

Respondent's Exhibit A

Expert Report of Professor Thomas T MacDonald

1. Qualifications:

A full CV is attached. Briefly, however, I am currently Professor of Immunology and Dean for Research at Barts and the London School of Medicine in London. I co-ordinate the research activities of 300 senior researchers in 6 different institutes. Our research budget in 2006-2007 was \$68 million. I also run an active, externally funded research group primarily working on immunology and inflammation in the human gastrointestinal tract. I have a particular interest in the lymphoid tissue of the human gut. Through my published works I have gained an international reputation in gut immunology and inflammation and am regularly invited to give keynote talks at international scientific meetings. I am a former associate editor of the British Society for Gastroenterology's official journal "GUT," and served on the editorial board of the American Gastroenterology Association's official journal "GASTROENTEROLOGY," from 2001-2006. I currently serve on the board of the journal "INFLAMMATORY BOWEL DISEASE," the official journal of the Crohn's and Colitis Foundation of America. I am president-elect of the Society of Mucosal Immunology. I serve on grant awarding bodies in the Netherlands, France and Sweden and am a member of the UK Medical Research Council Physiological Systems and Clinical Science panel (equivalent to a NIH study section) where I have a particular focus on applications dealing with the gut.

Of particular relevance to this case is the fact that from 1985 to 1995 I worked extremely closely with the pediatric gastroenterologist, Professor John Walker-Smith, at St Bartholomews Hospital in London. We developed a research programme on the immunology of inflammatory bowel disease in children and published many papers together. In addition, during this time, I also supervised the PhD studies of Dr Simon Murch, and again co-authored a number of papers with him. In 1995, Drs Walker-Smith and Murch moved to the Royal Free Hospital in London to work alongside the surgeon, Mr Andrew Wakefield.

2. Introduction:

I have been asked to comment on the expert witness report of Dr Jean-Ronel Corbier who supports the action of Rolf and Angela Hazelhurst and William Yates Hazelhurst against the Secretary of Health and Human Services. I have also been informed that the expert witness report and testimony of Dr Arthur Krigsman, from the case of Cedillo vs Secretary of Health and Human Services, will be relied upon by petitioners in this case as evidence of an autistic enterocolitis phenomenon. I have conducted PubMed searches for evidence of academic output on autism and/or gut inflammation by Drs Corbier and Krigsman but found nothing.

In particular, I wish to deal with the following linked allegations. For clarity, I will list some of these below.

2.1 Dr Corbier report

Page 3 “I was very impressed with the co-existing gastrointestinal and immunological abnormalities”

Page 4 “He has several gastrointestinal symptoms including gastro-esophageal reflux, abdominal bloating and abdominal pain”

“Frequent loose stools”

“Diagnosed at Harvard with: grade 1 reflux esophagitis; nodular lymphoid hyperplasia at the sigmoid colon; mild eosinophilic colitis”

Page 8 “the MMR vaccine has been implicated in a subcategory of children with autism found to have significant gastrointestinal pathology including lymphonodular hyperplasia and enterocolitis”

“extra-neurological symptoms such as gastrointestinal pathology including colitis”

Page 13. “Dr Andrew Wakefield and colleagues have raised the question of an association between *the between (Corbier typo)* the MMR vaccines and a form of autism with associated gastrointestinal disorder they called autistic enterocolitis”

Page 14 “Since that time several other studies have shown an association between the presence of measles virus and gut pathology in children with developmental disorders. (eg Uhlmann V 2002). Other studies (eg Kawashima, 2000) have looked at the measles virus strain in autistic colitis to try to determine whether these were wild versus vaccine related strains and found they were the latter. Other researchers (eg Ashwood 2006) have demonstrated systemic immune dysregulation in the cohort of autistic children with enterocolitis and lymphoid nodular hyperplasia”

Page 16 Conclusion “ Yates represents..... associated gastrointestinal pathology”
“gastrointestinal pathologies”

Page 17 “In Yate’s case, the additional presence of colitis and lymphonodular hyperplasia are important clues. . . .”

2.2 Dr Kringsman report

Space precludes reciting the numerous times in this report where reference is made to the purportedly undisputed diagnosis in Michele Cedillo of autistic enterocolitis.

