

treated with oral melphalan plus high-dose oral dexamethasone, the 3-year overall survival rate was 80%, showing that they were actually “good risk” patients. With censoring of data for patients who died early and patients who could not receive their assigned treatment, the results of the landmark analysis strongly argued against the superiority of high-dose melphalan, even in groups with 0% treatment-related mortality and 100% treatment feasibility. This probably resulted from the very similar hematologic response rates in the two treatment groups, in a disease in which a clonal response is mandatory for improved survival.

Our 24% rate of treatment-related mortality with high-dose melphalan is in keeping with the results of several other multicenter studies and can be considered as representative of the results with high-dose melphalan when used outside some tertiary referral centers. The better results obtained in these referral centers probably reflect not only better management of the disease but also better selection of candidates for high-dose melphalan. Both were likely factors in the impressive

results reported by Comenzo et al. Studies comparing new standard-dose regimens with (optimized) high-dose treatments should now be performed in tertiary referral centers. In our opinion, further improvements in the survival of patients with AL amyloidosis are likely to result from the use of new drugs and innovative therapeutic approaches.

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## Early Thimerosal Exposure and Neuropsychological Outcomes

**TO THE EDITOR:** Thompson et al. (Sept. 27 issue)<sup>1</sup> report the results of a study investigating the neuropsychological outcomes of early exposure to thimerosal. As a dissenting member of the panel of external consultants for this study, I object to the authors' conclusion that there is no causal association between thimerosal and children's brain function. The sample comprised children who were least likely to exhibit neuropsychological impairments. Specifically, children with congenital problems, those from multiple births, those of low birth weight, and those not living with their biological mother were excluded. The sample was skewed toward higher socioeconomic status and maternal education — factors that are associated with lower rates of neurobehavioral problems and higher intervention rates and that were not measured. The sampling frame included only children enrolled from birth in the health maintenance organization (HMO) and still enrolled after 7 to 10 years, excluding children in higher-mobility families, who tend to have lower academic and behavioral function.<sup>2</sup> Children with neurobehavioral

problems may have been less likely to remain with the HMO. Only 30% of families selected for recruitment participated, a low rate for scientific research. Among the families selected for recruitment, 26% refused to participate. Another 28% “could not be located,” which included families that did not respond to multiple recruitment attempts (internal documentation from the study contractor, Abt Associates) — another form of refusal.

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**TO THE EDITOR:** Recently, I summarized several nutritional factors that are likely to play a large

role in modulating the toxicity of the various forms of mercury.<sup>1</sup> These factors include plasma thiol levels, zinc and selenium status, and dietary fiber intake, and they have been shown in various studies to be important as regulating factors in both the biological transport and the distribution of the different forms of mercury and therefore as mediators of mercury toxicity. In addition, several genes have been identified that are also thought to affect the toxicity of mercury. These genes are currently known to include the *CPOX4* polymorphism<sup>2,3</sup> and the *BDNF* gene.<sup>4</sup> The *CPOX4* polymorphism is known to lead to an atypical toxicologic response to mercury from dental amalgam in up to 15% of the population.<sup>2,3</sup> Each of these nutritional and genetic factors represents a confounding variable of unpredictable magnitude that may have affected the results of the study by Thompson et al.

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**THE AUTHORS REPLY:** Bernard raises several points that we wish to address. First, children with low birth weight or serious congenital conditions or conditions developing in infancy that are known to be associated with an increased probability of neurodevelopmental problems were excluded from the study. It would have been difficult to distinguish the possible added influence of thimerosal exposure on neuropsychological deficits among such children. To do so, a larger study with a different design would be required.

Second, our sample was probably skewed toward higher socioeconomic status because par-

ticipating families were members of HMOs in which coverage was provided by employers. In the study population, thimerosal exposure was associated with both maternal education and maternal IQ. We therefore controlled for socioeconomic factors, maternal education, and maternal IQ in the statistical analyses.

Third, our study was less likely to include highly mobile families because the participants had to have been enrolled in the same HMO during the first year of life and during the time of testing 7 to 10 years later. These criteria ensured that we had all immunization records during the first year of life, as well as access to the participants' medical records during the time of testing. This enhanced the internal validity of our study but makes the results less generalizable to highly mobile families.

Finally, the 30% participation rate may have resulted in some unmeasured biases. Participation in the study required a substantial time commitment from mothers and their children. Although the 30% participation rate was relatively low, it was higher than we estimated when we planned the study. More discussion regarding participation and other issues can be found in the study technical reports, available on the Web site of the Centers for Disease Control and Prevention.<sup>1,2</sup>

Although nutrition and genetics play an important role in neurodevelopmental outcomes, we believe that the factors pointed out by Mr. Rooney were unlikely to confound the results of our study because they are unlikely to be correlated with thimerosal exposure.

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