reform Investigating Vaccines and the Autism Epidemic, to critique the Hviid study, conducted in Denmark on autism and thimerosal exposure, and he has also addressed the Food and Drug Administration (FDA) Advisory Committee regarding vaccine safety. He has testified as an

expert witness in about 100 cases before the National Vaccine Injury Compensation Program in the US Court of Federal Claims. Dr. Geier and his son have been invited to speak to many state houses that were or are considering state wide bans on Thimerosal containing vaccines.

Geier has published several scientific reports, with his son David Geier, showing a relation between mercury exposure during infancy and the onset of neurodevelopmental disorders. Geier has suggested his research shows a direct causal link between Thimerosal containing vaccines (TCVs) and the onset of neurological disorders, including autism.

An advocate for vaccine safety

Geier has supported efforts by Representatives Dave Weldon, MD, Dan Burton, and Carolyn Maloney, to pass legislation introduced in early 2005 to ban the use of mercury based preservatives (i.e., thimerosal) in vaccines in the United States. Although mercury preservatives have been removed or reduced from some vaccines in the US, several vaccines and most US influenza vaccines still contain the full dose of Thimerosal. Geier said in an interview that the link between thimerosal and autism was clear.

Credibility as expert witness

Dr Geier has been accepted as an expert witness in approximately 100 hearings for parents seeking compensation from the National Vaccine Injury Compensation Program for vaccine injuries to their children.

On November 25, 2003, Special Master French praised Geier's credentials and vast experience and said Dr. Geier "ranks high among those who have studied vaccine issues through the medical literature on vaccines, databases, studies, articles and information on vaccine safety and efficacy in vaccine policy. The tenor of his testimony in this case addressed the importance of statistical databases in providing statistical reliability and validity in interpreting the epidemiology and issues relating to autism and various vaccines...Dr.

Geier has recently proposed a data-sharing process that would improve the reliability of present statistical data that would include the present VAERS statistical database. It would be helpful in interpreting the epidemiology and issues relating to the autism controversy." [7]

Furthermore, Dr. Geier's testimony has been found to be relevant and credible, and resulted in petitioner's prevailing before the National Vaccine Injury Compensation Program in decisions reached in each of the following cases:

Alger v HHS - Special Master Baird

Allen v HHS - Special Master Hauptly

Bailey v HHS - Special Master Gerard

Batdorf v HHS - Special Master Bernstein

Caouette v HHS - Chief Special Master Golkiewicz

Ciotoli v HHS - Special Master Wright

Cline v HHS - Special Master Bernstein

Davis v HHS - Special Master Wright

Dileo v HHS - US Federal Court of Claims Judge Margolis

Essex v HHS - Special Master Wright

Estep v HHS - US Federal Court of Claims Judge Margolis

Estep v HHS - Special Master Baird

Freeman v HHS - Chief Special Master Golkiewicz

Gonzales v HHS - Special Master Abell

Gowan v HHS - Special Master French

Grant v HHS - Chief Special Master Golkiewicz

Grant v HHS - US Federal Court of Claims Judge Tidwell

Hailey v HHS - Special Master French

Ionescu v HHS - Special Master Hastings

Lambert v HHS - Special Master Wright

McClendon v HHS - US Federal Court of Claims, Chief Judge Archer

McClendon v HHS - US Federal Court of Claims Judge Gibson

McDermott v HHS - Special Master Hastings

Misenko v HHS - Special Master Millman

Monteverdi v HHS - Special Master Gerard

Newton v HHS - Special Master Gerard

Oetting v HHS - Special Master French

Overgard v HHS - Special Master French

Pollard v HHS - Special Master Bernstein

Pusateri v HHS - Special Master French

Raines v HHS - Special Master Hauptly

Richardson v HHS - US Federal Court of Claims Judge Andewelt

Richardson v HHS - Special Master French

Riggs v HHS - Special Master French

Sanders v HHS - Special Master Wright

Seman v HHS - Special Master Baird

Siegfried v HHS - Special Master Baird

Sumrall v HHS - US Federal Court of Claims Judge Turner

Sumrall v HHS - Special Master French

Tafoya v HHS - Chief Special Master Golkiewicz

Thomas v HHS - Special Master French

Waugh v HHS - Special Master Wright

Work Experience:

1969-1970 - Research (Student) at the National Institutes for Health, Bethesda, MD

