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Guest Editorial

From observational studies to randomized trials: asking the right question at the right time

Focused Perspective on Hujoel et al., J Clin Periodontol 2006; 33: 520–523.

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In an article in this issue, Hujoel et al. argue that associations between oral and general health awareness have the potential to result in spurious relationships being identified in oral epidemiological investigations (Hujoel et al.). The authors use the results of a survey of dental flossing and obesity to illustrate their point.

Their point has merit. Periodic reminders, such as the paper by Hujoel et al., on the importance of critical evaluation of data from epidemiologic studies are important. Scientists, and the public more generally, are inundated with health messages, and discerning which are based on good study designs and accurate data can be challenging. A few years ago a science reporter by the name of Victor Cohn wrote an article in a statistics journal about how scientists can help the media. Cohn realized that reporters were struggling to understand what was believable and what should be reported. He suggested always asking ''Are there any other possible explanations for what you are saying, or influences that you may be ignoring?'' (Cohn 2001). This is a healthy scientific practice in general and is a reporter's analog to identifying a differential diagnosis. Clearly, in the Hujoel et al. paper, general health awareness appears to be an important alternative explanation for the association between flossing and obesity.

Similar to the main point of Hujoel et al., Davey Smith et al. (1992) described associations between smoking and suicide and between smoking and homicide in a large cohort study to illustrate the dangers inherent in two common approaches for assessing causality from observational data: investigation of a dose–response relationship and assessing whether the effect was ''independent'' of other risk factors (meaning statistically significant even after adjusting for known confounding factors). Developing a plausible biological mechanism to explain a correlation does not substantially increase the likelihood that the finding is real or that the relation is causal, as post-hoc explanations are common and fraught with errors. Indeed, there is a whole body of philosophy and statistical methodology that falls under the rubric of ''Causal Inference'' that seeks to address these issues, but there is no substitute for conducting confirmatory randomized trials when they are possible. The commentary of Hujoel et al. helps to reinforce the importance of careful attention to study design (control of confounders and bias), critical interpretation of results of clinical studies (especially observational studies), and the importance of replication.

Although emanating from a longitudinal study, the analysis reported by Hujoel et al. is cross-sectional. In such analyses, in addition to confounding and bias, the temporal association between the risk factor (flossing) and the outcome (obesity) is not clear. Most would agree with the authors that the reported association between dental flossing and body mass index is not sufficiently compelling to initiate a randomized trial on whether dental flossing might help people lose weight. However, it is important that this study does not serve as a ''straw man'' for those who believe that randomized trials of oral health preventive measures on systemic health (e.g., the effect of interventions for periodontal disease on cardiovascular outcomes) should not be considered. Stronger evidence from epidemiologic studies may exist (e.g., data from cohort studies where the temporal sequence is clear, where changes over time in the oral and systemic health measures can be assessed, and where data can be evaluated from different populations that vary by general health awareness), and it is usually better to consider randomized trials sooner rather than later. Otherwise, treatment practices and public perceptions can develop based on inferior or incorrect information. Like any bad habit, these can be difficult to break.

The timing of randomized trials was eloquently discussed in a short letter by Chalmers several years ago (Chalmers 1968). He argued that the initial studies of new drugs in humans should begin with randomization because at this early point, when there are no data on efficacy and safety, randomization is most ethical. Once treatments become established, it is difficult to conduct trials to understand their effectiveness. Using data from non-randomized studies on the association of treatment and disease

outcomes (e.g., anti-infectives for periodontal disease and cardiovascular disease) to inform practice can be fraught with problems. The interventions are likely to have only modest effects on health outcomes, and bias and confounding in non-randomized studies might dominate the observed effects, leading to under- or over-estimation of benefit. Also, oral health interventions may be associated with long-term risks, particularly if they involve drugs rather than less benign interventions such as flossing.

