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Thimerosal and autism? A plausible hypothesis that should not be dismissed☆

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Summary The autism–mercury hypothesis first described by Bernard et al. has generated much interest and controversy. The Institute of Medicine (IOM) reviewed the connection between mercury-containing vaccines and neurodevelopmental disorders, including autism. They concluded that the hypothesis was biologically plausible but that there was insufficient evidence to accept or reject a causal connection and recommended a comprehensive research program. Without citing new experimental evidence, a number of observers have offered opinions on the subject, some of which reject the IOM's conclusions. In a recent review, Nelson and Bauman argue that a link between the preservative thimerosal, the source of the mercury in childhood vaccines, is improbable. In their defense of thimerosal, these authors take a narrow view of the original hypothesis, provide no new evidence, and rely on selective citations and flawed reasoning. We provide evidence here to refute the Nelson and Bauman critique and to defend the autism–mercury hypothesis.

Introduction

In 1999, the US Public Health Service and the American Academy of Pediatrics (AAP) called for the reduction or elimination of the ethylmercury preservative thimerosal from vaccines, saying that the cumulative amount of mercury in infant vaccines exceeded US Environmental Protection Agency (EPA) guidelines for methylmercury [1]. In 2000, Bernard et al. published an extensive literature review which outlined the shared traits and biological abnormalities between mercury poisoning and autism. They suggested that many cases of idiopathic autism may be induced by early mercury exposure and represent an unrecognized mercurial syndrome. They further postulated that genetic and non-genetic factors establish susceptibility whereby mercury's adverse effects do not occur in all children exposed to mercury [2,3]. Since then, the topic has generated a great deal of controversy. In 2001, the IOM reviewed the science literature on thimerosal and found insufficient evidence to accept or reject an association between thimerosal and neurodevelopmental disorders but found the hypothesis ''biologically plausible''. The IOM committee recommended a comprehensive program of research to resolve the

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issue [4]. Since 2002, thimerosal-containing vaccines have been largely eliminated for administration to infants under 6 months of age in the developed world, except for the influenza and diphtheria–tetanus vaccines in the US and the routinely recommended diphtheria–tetanus–peretanus–pertussis vaccine in the UK. Thimerosal is still widely used in infant vaccines in the developing world.

Since the IOM conducted its review, several articles on thimerosal have appeared or are in press in scientific and medical journals. While most papers have reported on original in vitro, in vivo, or epidemiological research investigations [5–10], one widely cited paper [11], ''Thimerosal and Autism?'', was an invited commentary which represented a literature review. This commentary, by Karen Nelson and Margaret Bauman, appeared in *Pediatrics*, the journal of the AAP, and was a direct rebuttal of the 2000 Bernard et al. autism–mercury paper. The commentary contains a number of assertions and conclusions that demand close examination. The current paper analyzes the contents of the Nelson–Bauman commentary and provides evidence that directly refutes the primary assertions and conclusions made therein. While the autism–mercury hypothesis encompasses more disease features, here we examine the four primary areas covered in Nelson and Bauman's review: (1) clinical manifestations of mercury poisoning; (2) the neuropathology of mercury toxicity; (3) evidence of increased mercury exposure and retention in autistic persons; and (4) epidemiological evidence in populations exposed to mercury.

Clinical manifestations of mercury poisoning

In a direct rebuttal to the autism–mercury hypothesis, Nelson and Bauman construct a table of six symptoms (reduced from 95 in Bernard et al.) that they use to compare the ''typical and characteristic manifestations'' of mercury poisoning and autism. The table suggests an absence of overlap in the clinical manifestations of the two conditions. Nelson and Bauman provide no definition or source for their inclusion of these ''typical and characteristic manifestations''. This omission is not surprising since no ''typical'' pattern of mercury poisoning can be or has been described. Rather, as expert toxicologists well know, ''no other metal better illustrates the diversity of effects caused by different chemical species than does mercury'' [12].

Clinical manifestations of mercury toxicity vary greatly depending on numerous factors, including:

- amount of exposure (dose relative to body weight),
- dosing patterns (intermittent bolus, chronic, and acute),
- species type (ethyl, methyl, di-methyl, metallic, mercuric, and mercurous),
- route of administration (cross-placental, ingested, injected, inhaled, mucosal, and transdermal),
- excretion context (in utero, with antibiotics, immature commensal flora and/or bile production, and milk diets),
- age and developmental context at exposure (prenatal, postnatal, infant, toddler, child, and adult).

