

# Mercury in Dental Amalgam— A Neurotoxic Risk?

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**D**ENTAL AMALGAM, WHICH CONTAINS 50% MERCURY by weight, has been used for at least 150 years. Because mercury is an acknowledged neurotoxin, concerns about the health effects of exposure to this chemical are widespread. Consequently, many individuals have submitted to removal of amalgam dental fillings, an uncomfortable, expensive procedure that is not free of hazard. In this issue of *JAMA*, Bellinger and colleagues<sup>1</sup> and DeRouen and colleagues<sup>2</sup> report the first 2 randomized controlled trials comparing the health effects in children treated with mercury amalgam fillings with those treated with a composite dental restorative material.

Mercury is a highly reactive metal that has widely recognized toxic properties at high dose, including paresthesias, cerebellar ataxia, dysarthria, and constriction of the visual fields.<sup>3</sup> The significance of lower-level asymptomatic exposures on brain function is less clear, and sound clinical studies are needed to define this risk. Amalgam mercury enters the bloodstream, and a number of investigations suggest that this has toxic consequences. Mercury levels in expired air are correlated with the number of amalgam fillings.<sup>4</sup> Dentists and dental assistants have deficits in motor function and cognitive scores in relation to their number of fillings and to their urinary mercury excretion.<sup>5</sup> Mercury also has been suggested as a risk factor for multiple sclerosis and Alzheimer disease.<sup>6</sup>

Sensitivity to mercury toxicity may have a genetic basis. Echeverria et al<sup>7</sup> recently reported that polymorphisms of coproporphyrinogen oxidase (*CPOX4*), the gene encoding urinary porphyrin excretion, altered the impact of mercury on cognitive and mood scores. Approximately 25% of the US population is polymorphic for this genotype.<sup>7</sup> Although the literature is sparse, other molecular effects of mercury exposure also are receiving attention. For example, in an *in vitro* study, mercury has been shown to affect heat shock protein levels in human cells<sup>8</sup> and in an animal model, mercury inhibited the binding of guanosine triphosphate (GTP) to tubulin in the rodent brain.<sup>9</sup>

With the application of better epidemiological designs and more robust statistical methods to investigate toxicity, the

usual consequence is uncovering effects at lower thresholds. The trajectory of discovery of the toxic effects of another metal, lead, has followed this path and may offer insight into the future path that mercury investigations may follow.

When childhood lead poisoning was first reported, it was believed to have only 2 outcomes: death or complete recovery with no sequelae. After long-term neurobehavioral deficits were found in survivors of lead poisoning, these effects were thought to occur only in children who had displayed signs of severe encephalopathy.<sup>10</sup> In the 1970s, studies of elevated lead burden in children who had displayed no symptoms revealed dose-dependent deficits in cognitive skills, attention, and behavioral control.<sup>11</sup> In the 1960s, the defined toxic threshold for lead was 60 µg/dL (2.90 µmol/L); however, over the next 30 years, on the basis of newer studies, this threshold was sequentially reduced to 10 µg/dL (0.48 µmol/L). A recent pooled analysis of 7 longitudinal cohort studies demonstrated that blood lead levels below 10 µg/dL (0.48 µmol/L) in children are associated with decrements in IQ scores.<sup>12</sup> These findings are the consequence of larger sample sizes, more sensitive outcome measures, and better multivariate techniques. History is likely to repeat itself with other neurotoxins.

The 2 clinical trials reported in this issue of *JAMA* examine the neuropsychological and renal effects of dental amalgam in children. In their study of 534 New England children aged 6 to 10 years, Bellinger et al<sup>1</sup> found that, at 5 years' follow-up, children randomly assigned to the amalgam group had higher mean mercury levels than those in the resin-based composite group, but there were no statistically significant differences between the groups in terms of 5-year change in full-scale IQ score, 4-year change in general memory index, or visual motor composite score, or urinary albumin levels. In the report by DeRouen et al,<sup>2</sup> 507 8- to 10-year-old children from Lisbon, Portugal, were randomly assigned to receive dental restorations using amalgam or resin composite. At 7 years of follow-up, children in the amalgam group had higher urinary mercury levels, but there were no statistically significant differences be-

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tween the groups' scores on neurobehavioral assessments of memory, attention/concentration, or motor/visuomotor performance.

Although the studies by Bellinger et al and by DeRouen et al provide important new data on the health effects of mercury containing dental amalgam in children, there are, as the authors clearly delineate, limits to the inferences that can be drawn from these data. It is predictable that some outside interests will expand the modest conclusions of these studies to assert that use of mercury amalgam in dentistry is risk free. This conclusion would be unfortunate and unscientific. The conclusions that can be extrapolated from these 2 studies are constrained by several factors.

First, the follow-up duration is limited to 5 years in the study by Bellinger et al and 7 years in the study by DeRouen et al. Although these follow-up periods are noteworthy, the delayed effects of early toxic exposure on health later in life, which are a subject of growing interest, are not, as acknowledged by the authors, addressed in these reports. The hints that mercury has an effect on the aging brain emphasize the salience of this question.

Second, although both studies were sufficiently powered to rule out clinically important neurocognitive effects, the statistical power may be insufficient for detecting smaller effects. Considering the huge exposure pool, a statistical power of 0.8 to detect a 3-point difference in IQ change scores or one adequate to find an effect size of 0.3 SD could miss some effects of mercury in a meaningful number of children. For instance, the estimated amount of mercury used in amalgam production each year is 100 tons,<sup>4,13</sup> and the number of children with amalgam fillings is estimated to exceed 50 million. If mercury caused subtle effects in 1% of those exposed, up to 500 000 children could be affected.

Third, the effect of dental amalgam among highly vulnerable groups (such as those with genetic predispositions to mercury toxicity) on the risk ratio is not considered. This factor has been shown for the *CPOX4* gene, and other variants undoubtedly will be discovered.

And, fourth, there are the potential effects of unavoidable measurement error. Both studies compared and contrasted children with and without dental restorations using amalgam. This binary classification, while an improvement over earlier studies, still is subject to error in measurement. This unavoidable error is nondifferential because it affects both randomized groups and biases study

results toward the null and thus underestimates the true effect size. Studies of more proximate body burden measures, such as urinary mercury concentrations treated as interval variables, are needed to sharpen the focus on this question. Much of this would require experimental studies in animals for which the dose and tissue levels are carefully controlled and measured. The true exposure measure is the level of mercury at critical brain sites but cannot be determined at this time.

The studies by Bellinger et al and DeRouen et al represent thoughtful and important contributions to understanding the question of dental amalgam risks in children, but the question of more subtle effects remains open. Given the numbers of children exposed to dental amalgam, it is critical that further rigorous studies examine the molecular effects of the toxicant at appropriate doses, measure exposure as precisely as possible, and explore the important question of vulnerability factors.

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