

Thimerosal Disappears but Autism Remains

SINCE AUTISM WAS DESCRIBED in the 1940s, multiple unfounded theories of causation and corollary “treatments” have been offered. Psychiatry, then a psychoanalytically oriented discipline, posited a psychosocial explanation that blamed “refrigerator” mothers for the child’s withdrawal into the autistic bubble, only to be reached by the interpretations of therapists engaged in long-term play therapy. To name only a few more recent such theories taken from both

See also page 19

the psychosocial and biological realm of explanations, facilitated communication and secretin infusion enjoyed widespread support up to the point when the systematic accumulation of carefully controlled clinical trials consistently failed to provide support for their efficacy.^{1,2} In the last decade, 2 hypotheses on autism-immunization links were raised that have had a profound impact in the field of autism research and practice and on public health at large. One incriminated the measles component of the triple measles-mumps-rubella (MMR) vaccine,³ the other the amount of thimerosal (about 50% of which is ethylmercury) contained in most other childhood vaccines.⁴ The 2 hypotheses are separate, since MMR vaccines never contained thimerosal. Both hypotheses relied on the claim of an autism “epidemic” that apparently coincided with the introduction of MMR and/or the increased exposure to ethylmercury due to the increased number of recommended childhood immunizations in the first 3 years of life.

In testing these hypotheses, critical epidemiologic investigations were immediately conducted by different investigators using a variety of designs (cohort, case-control, and ecologic) in different samples and coun-

tries. With the exception of studies conducted by the 1 single pair of authors,⁵ all studies failed to reject the null hypothesis of no association.⁶ Relative risks in studies in which it could be estimated were close or below unity, and studies were in most cases well powered to detect even small effects and could adjust for background confounding factors. In parallel, several studies were conducted that failed to identify a specific phenotype of mercury- or MMR-induced autism and failed to find evidence of mercury poisoning or of the persistence of the measles virus in children with autism. In 2004, the Institute of Medicine Immunization Safety Review Committee reviewed all evidence available from epidemiologic, biological, molecular, and animal model studies and concluded that the evidence favored the rejection of both hypotheses with respect to the risk of autism.⁷ Since then, more studies have accumulated that have reinforced this conclusion, one independently reached by scientific and professional committees around the world.⁸

The study by Schechter and Grether⁹ in this issue of the *Archives* provides additional evidence of the lack of association between thimerosal exposure and the risk of autism in the US population. Using an ecologic design and data from the California Department of Developmental Services, the authors showed that the prevalence rate of autism increased continuously during the study period even after the discontinuation of the use of thimerosal in US vaccines in 2001. Had there been any risk association between thimerosal-containing vaccines and autism, the rate of autism should have decreased in young children between 2004 and 2007. Instead, the rate increase did not attenuate, indicating that thimerosal exposure bears no relationship to the risk of autism. The findings of Schechter and Grether⁹ are

consistent with those of previously published cohort and case-control studies¹⁰ and similar ecologic studies conducted in Denmark and Canada.^{11,12} Ecologic studies can be powerful tools to test causal hypotheses in circumstances in which exposure to a risk factor (in this case, immunizations) is widespread and when the effects of variation in exposure level can be examined (either by contrasting different countries that systematically differ in their exposure levels or by testing trends across time when sufficient variation in the level of exposure, as in the case of discontinuation, occurs). The particular significance of the study by Schechter and Grether⁹ is that it relies on the California Department of Developmental Services database, which has been systematically used by proponents of the thimerosal hypothesis to argue that the rising number of children accessing these services—or the “epidemic” of autism—was linked to the increasing exposure to ethylmercury of US children occurring in the 1990s through the changes in the immunization schedule. To the contrary, the data analyzed by Schechter and Grether⁹ provide a clear and unambiguous test that shows that the expected decline in autism rates following discontinuation of thimerosal in US vaccines did not occur.

Despite the accumulation of scientific evidence rejecting these 2 hypotheses linking autism to various components of childhood vaccines, these theories and the practices that accompany them have not faded away. Why? How many more negative study results are required for the belief to go away, and how much more spending of public funds on this issue could even be justified? A full answer to this question is beyond the scope of this commentary, but some issues relevant to the development and persistence of this controversy can be identified in the complex in-

terplay between academic medicine, social policy influences, families of autistic children, and the public.

In the 1990s, most of the funding in autism research went initially to genetic research, consistent with the strong evidence of autism as a genetic disorder. As a result, the United States, as did most other countries, failed to track the incidence of autism and related disorders. Much-needed epidemiologic approaches to the study of autism and other disorders were not developed or funded. Thus, as the number of children diagnosed as having autism grew, concerns about an epidemic were appropriately raised in the public. Available data suggest that broadening of the autism concept, changes in diagnostic criteria, diagnostic substitution, improvements in educational policies, and increased awareness have played a major role in explaining the increasing numbers of children identified with autism.^{13,14} New monitoring programs such as those developed in recent years by the Centers for Disease Control and Prevention will help to address these questions in the near future.

Outside academic circles, powerful advocacy groups developed and started to lobby decision makers to influence decisions about which autism research to fund and even how to conduct it. Unaware of scientific studies, or worse, doubtful of their results, bestselling writers, journalists, and politicians were drawn to embrace conspiracy theories that portrayed vaccine manufacturers and the Centers for Disease Control and Prevention as public enemies.¹⁵ Law firms saw an opportunity to obtain large financial compensations from the US Vaccine Injury Compensation Court or before local federal courts, the viscous US legal process allowing for fermentation of misconceptions. Exploiting further families' beliefs and their understandable desire to try everything possible to help their children, charlatans developed alternative (and lucrative) "treatments" for autism, which included chelation therapy,

use of a hyperbaric oxygen chamber, and testosterone suppression.¹⁶ All are of unproven efficacy, and many are dangerous.

Childhood vaccines have been one of the most important advances of modern medicine in the 20th century. Unfortunately, once vaccine programs have been successful at controlling preventable infectious diseases, people shift their attention to the potential adverse effects of vaccines (which are rare but can nevertheless be serious). Deaths of young children occurred in Europe because of the MMR-autism scare, and as shown in a recent US measles outbreak,¹⁷ children's health was put at risk by parents who refused to vaccinate their children because of the supposed vaccine-autism link. Parents of autistic children should be reassured that autism in their child did not occur through immunizations. Their autistic children, and their siblings, should be normally vaccinated, and as there is no evidence of mercury poisoning in autism, they should avoid ineffective and dangerous "treatments" such as chelation therapy for their children.

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