Urinary Thromboxane, Prostacyclin, Cortisol, and 8-Hydroxy-2′-deoxyguanosine in Nonsmokers Exposed and Not Exposed to Environmental Tobacco Smoke

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This study tested the hypotheses that (1) increased platelet aggregation, as measured by 2,3-dinor-thromboxane B2 (Tx-M) and 2,3-dinor-6-keto-prostaglandin F1α (PGI-M), and (2) increased oxidative stress, as measured by 8-Hydroxy-2′-deoxyguanosine (8-OHdG), would occur in ETS-exposed nonsmokers as compared with non-ETS-exposed nonsmokers. The concentrations of the stable urinary metabolites of thromboxane (Tx-M) and prostacyclin (PGI-M), cortisol and 8-OHdG were measured in a 24-h urine sample from 3 groups of subjects: 21 nonsmokers with minimal (15 min or less per day) ETS exposure (termed non-ETS-exposed), 22 nonsmokers with at least 5 h per day of ETS exposure (termed ETS-exposed), and 20 cigarette smokers who served as a positive control group. The self-reported levels of ETS exposure were verified by personal air monitors. As compared with either group of nonsmokers, cigarette smokers excreted significantly more urinary Tx-M. Non-ETS-exposed nonsmokers showed a statistically significantly higher level of urinary Tx-M over that seen in nonsmokers with considerably more ETS exposure. Urinary concentrations of PGI-M were marginally higher in the smokers and did not differ between the nonsmoker groups. Nonsmokers exposed to at least 5 h of ETS per day did not have significantly higher excretion of 8-OHdG than non-ETS-exposed nonsmokers. The results from this study suggest that platelet aggregation, as measured by the thromboxane metabolite Tx-M and prostacyclin metabolite PGI-M, is not associated with ETS exposure. Therefore, platelet aggregation is not a plausible or quantitatively consistent mechanism to explain the nonlinear dose-response hypothesis of cardiovascular disease and ETS exposure.

Key Words: environmental tobacco smoke; platelets; thromboxane; cardiovascular disease.

A recent meta-analysis published by He et al. (1999) reports that nonsmokers exposed to environmental tobacco smoke (ETS) experience a 25% increased risk (relative risk 1.25) of coronary heart disease (CHD) as compared with non-ETS-exposed nonsmokers. In an accompanying editorial, John Bailar questioned the plausibility of an increased risk of this magnitude given the high dilution level of ETS (Bailar, 1999). Specifically, the meta-analytic relative risk of cardiovascular disease (CVD) in active smokers of 20 cigarettes per day (one pack) is reportedly 1.78 (Law et al., 1997). The ETS-CVD risk, as estimated by He et al. (1999), is approximately one-third of the CVD risk associated with actively smoking 20 cigarettes per day. Therefore, given that active smoking exposes the smoker to 100- to 300-fold the total smoke dose experienced by a nonsmoker, as estimated by cotinine (Ogden et al., 1996; Smith et al., 1992), the shape of the proposed dose-response relationship is highly nonlinear (Smith et al., 2000). Proponents of an adverse association between ETS and CVD have hypothesized that platelet aggregation induced by ETS could explain the highly nonlinear shape of the dose-response relationship (California EPA, 1997; Law et al., 1997; Matthews, 1999; OSHA, 1994; SCOTH, 1998). In essence, this hypothesis states that a small amount of ETS exposure would induce platelets to aggregate to a quantitative degree similar to that seen by exposure to a relatively larger amount of mainstream smoke (active smoking). Further, it is hypothesized that the induction of platelet aggregation may lead to the development of thrombi in occluded coronary arteries and contribute to myocardial infarction.

Thromboxanes are synthesized in platelets and can cause vasoconstriction and platelet aggregation after release (Hamberg and Samuelsson, 1974). Prostacyclins are potent inhibitors of platelet aggregation, produced by blood vessel walls (DeWitt et al., 1983) when endothelial cells are exposed to activated platelets. Therefore, thromboxanes and prostacyclins are considered to be antagonistic in their actions (Mayes, 1985). Several groups have previously shown that an increased urinary level of the thromboxane metabolite 2,3-dinor-thromboxane B2 (Tx-M) is a marker of in vivo platelet activation and that an increased urinary level of the prostacyclin metabolite 2,3-dinor-6-keto-prostaglandin F1α (PGI-M) potentially indicates “activated platelet” vessel wall interaction (Dotevall et
damage to DNA (Lagorio et al., 1992; Lassila et al., 1988; Murray et al., 1985; Nowak et al., 1987; Rangemark and Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). These groups have reported that cigarette smokers usually excrete higher levels of Tx-M and sometimes of Wennmalm, 1991). 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aggregation over a wide age range of smokers (Smith et al., 1998). Therefore, the somewhat older average age of the smoking group as compared with the 2 nonsmoking groups should not be physiologically significant vis à vis the use of this group as a positive control.

