Concerning Blood Mercury Levels and Autism: A Need to Clarify

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Response to Article by DeSoto and Hitlan on the Relationship Between Mercury Exposure and Autism

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In a recent article DeSoto and Hitlan[1] reanalyzed an original data set,[2] concluding that a relationship exists between blood mercury levels and the diagnosis of autism spectrum disorder (ASD). The conclusion is based on the reanalysis of hair to blood mercury ratios. Hair to mercury concentration ratios while informative need to be considered within the context of a temporal relationship. As elegantly demonstrated by Grandjean and colleagues,[3] mercury levels in the hair reflect a delayed average compared to the blood mercury level averages. That is, mercury hair concentrations at hypothetical time point T reflect blood mercury levels at T minus 1 to 2 months. Chelation therapy and changes in diet and fish consumption (both more likely to occur in the ASD group) in the 2 months preceding the mercury analysis are likely to affect blood, but not hair mercury sample concentrations. The analysis by DeSoto and Hitlan,[1] which presumes that the 2 biomarkers are equally affected, is clearly erroneous. Thus, absent appropriate corrections for the temporal fluctuations in mercury levels, the conclusions should be interpreted with utmost caution and revalidated taking the above issue into account.

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There are mistakes, and there are mistakes about mistakes. The article Robert Hitlan and I[1] wrote about the original Ip et al article[2] has generated unprecedented attention. Indeed, we have received about 100 contacts concerning the article. It was the most read article on the *Journal of Child Neurology* website for December 2007 and in the same month was the number two "Hidden Jewel" for all of biology as rated by Faculty of 1000 Biology. About 75% of the comments we have received have been positive and about 25% negative. The reactions have ranged from unmitigated glee to near death threats. Overall, it has given us the impression that this is a topic about which some have such strong feelings that it interferes with objective analysis. There have been a number of comments that represent misunderstanding of both articles.

Let me start by restating what Ip et al said in their 2004 article. Ip et al published statistics that did not fit with the data presented. This represents a serious mistake—it is not like disagreeing over what results mean, but is actually misstating the results themselves. Mean blood mercury level values as reported by Ip et al in 2004[2] were 17.68 (with a standard deviation of 2.48) for the autism group and 19.53 (standard deviation of 5.65) for the control group. With the sample size (n = 137), the degrees of freedom are 135. These values published by Ip et al can be found in a statistics book or punched into online *t*-test calculators. There is no question whatsoever that there was an error. These original numbers given by Ip et al yield a *t*-statistic of 2.3 which represents a significant difference ($P = .02$, two-tailed). This was the error that was discovered. (This occurred when trying to get some idea of a possible effect size for a potential grant; autism is a longstanding interest of mine in terms of a

testosterone and theory of mind connection).[3] Our analysis of the data set provided in 2007[4] (publicly available)[5] also shows a significant relationship exists.[1]

A case in point of apparent misunderstanding is the letter by Aschner in this issue of the *Journal of Child Neurology* about our article.[6] Aschner's opening sentences read, "DeSoto and Hitlan reanalyzed an original data set, concluding that a relationship exists between blood mercury levels and the diagnosis of autism spectrum disorder (ASD). The conclusion is based on the reanalysis of hair to blood mercury ratios . . . ". We believe it should be clear that our conclusion was not related to the hair analysis, and the statement by Aschner appears to reflect a misunderstanding of our article. We have some concern that Aschner's opening sentences may confuse the issue further, which is why we hope that this response is very clear. The relationship of mercury to blood levels is based on these statistics: $r = .20$, $P = .017$. The F ratio associated with the regression is $F(1,133) = 5.76$. This statistic is based on 2 numbers from each participant in the study: (1) their blood mercury level, and (2) a code for being either a member of the autistic group or the control group. These are the only numbers that are used. In contrast, the hair analysis is a distinct (separate) analysis and has nothing to do (at all) with the statistically significant link between blood mercury level and autism diagnosis.

