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LETTER TO THE EDITOR

Response to “Theoretical aspects of autism: Causes—A review” by Ratajczak, HV (Journal of Immunotoxicology 8:68–79, 2011)

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In a recent review paper by Ratajczak (2011) on theoretical aspects of autism, the lines between speculation and well-supported science were blurred with respect to how possible risk factors for autism were described. Considering the potential public health implications if speculation leads to action, we felt that we needed to respond to the way in which Dr. Ratajczak presented information in the review.

Autism is a childhood disease that has an estimated prevalence of 1 in 110 children in the United States (CDC, 2009). The accompanying social costs of treating autistic children have sky-rocketed, and the emotional costs endured by families with autistic children are impossible to estimate. Hindrances to the treatment and prevention of autism are directly related to the heterogeneity of risk factors that likely contribute to an autism diagnosis and the phenotypic heterogeneity of the disease itself. Genetic susceptibilities combined with a myriad of exogenous factors including maternal infections, stress, environmental pollutants, pharmaceutical agents, and dietary insufficiencies are thought to contribute to the etiology of autism. However, specific pathways are hypothetical at best and causality among putative risk factors has not been established. The review by Dr. Ratajczak goes beyond a discussion of scientific studies of putative risk factors of autism to assign both causes and specific preventative measures linked with those causes. In our opinion and based on the present state of the scientific literature, this is inappropriate.

In her review on autism, we feel that Dr. Ratajczak misrepresented the following points:

(1) Perhaps the most publicly and scientifically debated issue surrounding risk factors associated with autism is vaccine safety. Dr. Ratajczak writes that “The incidence and prevalence data indicate that the timing of introduction of vaccines and changes in the type and increasing number of vaccines given at one time implicate vaccines as a cause of autism.” Several recent studies indicate that vaccination, specifically the vaccination against measles-mumps-rubella (MMR), does not increase the risk of autism. Notably, a longitudinal study done in Japan over a 4-year period (1989–1993) demonstrated that the incidence of autism was not different across the interval before, during, and after this MMR vaccination window (Uchiyama et al., 2007).

The vaccine controversy arose from a *single* paper published in 1998 (Wakefield et al., 1998), suggesting that the MMR vaccine was linked to autism. For parents with autistic children looking for a reason to explain their child’s diagnosis, this paper seemed a blessing and led to anti-vaccination cries from celebrities and advocacy groups. The original Wakefield et al. 1998 paper was fully retracted by the *Lancet* on 2 Feb 2010 following a report of the United Kingdom’s General Medical Council. The British Medical Journal concluded that the study had been fraudulently concocted (Godlee et al., 2011). However, the damage to public health persists. The outcome of this flawed work included the resurgence of previously controlled diseases in the United States and United Kingdom that led to injuries and deaths in children who were not immunized against MMR. Numerous studies were unable to replicate the fraudulent Wakefield findings

and, in fact, produced additional data against the ability of the MMR vaccine or the preservative, Thimerosal, to induce autism in children or autistic-like effects in animal models. Similarly, a study by Price et al. (2011) indicated that no increased risk of Autism Spectrum Disorders was associated with thimerosal-containing vaccines given during prenatal, birth-to-1 month, birth-to-7-month, and birth-to-20-month age periods. Regarding the Wakefield controversy, an editorial by two scientists who study vaccine safety (Poland and Spier, 2010) emphasized that the movement from evidence-based medicine to media and celebrity based medicine lead to barriers to discovering causes and effective treatments for autism.

While we agree that a review article on the risk factors associated with autism must include a discussion of vaccine safety, not because it is scientifically meritorious but because it is an issue that the public seems to think is scientifically debatable, we do not feel that Dr. Ratajczak suitably addressed the issue. Although the cited articles were published in reputable journals, the language that Dr. Ratajczak used to discuss vaccines as risk factors in autism did not make it clear that the debate surrounding this issue has moved from the scientific arena to the arena of media hype and misinformation. In addition, although it is well accepted that the immune system of newborns and children is more sensitive to perturbations than the adult, there is no agreement on the specific age at which sensitivity is the highest. Therefore, asserting that the immune system of a 2-month-old is more or less compromised than a 1-month-old or a 1-year-old is hypothetical, at best, and misleading at worst.