Recruiting 3 different subject groups experiencing such disparate levels of exposure to cigarette smoke was problematic. First, smoking restrictions in the U.S. workplace are almost ubiquitous. Therefore, members of the heavily ETS-exposed subject group had to be employed at a workplace that permitted smoking and also, preferably, to live with a smoker. Conversely, the non-ETS-exposed subject group was required to work, recreate, and live in a smoke-free environment. Based on the 2 extremes of ETS-exposure criteria required, the ETS-exposed subjects and the cigarette-smoking subjects were recruited and enrolled from employees of R. J. Reynolds Tobacco Company (Winston-Salem, NC) and their primary relatives and friends. The non-exposed subjects were recruited and enrolled from employees and students at the University of North Carolina School of Medicine, Chapel Hill, NC.

The study was reviewed by the Ethics Committee of the University of North Carolina School of Medicine and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All persons gave written informed consent prior to their inclusion in the study. Subjects were not aware of the study hypothesis prior to completion of the experiment.

Chemical Analyses

**Tx-M and PGI-M analyses.** Radioimmunoassay analyses of the stable urinary metabolites of thromboxane (Tx-M) (Kuhn et al., 1993) and prostacyclin (PGI-M) (Demers et al., 1981) were performed without knowledge of study design or subject group by Clinical Laboratory Services, Department of Pathology, Milton S. Hershey Medical Center, Pennsylvania State University. One ml of straight urine was extracted once using 3 ml of ethyl acetate, 3 ml of saline, and a 3-ml mixture of ethyl acetate, isopropyl alcohol, and 0.1 N hydrochloric acid. The organic layer was layered off by drying down under nitrogen in a water bath. The sample was then brought back up to the original volume of 1 ml using BGG buffer. Therefore, there was no dilution of the urine samples. The measurements were validated by using internal standards. The detection limits for Tx-M and PGI-M are 5 pg/ml and 9 pg/ml, respectively. PGI-M and Tx-M antiserum were ordered from Advanced Magnetics (Cambridge, MA). Urinary creatinine was determined by the Jaffe method using a commercial test kit (Merck AG, Darmstadt, Germany).

**8-Hydroxy-*2-oxguanosine (8-OHdG).** ESA Laboratories, Inc. (Chelmsford, MA) determined 8-OHdG in 24-h urine by a liquid chromatography electrochemical (LCEC) column switching system, without knowledge of study design or subject group. This 30-min automated column switching, high performance LCEC method for 8-OHdG was developed based on the unique purge selectivity of integral porous carbon columns. Detection with series coulometric electrodes provides 500 fg sensitivity and quantitative certainty by 8-OHdG/creatinine response ratios.

**Urinary free cortisol.** Using the antibody-coated tube method (Diagnostic Products Corporation, Los Angeles, CA), urinary free cortisol was also measured by Clinical Laboratory Services at the Milton S. Hershey Medical Center.

