

**SCIENTIFIC CORRESPONDENCE****Thimerosal and autism**

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SIR – The paper by Richard Deth and coworkers titled ‘Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal’ states, ‘The discovery of the PI3-kinase/MAP-kinase/MS pathway and its potent inhibition by developmental neurotoxins, including vaccine components thimerosal and aluminum, provides a potential molecular explanation for how increased use of vaccines could promote an increase in the incidence of autism.’ The data presented by the authors do not support this statement.

(1) The authors, by examining cells exposed to various concentrations of ethylmercury *in vitro*, failed to consider issues of bioavailability *in vivo*. Previous studies showed that mercury is toxic to the central nervous system (CNS). However, environmental mercury (methylmercury) is far more likely to enter the CNS than mercury found in vaccines (ethylmercury). Methylmercury enters the CNS by an active transport mechanism whereas ethylmercury does not.<sup>1</sup> Also, because its half-life is much longer, methylmercury is more likely to accumulate than ethylmercury, causing higher levels of mercury in the blood.<sup>2</sup> Exposing cells *in vitro* to ethylmercury assumes absolute availability *in vivo*, eliminates the most important difference between those two forms of mercury, and ignores the fact that ethylmercury is unlikely to enter the CNS at concentrations likely to be harmful. Similarly, ethanol and methanol have different capacities to enter the CNS; a difference clearly reflected in their clinical effects.

(2) The authors chose to use a cell line derived from a metastatic peripheral nervous system tumor (neuroblastoma cells) to make predictions about developing healthy cells of the CNS. If the authors were interested in making claims about the developing CNS they should use cells derived from the developing CNS (eg primary neuronal cells at different stages of development). This failure is not trivial. Although the authors make statements in their introduction about developmental disorders such as fetal alcohol syndrome, Rhett’s syndrome, or Fragile-X syndrome, they fail to consider the fact that all of these diseases have their origins in the developing embryo and fetus, not postnatally. Children exposed to alcohol after they are born do not develop fetal alcohol syndrome.

(3) The authors found that, with the exception of divalent copper, all substances tested (including the non-heavy metal, ethanol) modified methylation reactions in neuroblastoma cells. This cell line used has gross cytogenetic abnormalities including 47 chromosomes. The broad response to many different stresses calls into question inherent changes in transformed cells that might make them more sensitive to stresses *in vitro*. At the very least, the authors should confirm their observations in other cell types, including several other cell lines.

(4) The authors’ reference a study that evaluated the causal association between thimerosal and vaccines using the Vaccine Adverse Events Reporting System (a passive surveillance system) but fail to mention two retrospective studies performed in the United States and Denmark that were more comprehensive, better controlled, and better analyzed.<sup>3,4</sup> Both of these studies found no evidence for an association between thimerosal in vaccines and autism.

Lastly, these criticisms should have been addressed prior to, not after, publication. People whose children suffer autism are desperate to find the cause or causes of the disease. Studies like this, although severely limited by their design, may be a focus of media and parental attention and offer the false hope that avoidance of thimerosal will lessen the risk of autism. However, by avoiding vaccines the risk of autism will not be lessened and the risk of vaccine-preventable diseases will be increased. The editors should be mindful that unreasonable extrapolations from *in vitro* studies to *in vivo* events may do more harm than good.

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3 Verstraeten T *et al.* *Pediatrics* 2003; **112**: 1039–1048.

4 Hviid A *et al.* *JAMA* 2002; **290**: 1763–1766.