However, I would particularly like to refer to the comment on Page 7

“that Michele has an inflammatory bowel disease” and “ that Michele had colitis beyond question as evidenced by colonic aphthous ulcerations...”

and on page 8 of the report where it is stated that

“It therefore appears that the ongoing measles viral presence within the lymphoid tissue of the gut is the catalyst for the observed inflammatory response seen on biopsy”

“the presence of a mild, diffusely patchy non-specific lymphocytic infiltrate of the gastrointestinal mucosa coupled with lymphonodular hyperplasia. . . .”

There seems very little doubt from these expert witness statements that a clear attempt is being made to suggest that Michele Cedillo and Yates Hazelhurst have an inflammatory bowel disease (“IBD”) and that it is caused by measles virus from MMR. The experts’ comments on the gut seem largely to be derived from the work of Dr Andrew Wakefield.

3. What exactly are the findings in Yates Hazelhurst’s small and large intestine?

At colonoscopy, Dr Timothy Buie noted a normal colon and nodular lymphoid hyperplasia at the sigmoid colon and rectum. Biopsies from the ileum were histopathologically normal. In the cecum, transverse colon and sigmoid colon, mild eosinophilic colitis and increased cellularity were noted. Since eosinophils are typically found in allergic tissues, and Yates has multiple food allergies, it was suggested that allergy was the reason for the increased number of eosinophils.

Although Yates was considered to have enlarged lymphoid tissue in his gut, there was no evidence of aphthous ulcers, the inflammatory lesions which occur over lymphoid follicles in Crohn’s disease. On their own, however, without accompanying mucosal inflammation and the characteristic features of Crohn’s disease, such as granulomata, aphthous ulcers are not diagnostic of inflammation.

4. What is the significance of lymphoid hyperplasia in the gut?

Lymphoid hyperplasia (LH) is a poorly defined phenomenon, which is seen in some children with sufficient symptoms to justify colonoscopy, but who display no obvious pathological abnormality. There is gut lymph node hyperplasia in a well-defined group

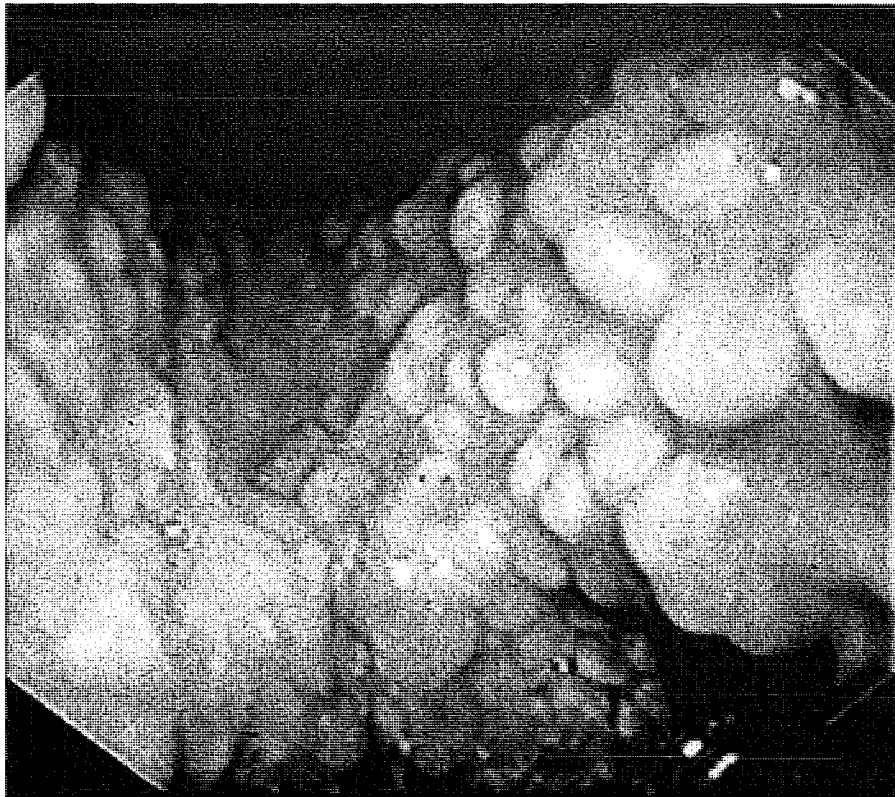
of patients, namely those with profound antibody deficiencies, but the reason for the increased incidence is not known.