ETS Exposure Assessment

Markets of ETS exposure were assessed for each subject during the 24-h study period by personal monitoring for 3 vapor phase analytes and 4 particulate phase analytes. The vapor phase analytes were nicotine, 3-ethenylpyridine, and myosmine. The 4 particulate phase analytes were gravimetric respirable suspended particulate matter (RSP), ultraviolet particulate matter (UVPM), fluorescent particulate matter (FPM), and solanesol particulate matter (Sol-PM). The vapor phase analytes were collected on XAD-4 solid sorbent tubes (SKC, Inc., Eighty Four, PA), and the respirable (4.0 μm median cutoff) particulate phase analytes were collected on 37-mm diameter, 1.0-μm pore size Fluoropore filters (Millipore Corp., Bedford, MA). Simultaneous collection was achieved by using personal Double Take Samplers (SKC, Inc.). Nicotine and 3-ethenylpyridine analyses were performed by ASTM Method D 5075–96 (ASTM Method D 5075–96; Ogden et al., 1996; Ogden and Nelson, 1994). Myosmine analyses were performed as reported by Ogden et al. (1996) and Ogden and Nelson (1994). The XAD-4 resin was transferred to an auto-sampler vial, extracted with ethyl acetate modified with 0.0125% triethylamine, and analyzed by capillary gas chromatography with N-thermionic detection using quinoline as an internal standard. Instrumentation used included a Hewlett-Packard Model 5890 A gas chromatograph (Palo Alto, CA) equipped with a Hewlett-Packard Model 7673 auto-sampler, a split/splitless injector, a 30 m × 0.25 mm J&W capillary column (J&W Scientific, Folsom, CA), and a nitrogen-phosphorus detector. Quantification was achieved using EZChrom data software (Scientific Software, Inc., Pleasanton, CA). This method allows for simultaneous determination of nicotine, 3-ethenylpyridine, and myosmine. Gravimetric RSP, UVPM, and FPM analyses were conducted by ASTM Method D 5955–96 (ASTM Method D 6271–98; Ogden et al., 1996). The pre-weighed filters were conditioned at 50% relative humidity for a minimum of 12 h (static inhibited) and the final weight was determined. After gravimetric determination of RSP, the filters were placed in vials and extracted with methanol. Determinations of UVPM and FPM were performed simultaneously, using standard HPLC equipment (Waters Chromatography Division, Millipore Corp., Milford, MA) without a column installed; Model M-45 Solvent Delivery System; Model 712 WISP autosampler; Model 490E Programmable Wavelength Detector at 325 nm absorbance; and a Hitachi Corporation (Danbury, CT) Model F1000 Fluorescence Spectrophotometer at 300 nm excitation and 420 nm emission. Sol-PM analyses were performed using ASTM Method D 6271–98 (ASTM Method D 6271–98; Heavner et al., 1996). Determination of solanesol and Sol-PM was performed on the same methanol extract using a Waters Model 510 pump, Waters Model 712 WISP auto-sampler, and Hitachi Model L-4200 UV-Visible detector at 205 nm absorbance with a Keystone Scientific (Bellefonte, PA) 250 mm × 4.6 mm, 5 μm DELTABOND ODS LC column at isocratic conditions of 95% acetonitrile/5% methanol. Quantification for UVPM, FPM, and solanesol was achieved using Scientific Software, Inc. (Pleasanton, CA) EZChrom data software. The readings were field blank corrected with nominally negative values being assigned a value of zero. A saliva sample was collected from each subject at the beginning of the 24-h study period using Salivettes (Starstedt Inc., Newton, NC). Salivary cotinine was determined by radioimmunoassay (Langone et al., 1973; Langone and van Vunakis, 1982).

Statistical Methods

Thromboxane, prostacyclin, cortisol and 8-OHdG comparisons were all performed in a similar fashion. The primary comparison in each case related to whether the exposure groups (smokers, ETS-exposed nonsmokers, and non-ETS-exposed nonsmokers) were different from one another. All comparisons utilized analysis-of-variance techniques. The potential confounding factors taken into account were gender, creatinine level, and age in a subset of calculations. Creatinine is formed and excreted in constant amounts and serves as an internal standard. The analysis was done using the following combinations of covariates: (1) gender; (2) gender and creatinine; and (3) interactions of gender and creatinine with exposure group. Typically the terms accounting for the interaction of creatinine with exposure group were necessary, but the interaction term with gender was not, effectively, fitting a model with an interaction between creatinine and exposure group is equivalent to fitting separate regression lines for each exposure group to account for the relationship between creatinine and the various response variables. This model was chosen because the slopes often differed among the different groups. Note that this is not equivalent to the common practice of dividing the response by creatinine. This approach appears to be more appropriate than the common practice, because the regression lines had a non-zero intercept. Terms were retained in the model only when significant.

