

## Cardiovascular Effects of Secondhand Smoke Nearly as Large as Smoking

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**Background**—Secondhand smoke increases the risk of coronary heart disease by  $\approx 30\%$ . This effect is larger than one would expect on the basis of the risks associated with active smoking and the relative doses of tobacco smoke delivered to smokers and nonsmokers.

**Methods and Results**—We conducted a literature review of the research describing the mechanistic effects of secondhand smoke on the cardiovascular system, emphasizing research published since 1995, and compared the effects of secondhand smoke with the effects of active smoking. Evidence is rapidly accumulating that the cardiovascular system—platelet and endothelial function, arterial stiffness, atherosclerosis, oxidative stress, inflammation, heart rate variability, energy metabolism, and increased infarct size—is exquisitely sensitive to the toxins in secondhand smoke. The effects of even brief (minutes to hours) passive smoking are often nearly as large (averaging 80% to 90%) as chronic active smoking.

**Conclusions**—The effects of secondhand smoke are substantial and rapid, explaining the relatively large risks that have been reported in epidemiological studies. (*Circulation*. 2005;111:2684-2698.)

**Key Words:** smoking ■ cardiovascular diseases ■ endothelium ■ epidemiology ■ tobacco smoke pollution

Secondhand smoke (SHS) increases the risk of heart disease by  $\approx 30\%$ ,<sup>1-7</sup> accounting for at least 35 000 deaths annually in the United States.<sup>2,8</sup> Protection of nonsmokers through smoke-free environments leads to a decrease in heart disease mortality through a combination of reduced exposure to SHS and an environment that makes it easier for smokers to stop smoking.<sup>9</sup> The California Tobacco Control Program that stressed smoke-free policies has been associated with preventing 59 000 deaths resulting from heart disease between 1989 and 1997.<sup>10</sup> An evaluation of a geographically isolated community (Helena, Mont) showed that the number of hospital admissions resulting from acute myocardial infarction decreased after the implementation of a law ending smoking in public and workplaces, an effect that partially reversed when enforcement of the law was suspended by a lawsuit.<sup>11</sup> The effects observed in epidemiological studies are both larger and faster than one would expect if there were a simple linear dose-response relationship between level of smoke exposure in passive smokers and active smokers.<sup>12</sup> Despite the fact that the dose of smoke delivered to active smokers is 100 times or more that delivered to a passive smoker, the relative risk of coronary heart disease for smokers is 1.78,<sup>5</sup> compared with 1.31 for passive smokers (Figure 1). Rapidly accumulating evidence, however, indicates that many important responses of the cardiovascular system (Table 1) are exquisitely sensitive to

the toxins in SHS. These mechanisms, rather than isolated events, interact with each other to increase the risk of heart disease.

The present article extends earlier reviews of the biological effects of SHS on the cardiovascular system,<sup>3-5,14-21</sup> with particular emphasis on literature on the effects of low doses of tobacco smoke exposure and the speed of the effect on the cardiovascular system. In many cases, the effects of even brief (minutes to hours) passive smoking are nearly as large as those from chronic active smoking.

### Epidemiological Studies

Epidemiological data on the relationship between passive smoking and heart disease have been accumulating since the mid-1980s. Six meta-analyses have been published,<sup>3-7,22</sup> all yielding relative risks of heart disease from passive smoking that range between 1.2 and 1.3. Since the last meta-analysis was published, we found 6 new epidemiological studies on the association of passive smoking with heart disease (4 case-control<sup>23-26</sup> and 2 cohort studies<sup>27,28</sup>). We excluded 2<sup>23,25</sup> of 3<sup>23-25</sup> case-control reports on the same data set and 1 cohort study because of serious misclassification bias.<sup>27,29</sup> Figure 1 shows the results of the 29 studies as the risk of ischemic heart disease in never-smokers exposed to SHS relative to the risk in those who were not exposed to SHS. The pooled relative risk computed with a random-effects