1970-1971 - NIH Traineeship at Columbia University, Department of Human Genetics and Development, New York, NY

1971-1973 - Research Geneticist, Laboratory of General and Comparative Biochemistry, National Institute of Mental Health (NIMH), National Institutes of Health (NIH), Bethesda, Maryland

1973-1974 - Staff Fellow, Laboratory of General and Comparative Biochemistry, NIMH, NIH, Bethesda, MD

1974-1978 - On Professional Staff Laboratory of General and Comparative Biochemistry NIMH, NIH, Bethesda, MD

1978-1979 - Intern and Fellow, Department of Obstetrics and Gynecology, the Johns Hopkins Hospital, Baltimore, Maryland

1979-1982 - Assistant Professor, Department of Gynecology and Obstetrics, the Johns Hopkins School of Medicine, Baltimore, MD

1980-1982 - Guest worker Laboratory of General and Comparative Biochemistry, NIMH, NIH, Bethesda, MD

1981-1984 - Assistant Research Professor, Psychiatry Department, Uniformed School of the Health Sciences, Bethesda, MD

1988-1994 - Director of Genetics of Maryland Medical Laboratory, Inc. Baltimore, MD

1989-1994 - Member of the Substance Abuse and Doping Committee and the Sports Medicine and Science Committee of the United States Bobsled and Skeleton Federation (Olympic Committee)

Board Certification:

1987 - American Board of Medical Genetics

1993 - Associate Founding Member of the American College of Medical Genetics

1996 - Board Certified by the American Board of Forensic Examiners

1996 - Diplomate of the American Board of Forensic Medicine

Other Positions:

1980-2003 - Laboratory Director, Molecular Medicine, MD

1980-Present - Co-director of Genetic Consultants, Bethesda, MD

1981-Present - Director of Institute of Immuno-Oncology and Genetics, MD

1986-Present - President of Genetic Counseling and Research, Inc., T/A The Genetic Center, Baltimore, MD

1997-Present - President of Genetic Counseling and Research, Inc. T/A The Ultrasound Institute of Baltimore

1997-Present - President of the Genetic Centers of America

2001 - Host of one hour weekly medical talk show “The Dr. Mark Geier Show” on KFNX in Phoenix, Arizona, WALE in Provident, Rhode Island, and on the World Wide Web.

Journal Peer-Reviewer:

Annals of Internal Medicine

Clinical and Experimental Rheumatology

Environmental Health Perspectives

Expert Review of Vaccines

Expert Opinion on Emerging Drugs

Vaccine

Major Presentations:

Addressed United States’ State Department, Foreign Service Institute (Washington, DC) on Contemporary Genetics

Addressed the Institute of Medicine of the U.S. National Academy of Sciences (Washington, DC) on Vaccine Safety & Vaccine Policy Issues

Addressed the Government Reform Committee of the United States’ House of Representatives (Washington, DC) on Vaccine Safety Issues

Addressed the Food and Drug Administration’s Vaccine Advisory Committee (Silver Spring, MD) on Vaccine Safety Issues

References

JPandS.org (pdf) - 'Thimerosal in Childhood Vaccines, Neurodevelopment Disorders and Heart Disease in the United States', Mark and David Geier, Journal of American Physicians and Surgeons, vol 8, no 1, Spring, 2003

JPandS.org (pdf) - 'A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders', Jeff Bradstreet, MD, David A. Geier, BA, Jerold J. Kartzinel, MD, James B. Adams, PhD, Mark R. Geier, MD, PhD Journal of American Physicians and Surgeons, vol 8, no 3, Summer, 2003

MedSciMonit.com (pdf) - 'A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow up analysis', David A. Geier and Mark R. Geier, Med Sci Monit, vol 11, no 4, April 1, 2005

A-Champ.org (pdf) - 'Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines', David A. Geier, BA, and Mark R. Geier, MD, PhD, Journal of American Physicians and Surgeons, vol 11, no 1, Spring, 2006

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SUNDAY EXPRESS MAY 28 2006-Study finds MMR is linked with autism.

By Lucy Johnston: HEALTH EDITOR

Scientists have confirmed the controversial link between MMR and autism.

The findings corroborate research by Dr Andrew Wakefield, discredited by the Department of Health for suggesting the combined measles, mumps and rubella jab may have
contributed to rises in the disorder.