Distinct groupings of these exposure variables produce distinctive disease patterns that have carried different labels through the years: e.g., Hunter–Russell syndrome, Minamata disease, Pink disease, mad-hatter's disease, and so forth. In the specific case of thimerosal-containing vaccines in infants, a new combination of exposures and timing that has contributed to recent increases in autism has been hypothesized. Hence, the proposition in Bernard et al. that this combination describes a ''novel form of mercury poisoning''.

Age at exposure is critically important for the autism–mercury hypothesis, since the proposed mechanism of mercury toxicity is specifically related to the developmental timing and consequences of mercury exposure. Only two well-documented mercury exposure patterns lie close to the developmental window proposed in the autism–mercury hypothesis: congenital Minamata disease (CMD) and Pink disease or acrodynia. Each of these disorders involves unique mercury exposure patterns. CMD results from fetal exposures via cross-placental transfer of relatively high doses of methyl mercury ingested by the mother through contaminated fish. Acrodynia results from direct trans-dermal and mucosal exposures in infants and small children (often via teething powders) to inorganic mercury, specifically, mercurous chloride in calomel.

The ''typical and characteristic manifestations'' subsequent to the known mercury exposures in CMD and acrodynia bear little resemblance to the vague manifestations of ''mercurism'' (*sic*) that Nelson and Bauman describe. Indeed, each disorder has vivid and unambiguous symptoms neither set of which resembles the other. Expert observers cannot distinguish CMD victims from patients with cerebral palsy and mental retardation [13]. By

contrast, children with acrodynia typically suffer from mild to severe peeling of the skin, with associated redness on their hands and feet (hence ''pink disease''), ''extreme misery'', social withdrawal, profuse perspiration, and heightened sensitivity to light or photophobia [14,15]. More to the point, not one of Nelson and Bauman's six characteristics of mercurialism is commonly reported in *both* CMD *and* acrodynia. CMD sufferers show no evidence of peripheral neuropathy [16], whereas no contemporary accounts [14,15,17] of acrodynia symptoms make mention of ataxia, dysarthria, visual field constriction or microcephaly.

By contrast, both CMD and acrodynia share many of the autism symptoms cited by Nelson and Bauman, including mental retardation in CMD [13] and loss of speech, social withdrawal, sensory defensiveness and ''bizarre positions'' in acrodynia [15,17].

Nelson and Bauman derive their list of mercurialism symptoms largely from relatively high dose, ingested, methyl mercury exposures in adults. These exposure patterns are not closely comparable to the relatively low dose, injected, ethyl mercury exposures hypothesized to provoke autism symptoms in infants. Their claim that ''the typical clinical symptoms of mercurism (*sic*) are not similar to the typical clinical signs of autism'' is therefore inaccurate, misleading and unsupported by evidence from any comparable childhood disorder of mercury exposure.

Neuropathology of mercury toxicity

Nelson and Bauman make similar errors in their claims that mercury exposure produces different neuroanatomic effects than those observed in autism. They cite several references to the neuropathological effects of mercury poisoning, but generally fail to distinguish between the degenerative and developmental effects of mercury exposure. All of their references to mercury neuropathology in humans [18–20] are based on ''severe'' exposure levels resulting in death.

Their suggestion that ethylmercury does not readily cross the blood–brain barrier is contradicted by the single study [21] that directly compares the brain levels of mercury following comparable doses of methyl and ethlymercury. In this study by Magos (using Wistar rats), both ethyl and methyl mercury entered the brain in significant amounts. They also overstate the difference between the brain volumes of ethyl and methyl mercury-exposed rats. Male Wistar rats exposed to ethylmercury had brain levels of mercury that were two-thirds the levels of methylmercury treated rates [22,23].

Nelson and Bauman repeat Magos' later assertion [23] that ethylmercury lacks the active transport mechanism across the blood–brain barrier that others [24] have found available to methylmercury. But neither Nelson and Bauman nor Magos support this claim with evidence, whereas the available evidence suggests a contrary conclusion. Kerper et al. described the characteristics of this transporter in ways that fail to exclude an available transport mechanism for ethylmercury. ''The L system is the major route of entry of neutral amino acids from blood into the brain. This system has a *broad specificity for neutral amino acids, with preference for those with bulky, hydrophobic side chains* [emphasis added]. These properties are more important than the actual stereo-chemistry of the side chain, as evidenced by the transportof several different amino acids with similar affinities. This broad specificity may enable MeHg–L-Cys to be transported by the L system as well. MeHg–L-Cys fits the criteria for preferred substrates, containing a bulky, hydrophobic side chain similar in structure to that of methionine''. In fact, the L system mediates transport of 14 of the 16 neutral amino acids [25]. Since ethylmercury is both slightly bulkier and more hydrophobic than methylmercury, the broad specificity of the L system transporter might allow transport of an ethylmercury–thiol complex such as EtHg–L-Cys across the blood–brain barrier in similar fashion. This hypothesis deserves testing rather than a priori dismissal.