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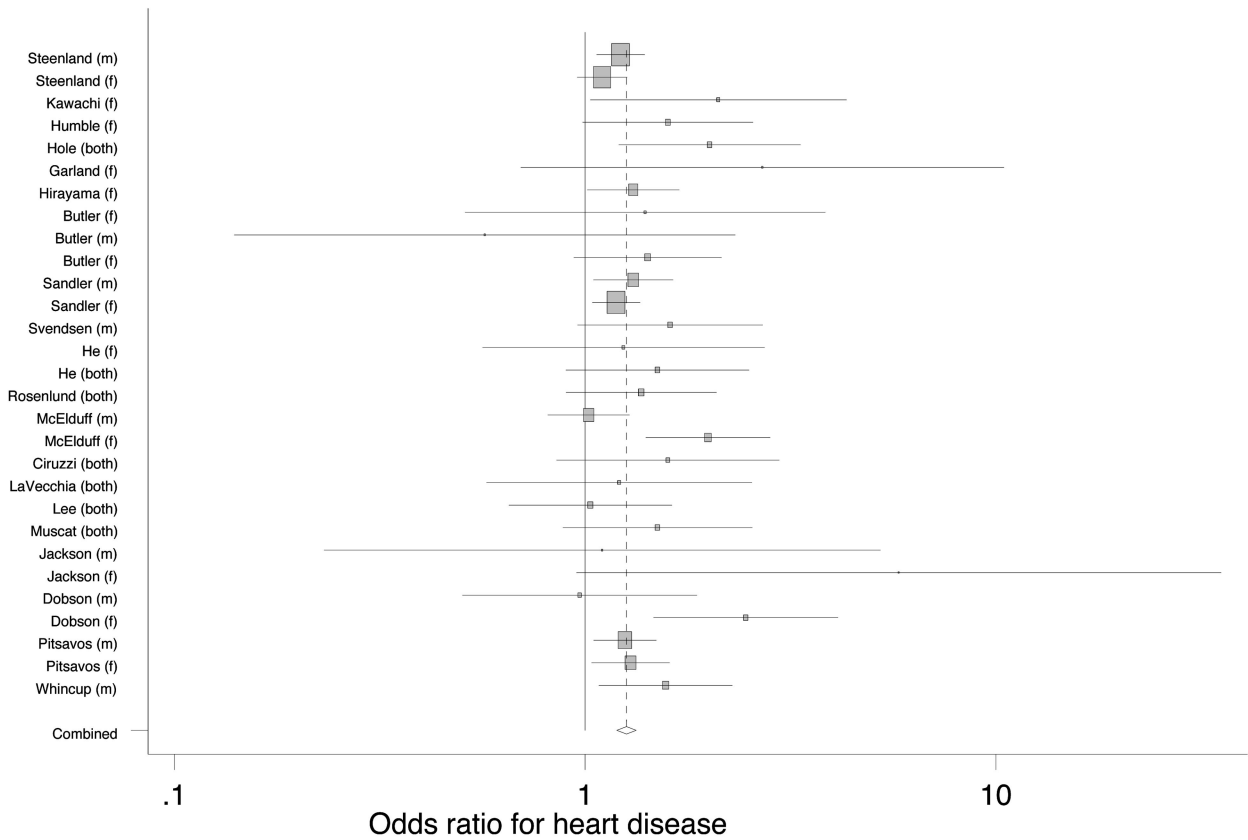
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**Figure 1.** Summary of epidemiological studies on passive smoking and coronary heart disease, together with results of random-effects meta-analysis. There was no significant heterogeneity ( $P=0.1$ ), but we used random-effects model to be conservative. Citations for individual studies are as follows: Steenland et al,<sup>152</sup> Kawachi et al,<sup>153</sup> Humble et al,<sup>154</sup> Hole et al,<sup>155</sup> Garland et al,<sup>156</sup> Hirayama,<sup>157</sup> Butler,<sup>158</sup> Sandler et al,<sup>159</sup> Svendsen et al,<sup>160</sup> He et al,<sup>6</sup> Roselund et al,<sup>26</sup> McElduff et al,<sup>161</sup> Ciruzzi et al,<sup>162</sup> LaVecchia et al,<sup>163</sup> Lee et al,<sup>164</sup> Muscat and Wynder,<sup>165</sup> Jackson,<sup>166</sup> Dobson et al,<sup>167</sup> Pitsavos et al,<sup>24</sup> and Whincup et al.<sup>28</sup>

model (computed with Stata Version 7) was 1.31 (95% CI, 1.21 to 1.41), similar to the estimates of earlier meta-analyses.<sup>3-7,22</sup>

In 2004, Whincup et al<sup>28</sup> published a 20-year prospective study of passive smoking and coronary heart disease that estimated that the risk associated with passive smoking was between 1.45 (95% CI, 1.10 to 2.08) and 1.57 (95% CI, 1.08 to 2.28), depending on the level of SHS exposure. These estimates are about twice as high as earlier estimates (Figure 1) and nearly as high as observed in light (1 to 9 cigarettes/d) active smokers (1.66; 95% CI, 1.04 to 2.68). Earlier epidemiological studies that used marriage to a smoker as a surrogate for exposure did not capture the entire exposure to SHS, including from workplaces and public places such as restaurants and bars. As a result, they underestimated SHS exposure and simply compared more exposed people (nonsmokers married to a smoker but exposed to SHS elsewhere) to less exposed people (nonsmokers married to nonsmokers but exposed to SHS elsewhere). This comparison biases the risk estimate of the effect of SHS downward. By using cotinine, a stable metabolite of nicotine,<sup>30</sup> as the measure of exposure, Whincup et al<sup>28</sup> were able to capture more of the total SHS exposure. (The reference group consisted of the lowest quartile of cotinine levels, 0 to 0.7 ng/mL, which means

that even people in the control reference group had some SHS exposure.) These results suggest that passive smoking leads to between 68% and 86% of the risk of light smoking, depending on the level of SHS exposure (Table 2).

