Respondent's Exhibit X

Report #4: Colten Snyder

Submitted October 2, 2007

General Comments

The reports submitted by Drs Kinsbourne and Kennedy in the Colten Snyder case are largely identical to their reports in the Cedillo case. Having addressed almost all of the general points raised in Cedillo, I will limit my current response to the subtle changes in their persistently flawed argument about measles virus persistence in children with ASD. The supplemental report provided by Dr Bradstreet contains little information of relevance and will not be discussed.

Kinsbourne & Kennedy: Immunosuppression vs Immune Dysregulation

Both Dr Kinsbourne and Dr Kennedy stress the point that the vaccine-strain measles virus is similar to the wild-type virus. They point out that the wild-type virus is powerfully immunosuppressive and potentially neurovirulent (both true). They further stress that wild-type measles virus can persist for prolonged periods in some subjects (also true but **only** in the rare cases of sub-acute sclerosing panencephalitis or severe immunocompromise such as HIV). They then extrapolate to state that the vaccine-strain virus acts in the 'same way' to cause ASD. Their argument denies almost half a century of experience with measles-containing vaccines.

- *There is no evidence of clinically-relevant immune suppression after MMR*
  Although subtle immunologic changes can be observed for a short period after MMR vaccination in both the test tube (*in vitro*) and in study subjects (*in vivo*), there is no evidence that these changes reflect any significant degree of immunocompromise. Hundreds of millions of children have received measles-containing vaccines and, to my knowledge, there has never been a convincing report of either increased incidence or severity of **any** viral, bacterial, fungal or parasitic disease following vaccination.

- *There is little evidence that vaccine-strain measles virus is neurovirulent*
  Vaccine-strain measles virus can bind to a number of receptors (SLAM, CD46 and possibly others) and replicate in a wide range of primary and immortalized human cells *in vitro*, including CNS cells. To date however, the only neurologic events that have been convincingly documented following exposure to MMR formulations are aseptic meningitis (AM) and (possibly) post-infectious encephalomyelitis (PIEM). The former has been most convincingly associated with solo mumps vaccines and with early MMR formulations containing the Urabe-strain mumps virus. In Urabe-containing MMR, AM occurred at a rate of up to 1:14,000 doses (Duardo 2000). The Urabe strain was removed from MMR formulations sold in the USA more than a decade ago. Whether or not serious neurologic sequelae follow the MMR vaccine that Colten received is much more tenuous. Dr Kennedy (sort of) acknowledges this fact when he states (Page 8) that such 'neurologic disorders *might* also occur with the combined MMR vaccine' (my italics). PIEM is an T cell-mediated autoimmune attack against brain antigens and

occurs with a frequency of approximately 1:1000 following both natural measles and less frequently after natural mumps infection. If this complication occurs after MMR vaccination, it is estimated to do so at a rate of less than 1:1,000,000 (Weibel 1998).

- *The most common situation of measles virus persistence (SSPE)*
  For unknown reasons, wild-type measles can persist in heavily mutated form in ~1:1,000,000 children who acquire natural disease. Oddly, given the petitioners' experts' argument of viral persistence, SSPE has largely disappeared wherever measles vaccination has been introduced. Furthermore, children with proven persistent measles virus (ie: SSPE) typically have marked elevation in anti-measles antibody titers, especially in the CSF (titers are low or absent in Colten's case). Finally, children with SSPE almost invariable die. Colten is still alive despite the putative discovery of extraordinarily high copy numbers of measles virus nucleic acids in his CSF several years ago. The petitioner's experts argue that this is an example of new and 'unexpected' biology. A far more plausible explanation is that the 'positive' PCR result is actually a 'false positive' result (see below).

Dr Kennedy repeatedly states that the vaccine-strain virus has qualitatively similar effects to the wild-type virus (Page 6). This seems logical until one considers that the same type of argument could be made for qualitative similarities between a back-yard sprinkler and a tsunami (both are water and both make you wet). The wild-type and vaccine-strain viruses are very similar in their genetic sequences (estimated sequence divergence of ~3%)(Rota 1992). However, it is obvious that they are very different agents biologically, when one considers that the current estimates for genetic differences between chimpanzees and humans range from 1.5-6% (Demuth 2006).