The new study, led by Dr Arthur Krigsman, a child gastroenterologist from New York University School of Medicine, has led to calls for an immediate overhaul of Britain's child vaccination programme.

The research, presented at the International Conference for Autism Research in Montreal, is still going on but, unusually early findings have been released because of the significance.

The study, which covers 275 children and is being carried out at different medical centres in America, found serious intestinal inflammation in autistic children identical to that described by Dr Wakefield and his colleagues eight years ago.

Gut biopsy tissue from 82 of these children reveals that 85 per cent have evidence of the measles virus in their inflamed intestines. Fourteen have so far been confirmed by more stringent DNA tests.

The news will be a huge embarrassment for the Department of Health which rubbished Dr Wakefield's research on the grounds it was uncorroborated "bad

science". Steve Walker, assistant professor at Wake Forest University Medical Centre, North Carolina, who analysed the gut samples, said the work mirrored Dr Wakefield's study.

"We're very excited by our findings," he said. "Wakefield's study was criticised because it lacked replication. Our goal is to see if the finding was real. Preliminary results show that it was."

Just as Dr Wakefield discovered in his work on the children with a previously unidentified bowel condition, Dr Krigsman's patients had all inexplicably deteriorated, losing language and other skills at around 12 to 18 months of age.

All of the children under both doctors were diagnosed with autism and had come to them seeking help for symptoms of serious digestive problems for which no explanation could be found.

Dr Wakefield, who was forced to resign his job as a gastroenterologist at the Royal Free Hospital in north London after he publicised his theory, welcomed the research. He said: "The Department of Health was able to discredit our research by saying no one else had found similar results to ours but no one else had looked.

"In the light of these results - which are strikingly similar to ours - the Government and its regulators are obliged to act. At this stage it would be prudent and in the best interests of vaccine uptake to make single vaccines available."

Dr Richard Halvorsen, a GP from the Holborn Medical Centre in central London, who is writing a book on the child vaccination programme, said: "This is incredibly powerful evidence confirming the link between autism, MMR and bowel disease.

"The Government should withdraw MMR until its safety can be proven, particularly as we have safer and effective alternatives."

Jackie Fletcher, founder of **JABS**, a support group for parents who believe their children have been damaged by vaccines, said: "This study confirms that the measles virus is present in the guts of these children when it shouldn't be.

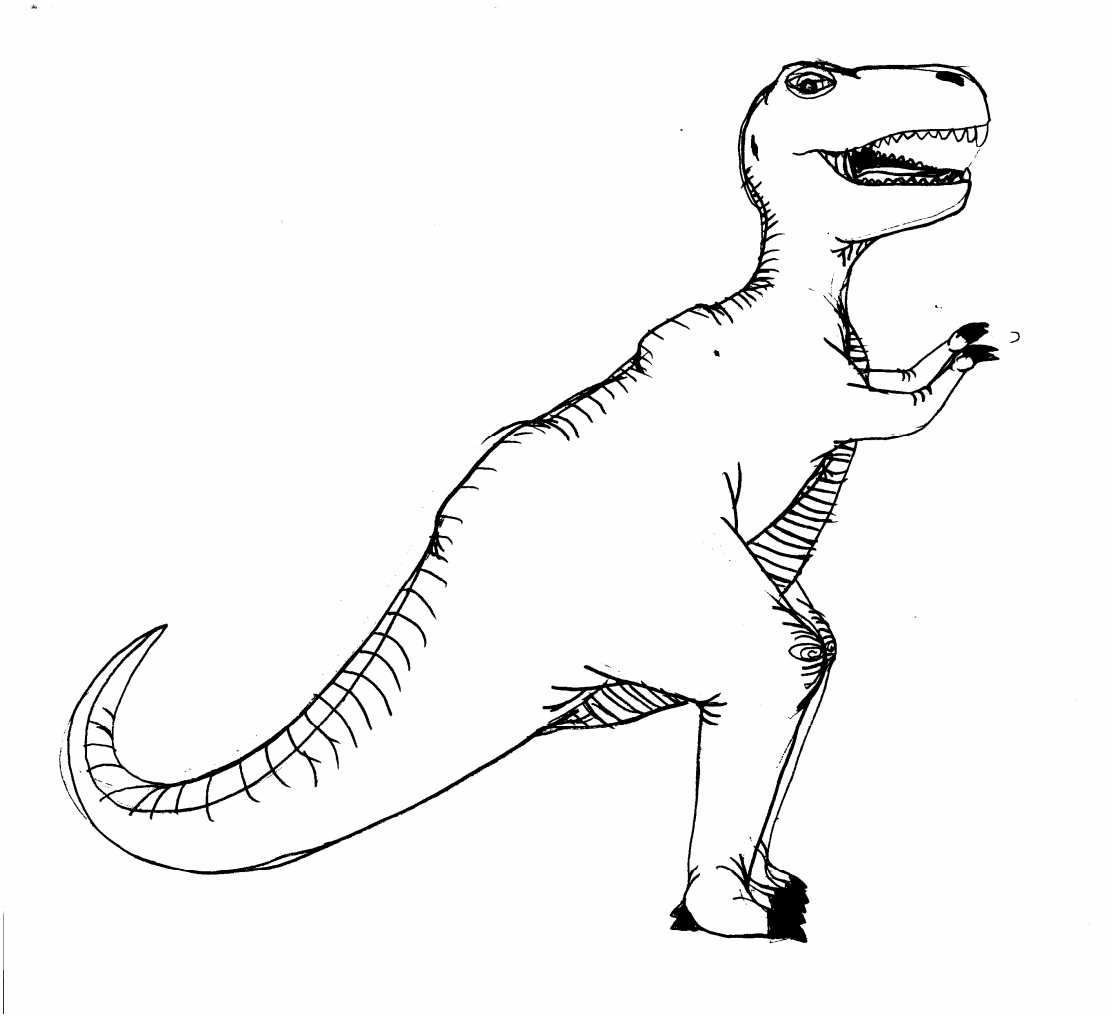
"This also shows that the studies, which the Government use as proof of the safety of MMR vaccine, are inadequate. The MMR should be suspended and single jabs reinstated immediately. We cannot take risks with our children."