**TABLE 1. Effects of SHS on the Cardiovascular System**

Platelet activation
Endothelial dysfunction
Inflammation and infection
Atherosclerosis
Low HDL levels
Plaque instability
Increased oxidized LDL
Increased oxidative stress
Decreased energy metabolism
Increased insulin resistance
Outcome measures
Increased infarct size
Decreased heart rate variability
Increased arterial stiffness
Increased risk of coronary disease events

TABLE 2. Comparative Effects of Passive and Active Smoking\*

	SHS Effect†	Exposure	Active Effect‡	SHS/Active Effect, § %
Risk of heart disease (95% CI)				
Figure 1	1.31 (1.21 to 1.41)	Chronic	1.78 (1.31 to 2.44)	40
20 y <sup>28</sup>	1.57 (1.08 to 2.28)¶	Cotinine at study entry	1.66 (1.04 to 2.68)	86
First 4 y <sup>28</sup>	3.73 (1.32 to 10.98)	Cotinine at study entry	3.32 (0.87 to 12.64)	122
Platelet function				
Platelet activation <sup>31</sup> (SI PGI <sub>2</sub> )#	0.55±0.059	20 min	0.54±0.069	96
Platelet aggregate ratio <sup>32,32a</sup> (change)	-0.09	20 min	-0.15	60
Fibrinogen, <sup>87</sup> mg/dL (95% CI)	5.2 (-1.2 to 12)	Chronic	6.9 (-0.9 to 14)	75
Fibrinogen, <sup>38</sup> mg/dL (SE)	11.2±4.1	Chronic	18.1±6.7	62
Plasma thromboxane, <sup>40</sup> pg/mL	3.30±0.35	Acute	2.93±0.07	113
Plasma malondialdehyde, <sup>40</sup> nmol/L per 10 <sup>9</sup> platelets	4.2±0.17	Acute	3.9±0.07	108
Endothelium and arterial function				
Endothelial cell count, <sup>32,32a</sup> mean No. of anuclear cell carcasses on 0.9- $\mu$ L chamber (change)	0.9	20 min	2.0	45
Coronary flow velocity reserve, <sup>43</sup> cm/s	68.8±22.7	30 min	67.1±15.0	91
Flow-mediated dilation, <sup>45</sup> %	3.1±2.7	≥3 y	4.4±3.1	134
Aortic stiffness, <sup>67,68</sup> mm Hg/mm	58	4 minutes	49	110
HDL, <sup>77</sup> mg/dL	48.26±3.47	Chronic	45.59±4.6	73
Increase in IMT, <sup>98</sup> $\mu$ m/3 y	5.9	Chronic	14.3	41
Inflammatory markers <sup>87</sup> (95% CI)				
White blood cells, $\times 10^3$ per 1 $\mu$ L	0.6 (0.3 to 0.8)	Chronic	0.6 (0.5 to 0.7)	100
C-reactive protein, mg/dL	0.08 (0.02 to 0.1)	Chronic	0.1 (0.08 to 0.2)	80
Homocysteine, $\mu$ mol/L	0.4 (0.2 to 0.6)	Chronic	0.5 (0.1 to 0.9)	80
Oxidized LDL, mg/dL	3.3 (0.5 to 6)	Chronic	3.9 (1.4 to 7)	85
Antioxidants				
Vitamin C, <sup>120</sup> median (interquartile range), $\mu$ mol/L	53 (41 to 79)	Chronic	40 (25 to 58)	57
Hypovitaminosis <sup>120</sup> (vitamin C <23 $\mu$ mol/L), %	12	Chronic	24	50
Ratio of DHAA to ascorbic acid <sup>122</sup>	10.3±7.00	>6 mo	11.2±6.9	78
Vitamin C in children <sup>123</sup> (mean±SE), mmol/L	-8.8±1.5**	Chronic	-9.0±2.3	98
$\beta$ -Carotene <sup>125</sup> (mean±SE), $\mu$ mol/L	0.129±0.022	Chronic	0.155±0.021	174
$\beta$ -Carotene, <sup>127</sup> $\mu$ mol/L	0.15	Chronic	0.17	128
Red blood cell folate mean decrease, <sup>130</sup> nmol/L (95% CI)††	-50 (-69 to -31)	Chronic	-86 (-101 to -71)	58

\*Data are presented as mean±SD unless otherwise noted.