The mean values for exposure groups are compared after adjusting for other terms in the model. For instance, in the models that include creatinine, the exposure group values are adjusted to the average level of creatinine over all of the subjects.
The air concentration data similarly showed statistically significant differences among the 3 exposure groups. Two of the 8 air concentration measures are of particular interest because of their relative specificity to tobacco smoke: air nicotine and solanesol particulate matter (SOL-PM). In ETS, nicotine exists primarily in the vapor phase, and SOL-PM exists in the particulate phase of the cigarette smoke aerosol. As in the case of salivary cotinine, power transformations of the nicotine and SOL-PM data were performed. The nicotine and SOL-PM values for the smokers, ETS-exposed nonsmokers and the non-ETS-exposed nonsmokers are 18.58 μg/m³, 90.8 μg/m³, 2.65 μg/m³, 11.7 μg/m³; and 7.93 × 10⁻³ μg/m³, not applicable (below the limit of detection), for the 3 groups, respectively.

### RESULTS

#### Biological Measurements (Table 4)

As noted above, thromboxane was compared using the 3 different analysis-of-variance models, i.e., gender, gender and creatinine, and interactions of gender and creatinine with exposure group. All show that the thromboxane levels differ among exposure groups ($p < 0.0001$ for each pairwise comparison). The thromboxane levels are highest for the smokers ($0.0001$), followed by the nonsmokers ($0.0001$), and non-ETS-exposed nonsmokers ($0.001$).

Note. Tx-M, 2,3-dinor-thromboxane B₂; PGI-M, 2,3-dinor-6-keto-prostacyclin F₁₂; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; RSP, Respirable Suspended Particulate Matter; UVPM, Ultraviolet Particulate Matter; FPM, Fluorescent Particulate Matter; SOL-PM, Solanesol Particulate Matter; 3-EP, 3-ethenylpyridine.

