

Letter to the Editor

Dental Amalgam and Multiple Antibiotic Resistance: an Untested Hypothesis

In a recent article in your journal, Summers et al. (3) suggested that exposure to mercury (Hg) from dental amalgams resulted in an increased incidence of multiple antibiotic-resistant bacteria in the normal floras of nonmedicated subjects. However, the study does not allow such conclusions, and the authors' inferences are unwarranted.

The investigators first reported the results of a study that attempted to correlate the incidence of Hg resistance with that of antibiotic resistance in human fecal flora. This study was meaningless in the context of the paper. The authors failed to obtain data on the amalgam status of their study subjects, and the accuracy of the estimates used is doubtful, considering the age range of the population; inferences relating amalgam placement with increases in the incidence of antibiotic-resistant fecal flora in this population therefore cannot be made.

The authors did attempt to directly correlate placement and/or removal of amalgams with an increased incidence of antibiotic resistance in a subsequent investigation using six monkeys. The oral and intestinal floras of each monkey were sampled at intervals before and after amalgam placement and/or removal; bacterial isolates were then screened for Hg and antibiotic resistance. The researchers reported an increase in the frequency of bacterial resistance to mercury immediately following amalgam placement and suggested an "overgrowth of either rare preexisting Hg-resistant strains or of strains contaminating the food. . . ." However, the authors did not report total microbial counts and therefore are unable to conclude that Hg-resistant strains represented a significant portion of the total floras, never mind conclusions relating to "overgrowth."

The study further attempted to correlate increased numbers of Hg-resistant bacteria with an increased incidence of resistance to two antibiotics, tetracycline and ampicillin. First, I address tetracycline resistance: the authors found that "tetracycline resistance occurred in all bacterial populations even prior to the installation of the fillings . . . it did not fluctuate with Hg resistance profile." Such results would clearly disassociate tetracycline resistance from any procedures relating to amalgam placement and/or removal.

Second, results for the antibiotic ampicillin were reported for only two of the six monkeys studied; resistance to this drug was "not detected in either gram-positive population," i.e., the enterococci and the oral streptococci (p. 831, Fig. 4B). Resistance trends were reported for members of the family *Enterobacteriaceae*; however, the second highest level of ampicillin resistance was observed 6 weeks prior to amalgam placement, clouding any meaningful association between amalgam placement and ampicillin resistance.

To conclude, the researchers attempted to directly relate amalgam placement and/or removal with an increased incidence of resistance to only two antibiotics; they found no correlation for one of the drugs (tetracycline) and obtained inconsistent (and unexplained) results for the only remaining antibiotic (ampicillin). Statements "implicating the exposure to mercury from dental amalgams in an increased incidence

of multiple antibiotic resistance plasmids" are clearly unwarranted.

The researchers finally reported the resistance phenotypes and biotypes of representative Hg resistance isolates. Once again it is difficult to ascertain the relevance of this work to the context of the paper. Antibiotic resistance patterns were not reported in relation to total microbial count and were not reported in relation to amalgam placement. At best, all that these data would suggest is that mercury resistance and resistance to some antibiotics may be encoded on the same transmissible genetic elements, a fact that has been known for many years (1, 2, 4) and whose physiological significance is unknown.

Hg is ubiquitous in our environment, and its selective influence has always been present—certainly since the introduction of antimicrobial agents in the mid-1930s. On this basis, it is difficult to associate recent increases in antibiotic resistance with Hg, when a potential niche for Hg- and antibiotic-resistant microorganisms has existed for almost 60 years.

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Author's Reply

Dr. Brian Shearer of the American Dental Association raises some objections to our recent paper. His first objection relates to the absence of specific dental amalgam data for individual members of the human population described. In our article, we do not claim to show a relationship between amalgams and antibiotic resistance in the individuals tested. What we do show is a statistically significant relationship between Hg resistance and antibiotic resistance in the fecal floras of these 356 persons (Fig. 1, p. 828), none of whom had recently consumed an antibiotic. Therefore, we made the hypothesis (not an inference) that environmental exposure to Hg (perhaps from amalgams) might be related to the occurrence of multiresistant plasmids in these subjects. We tested this hypothesis with primates and proved that

amalgams released mercury which selected for mercury- and antibiotic-resistant bacteria.

Dr. Shearer's second objection seems to be that the antibiotic resistance should have been reported in relation to the "total microbial count." It is simply not technically feasible to make a "total microbial count" of the intestinal and oral floras. In both niches, the multitude of different kinds of bacteria growing on and within complex surfaces precludes precise quantitation of their absolute total numbers. The three populations of bacteria whose percent resistance we examined by standard methods (5) were chosen for their well-documented significance in primary and opportunistic human infections and because antibiotic resistance in these families of bacteria is an increasing problem in human medicine (2, 4, 6).

Third, Dr. Shearer is simply incorrect in stating that we did not detect ampicillin resistance in the oral streptococci. As reported (p. 830), we observed ampicillin resistance in the oral streptococci and also found many other antibiotic resistance phenotypes (including those for streptomycin, kanamycin, chloramphenicol, and erythromycin) on subsequent screening of typical Hg-resistant isolates of all genera. Moreover, the single pre-amalgam occurrence of ampicillin and tetracycline resistances in one pair of monkeys is to be expected with animals arriving from an uncontrolled environment. During the subsequent 5 weeks before the amalgams were installed, both resistances in these two animals fell to barely detectable levels (Fig. 3, p. 830). However, once the amalgams were installed both resistances increased and persisted over the entire time of exposure to Hg. Following the removal of the amalgams, antibiotic resistance in these animals became undetectable. Thus, if amalgam installation provokes an increase in Hg-resistant bacteria (demonstrated in Fig. 3A and 4A, p. 830 and 831) and individual Hg-resistant isolates obtained during those peak periods are resistant to many antibiotics, then amalgam installation is indeed provoking an increase in multiply resistant bacteria.

Dr. Shearer's fourth objection is that if amalgam Hg is fostering an increase in antibiotic resistance, it should have been noticed before. In fact, the selection by antibiotics of antibiotic resistance genes in the general human population could only have begun with the introduction of widespread antibiotic use ca. 50 years ago (4). Since Hg-containing dental fillings had been in use for 100 years prior to the introduction of antibiotics (1), Hg-resistant plasmids might have already spread throughout the human population and could have provided a ready substrate for the accretion of multiple antibiotic resistance loci once antibiotic use began. Indeed, the very earliest antibiotic resistance plasmids described also carried genetically linked Hg resistance loci (3, 7).

Finally, Dr. Shearer's statement that "Hg is ubiquitous in our environment" misleadingly implies that there are envi-

ronmental sources of Hg exposure equivalent to amalgam. Quite the contrary; as recently reported, dental amalgam is the major source of human exposure to Hg, substantially exceeding that available from all other nonoccupational sources combined, including food (8). Because of the ominous increase in and persistence of multiple antibiotic resistance in the floras of healthy, unmedicated persons (2, 4, 6) and in light of the known genetic linkage of Hg and antibiotic resistances on bacterial plasmids, we are currently examining (in a longitudinal, multifactorial experiment) how amalgam installation affects the oral and intestinal floras of humans.

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