†Change in variable associated with passive smoking among nonsmokers (after minus before SHS exposure).

‡Difference in variable between smokers and nonsmokers (smoker minus nonsmoker).

§Represents the difference between passive smoking effect divided by active smoking effect times 100%.

||Risk of death at 65 years of age, smoking 20 cigarettes per day (from Law et al<sup>5</sup>).

¶Cotinine levels 2.8 to 14.0 ng/mL.

#Sensitivity index to prostacyclin.

\*\*High-dose SHS group.

††High exposure to SHS.

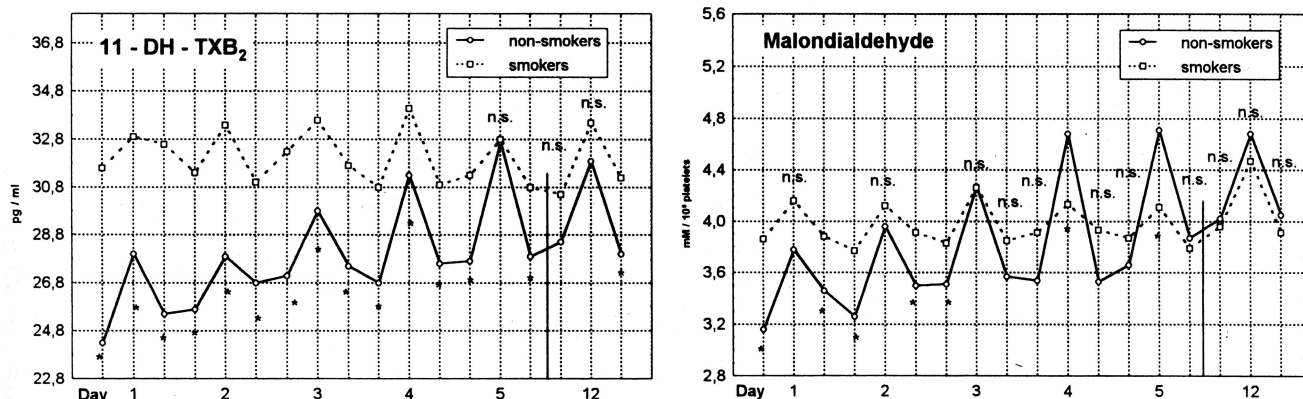
## Platelet Function

The first mechanistic evidence explaining why SHS leads to an increase in the risk of heart disease incidence or death came from studies on platelet activity. SHS activates blood platelets, increasing the risk of thrombus formation and damaging the lining of arteries, which facilitates the development of atherosclerosis.<sup>4,5,19,31,32,32a</sup>

Platelet activation in response to SHS was first evaluated in an experiment that exposed smokers and nonsmokers to 20 minutes of SHS (Table 2).<sup>31</sup> At baseline, platelet activation

among smokers was higher than activation in nonsmokers. After the experiment, activation remained the same in smokers but was significantly increased in nonsmokers, to the point that their platelet activation was not discernibly different from that of the smokers. Bleeding time, another measure of platelet activation (decreased bleeding time indicates increased activation), is decreased in rabbits<sup>33,34</sup> and rats<sup>35</sup> exposed to realistic doses of SHS.

In *in vitro* experiments, extracts of sidestream smoke (the smoke emitted directly from the burning tip of the cigarette



**Figure 2.** Exposure to 60 minutes of SHS increased measures of platelet activation; repeated exposures over several days led to levels in nonsmokers comparable to smokers. \* $P < 0.05$ . Reproduced from Figure 1 of Schmid et al,<sup>40</sup> copyright 1996, with permission from Elsevier.

into the air, the main component of SHS), show that, at equal doses, sidestream smoke is a more potent platelet activator than extracts of mainstream smoke (the smoke inhaled by active smokers). Rubenstein et al<sup>36</sup> exposed human platelets to sidestream and mainstream smoke extract from 1 Marlboro cigarette. Platelet activation was evaluated under static and flow conditions (blood flow increases platelet activation). Under both conditions, sidestream was about 1.5 times more potent than mainstream smoke in activating platelets.