Again, the link between blood mercury level and autism diagnosis is based only on these 2 variables: blood level of mercury and autism diagnosis. This is the finding that is most important and should not be overlooked—this is what necessitated the correction regarding the original paper.[4]

The hair analysis data is, in fact, interesting. But it is of secondary importance. That said, because it was brought up in Aschner's critique, we address the rest of his criticism. Aschner writes, "Chelation therapy and changes in diet and fish consumption (both more likely to occur in the ASD group) in the 2 months preceding the mercury analysis are likely to affect blood, but not hair mercury sample." Chelation is sometimes recommended to decrease levels of toxins in the blood by practitioners who think toxins might play a role in autism symptoms. Because hair is formed and grows slowly, hair levels actually reflect the amount of mercury in the blood from several weeks previous. Essentially, Aschner has suggested that the discrepancy in hair to blood mercury correlation in autistics versus controls is likely to be related to the ASD group being more likely to have effectively removed levels of mercury from the blood in the recent past. His argument is this:

1. Chelation, if it occurred, would lower blood levels, but hair mercury would still be high for a month or so after the chelation therapy. [We agree.]
2. Chelation is more likely to occur in the ASD group than controls. [We could agree with this as well.]
3. The ASD group would therefore be expected to have higher hair levels than the blood levels would predict. [We agree this would be so if chelation were the underlying reason for the discrepancy in the autistic person's blood/hair mercury correlation.]

To sum, chelation among autistic patients could, as Aschner suggests, cause the correlation between blood and hair to be different in the autistic group compared to controls. So, do we agree with Aschner's critique? No. There is a statistical way to test Aschner's idea and it was performed and reported in our article. Although the autism group would have higher hair levels than the blood would predict if recent chelation therapy among some in the autistic group caused the results (what Aschner argues), the exact OPPOSITE was found.

In our article we performed additional analyses (reported in the second paragraph of the "exploratory analysis" section) that directly speak to this: "A t-test on the residuals showed that autistic participants were significantly more likely to have lower hair mercury levels than would be predicted as a function of their blood levels, $t(133) = 2.92$, $P < .005$".[1(p1310)] In other words, the autistic sample had LOWER hair levels of mercury than their blood levels would predict and not the higher levels as would be the case if they had undergone successful chelation therapy; these results are opposite to the argument put forth by Aschner. They are consistent with the idea that the autistic sample might perhaps be worse at ridding the body of circulating mercury, and not consistent with the idea that the autistic group might have recently experienced a higher level of mercury removal from the blood circulation than controls (via chelation).

Aschner writes that DeSoto and Hitlan "presume that the 2 biomarkers are equally affected" and that we are "clearly" in error on this. That seems to be a misreading of our article. We are actually, if anything, suggesting the possibility that the biomarkers are NOT equally affected (if one group is a poor excreter of mercury relative to the other, then this assumes hair and blood biomarkers are NOT equally affected). In fact, this is essentially the point of the exploratory analysis—that the degree of coupling of the 2 biomarkers were not equal in the autism and control groups.

To reiterate, the link between mercury blood levels and diagnosis of autism is the fundamental issue and was initially incorrectly reported by Ip et al. This is independent of the hair analysis, which was a separate (but interesting) exploratory analysis on the included data. If the autism spectrum disorder group had undergone chelation therapy (or avoided fish) as Aschner suggests, the autism spectrum disorder group would have higher hair levels compared to blood levels, but the opposite pattern was observed and reported. Finally, although Aschner suggests we have assumed that mercury blood levels and mercury hair levels

must be "equally affected," the entire exploratory analysis section is, in fact, suggesting the very opposite.

Because our article has been so widely read, we have developed a Frequently Asked Questions (FAQ) website to help interested persons understand the article.[7] Researchers who have used the Ip et al citation to reject the possibility that mercury and autism could be related should reevaluate their acceptance of the original Ip et al findings. It is reasonable that a correction of a widely cited article might change the debate, at least somewhat. Faculty of 1000 Biology is an independent body of experts, with an understanding of how statistics are (and are not) properly used. The review of our paper was given a high impact factor and listed as a must read.[8] The review describes the paper thusly: "... oddly exciting and disturbing because it involved the re-analysis of a classic paper used to debunk the mercury hypothesis of autism spectrum disorder and the original conclusion is now in doubt. This re-analysis does not prove the mercury hypothesis by any stretch of the imagination but it does suggest that we have been too definitive in ruling it out." We agree entirely. And as of this writing, there are no dissenting opinions by the Faculty of 1000 experts.

This brings us to another point. It is also imperative not to overstate the importance of these results. Our results do not prove that vaccines cause autism. In fact, although these results should properly be seen as moving the consensus opinion more toward than away from a link between mercury and autism, it should be considered that the link, if it exists at all beyond this sample, might or might not come from vaccines. For example, approximately 8% of women of child-bearing age in the United States have existing mercury levels in their blood that are above the levels considered safe.[9] Furthermore, mercury, even at these relatively low levels, has been shown to be deadly to developing neural stem cells.[10] There is compelling evidence that reaction to mercury is likely not the same for all individuals (that individuals' genetics matter).[11] As a whole and in light of these findings, logic compels us to keep an open mind and avoid adhering to an inflexible doctrine that often stifles scientific advancement.

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