Several recent examples confirm the problem of relying on observational studies for understanding the effectiveness of treatment: while a number of observational studies report inverse associations between antioxidant vitamin intake and cardiovascular disease and cancer, randomized trials have shown that supplementation with antioxidants does not prevent these conditions (Rimm et al. 1993, Stampfer et al. 1993, The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group 1994, Khaw et al. 2001, Heart Protection Study Collaborative Group 2002). Likewise, observational studies on the protective effect of hormone replacement therapy led to large randomized trials in which the beneficial effects of hormone replacement therapy were not confirmed (Stampfer & Colditz 1991, Rossouw et al. 2002).

In summary, good epidemiologic studies on oral health and systemic health that account for general health awareness are important, and a critical interpretation of such studies is essential. The paper by Hujoel et al. is a valuable reminder of this. As MacMahon and Collins noted in a recent review article, well-done observational studies can play an important role in determining the potential effects of treatments (this is often important in considering whether a substantial investment in a trial is warranted) and in determining the rates of disease in the absence of the treatment (this is important both for the design of randomized trials and in determining to which populations the intervention should be targeted if it is found to be effective); however, in most situations they are no substitute for randomized trials (MacMahon & Collins 2001).

The process of determining when a confirmatory outcomes trial is warranted should be based largely on consensus, with several identifiable elements. First, consensus should be reached that a strong independent association between a modifiable risk factor (e.g., periodontal disease) and an outcome of interest (e.g., cardiovascular disease) exists. This can be reasonably inferred from carefully conducted epidemiologic studies that examine temporal associations and control for confounding factors such as general health habits. Second, consensus should be reached that an intervention (e.g., an effective antibiotic) that modifies the risk factor (e.g., periodontal disease) has the potential to modify the disease outcome (e.g., cardiovascular disease). Third, once the first two elements are established, consensus should move rapidly to determine whether a trial is feasible and should be carried out (i.e., to consider whether it is the right time to address the question). This consensus process should not only consider the strength of the observational evidence and the potential for improving public health, but also trial feasibility, including recruitment and follow-up of patients, cost, and the nature of the intervention. This process needs to be ongoing, as new data accumulate rapidly, and timing is everything. The Women's Health Initiative trial (Rossouw et al. 2002) was almost too late in coming. Many opposed the trial of hormone replacement therapy because women were to be randomized and some would not receive the presumed benefits of hormone replacement therapy that had been seen in observational studies. The timing of randomized clinical trials is critical: strike too soon, and you may fail to answer the right question. Procrastinate, and practice patterns may be so ingrained that it is impossible to conduct a randomized trial. It is important that the window of opportunity for doing trials on oral health interventions that have the potential for making an important impact on systemic health not be missed.

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Editorial note

The authors of this editorial are faculty in biostatistics who are very active in the design and conduct of large clinical trials in medicine. The editors of the *Journal of Clinical Periodontology* are most apprciative for their thoughtful discussion of observational studies and clinical trials as they relate to the association of periodontal disease with ''systemic diseases''. Such discussion is essential as

our field moves forward in this exciting area that has the potential to dramatically change our profession in the field of disease prevention and health care.

As an addiitional comment, the editors feel that researchers and clinicians alike should discontinue using the term ''systemic disease'' because it only serves to perpetuate the separation of oral disease and dentistry from the rest of the body and medicine in general. Medical specialties do not use similar nomenclature and we recommend that dentistry discontine use of this terminolgy. As an example, opthamologolgists or cardiologists do not use terminology such as 'the link between eye diseases or cardiovascular disease with ''systemic disease'''.

We recommend that use of the term ''systemic diseases'' be discontinued and that the term ''other diseases'' be adopted. As an example of using such terminology, one could state ''that there is observational evidence that periodontal disease may be associtated with other diseases, but that a causal association between periodontal disease and other diseases has not been established. Moreover, it has not been shown that treating periodontal disease will prevent the occurence of other diseases.'' Note that the term ''systemic disease'' has been omitted from this statement.

Terminology is important because it often shapes perception. As long as researchers and clinicians continue to use terminology that separates oral disease and dentistry from medicine, our profession and the diseases it seeks to prevent and treat will continue to be percieved as separate from the rest of the body and from medicine in general.