Fibrinogen, a mediator of platelet activation and an inflammatory marker associated with a higher risk of heart disease,<sup>37</sup> is elevated in passive smokers.<sup>5</sup> Iso et al<sup>38</sup> found that Japanese exposed to SHS had an  $11.2 \pm 4.1$ -mg/dL (mean  $\pm$  SE) higher mean covariate-adjusted fibrinogen level than nonexposed nonsmokers. This increase is 62% of the difference between active smokers and nonexposed nonsmokers,  $18.1 \pm 6.7$  mg/dL (Table 2). Another study found that teenagers living with a smoker at home had higher fibrinogen levels than those living in a smoke-free home (mean  $\pm$  SD,  $241 \pm 51$  and  $218 \pm 33$  mg/dL, respectively).<sup>39</sup>

Thromboxane, another marker of platelet activation, is also increased in passive smokers, in some cases to levels observed in active smokers (Figure 2 and Table 2).<sup>40</sup> Healthy smokers and nonsmokers were exposed to the smoke of 30 cigarettes for 60 minutes in an 18-m<sup>3</sup> room for 5 consecutive days and one more time on day 12. Before the first exposure to SHS, all measures of platelet activation (malondialdehyde [MDA], serum and plasma thromboxane B<sub>2</sub> [s-TX B<sub>2</sub> and p-TX B<sub>2</sub>], and 11-dehydro-thromboxane B<sub>2</sub> [11-DHTXB<sub>2</sub>]) were higher in smokers than nonsmokers. Exposure to SHS for 1 hour increased these measures of platelet activation (except s-TX B<sub>2</sub>) more in nonsmokers than in smokers, to the point that several of them approached the baseline levels observed in smokers (Table 2). Six hours after exposure ended, activation markers in nonsmokers remained significantly elevated for MDA and p-TX B<sub>2</sub> compared with baseline. After repeated daily 60-minute exposures to SHS, the baseline levels of these markers in nonsmokers increased (Figure 2 and Table 2).<sup>40</sup> These results indicate that repeated exposures to SHS renders platelet function measures of

nonsmokers more activated and close to the behavior of smokers.

Platelet activation, however, is not the only player in thrombus formation. Blood vessel integrity is vital to prevent thrombus formation. A pathological event such as rupture of an atherosclerotic plaque will lead to platelet adhesion to the arterial wall and platelet activation, culminating in the formation of a platelet plug (thrombus) and potentially vessel occlusion and ischemia or infarction.<sup>41</sup> Platelets activated by SHS also damage the endothelium, a vital layer of the arterial wall.

### Endothelial Dysfunction

The endothelium is the first layer in the arterial bed that is in contact with the blood; it maintains vessel integrity and controls vascular tone and the vascular inflammatory process.<sup>18</sup> In response to hemodynamic changes (eg, increased blood flow) and acetylcholine, the endothelium secretes nitric oxide (NO), leading to vasodilation. In response to epinephrine, the endothelium secretes endothelin, leading to vasoconstriction. Endothelial damage can result in decreased vessel dilation and increased contraction, prothrombotic and proinflammatory states, and cell proliferation in the arterial wall. As a result, endothelial dysfunction contributes to atherosclerotic plaque formation and progression, plaque rupture, and decreased blood flow because of thrombosis and vasospasm, leading ultimately to cardiovascular disease.<sup>42</sup>

### Endothelium-Dependent Vasodilation

SHS has immediate effects on endothelium-dependent vasodilation, which is manifest clinically in 15 to 30 minutes.<sup>17,43,44</sup> Using the coronary flow velocity reserve, a clinical surrogate measure of endothelial function, Otsuka et al<sup>43</sup> showed that 30 minutes of breathing SHS (at levels comparable to those in a bar) impaired endothelium-dependent vasodilation in coronary arteries of nonsmokers almost to the same extent as seen in habitual smokers (Table 2).

Chronic SHS exposure also has deleterious effects on endothelium-dependent vasodilation. Arterial flow-mediated dilation, another measure of endothelium-dependent vasodilation, was impaired in subjects with a history of SHS

exposure for  $\geq 3$  years. This impairment was dose dependent; arterial dilation (measured as percentage change in vessel diameter at rest and during reactive hyperemia) in response to increased flow was  $1.8 \pm 2.0\%$  (mean  $\pm$  SD),  $3.1 \pm 2.2\%$ , and  $4.1 \pm 3.3\%$  in subjects with heavy ( $>6$  h/d), moderate (4 to 6 h/d), and light (1 to 3 h/d) exposure, respectively.<sup>45</sup> In addition, the level of impairment was similar in passive and active smokers (Table 2).<sup>45</sup> These results were also confirmed in healthy women.<sup>46</sup>

Studies in animals have confirmed the phenomena observed in humans.<sup>47</sup> Rabbits exposed to SHS for 30 minutes twice a day for 3 weeks showed an  $\approx 50\%$  decrease in endothelium-dependent vasodilation compared with unexposed rabbits. Other animal data show that high cholesterol and SHS have additive effects on endothelial dysfunction.<sup>48</sup> In utero and neonatal exposure to SHS leads to endothelial dysfunction. Hutchinson et al<sup>49</sup> found that newborn rats exposed in utero to SHS for 21 days had impaired endothelium-dependent relaxation (measured as a decrease in the vasodilation effect of acetylcholine).