Finally, if ASD is as common after MMR vaccination as the petitioners' experts suggest, then why does their genetic similarity argument not apply in reverse? Why is ASD not a common consequence of natural measles virus infection? As discussed in the Cedillo case, there is remarkably little evidence that the risk of ASD is increased following natural measles virus infection. In support of such an association, Dr Kinsbourne can cite only Deykin & MacMahon (1979) (and he carefully uses the word 'incriminated')(Page 18). These authors studied 183 children in Massachusetts with ASD (and 355 sibling controls) between 1975-1977 to assess the risk associated with preterm and early infancy infection or exposure to four common viral illnesses (measles, mumps, rubella and chickenpox). This study included only 28 cases of measles virus infection or exposure either pre-term or between birth and 18 months of age (11 in ASD children). They found no significant association with measles infection or exposure after birth and a borderline significant effect for measles exposure/infection preterm ($p = 0.04$). Apparent effects of similar magnitude were also seen for rubella and mumps (preterm) and mumps and chickenpox post-term ($p = 0.5$-0.004). The authors conclude that '*the proportion of cases with histories of viral experience during the periods of interest was small, indicating that these four viruses were un-likely to have played a major role in any substantial proportion of the cases.*' Given the fact that natural measles virus infected millions of children in the developed world countries through the 1970s, the absence of any real literature to support Dr Kinsbourne's statement is significant.

Kinsbourne & Kennedy: Models of Viral Persistence

Several disease models are mentioned in the reports of Drs Kinsbourne and Kennedy. They either state or imply that observations in these models can or should be extrapolated to inform the court's decision in the Colten Snyder case. In several instances (eg: Kinsbourne page 11), it is very difficult to know what model is being used without very close attention to (and thorough knowledge of) the literature being cited.

- *Canine distemper virus (CDV) and close relatives as relevant models*

  It is widely acknowledged that several members of the Morbillivirus family are neurovirulent, including measles virus, CDV and phocine distemper virus. As a general rule however, when these viruses invade the brain (human, canine and seal respectively), the host typically dies. Dr Kennedy discusses 'distemper' and prolonged behavioural changes (implying that vaccine-strain measles virus could do the same). The onset of behavioural changes in a canines infected with either the wild-type **or attenuated vaccine-strain CDV** is typically a harbinger of death (pers comm. von Messling (von Messling 2005).

- *LCMV and Borna virus models*

  Dr Michael Oldstone's work on persisting viruses is given great prominence in Dr Kinsbourne's report. In particular, he gives considerable play to Dr Oldstone's suggestion that the type of disease that persistent viruses can cause is often '*novel and unexpected*' and implies that the MMR-ASD hypothesis 'fits' perfectly into this paradigm. However, the medical-scientific community has long known how measles virus presents when it infects the CNS: this syndrome is called SSPE and it is almost invariably fatal. In the middle of his argument, Dr Kinsbourne transitions from measles virus to an unrelated mouse virus (LCMV) without warning the reader that he is switching models (page 11 and 15). In addition, both Dr Kinsbourne (page 18) and Dr Kennedy refer to Borna virus in support of their hypothesis, without making it clear that this model requires the virus to be injected directly into the brain of a neonatal animal. It is not clear to me how these 'models' are relevant to Colten's case.

Dr Kennedy states in his report that '*The fact that MV RNA is present at high copy numbers in the CSF of Colten Snyder [sic] this would result in CNS disorders similar to that reported in the literature for MV and other morbilliviruses*'. Again, the presence of a neurovirulent morbillivirus at high copy number in the brain would typically be expected to lead to the death of the host, be it human, canine, seal, horse or pig (Sips 2007).

Kinsbourne & Kennedy: Defense of PCR Data Generated by O'Leary

Virtually all of the PCR data presented in support of the MMR-ASD hypothesis to date have originated either in Dr O'Leary's research laboratory or in the biotech start-up company founded by Dr O'Leary (Unigenetics – not 'Neurogenetics' as stated in Dr Kinsbourne report). Given the critical nature of these data to the case, it is not particularly surprising that Dr Kennedy and Dr. Kinsbourne attempt to defend the data. Neither defense is credible in light of the facts:

- Almost all of Dr Wakefield's co-authors on the pivotal Lancet paper have distanced themselves from this work
- Dr Wakefield has been severely censured by the Lancet and is currently facing professional disciplinary action for related work