(2) The title of the article *Theoretical aspects of autism: Causes—A review* implies that autism has a sufficient number of theoretical causes to warrant a review. A parent or health care provider searching through scientific literature databases could easily read the title and make the assumption that the etiology of autism has a theoretical basis. Skimming through the article would lead such readers to suspect that being pregnant or getting exposed to agricultural pesticides can cause autism, even though no strong scientific evidence points to these factors as causal. At best, the article reviews the hypotheses that have been proposed as risk factors for autism, not theoretical causes. This may seem a point of semantics, but given the media focus on the search for causes of autism, any assertions about causative factors should be strongly supported by well-documented epidemiological findings backed by rigorously-controlled animal studies that establish biological plausibility. Currently, such data simply do not exist to assign causality.

(3) Deductive logic is part of the scientific method and allows scientists to base conclusions on empirical observations. In the absence of empirical evidence, scientists develop ideas based on relatively little data, with the understanding that asserting such ideas often drives the development of additional empirical evidence. This is the creative aspect of science and helps to push the boundaries of knowledge. However, stating such ideas as theory

removes the experimental piece required to move an idea to theory. It glosses over gaps in data and forces a reader to fill in the missing information with speculation and supposition. For example, under the “pregnancy” section of “conditions,” pregnancy is not really a theoretical cause of autism; prenatal viral exposures during pregnancy may affect the blood-brain-barrier, which may increase the risk of autism. In one cited study (Atladóttir et al., 2010), the authors indicated that “...this study is an exploratory study” and that “...the significant associations observed could therefore be chance findings (Type I error).” In the review article by Dr. Ratajczak, this study is presented as evidence that viral infections in the first trimester and bacterial infections in the second trimester of pregnancy are associated with a diagnosis of autism in the offspring. In reality, the Atladóttir et al. (2010) study merely indicated that maternal infection increased the risk of autism, not the diagnosis. In addition, the possibility of a Type I error indicates that if it was assumed that viral infections were associated with autism, the reality is that they really were not. Dr. Ratajczak’s critical error is not citing the article(s), but overstating the conclusions of specific articles particularly in light of the authors’ own stated conclusions. Doing so takes this review article from a critical assessment of the literature to significant over-speculation.

The absence of definitive causes for autism is a powerful force that turns mild associations and even assertions into key risk factors. The search for causes to explain why a particular child succumbed to an autism diagnosis leads down a slippery slope from strongly supported scientific hypotheses to a desperate search for answers in the milieu of questions with little to no scientific support. Such questions often receive a multitude of media attention because the answers seem so simple. However, with a disease as heterogeneous as autism, no answer concerning its etiology will be simple, linear, or absolute. It is, therefore, imperative that scientists in the autism research arena appreciate that over-speculation may lead to sensationalism.

The decision of the Editorial Board of the *Journal of Immunotoxicology* to publish Dr. Ratajczak’s manuscript reflects the need to improve and expand upon the scientific literature surrounding the etiology of autism. We laud the journal for their desire to contribute to the discourse on autism and appreciate the efforts of the reviewers to ensure that reviews are timely and supported by relevant peer-reviewed literature. Considering that the scientific debate on vaccine safety has concluded that vaccines do not contribute to the incidence of autism, neither the editors nor the reviewers likely anticipated the negative impact on public safety if parents fail to vaccinate their children as a result of reading Dr. Ratajczak’s misleading statements about vaccine safety. Similarly, asserting that autism has theoretical causes may mislead casual readers into believing that the scientific community has reached a consensus on the specific risk factors that contribute to autism etiology.

We agree that certain risk factors have a greater probability of contributing to autism than others; we do not

agree that any risk factors have been deemed causal. We hope that we have emphasized that while Dr. Ratajczak's review was timely and necessary, it over-speculated, relied heavily on exploratory studies, and discounted the conclusions of the scientific community with regard to the safety of vaccines. We hope that we have clarified some of the misconceptions that may have been raised by Dr. Ratajczak's review and appreciate the opportunity to comment.

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Declaration of interest

The authors report no conflicts of interest.

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