A spokeswoman for the Department of Health said it could not comment on the research until it had been presented but she defended the triple jab. "There is no link between autism and the MMR vaccine," she said. "MMR remains the best form of protection against measles, mumps and rubella."

SUNDAY EXPRESS MAY 28 2006-OPINION-MMR: it's time to find out

New research by top scientists in America appears to have confirmed the controversial link between MMR and autism. The findings corroborate the research by Dr Andrew Wakefield, who was discredited by the Department of Health for suggesting the combined measles, mumps and rubella jab may have contributed to a rise in the devastating brain disorder.

In light of these revelations, the time has now come to stop messing around and give fraught parents peace of mind by holding a public inquiry on the issue. For far too long, the Government has been keen to sweep the matter under the carpet but we all deserve better.



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PRIVATE EYE 9 June - 22 June 2006

The MMR controversy has been rekindled by last week's announcement in Canada that vaccine-strain measles virus has been found in the guts of a large group of children in New York suffering from regressive autism and bowel disease.

This discovery in an entirely separate group of children across the Atlantic is significant in that it replicates the research findings of Professor John O'Leary in Dublin and Dr Andrew Wakefield in London.

Before legal aid was suddenly withdrawn from families of autistic children mounting a group legal action against the drug companies, the judge in the case, Mr Justice Keith, said that Prof O'Leary's discovery of measles virus lodged in the guts and spinal fluid of some autistic children was "pivotal to the claimants' case".

As Eye readers will be well aware, health chiefs and the drug company defendants always responded to these findings by saying that the work could not or had not been replicated. Well now it has been by an American team of researchers, led by Dr Steve Walker of Wake Forest University School of Medicine in North Carolina.

The US team is examining 275 autistic and bowel-diseased children. Of the 82 tested so far, 70 (or 85 percent) show evidence of vaccine-strain measles virus lodged in the inflamed tissue of their guts.

Last week, when Dr Walker presented his interim findings to the International Meeting for Autism Research in Montreal, he made it quite clear that this does not in any way suggest that MMR causes autism. What it does show, however, is that a virus that one would expect to be ordinarily cleared by the