- Dr Wakefield was Dr O'Leary's close collaborator for his MMR-ASD studies
- The samples used in the Uhlmann manuscript were provided by Dr Wakefield
- The primers used in Uhlmann yield non-specific products of human origin from both PBMC and gut biopsies (D'Souza 2006, D'Souza 2007)
- Other groups have not been able to replicate any aspect of Dr O'Leary's work (see references in Cedillo report)
- Despite a 5 year interval since Uhlmann was published, Drs O'Leary and Shiels have not produced measles virus sequence data to support their work. Sequence data is the gold standard technique in PCR diagnostics (as was acknowledged by the petitioner's experts in the Cedillo trial).
- Unigenetics was never accredited as a diagnostic laboratory
- Unigenetics declined to participate in a quality assessment exercise offered by the UK National Institute for Biologic standards and Control (NISBC) (see Cedillo trial transcripts)
- An independent inspection of Unigenetics was mandated within the context of the UK MMR lawsuit. A panel of experts (including Drs Bustin and Rima) identified significant problems with the practices of the company. Their review make all of the reports generated by this 'purpose-built' company suspect.
- Shortly after this review, the UK lawsuit was abandoned and Unigenetics went out of business.
- Dr O'Leary has not formally retracted the Uhlmann manuscript but he has not published any further work dealing with ASD or MMR since 2002 (despite an otherwise active and apparently successful research agenda including the introduction of new, PCR-based assays for viral illnesses) (Logan 2006, Logan 2007)

It is ironic that Dr O'Leary's laboratory has meticulously included sequence data in these more recent forays into virus diagnostics. For example, he and his collaborators write '*The nucleotide base sequence of the insert DNA from each plasmid was determined by nucleotide sequencing of both DNA strands, using the universal M13 forward and M13 reverse primers (Lark Technologies, Inc., Essex, United Kingdom). Sequence data generated from forward-and reverse-sequencing reactions was assembled, and a consensus sequence was imported into MEGA version 3.1 software for molecular typing determination by sequence homology (9).*' (Logan 2006). It is perplexing that the O'Leary lab did not sequence their putative 'measles virus' amplicons, especially given the subsequent years of controversy and class-action lawsuits.

It is not really relevant to ask whether or not O'Leary's laboratory or Unigenetics ***can*** perform research-quality RT-PCR or even Good Laboratory Practice (GLP)-quality RT-PCR in 2007. The issue is whether or not the laboratory performed the measles virus RT-PCR on Colten Snyder's intestinal biopsy and CSF to a reasonable standard of confidence. Colten's samples were among those tested during the period covered by the UK independent review and their conclusion was unambiguous. These results cannot be trusted.

What is the Relevance of CNS Inflammation if there is No Measles Virus?

The fact that there may be a degree of inflammation in the brains of some ASD children (Pardo 2005) is fascinating but is largely irrelevant in Colten Snyder's case if measles virus wasn't there. It is certainly noteworthy that NIMH did **not** fund Dr Pardo and his team at Johns Hopkins to use an anti-viral drug in ASD (as might be logical if a persisting virus were suspected).

Administration of measles vaccine or MMR to Children with Immunocompromise

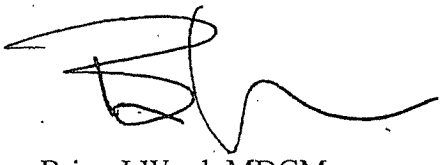
Dr Kennedy states (Pg 8) that '*If the MMR vaccine was administered in an infant that was immunosuppressed or had evidence of immune dysregulation, the potential for an adverse neurologic event to occur is reasonable.*' He then proceeds to discuss progressive and fatal measles cases in children with severe immune compromise (eg: leukemia). However, he ignores that fact that many millions of children with varying degrees of HIV-induced immune suppression receive measles-containing vaccines every year without any evidence of increasing incidence of neurologic sequellae. Furthermore, it is not documented anywhere that Colten was immunocompromised or immune dysregulated at any time. In fact, there is no evidence that Colten suffered any degree of significant immunocompromise either before or after the MMR immunization.

Inaccurate Statements About PCR

Dr Kennedy states (Pg 9) that '*The detection of high levels of MV F gene RNA in the CSF of Colten Snyder further supports the contention that this was not the result of contamination or a weak false positive result.*' This finding could just as easily support the contention that the specimen in question was contaminated. Dr Bustin's thorough review of the Unigenetics laboratory data demonstrates that such contamination occurred and was, at least occasionally, ignored by technical staff.

My response is the same to Dr Kennedy's further comment that because the RNA '*levels were much higher than one would anticipate as the result of a natural MV infection, it most likely reflects the detection of mRNA that has been amplified by replication to some extent*'. The levels of measles virus RNA detected in Colten's CSF were indeed very high and are completely compatible with contamination. Such contamination (documented at Unigenetics) is a far more plausible explanation than speculation about the vaccine-strain virus replicating to high copy number (Page 9).

If you have any questions regarding this report, please do not hesitate to contact me.
Sincerely,



Brian J Ward MDCM
McGill University Infectious Diseases Division

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