Nelson and Bauman place particular emphasis on the ''relative sparing'' of Purkinje cells as compared to granule cells after mercury exposure, since reduced numbers of Purkinje cells are a common finding in autistic brains. They also state that ''involvement of granule cells has rarely been reported'' in autism. Yet in a review of the studies they cited in order to demonstrate ''relative sparing'' of Purkinje cells after Hg exposure, one study [21] actually describes ethylmercury treated rats in which ''silver-mercury deposits...are in the large Purkinje neurons but are absent in the granular layer'' while another [18] describes a single ethylmercury case in which ''Purkinje's cells were more spared, though in certain areas silver impregnation for neurofibrils showed empty basket cells and torpedo-shaped Purkinje cell axons''. Other studies, not cited by the authors, show clear evidence in favor of Purkinje cell involvement in mercury poisoning, with increased levels of Purkinje cell loss or dysplasia following exposure

[26–28]. Regarding autism and granule cells, in a postmortem study of autistic brains, Bauman [29] herself found ''a variable decrease in granule cells throughout the cerebellar hemispheres'' in all brains examined. Nelson and Bauman's references are thus inaccurate and incomplete. They provide definitive proof neither for the lack of involvement of Purkinje cells in mercury exposure nor the lack of involvement of granule cells in autism.

Finally, Nelson and Bauman mention brainstem lesions as being an important neuroanatomical observation in autism and imply that such lesions are not reported in the mercury literature. Yet brainstem abnormalities are among the most common features of prenatal and postnatal mercury exposure [30,31].

Nelson and Bauman assert ''material differences in the neuroanatomic findings in autism as compared with those in mercury toxicity''. This assertion is based on a handful of selectively chosen studies of mercury neuropathology in rats and severely poisoned adults, yet even these studies provide meager direct support for their claims. Other studies [26–28] that they choose not to cite contradict their claims. None of these studies provide even a marginally comparable test of the hypothesized exposure levels and timing involved in the autism–mercury hypothesis. Consequently, Nelson and Bauman's assertion of ''material difference'' in the neuropathology of autism and mercury poisoning has little evidentiary support.

Evidence of increased mercury exposure and retention in autistic persons

Emerging evidence supports a finding of elevated mercury exposure and unusual mercury metabolism in autistic children. In their brief treatment of this issue, Nelson and Bauman imply that reliable evidence of increased mercury exposure will not be found. They are premature in their assessment.

- Higher levels of exposure to thimerosal-containing vaccines have been observed among children with autism as compared to controls in one unpublished study [32] using the Vaccine Safety Datalink (VSD) database and another published study [9] using the Vaccine Adverse Events Reporting System (VAERS) database. The VSD study found a relative risk of autism of 2.48 in infants receiving 62.5 mcg or more of ethylmercury by three months of age.
- Increased levels of prenatal exposure to mercury in autistic children have been found, resulting from both higher numbers of maternal amalgam fillings [10] and higher probability of receiving thimerosal-containing Rho D immunoglobulin injections [10,33]. Any such prenatal mercury exposures occur against a background of elevated mercury blood levels in women of child-bearing age, with over 8% of women in a recent study showing blood mercury readings in excess of the EPA's allowable levels [34].
- Lower levels of mercury have been found in the first baby haircuts of autistic children as compared to controls [10], suggesting reduced excretion rates, since the autistic group had elevated mercury exposures as compared to controls.
- High levels of mercury have been detected in the urine of autistic children following chelation therapy with DMSA [35].

One obstacle to more definitive biomedical findings in this area has been the slow pace of research. We wonder why Nelson and Bauman choose not to call for more research to test the autism–mercury hypothesis, an argument that would align them with the IOM position, but instead choose to criticize a plausible hypothesis in advance of comprehensive testing. The only practical effect of their position will be to cast a disapproving gaze over researchers with an interest in taking up this subject, an unwise and inhibitory gesture.

Epidemiological evidence in populations exposed to mercury

Nelson and Bauman cite the only instance in which a known, large-population mercury exposure occurred in close geographic and temporal proximity to a major autism epidemiology study [36]: Fukushima prefecture in Japan, a province that borders Niigata prefecture and lies only a few kilometers from the source of the mercury emissions that led to Japan's second major outbreak of Minamata disease around 1965. This study is notable for two reasons: (1) the child populations covered in the survey were born between 1960 and 1977, thereby including pregnancies that preceded and followed the Niigata mercury exposures and (2) the autism prevalence rates reported in children born after 1965 showed a sharp increase over rates before 1965. The inference is clear: the time trends in autism prevalence in Fukushima prefecture are consistent with an etiological role for mercury.

