nature neuroscience

A mercurial debate over autism

In June, environmental lawyer and activist Robert F. Kennedy, Jr., accused the scientific community of covering up evidence that mercury in childhood vaccines causes autism[1]. Before 2001, US childhood vaccines contained thimerosal, a preservative that includes ethyl mercury. As more vaccinations were recommended beginning in the 1980s, cumulative exposure increased, eventually exceeding the safety limit set by the US Environmental Protection Agency for mercury, a known neurotoxin. During this period, the number of autism cases increased, and thimerosal was suggested as a possible cause[2]. The hypothesis seemed plausible when first proposed, but recent epidemiological data do not support a causal relationship[3]. Some supporters of the hypothesis are not convinced by these data, and the scientific community has not helped its case with the public by appearing defensive or dismissive of this position.

Autism is the most severe of the autism spectrum disorders, pervasive developmental disorders characterized by impaired language, non-verbal communication and social interaction, and repetitive or stereotypically restricted behaviors. Autism is strongly heritable, and epigenetic and environmental factors are likely to interact with a predisposing genetic background involving multiple risk genes. According to the US Centers for Disease Control and Prevention, the prevalence of autism spectrum disorders ranges from 2–6 per 1,000, and the number of cases has risen about tenfold over the last 20 years in the US and other western countries, with some reports claiming more dramatic increases. Some or all of this apparent increase, however, may be due to changes in diagnostic definitions and recognition of the disorder by parents and doctors. Yet, with so many affected children and so few answers, parents of autistic children are understandably frustrated. This feeling may enhance the attractiveness of the thimerosal hypothesis, which allows parents to identify a discrete cause and suggests avoiding future exposure as a reassuring preventative action.

Unfortunately, epidemiological studies do not support this link. In May 2004, a review by the Institute of Medicine (IOM)[3] of over 200 studies (available online at http://www.nap.edu/catalog/10997.html) concluded "that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism," a view held by most of the international scientific community. The World Health Organization also maintains that "there is no evidence supporting a causal association between neurobehavioural disorders and thiomersal-containing vaccines."

Nonetheless, supporters of the thimerosal hypothesis continue to campaign aggressively for removal of any remaining trace of the preservative from medical products and for research that would confirm their hypothesis or develop therapies based on it. Largely through one vocal parent organization, Safe Minds, the idea has attracted media and political attention. However, according to Marie McCormick of the Harvard School of Public Health, chair of the IOM panel, other parent groups fear that the research process has been hijacked by the ongoing controversy. Many scientists see it as a distraction from other avenues of research that are more likely to yield insights into the disorders' causes, prevention and treatment.

One promising avenue is to use the variability in clinical characteristics of autism to build more focused hypotheses. For example, most children with autism show abnormalities within the first year of life. In contrast, about a quarter of autistic children seem to develop normally until about 15–24 months of age, when their development appears to regress. Geraldine Dawson at the University of Washington, who studies regressive autism, notes that distinguishing between early-and late-onset Alzheimer disease led to important breakthroughs and hopes that the same may be true for autism. A planned intramural program at the US National Institutes of Health will look at psychological, immune and other measures across regressive and non-regressive cases to examine what might precipitate the disease.

Improved understanding of phenotypic diversity is also guiding the search for autism risk genes. A subset of the symptoms of autism are often variably expressed in unaffected family members. The use of these endophenotypes increases the power of genetic analyses and may lead to identification of genetic homogeneities underlying individual traits. The hope, says Daniel Geschwind at UCLA, is to "take these genetic homogeneities and then work backward" to generate hypotheses about disease etiology, or about what types of gene-environment interactions may contribute to autism spectrum disorders.

In addition to interfering with such promising lines of research, the thimerosal controversy threatens to undermine the public's trust that scientists are committed to studying the problem. Overcoming this mistrust will require continued efforts from scientists to collaborate with the public. A good example is the US Department of Health and Human Services' Interagency Autism Coordinating Committee, which includes parents or legal guardians of autistic patients. These members represent the autism community and help guide policy decisions on autism research. Through this committee, the National Institutes of Health and other governmental agencies have developed partnerships for research and public education with national autism associations (http://www.nimh.nih.gov/autismiacc). Another successful collaborative effort is the Autism Genetic Resource Exchange (AGRE) program[4] founded by the Cure Autism Now organization, which has provided researchers with biomaterials from hundreds of families with autistic children.

In the end, McCormick may be correct that some supporters of the thimerosal hypothesis are unlikely to be swayed in their beliefs by anything short of finding the "silver bullet that causes autism." In the meantime, the absence of a clear mechanistic explanation should not be used to direct resources toward a single weak hypothesis. Parent groups should instead seek reassurance in continued collaboration with the scientific community as it moves forward in more promising directions.

1. Kennedy, R.F, Jr. Rolling Stone, published online 20 June 2005 <http://www.rollingstone.com/politics/story~/id/7395411>.
2. Bernard, S., Enayati, A., Redwood, L., Roger, H. & Binstock, T. *Med. Hypotheses* **56**, 462–471 (2001).
3. *Immunization Safety Review: Vaccines and Autism* (National Academies Press, Washington, DC, 2004).
4. Geschwind, D.H. *et al. Am. J. Hum. Genet.* **69**, 463–466 (2001).