Passive Smoking and Heart Disease

The recent article in *Circulation* on passive smoking by Glantz and Parmley addresses a very important issue—an estimate of adult mortality from heart disease attributable to environmental tobacco smoke (ETS). This is a very timely contribution, but it includes several issues that deserve clarification. Having reviewed recently the literature on the association of tobacco use and cardiovascular disease in the active smoker, with an emphasis on risk factors, mechanisms of disease, and risk modification, we would like to raise some considerations about exposure to ETS and coronary heart disease.

ETS is generated by about 50 million active smokers in the United States, resulting in widespread exposure of the nonsmoking majority to some of the residual constituents of mainstream and sidestream smoke. Efforts to assess the health effects attributable to ETS have used risk factor analysis, an epidemiological concept that describes a consistent association of characteristics in healthy individuals that are related to the development of disease in the exposed population. Using this approach, the risk for the nonexposed population is set at unity, or 1.0, and the risk of the exposed group then is some variation of unity. When this multiple is high, the risk factor is strong, implying a high probability for a true causal relation; even then, however, it still remains only a statistical association that must be considered in the context of other scientific information. When the risk factor for the development of disease is less than 3.0, the risk is considered to be weak.1,2

With weaker risk factors, greater care is required for interpretation. For instance, when the risk ratio is 2.0 or less, "... the possibility that the finding is artificial and a consequence of problems in case-control selection or due to the presence of confounders and biases needs to be carefully considered."3

The pooled relative risk for coronary heart disease as a function of exposure to ETS reported by Glantz and Parmley was in fact very weak, at 1.3. At this level of risk, there are at least 300 or more reported risk factors for cardiovascular disease.4,5 It thus becomes extremely difficult, and even precarious, to attribute causality to any one such risk factor without appropriate control for the confounding effects of others. For cardiovascular disease, this is an almost impossible task to undertake with certainty for very weak risk factors, when only about 50% or less of all mortality and morbidity from coronary heart disease can be accounted for by specific identifiable risk factors of any kind.6

The epidemiological studies of ETS and heart disease cited by Glantz and Parmley all report negative (less than 1.0 relative risk) or only weak associations. When multiple studies report weak relations, strengthening of the statistical analyses sometimes may be improved by combining the data from all studies into one comprehensive assessment or meta-analysis. There are, however, recognized guidelines that must be used in pooling data.7 One cannot determine from the text of their article how Glantz and Parmley pooled the epidemiological results cited, but clearly no known guidelines for combining such data for any such compilation of effects permit mixing mortality data with disease prevalence data.8,9 Likewise, no known criteria for meta-analysis permit incorporating the same data twice, as Glantz and Parmley have done by citing the results of a preliminary report9 and the final report8 on the same population study.

In support of their hypothesis, Glantz and Parmley developed a comprehensive overview of "... a variety of physiological and biochemical data that show that ETS adversely affects platelet function and damages arterial endothelium in a way that increases the risk of heart disease."10 This supports the theory that the polycyclic aromatic hydrocarbons (PAHs), 7,12-dimethylbenz[a]anthracene (DMBA) and benz[a]pyrene (BAP), initiate endothelial injury, ultimately leading to platelet aggregation and plaque formation. Chronically delivered high doses of 10–100 mg per kilogram of DMBA and BAP consistently enhance rates of atherogenesis in certain animal models; chronic administration of lower dosages of these PAHs does not appear, however, to have an atherogenic effect. Although reported in a very limited number of citations, the various surgeon generals' reports do not list DMBA as a constituent of mainstream or sidestream tobacco smoke. BAP, however, is present in mainstream smoke (30 μg per cigarette) and in very low concentrations in sidestream smoke (70 ng per cigarette), but neither DMBA nor BAP have ever been reported as present in readily measurable quantities in ETS. In studies on humans, no differences in urinary markers of PAHs after exposure to ETS have been detectable, even at extraordinarily and unrealistically high levels of exposure.10

There is no evidence that the polycyclic aromatic hydrocarbons of ETS "... accelerate, and may initiate, the development of atherosclerotic plaque," as Glantz and Parmley claim.1 There is no compelling evidence that these polycyclic aromatic hydrocarbons can even be detected in ETS. In fact, it is hard to define exactly what ETS really is. Of the 3,400 or more identifiable substances in mainstream smoke and of the 150 components that have been consistently identified in sidestream smoke, only 50 are so highly diluted residual constituents of tobacco smoke have been measured reproducibly in ETS.11,12 By denudation, chemical reaction, and other processes, most of the mainstream and sidestream smoke constituents are lost or remain present only in extremely low levels that are below our capacity to detect as environmental pollutants.

The considerations raised by Glantz and Parmley are very important. It is essential, however, not to compromise scientific accuracy simply because the subject is ETS. To do so detracts from the significance of this important topic and diminishes the credibility of contributions otherwise critical to the development of responsible public policies governing these matters.

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References

Reply

Huber and Brockie say that one should ignore epidemiological associations with relative risks below 3.0. This is a philosophical, not a scientific point. The simple fact is that the 1.3 relative risk we obtained by pooling across studies was statistically significantly elevated above 1.0 (p<0.001). This 30% change in relative risk is about the same magnitude obtained when one pools all studies on the benefits of treating myocardial infarction with β-blockers, which led to the use of β-blockade after myocardial infarction as standard clinical practice.