Nelson and Bauman concede that this Japanese study ''might have tested the question as to whether autism was more frequent near to outbreaks of mercury poisoning'', but instead of accepting the validity of the test, they choose to attack the methods of the original investigators. They offer numerous criticisms designed to ''invalidate the time trend analysis''. Most notably:

- They estimate (in a calculation not provided by the original authors) that population coverage in the screening stage fell below 40%. This is a misleading calculation that excludes coverage from nearly 700 pediatric practices and public health centers;
- They allege a temporal bias in case ascertainment for the years spanning the mercury exposure period without specifying the mechanism or temporal locus for the alleged bias. Ascertainment biases are an important source of error in autism prevalence surveys but there is no evidence supporting a large effect in the age range (8—12 year olds) in which the Fukushima increases took place.

They rely on these claims of methodological bias to dismiss a dramatic increase in autism rates from less than 1 per 10,000 in children born in or before 1965 (the year of the Niigata disaster), to over 4 per 10,000 just three years later. The evidence, we submit (and not methodological concerns), speaks for itself here.

Nelson and Bauman also cite two well-known studies in the mercury literature, the Faroe and Seychelles Islands investigations [37,38], which examined long-term, neurodevelopmental outcomes in two populations exposed to dietary methylmercury. They cite the absence of autism cases reported in these two studies while observing that these studies ''were probably large enough to detect a substantial but not minor increase in autism, if it was present'', in the exposed populations. This argument fails for several reasons. First, both studies were conducted on very small populations of children, well under one thousand, neither of which could be expected to yield a significant number of children with autism at historic prevalence rates (more relevant to dietary exposures) and would yield only 2—3 autistic children at more recent prevalence levels (which would only prevail under the recent, elevated exposure conditions). Second, children with neurological disease, particularly those with seizure disorders (which can affect as many as one-third of children with autism), were excluded from the Faeroe investigations. Third, neither of these populations were exposed to thimerosal in vaccines at the levels of recent concern: the Seychelles are a developing nation and the Faeroes, under Danish control, operated under childhood immunization schedules that kept thimerosal exposures low (Grandjean, personal communication). Therefore, the fact that autism was not cited in either of these studies provides little reassurance of any kind, contrary to the authors' suggestions.

Finally, Nelson and Bauman run through a familiar litany of arguments designed to obscure the strong evidence of increasing incidence of autism, including: diagnostic substitution [39], lower diagnostic standards, and methodological non-comparability [40]. Although many have offered speculative theories [41] with an eye to dismissing the mounting evidence of increasing incidence of autism, none of these hypotheses have been effectively tested and replicated. To the extent that they can be quickly tested, several recent authors have either falsified the hypothesis of diagnostic substitution and lower diagnostic standards [39,42—45] or failed to find any evidence in favor of them [46,47].

Conclusion

In the March 2003 issue of *Pediatrics*, Nelson and Bauman's ''Thimerosal and Autism?'' [11] answers the title's question through a unilateral dismissal of the autism—mercury hypothesis. In the process, the authors effectively oppose the findings of the Institute of Medicine [4], which in its October 2001 report found the connection between thimerosal exposure and neurodevelopmental disorders to be ''biologically plausible''. Although the IOM found insufficient evidence to accept or reject an association, their report expressed concern that ''action might be delayed'' and ''recommend[ed] that full consideration be given... to removing thimerosal from vaccines administered to infants, children or pregnant women in the United States''. The IOM also ''recommend[ed] a diverse public health and biomedical research portfolio... [that] provides some findings fairly quickly''.

Just over a year after the IOM issued its report, Nelson and Bauman, while offering no new evidence, ''consider it improbable that thimerosal and autism are linked''. In addition, ''when information is incomplete'', they offer the startling suggestion that infant exposures to mercury in vaccines should be continued. Their positions violate principles of both precaution and scientific method. If the arguments in their review were well-supported by evidence, such an aggressive

posture might be defensible. Yet, as demonstrated in this analysis, their arguments misinterpret the evidence on early mercury exposure and autism characteristics and require correction. When the comparisons are fairly presented, characteristics of autism do in fact mirror those of mercury exposure, on symptom, neuroanatomical, body burden, and epidemiological bases.

The facts are increasingly clear. The incidence of autism has increased 10-fold in a decade (compare [48—50] to [51,52]). Such order-of-magnitude increases must have environmental roots. Increased mercury exposure is both biologically and epidemiologically plausible as a sole or contributing causal factor. Instead of speculative dismissals of this model, as offered by Nelson and Bauman, we need more evidence-based research. This is what the IOM has recommended and we should get on with it.

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