The interpretation of lymph node hyperplasia in the gut as a pathological entity is wrong. Many children without disease display an increased number of protuberant lymphoid follicles in their ileum.

5. Detection of lymphoid hyperplasia

The gut is richly endowed with lymphoid tissue in all healthy individuals, especially in children.

The figure below shows pronounced lymphoid hyperplasia in the ileum of a child who was colonoscoped for suspected inflammatory bowel disease under the clinical management of Professor John Walker-Smith at St Bartholomews Hospital. The child was discharged with no treatment.



At issue is whether an endoscopically visible exuberance of lymphoid tissue in the gut is reflective of some underlying disease process or is expected to be seen in a proportion of healthy individuals, especially children. It must however be emphasized that the latter view is almost universally accepted (Bartram and Halligan 1994, Williams and Nicholls 1994) and is discussed in a book on pediatric gastroenterology edited by MacDonald and Walker-Smith. Although this book is now 13 years old, views on lymphoid hyperplasia in the gut have not changed.

There are however important caveats before one analyses the published data.

1. It is unethical to carry out a colonoscopy on a healthy individual so the question as to whether LH is seen in individuals without gastrointestinal symptoms cannot be systematically answered.
2. Lymphoid hyperplasia as seen endoscopically is very much a subjective interpretation.
3. Lymphoid hyperplasia is an endoscopic and/or radiological observation and is not a histological diagnosis, although when present in sections, large lymph nodes are noted by histopathologists.

6. Is there a definition of LH?

Earlier studies defined LH on the large amount of lymphoid tissue seen histologically in ileum removed from the patients on medical grounds (Cornes and Dawson 1963, Fieber and Schaefer 1966). Wakefield et al (2000) developed a non-quantitative 4 point score (0-3) to try to quantitate the degree of ileal LH, and Kokkonen and Karttunen (2002) defined ileal lymphonodular hyperplasia endoscopically as a cluster of lymphoid tissue which contained greater than 10 nodules. These nodules were not defined but probably represent follicles. Furlano et al (2001) considered LH to be present when the follicles were extruding, prominent, and greater than 2mm in diameter. It is not clear why the

same investigators at the same institution (ie Wakefield and Furlano) should use 2 different scoring systems on consecutive series of autistic children. All of these scores are subjective, subject to observer bias, and are not validated. There is no evidence for any significance in having a follicle greater than 2mm.

7. Is lymphoid hyperplasia a pathological condition?

There is no evidence that LH is a pathological, inflammatory condition, and it is very important that it not be confused with ileitis or colitis, which is inflammation of the mucosa, as in Crohn's disease. The histological appearance of the enlarged follicles in LH is identical to that seen in the follicles of patients without gut disease, and both show extensive immune reactivity (such as large germinal centres containing tingible body macrophages, Webster et al 1977, Spencer, Finn and Isaacson 1986). This is also quite different to early Crohn's disease, where ulcers form above lymphoid follicles and there is concomitant inflammation in the mucosa.

8. Is LH associated with any diseases?

The classical association of increased lymphoid tissue in the gut is with antibody deficiency states (Nagura et al 1979, Hermans et al 1966, Ajdukiewicz et al 1972, Bastlein et al 1988, Eidelman 1976, Van den Brande et al 1988, Webster et al 1977). These are not patients with low levels of antibodies at the lower level of the normal range or patients with isolated subclass deficiencies, but are patients with conditions such as primary hypogammaglobulinemia (gamma globulin is another word for antibody) who for genetic reasons cannot make antibodies, or patients with common variable immune deficiency. These patients display nodular lymphoid hyperplasia of the upper and lower small bowel and colon, and often are infected with the parasite *Giardia lamblia* (Eidelman 1976). It is not known why patients with antibody deficiencies show lymphonodular hyperplasia, although these patients probably are infected with *Giardia lamblia* because they do not make secretory IgM or IgA, which is needed to prevent this microbe from binding to the surface of gut epithelial cells.