# Table 1

**Individual Smoker Data**

<table>
<thead>
<tr>
<th>Sample D</th>
<th>Gender</th>
<th>Age</th>
<th>Tx-M pg/ml</th>
<th>PGI-M pg/ml</th>
<th>8-OHdG ng/ml</th>
<th>Cortisol μg/24 hr</th>
<th>Creatinine mg/dl</th>
<th>Cotinine ng/ml</th>
<th>Air concentration data μg/m³ (field blank corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHILL001 Female</td>
<td>42</td>
<td>49</td>
<td>130</td>
<td>2.79</td>
<td>21</td>
<td>74.2</td>
<td>421.5</td>
<td>67</td>
<td>41.0</td>
</tr>
<tr>
<td>CHILL003 Male</td>
<td>37</td>
<td>47</td>
<td>239</td>
<td>5.22</td>
<td>51</td>
<td>124.6</td>
<td>606.9</td>
<td>132</td>
<td>102.8</td>
</tr>
<tr>
<td>CHILL006 Male</td>
<td>49</td>
<td>44</td>
<td>133</td>
<td>1.69</td>
<td>55</td>
<td>66</td>
<td>338.8</td>
<td>300</td>
<td>260.8</td>
</tr>
<tr>
<td>CHILL007 Male</td>
<td>25</td>
<td>88</td>
<td>247</td>
<td>5.49</td>
<td>40</td>
<td>146.3</td>
<td>575</td>
<td>286</td>
<td>240.2</td>
</tr>
<tr>
<td>CHILL008 Male</td>
<td>43</td>
<td>37</td>
<td>105</td>
<td>2.69</td>
<td>68</td>
<td>51.4</td>
<td>566.3</td>
<td>96</td>
<td>70.9</td>
</tr>
<tr>
<td>CHILL009 Male</td>
<td>43</td>
<td>48</td>
<td>169</td>
<td>4.88</td>
<td>51</td>
<td>144.1</td>
<td>459.3</td>
<td>154</td>
<td>106.9</td>
</tr>
<tr>
<td>CHILL010 Male</td>
<td>46</td>
<td>45</td>
<td>92</td>
<td>2.73</td>
<td>62</td>
<td>37</td>
<td>486.3</td>
<td>211</td>
<td>183.8</td>
</tr>
<tr>
<td>CHILL011 Female</td>
<td>38</td>
<td>36</td>
<td>147</td>
<td>1.30</td>
<td>29</td>
<td>48.7</td>
<td>606.6</td>
<td>113</td>
<td>91.0</td>
</tr>
<tr>
<td>CHILL012 Male</td>
<td>42</td>
<td>58</td>
<td>228</td>
<td>4.30</td>
<td>40</td>
<td>79.4</td>
<td>840.4</td>
<td>77</td>
<td>58.6</td>
</tr>
<tr>
<td>CHILL013 Male</td>
<td>38</td>
<td>111</td>
<td>1.57</td>
<td>70</td>
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<td>488.4</td>
<td>224</td>
<td>161.1</td>
<td>148.9</td>
</tr>
<tr>
<td>CHILL014 Male</td>
<td>41</td>
<td>57</td>
<td>285</td>
<td>2.31</td>
<td>47</td>
<td>116</td>
<td>281.1</td>
<td>154</td>
<td>132.2</td>
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<tr>
<td>CHILL015 Male</td>
<td>47</td>
<td>84</td>
<td>293</td>
<td>11.70</td>
<td>50</td>
<td>116.3</td>
<td>402.2</td>
<td>136</td>
<td>101.8</td>
</tr>
<tr>
<td>CHILL016 Female</td>
<td>34</td>
<td>52</td>
<td>190</td>
<td>2.19</td>
<td>22</td>
<td>68.8</td>
<td>129.9</td>
<td>198</td>
<td>177.7</td>
</tr>
<tr>
<td>CHILL017 Female</td>
<td>39</td>
<td>121</td>
<td>1.29</td>
<td>15</td>
<td>65.5</td>
<td>375.1</td>
<td>254</td>
<td>227.2</td>
<td>207.8</td>
</tr>
<tr>
<td>CHILL018 Male</td>
<td>45</td>
<td>26</td>
<td>97</td>
<td>4.26</td>
<td>25</td>
<td>51.5</td>
<td>331.1</td>
<td>182</td>
<td>121.2</td>
</tr>
<tr>
<td>CHILL019 Male</td>
<td>43</td>
<td>56</td>
<td>285</td>
<td>9.95</td>
<td>54</td>
<td>147.8</td>
<td>472.1</td>
<td>97</td>
<td>33.6</td>
</tr>
<tr>
<td>CHILL020 Male</td>
<td>39</td>
<td>166</td>
<td>3.27</td>
<td>20</td>
<td>69.5</td>
<td>365.9</td>
<td>79</td>
<td>43.6</td>
<td>39.8</td>
</tr>
<tr>
<td>CHILL021 Male</td>
<td>38</td>
<td>32</td>
<td>114</td>
<td>3.07</td>
<td>40</td>
<td>79.4</td>
<td>492.4</td>
<td>86</td>
<td>65.1</td>
</tr>
<tr>
<td>CHILL022 Male</td>
<td>42</td>
<td>58</td>
<td>100</td>
<td>5.97</td>
<td>58</td>
<td>60.7</td>
<td>388.4</td>
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<tr>
<td>CHILL023 Male</td>
<td>30</td>
<td>52</td>
<td>190</td>
<td>2.19</td>
<td>22</td>
<td>68.8</td>
<td>129.9</td>
<td>198</td>
<td>177.7</td>
</tr>
</tbody>
</table>

The air concentrations and salivary cotinine values were compared using an analysis-of-variance model, taking only the exposure group into account. Formal comparison of these data required that the values be transformed to make the variances within the exposure groups comparable. This was done using a power transformation, $y^\lambda$, where $\lambda = \frac{n}{n-1}$, $(n = 1, 2, \ldots)$. The value of $\lambda$ was chosen to make the variances similar to one another.

Several of the subjects in the ETS-exposed and non-ETS-exposed groups had salivary cotinine levels below the limit of detection of about 0.40 ng/ml. There are a number of different comparison procedures that are possible with different approaches for handling the values that are below the limit of detection. All of the procedures reach the same conclusions for these data. The approach reported here used all of the readings in their raw form whether they were above or below the limit of detection.

All of the comparisons were conducted using PROC GLM in the SAS® system (SAS Institute, 1990).

**Markers of Tobacco Smoke Exposure (Tables 1–3)**

After appropriate transformation ($\lambda \leq 0.5$ or so), exposure group variances are similar and the salivary cotinine means differ significantly ($p < 0.0001$ for pairwise comparisons) among the 3 groups, i.e., smokers (451.1 ng/ml), ETS-exposed nonsmokers (1.3 ng/ml), and non-ETS-exposed nonsmokers (0.2 ng/ml).
separate analyses were performed with an age term included as a covariate in the models for thromboxane and prostacyclin. All of the conclusions with respect to thromboxane and prostacyclin were identical, whether or not age was included in the model.