NO mediates endothelium-dependent vasodilation. In passive and active smokers,<sup>50</sup> decreased production of endothelial NO is a mechanism by which the risk of heart disease is increased. In response to acetylcholine, the enzyme NO synthase uses L-arginine to generate NO in the endothelium, leading to vasodilation (hence the term endothelium-dependent vasodilation). Light ( $<1$  pack per week) and heavy ( $\geq 1$  pack per week) smokers have similarly decreased levels of endothelial NO,<sup>51</sup> suggesting that cigarette smoke has an effect at low exposure that saturates at high exposures.

Rabbits exposed to SHS for 10 weeks have larger aortic intimal-medial lesions and decreased endothelium-dependent vasodilation and NO production compared with unexposed control rabbits.<sup>52</sup> Rabbits fed a diet with the NO precursor L-arginine while exposed to SHS did not suffer the decrease in endothelium-dependent vasodilation that was observed in the rabbits exposed to SHS and eating a normal diet.<sup>53</sup> The effects of SHS on NO production observed in the aortic endothelium have also been described in the pulmonary artery endothelium.<sup>54</sup> Therefore, SHS might also contribute to the pathophysiology of pulmonary hypertension.

SHS leads to endothelial dysfunction after short- and long-term exposure through inhibition of NO synthase. The level of endothelial dysfunction observed in passive smokers is comparable to the dysfunction observed in active smokers in both short- and long-term settings.

### Direct Damage to the Endothelium

Direct endothelial cell injury has also been described. SHS exposure for 20 minutes is associated with increased levels of circulating endothelial cell carcasses<sup>22</sup> (Table 2). Mullick et al<sup>55</sup> exposed rats to 6 weeks of SHS (6 h/d, 5 d/wk) and found damage to carotid artery endothelial cells. The cytoplasm of exposed cells contained abnormal vacuoles and bundles of compromised microtubules. In addition, there was disruption of the junctional complexes between adjacent cells and elevation of the basal surface of endothelial cells off the internal elastic membrane.<sup>55</sup> These injuries in the endothelial

cells in the artery wall lead to increased vascular permeability and atherosclerosis.

The endothelial cytoskeleton is vital to repair endothelial cell disruption resulting from multiple insults (eg, SHS and atherosclerosis). Actin filaments, part of the cytoskeleton, are important regulators of cell signaling, locomotion, and adhesion and wound repair mechanisms.<sup>56</sup> To evaluate the effects of nicotine on actin filament organization in endothelial cells, Cucina et al<sup>57</sup> cultured endothelial cells from the aorta of calves with nicotine at concentrations between  $6 \times 10^{-4}$  and  $6 \times 10^{-8}$  mol/L, which includes levels found in passive smokers, and found disruptions of actin filament organization after 24 hours of exposure to nicotine. These changes disappeared when anti-platelet-derived growth factor BB antibodies were added to the culture, suggesting that anti-platelet-derived growth factor BB is responsible for the changes. This same cytoskeletal reorganization was observed in aortic smooth muscle cells cultured with similar nicotine concentrations for 24 hours.<sup>58</sup> In addition to causing endothelial damage, passive smoking disrupts the endothelial repair system.<sup>56</sup>

### Oxidant Damage to the Endothelium

Cigarette smoke extract impairs NO-mediated endothelial function in isolated endothelial cells from both humans and animals as a result of increased production of superoxide anion ( $O_2^-$ ).<sup>59</sup> Cigarette smoke extract increases  $O_2^-$  by stimulation of NADPH, which, in turn, reduces NO bioactivity and results in endothelial dysfunction.<sup>60</sup> Acrolein, an important constituent of SHS,<sup>61</sup> is a compound in SHS that causes these effects.<sup>60</sup> Acrolein and other gas-phase oxidants in cigarette smoke remain stable in blood and thus are capable of acting directly on the vascular endothelium.