Mice have been made who are only able to make IgM antibody responses and cannot make IgG or IgA responses (Fagarasan et al 2002). A striking feature of these animals is that they also develop lymphoid follicle hyperplasia in the gut with large germinal centres, and this is associated with a massive increase in the numbers of bacteria in their small intestine. If the bacteria are cleared with antibiotics, the hyperplasia subsides. The genetic defect made in these mice produces very much the same immunological effects as is seen in patients with common variable immunodeficiency. Taken together, the mouse data give an indication that the LH seen in patients with antibody deficiencies may be driven by colonisation of the small intestine with large numbers of bacteria. Consistent with this, there is evidence that patients with antibody deficiencies also show increased colonisation of the small bowel with bacteria (Brown et al 1972, Borriello et al 1985).

In immunologically normal children there is very little data on LH. Wakefield et al (1998, 2000) reported that children with autism had LH, but there is no evidence that these children were antibody deficient. The same authors suggested that 14% of normal children undergoing colonoscopy, but who had no detectable gut abnormality, had ileal LH (Wakefield et al 2000). Kokkonen and Karttunen (2002) reported that 85% of children who had no evidence of colonic inflammation after investigation for suspected IBD had ileal lymphoid hyperplasia, and this was weakly associated with food allergy. The same authors also carried out colonoscopies on a large number of developmentally normal, constipated children (Turunen et al 2004). Forty six percent had LH in the colon compared to 7% of non-constipated controls. In the ileum, 81% of constipated children had LH compared to 20% of controls. None of the children was reported to have increased mononuclear cells in the colonic mucosa. Interestingly, lymphoid hyperplasia was associated with food allergy.

Lymphoid hyperplasia as a pathological entity appears in no textbooks. However, Andrew Wakefield has attempted for a number of years to suggest that lymphoid hyperplasia in the gut of autistic children is an abnormal finding. This, however, flies in the face of scientific and medical consensus and data from his own laboratory, which

found lymphoid hyperplasia in constipated, developmentally normal children (Furlano et al 2001), and confirmed by Finnish studies (Turunen et al 2004) .

I have also recently co-published a critique of the papers published by Wakefield (MacDonald and Domizio 2007) and suggested that Wakefield used the claim of lymphoid hyperplasia as pathology as a deliberate subterfuge to suggest that children with autism have an ileitis (inflammation of the small intestine) and a colitis (inflammation of the colon). Indeed, autistic enterocolitis almost certainly does not exist. Almost 10 years on, the data of Wakefield and colleagues have not been confirmed, indeed a small US study found that autistic children had a histopathologically normal colonic mucosa (DeFelice et al 2003). A more recent study (Fernell et al 2007) used well-accepted biomarkers, nitric oxide and fecal calprotectin, to look for gut inflammation in 24 autistic children. Only 2 children gave increased levels of these biomarkers, one who had a previous severe gut infection and another severely constipated child who only passed a stool every 6 weeks. Furthermore, the slides of the alleged enterocolitis seen in autistic enterocolitis have never been made available for anonymised objective examination by independent experts, essentially a trivial exercise, but which would throw a lot of light on this controversial area.

The purported increased incidence of lymphoid hyperplasia in autistic children cannot credibly be related to autism itself when there are data to suggest that LH is seen in developmentally normal children with chronic constipation (Furlano et al 2001, Kokkonen and Karttunen 2002, Turunen et al 2004), and the fact that autistic children also frequently suffer from chronic constipation (Afzal et al 2003).

9. Is there a reasonable immunological explanation as to why autistic children could have LH?

Autistic children are frequently severely constipated (Afzal et al 2003). Constipation results in stasis of the luminal contents proximal to the fecal mass. Luminal contents normally pass through the ileum and through the ileocecal valve into the cecum by peristalsis. Colonic bacteria can colonise the ileum in large numbers and cause disease

(small bowel overgrowth) unless constantly washed distally by peristalsis. In constipation, when the colon is filled with stool, stasis will occur and bacteria, fibre, and undigested food antigens will pool in the colon and terminal ileum. This will increase the antigen exposure of the lymphoid follicles in the gut, and there will be antigen-driven lymph node hyperplasia. The local nature of this expansion in autistic children is emphasised by the fact that, although the upper bowels of autistic children have been endoscopically examined and biopsies taken (Torrente et al 2002), lymph node hyperplasia has not been reported. This stands in marked contrast to the situation in the LH seen in children with antibody deficiencies, where hyperplasia is seen in the upper small bowel as well as the ileum (Nagura et al 1979, Hermans et al 1966, Ajdukiewicz et al 1972, Bastlein et al 1988, Eidelman 1976, Van den Brande et al 1988, Webster et al 1977).