The statement that there are “at least 300 or more reported risk factors for cardiovascular disease” is misleading. Hopkins and Williams (their reference 5) list 246 risk factors that have been identified in at least one paper as risk factors for cardiovascular disease. These risk factors, however, are not mutually exclusive or equally important. In particular, they list cigarette smoking, blood carboxyhemoglobin, blood nicotine, 16 different aspects of platelet and coagulation function, and a variety of hemodynamic changes associated with exposure to tobacco smoke. Huber and Brockie also cite a paper written by themselves (their reference 2) in support of the multiplicity of risk factors. We cannot comment on this paper because we could not locate this paper in Medline, either by authors, title, or journal. The journal is not in the UCSF library or any other University of California library.

Their statement that “the epidemiological studies of ETS and heart disease cited by Glantz and Parmley all report negative (less than 1.0 relative risk) or only weak associations” is misleading at best. Only one of the studies (the one funded by the tobacco industry) had a relative risk below 1.0.

Their statement that we “incorporated the same data twice” is incorrect. The footnote to Table 1 in our paper clearly states that we reported both the Gillis and Hole papers for completeness but only used the data from Hole in the pooled risk estimate to avoid double counting the data.

Their statement that benzo[a]pyrene (BAP) has never been reported in measurable quantities in air polluted with environmental tobacco smoke is incorrect. Concentrations in the range 3.3–23.4 ng/m³ have been measured in restaurants and public places (1989 Surgeon General’s Report, page 91).

Huber and Brockie are correct that 7,12-dimethylbenz[a,h]anthracene (DMBA) has not been reported in ETS. The question of whether DMBA is in ETS is, to some extent, a side issue. The essence of the monoclonal hypothesis of atherogenesis is that carcinogens such as polycyclic aromatic hydrocarbons (PAH) can initiate or accelerate the development of lesions. The distinction is between carcinogenic and noncarcinogenic PAHs in general. While DMBA has not been measured in ETS yet, many other carcinogenic PAHs have been identified, including the related PAH benzo[a]anthracene.

The letter closes with the innuendo that our findings are somehow dictated by a desire to affect public policy rather than to discover the truth. Even if this were true, it hardly applies to the editors or reviewers of Circulation who decided the manuscript warranted publication.

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The Dipyridamole-Thallium Test

We appreciate Dr. Pohost’s comments about our article, “Dipyridamole Thallium-201 Scintigraphy as a Preoperative Screening Test: A Re-examination of its Predictive Potential,” but take issue with his response. Our findings differ from those of previous studies by demonstrating that dipyridamole 201TI scintigraphy has limited sensitivity for the detection of perioperative ischemia or adverse cardiac outcome and a lower negative predictive value than previously appreciated. Consequently, we have suggested that routine use of dipyridamole scintigraphy for preoperative screening of patients undergoing vascular surgery may not be warranted.

Dr. Pohost believes that we are derailing “a useful approach for preoperative risk assessment in this surgical population,” and notes that dipyridamole thallium testing is “a widely documented technique” with a “substantial body of literature” that demonstrates that it has “considerable value for predicting postoperative events.” However, most of the favorable studies that are quoted come from a small number of hospitals with some overlap of subjects. Additionally, intravenous dipyridamole has become available only very recently to most practicing physicians, resulting in relatively circumscribed clinical experience. We believe that such experience is too limited to allow a conclusive comment regarding this test’s merits and certainly too limited to declare this test a “standard” preoperative procedure. Such uncritical acceptance also would have enormous cost implications.

Why did dipyridamole 201TI scintigraphy fail to consistently predict adverse perioperative cardiac outcomes in our patients? Dr. Pohost suggests that a patient selection bias may account for our finding; that is, we excluded the high-risk patients who would most likely benefit from the test. However, we excluded only those patients in whom we could not perform continuous perioperative electrocardiographic and transesophageal echocardiographic monitoring, such as those with paced rhythms, left bundle branch block, or esophageal disease; otherwise, we prospectively studied an unselected consecutive series of patients. Most previous studies, in contrast, have been retrospective, with no defined entry criteria other than referral for a scintigraphic study.

In our study, unlike previous studies, the results of the dipyridamole 201TI scintigrams were blinded and unavailable to the clinicians providing care and to the investigators making the diagnosis of perioperative complications. We did not intend to suggest that such blinding was responsible for the “poor performance” of dipyridamole 201TI scintigraphy in our study. Our blinding strategy was designed to optimize unbiased data acquisition and interpretation. Although blinding may be difficult to institute in clinical studies, we believe that it is only by blinding clinicians and investigators from test results that a number of sources of bias can be avoided and the independent value of a test be determined accurately.

Dr. Pohost correctly notes that the number of serious outcomes (death, myocardial infarction) in our patient series was small. However, the number of serious outcomes was similar to that obtained in several other series. Additionally, our outcome results were substantiated by our finding that more than one half of our patients who developed perioperative electrocardiographic and echocardiographic evidence of ischemia did not have a reversible defect on preoperative scintigraphy. This result is particularly noteworthy given the strong association of postoperative ischemia to adverse outcome. We are not surprised that patients without potentially jeopardized myocardium, as detected by dipyridamole scintigraphy, develop major postoperative complications. For example, myocardial infarctions usually are due to thrombosis, which may occur at the site of both noncritical and critical lesions during the postoperative hypercoagulable state. Heart failure and arrhythmias are more likely to be due to prior infarction and left ventricular dysfunction than de novo ischemia. Additionally, substantial increases in myocardial oxygen demand occur perioperatively that
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