### Recovery of Function After SHS Exposure Ends

Endothelial function partially recovers in humans after long-term exposure to SHS ends. One year after exposure ( $\geq 1$  h/d for  $\geq 2$  years) to SHS had ended, endothelium-dependent dilation (measured as the percentage change in arterial diameter at rest and during reactive hyperemia) was significantly better in former passive smokers (percentage change,  $5.1 \pm 4.1\%$ , mean  $\pm$  SD) than in current passive smokers ( $2.3 \pm 2.1\%$ ;  $P=0.01$ ), although both groups were impaired compared with control subjects ( $8.9 \pm 3.2\%$ ).<sup>62</sup> Only partial endothelium recovery might be attained because of the damage that SHS produces in the endothelial repair mechanism.<sup>57</sup>

Antioxidants may improve endothelial dysfunction in passive smokers. Schwarzacher et al<sup>63</sup> evaluated the effects of an antioxidant diet on endothelium-dependent vasodilation in hypercholesterolemic rabbits exposed to SHS. Rabbits breathed SHS for 6 h/d for 10 weeks and were given either an antioxidant supplement (vitamin E 1000 U/kg chow and  $\beta$ -carotene 600 mg/kg chow) or no supplement for 21 weeks. Through an intact endothelium, acetylcholine leads to a reduction in mean blood pressure. A decreased response to the blood pressure-lowering effects of acetylcholine was observed in hypercholesterolemic rabbits, and a larger decrease was observed in those exposed to SHS (percent decrease in blood pressure at a high dose of acetylcholine in

SHS/hypercholesterolemic,  $-22 \pm 10\%$  [mean  $\pm$  SE]; in controls,  $-80 \pm 2\%$ ). The antioxidant diet partially blocked the SHS-induced impairment of blood pressure responses (percent change in blood pressure at high dose of acetylcholine in SHS/hypercholesterolemic/vitamin supplemented,  $-68 \pm 21\%$ ).

The reduction in heart disease morbidity and mortality with the implementation of smoke-free environments that has been documented in epidemiological studies<sup>10,11</sup> can be partially explained by these data demonstrating endothelial recovery after SHS exposure ends.

### Effects on Arterial Stiffness

In addition to impairing the ability of blood vessels to dilate, SHS also increases arterial stiffness (Table 2).<sup>64–67</sup> Healthy male subjects breathing SHS from 15 cigarettes in an unventilated room for 1 hour experienced a significant increase in aortic arterial stiffness. The augmentation index, a measure of arterial wave reflection that is closely related to aortic stiffness, increased by 15.7%, from  $-1.7 \pm 5.2\%$  (mean  $\pm$  SE) at baseline to  $14 \pm 4.8\%$  at the end of 1 hour. About half the increase had occurred at 15 minutes, and it reached steady state after 30 minutes, the time at which the rise in both brachial and aortic systolic blood pressure occurred.<sup>65</sup> The effects of SHS on arterial stiffness occur before they are clinically manifest. These changes are larger than the ones that occur when a nonsmoker smokes a single cigarette.<sup>66</sup>

Another human experimental study showed that aortic stiffness, measured with the aortic pressure-diameter loop, increased within 4 minutes of passive smoking, similar to the effects observed in active smokers.<sup>67,68</sup> Increased arterial stiffness with SHS exposure has also been reported in a cross-sectional epidemiological study.<sup>64</sup> Adults chronically exposed to SHS at home, work, and other places with a body mass index (BMI) of  $\geq 27$  kg/m<sup>2</sup> (but not less) experienced an increase in carotid stiffness index with SHS exposure (adjusted carotid stiffness index from  $12.23 \pm 1.28$  [mean  $\pm$  SE] in the unexposed to  $20.67 \pm 4.18$  in those exposed to SHS). Significant interactions were found between SHS, age ( $\geq 55$  years), and carotid intima-media thickness (IMT  $\geq 0.707$  mm) on carotid arterial stiffness index. SHS is also associated with increased carotid intimal thickness.<sup>69</sup>

SHS has immediate and substantial effects on arterial stiffness. It is possible that these effects are related to the changes in endothelial function discussed earlier.

### Effects on HDL

In addition to endothelial damage, passive smokers are at increased risk of heart disease because SHS accelerates the development of atherosclerosis.<sup>33,70–72</sup> HDL is vital in preventing atherosclerosis.<sup>73</sup> It mediates cholesterol efflux from macrophage cells, inhibits foam cell formation, restores and protects from endothelial dysfunction, and prevents the oxidation of LDL. As a result, low HDL levels have been associated with an increased risk of heart disease.<sup>74</sup>