Further clues that stasis and stagnation of luminal contents might cause lymphoid hyperplasia come from studies of children with Hirschsprungs disease. This is a rare condition where there is abnormal development of the nerves that control peristalsis at the end of the colon and rectum, which results in a failure of the muscular tube of the gut to move luminal material through the end of the intestine, and the children become severely constipated. One way of dealing with this is to cut across the bowel proximal to the segment of gut which does not work and exteriorise it as a colostomy. Peristalsis then propels the gut contents into a bag. The piece of gut distal to the resection is thus defunctioned. Histological examination of the mucosa in the defunctioned bowel shows massive lymphoid hyperplasia, postulated to be due to persistent antigenic stimulation from the stagnant contents of the defunctioned loop of bowel (Drut and Drut 1992, Grant et al 1997).

10. Relevance of these findings to Yates Hazelhurst.

Yates suffers from abdominal pain and bloating and, like many autistic children, is almost certainly constipated, though I will defer to a clinical judgement of whether this is the case or not. If he is constipated, this is the most likely explanation for the enlarged

lymphoid tissue in his colon. It again needs to be re-emphasised that this is not pathology and is not suggestive of an IBD. He also had a mild eosinophilic colitis, which may have been caused by food allergy. However, it should again be noted that increased eosinophils have been seen in developmentally normal children with LH and constipation (Furlano et al 2001).

It was also stated that Yates had increased cellularity of the lamina propria but this is a non-specific feature and does not indicate an IBD.

To emphasise this final point, below is a copy of the published details of a series of 46 children without an IBD (Breese et al 1994). Of note is the fact that these children underwent colonoscopy under the supervision of Prof John Walker-Smith when he was at St Bartholomews Hospital in London, prior to his move to the Royal Free in London. Transcribed directly from the pathology reports are the histology findings in these children. Note the 15 children who had changes worthy of mention and in whom eosinophils, non-specific increases in inflammatory cells and follicles, feature prominently. These are control, non-inflammatory bowel diseased children in a study in the pre-eminent gastroenterology journal with Prof. Walker-Smith as a co-author. The reason why Prof. Walker-Smith subsequently put his name to papers where lymphoid hyperplasia and trivial changes were considered pathologically significant is not clear (Wakefield et al 1998, 2000). Nonetheless, all of the 15 children reported by Breese et al were discharged and told to return if bowel symptoms persisted; none returned.

Table 1. Clinical Characteristics and Histology of Patients With Noninflammatory Bowel Disease

Patient	Age (yrs)	Sex	Biopsy site	ESR	CRP	Histology
1	9.3	M	C	—	<5	Normal
2	9.8	M	C	—	<5	Normal
3	4.6	F	C	6	<5	Normal
4	12.4	M	C	—	6	Normal
5	3.6	M	C	—	<5	Normal
6	12.6	M	C	3	<5	Normal
7	12.1	M	C	6	<5	Normal
8	3.0	M	C	7	<5	Normal
9	9.4	M	C	6	<5	Normal
10	2.9	F	C	8	<5	Normal
11	9.0	F	C	<1	<5	Normal
12	13.4	F	C	9	15	Normal
13	12.7	F	C	3	<5	Normal
14	1.9	M	C	12	<5	Normal
15	13.4	F	C	7	<5	Normal
16	15.3	M	C	9	<5	Normal
17	11.8	F	C	<1	<5	Normal
18	8.9	F	C	25	<5	Normal
19	13.2	F	C	8	9	Normal
20	2.8	M	C	11	<5	Normal
21	9.3	F	C	6	<5	Normal
22	12.0	M	C	5	<5	Normal
23	8.9	M	C	6	<5	Normal
24	15.4	M	I	<1	<5	Normal
25	11.0	F	C	—	<5	Normal
26	5.4	F	C	—	<5	Normal
27	8.2	M	C	15	<5	Normal
28	2.1	M	C	3	<5	Normal
29	11.3	M	C	7	7	Normal
30	14.2	M	C	6	<5	Normal
31	3.5	M	C	<5	3	Normal
32	11.6	F	C	3	<5	Pigment-laden macrophages
33	2.8	M	C	11	<5	Lamina propria eosinophils
34	2.4	M	C	—	7	Eosinophils and follicles
35	8.4	M	C	12	7	Aggregates of macrophages
36	9.5	F	C	5	<5	Eosinophilic ileitis
37	13.4	M	C	39	55	Prominent follicles
38	6.8	M	C	8	<5	Chronic inflammation
39	13.9	M	C	4	<5	Pigment-laden macrophages
40	3.8	M	C	6	<5	Lamina propria polymorphs
41	9.8	M	C	11	<5	Mild focal inflammation
42	11.3	F	C	—	<5	Inflammatory cells
43	6.7	M	C	12	<5	Lamina propria eosinophils
44	14.7	M	C	5	<5	Increase in neutrophils
45	9.8	M	I	8	<5	Lymphoid follicles
46	7.9	F	C	11	<5	Epithelial macrophages