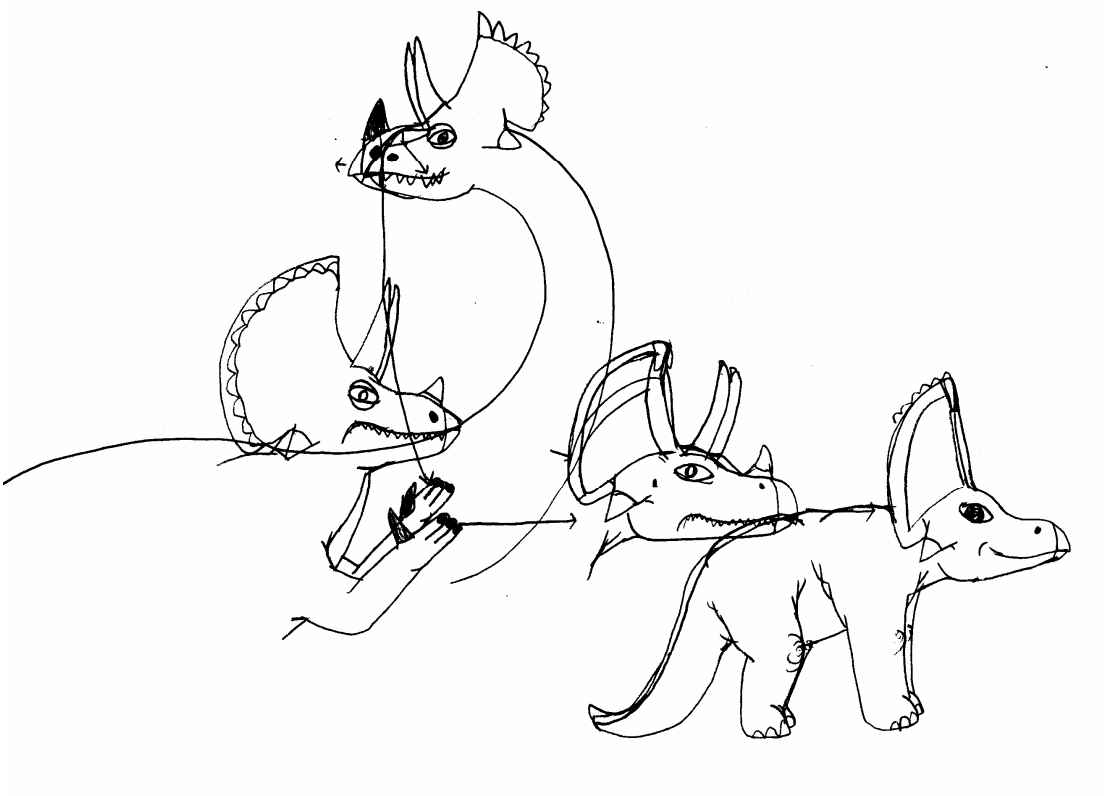
body is persisting in the inflamed tissues of children with regressive autism and gut disease - and that the virus was introduced via vaccination. There is therefore an association between the measles vaccine and the combined diagnosis of gut disease and autism that demands further investigation. No one knows what it is doing there.

The Walker study has already been attacked by critics because - at the moment - it lacks a "control" group of normally developed children and because it is not yet complete and properly published. But the Dublin researchers led by Prof O'Leary did have control subjects, the majority of whom did not appear to harbour the measles virus.

The same Montreal conference heard details of a study looking at the blood of autistic children, which was published last month in the Journal of Medical Virology, which did not find any measles traces. However, two more gut replication studies are due to be published soon, including that by Ian Lipkin, professor of neurology at Columbia University and a world authority on the role of genetic, immune and infection factors in brain disease. He told the Eye that replication work should have been done the moment the alarm bells were rung by Dr Wakefield.

But of course that is the real scandal in the MMR saga. Instead of investigating what was happening with this sub-group of around 3,000 autistic children when the issue was first quietly raised with them back in 1996, health chiefs responded by rubbishing Dr Wakefield and his work. Subsequently they also stopped giving parents the "choice" of single vaccines even though when MMR was first introduced, the department explicitly said that single measles vaccine would continue to be available.

Two and half years ago, Dr Elizabeth Miller, head of the immunisation division of the Health Protection Agency, was shown in the docu-drama Hear the Silence saying: "There have been no studies which have shown evidence that



the virus is present in these children. So really, there is no basis for now supporting a hypothesis that there is any link between MMR vaccine and autism."

Now there is evidence from two separate cohorts of children, and two separate teams of researchers, that the virus is present in these children; but health chiefs have no plans for a clinical study or to reintroduce single jabs.

The Eye asked the department to respond to the Walker study. It said MMR remains the safest way to protect children.

Release Date: 02/06/2006