The method of comparison for 8-OHdG levels among exposure groups was similar to that used for thromboxane and prostacyclin. Gender was statistically significant, and was therefore retained in the model ($p = 0.042$). Smokers ($4.94 \pm 1.8 \text{ ng/ml}$) were statistically significantly higher than the ETS-exposed group ($2.60 \pm 1.8 \text{ ng/ml}$) ($p = 0.001$). The non-ETS-exposed group ($3.70 \pm 1.8 \text{ ng/ml}$) was not statistically significantly different from either the smokers or the ETS-exposed group ($p = 0.082$ and 0.062, respectively).

The above analyses used a statistical model that assumes that the relationship between 8-OHdG and creatinine differs among exposure groups ($p = 0.067$). A model assuming no difference in the slope of creatinine among the three exposure groups gives slightly different conclusions. The 8-OHdG level in the ETS-exposed group remains significantly lower than in smokers ($p = 0.005$). The test comparing the ETS-exposed and non-ETS-exposed groups becomes statistically significant ($p = 0.029$) (non-ETS-exposed group is higher) and the test comparing the ETS-exposed and smokers groups ($p = 0.005$) is nominally significant ($p = 0.066$). If the outlier point is excluded from the data set, then both the ETS-exposed and the non-ETS-exposed groups are statistically significantly different from the smokers group ($p = 0.005$ and $p = 0.001$, respectively) and not statistically significantly different from each other ($p = 0.57$).

Because of age differences among the exposure groups, separate analyses were performed with an age term included as a covariate in the models for thromboxane and prostacyclin. All of the conclusions with respect to thromboxane and prostacyclin were identical, whether or not age was included in the model.

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respectively) and not significantly different from one another ($p = 0.082$) or the ETS-exposed group ($p = 0.062$). In addition to the meta-analysis of He et al. (1999), two studies were employed at the University of North Carolina School of Medicine showed a statistically significantly higher urinary thromboxane metabolite Tx-M and a marginally higher level of excreted prostacyclin metabolite (though at $p = 0.066$, the difference was not quite statistically significant), suggesting some degree of activation of their platelets. Several researchers have hypothesized that elevated levels of catecholamines play a central role in platelet responses to inhalation of mainstream cigarette smoke (Cryer et al., 1979).}

Interestingly, the group of non-exposed nonsmokers who were employed at the University of North Carolina School of Medicine showed a statistically significantly higher urinary thromboxane excretion as compared with the ETS-exposed nonsmokers. Whether the UNC Chapel Hill group experienced increased physical (Burghuber et al., 1981; Wang et al., 1994) or psychological occupational stress, thereby leading to catecholamine-induced platelet priming, remains unknown. One possible marker of "physiological stress," i.e., urinary free cortisol, showed no differences among the 3 groups.

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In addition to the meta-analysis of He et al. (1999), two
published government reports have also suggested a causal association between ETS and the incidence of CHD (California EPA, 1997; SCOTH, 1998). The California Environmental Protection Agency (CALEPA) and the Scientific Committee on Tobacco and Health (SCOTH) in the United Kingdom have estimated the relative risk for CHD in ETS-exposed nonsmokers at 1.30 and 1.23, respectively. However Bailar (1999) has suggested that the large differential in exposure between ETS and active smoking stands in contrast to the small difference in CVD risk estimates. One hypothesis has been that the platelet response to cigarette smoke is highly nonlinear, with only a tiny “dose” needed to activate platelets. Since ETS-exposed nonsmokers did not demonstrate increased indicators of platelet aggregation, the results from the present study suggest that platelet aggregation is not a plausible or quantitatively consistent mechanism to explain such a nonlinear dose-response anomaly.

Exposure to reactive oxygen species is reportedly a risk factor for chronic diseases including CVD (Mehta and Mehta, 1999; Palace et al., 1999). Several studies have examined oxidative stress levels in cigarette smokers by measuring urinary 8-OHdG levels (Howard et al., 1988; van Zeeland et al., 1999). In the present study, smokers displayed significant increases in urinary 8-OHdG as compared with ETS-exposed nonsmokers. ETS exposure did not result in increases in urinary 8-OHdG.

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REFERENCES


ETS AND URINARY THROMBOXANE AND PROSTACYCLIN