NOTE. None of the patients with noninflammatory bowel disease received medical treatment before endoscopic examination. C, colon; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; I, ileum.

11. Lymphoid hyperplasia and measles virus

Both Drs Kringsman and Corbier make reference to measles virus and/or MMR in their reports. Put more explicitly by Dr. Kringsman than Dr. Corbier is the notion that for unknown reasons, in some children, the measles component of the MMR vaccine persists in the gut, causes lymphoid hyperplasia, which then by an unknown mechanism causes an enterocolitis, which is then somehow related to the development of autism. Many years later, the enterocolitis allegedly present in the gut of autistic children and measles virus are the remnants of the catastrophic events which led to regression into autism.

I have argued above that autistic enterocolitis does not exist, however, I would like briefly to deal with the data on persistence of measles virus from MMR in the gut and its alleged role in lymphoid hyperplasia.

The evidence for the presence of measles virus in the lymphoid follicles is based on 2 pieces of data. Firstly, presented in abstract form but never published in a peer-reviewed journal, in 1998, Andrew Wakefield claimed that by immunohistochemistry he could detect measles virus in the lymphoid follicles of autistic children but not control children (Wakefield, Anthony et al 1998). Wakefield's immunohistochemistry for measles virus has been widely criticized because at the same time he was also claiming he could see measles virus in the gut of patients with Crohn's disease using reagents that were not specific for measles virus (Liu et al 1995, Iizuka et al 2000). In view of the 9 years that have elapsed since Wakefield's data was first presented, and despite the fact that Wakefield regularly shows these slides in oral presentations, these results have been discounted as not reliable by experts in this area.

The second piece of data comes from a paper published by Uhlmann et al in 2002 where a technique called in cell PCR was used to identify measles virus in gut lymphoid tissue of autistic children. This is a technique where measles virus genetic material is amplified on a glass slide containing a thin tissue section of gut, and then visualized. It is important to emphasise that this technique is quite different from the PCR techniques used to

amplify measles virus genetic material from whole samples of gut tissue (also used in Uhlmann et al 2002) where the cellular localization of the measles virus cannot be identified. The problems with the PCR on whole biopsies of gut were well enunciated by Professor Stephen Bustin in the Cedillo case.

In the case of in cell PCR where it is claimed that measles virus genetic material was localized in the lymphoid follicles and was responsible for the LH, the interpretation of whether there was positivity for measles virus in tissue sections of gut lymphoid tissue of autistic children was made solely by Professor John O'Leary, the senior author of the Uhlmann et al paper. Professor O'Leary's profit-making venture, Unigenetics, received £800,000 from the Legal Aid Board in the UK to perform tests on samples in the study. Professor O'Leary's analysis was subjective and it is worth noting that Professor O'Leary used this technique despite the fact that it is widely considered to be unreliable.

I have had the opportunity to examine the majority of those so-called positive in cell-PCR slides and discovered worrying discrepancies between the methodologies reported in the Uhlmann et al paper and what was actually done in the lab. The technique is completely unreliable with an unacceptably high experimental failure rate, many of the control sections were destroyed during the processing, the wrong technical controls were being used, and the claims of positivity or negativity were subjective and spurious. In cell-PCR does not detect measles virus in the lymphoid tissue of children with autism.

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