Passive smoking leads to lower levels of HDL in adults.<sup>75,76</sup> Passive smokers (exposed to SHS for  $\geq 6$  h/d for  $\geq 4$  d/wk for at least the past 6 months) had HDL levels of  $48.26 \pm 3.47$  (mean  $\pm$  SD) mg/dL compared with  $55.59 \pm 4.24$  mg/dL in those unexposed to SHS. HDL levels in passive

smokers were indistinguishable from levels in active smokers ( $45.59 \pm 4.6$  mg/dL) (Table 2).<sup>77</sup> HDL levels are also lowered with increasing smoking intensity (sum of cigarettes consumed by all workers in an office in 1 day divided by the number of all workers in the office). Nonsmoking women in the middle tertile and highest tertiles of SHS exposure were 1.7 (95% CI 1.2 to 2.5) and 1.6 (95% CI 1.1 to 2.4) times more likely to have low levels ( $<45$  mg/dL) of HDL than those in with the lowest intensity of exposure, respectively.<sup>76</sup>

Acute exposure to SHS also lowers HDL levels. Moffat et al<sup>78</sup> exposed 12 male subjects to 6 hours of SHS at concentrations similar to those found in a bar. HDL levels 8, 16, and 24 hours later were significantly reduced from baseline at all 3 times (18%, 14%, and 13% reductions, respectively). At the time of the last measurement (24 hours after the exposure), HDL levels still remained significantly below baseline ( $39.7 \pm 7.3$  [mean  $\pm$  SD] versus  $45.2 \pm 7.1$  mg/dL, respectively). There were no differences in dietary and exercise patterns between exposed and control groups.<sup>78</sup>

HDL<sub>2</sub>, the antiatherogenic subfraction of HDL, is decreased by SHS exposure.<sup>78,79</sup> Women exposed at work to SHS for 6 h/d for at least the past 6 consecutive months had HDL<sub>2</sub> levels significantly lower than those of unexposed women. The decrease in passive smoking women was similar to the decrease in smokers (31% and 33% HDL<sub>2</sub> percentage decrease from the levels in unexposed, respectively).<sup>77</sup> In men, acute exposure (6 hours) also reduces HDL<sub>2</sub>.<sup>78</sup> A significant reduction from baseline values was found as early as 8 hours and persisted even after 24 hours after exposure (37% and 28% reductions from baseline, respectively).

Passive smoking is also associated with lower levels of HDL in children.<sup>79–81</sup> After adjusting for potential confounders, Neufeld et al<sup>82</sup> found that exposed children had an HDL concentration that was 3.7 mg/dL lower than in unexposed children. In adults, a 1-mg/dL decrease in HDL level is associated with a 2% to 3% increase in coronary heart disease.<sup>73</sup> Racial and gender differences have been noted in the effects of SHS on lipid metabolism in children; data from cohorts of white and black twin children have shown an interaction between race and gender.<sup>79</sup> In children exposed to SHS, HDL levels were lower in whites than in blacks ( $43.2 \pm 8.0$  [mean  $\pm$  SD] versus  $52.7 \pm 8.4$  mg/dL, respectively). These data suggest that white males exposed to passive smoking may be more susceptible to the effects of SHS than blacks or females.

### Inflammation and Infection

Inflammation is a precursor of atherosclerotic plaque.<sup>83</sup> Both passive smoking children and adults have higher levels of inflammatory markers.

Acute-phase proteins (inflammatory markers) are increased in children breathing SHS at home compared with children not breathing SHS.<sup>84</sup> These proteins were higher among Japanese boys living with smokers than in boys not exposed to smoke after adjustment for potential confounders, including asthma or wheezing history, allergic diseases, feeding method in infancy, and heating type in the home. In boys exposed to  $\geq 11$  cigarettes per day at home, there was an increase in levels of component of the complement (C3c),

haptoglobin (Hp),  $\alpha_1$  acid glycoprotein ( $\alpha_1$ -AG), and ceruloplasmin (not significant). In girls exposed to  $\geq 11$  cigarettes per day, there was an increase in Hp,  $\alpha_1$ -AG, and ceruloplasmin (not significant). No association was found between SHS exposure and C3c in girls, perhaps because of the small number of girls with high exposure levels included in the study.<sup>84</sup>

Activated neutrophils and leukocyte count<sup>85</sup> increase in nonsmokers with as little as 3 hours of breathing SHS.<sup>86</sup> Chronic SHS exposure also increase inflammatory markers.<sup>87,88</sup> Panagiotakos et al<sup>87</sup> found that adults breathing SHS for >30 minutes at least 1 d/wk had higher leukocyte count, C-reactive protein, and homocysteine, but not fibrinogen, than did unexposed adults (adjusted for several potential confounders). Another study done in Poland also found a significant increase in plasma homocysteine levels in male passive smokers.<sup>89</sup> The effect of passive smoking ranged from  $\approx 100\%$  (white blood cell count) to 75% (fibrinogen) of the effect observed in active smokers (Table 2).

Animal data also support the hypothesis that the effects of SHS on the cardiovascular system are mediated in part through inflammation. After exposing mice to SHS from 2 cigarettes for 30 minutes/d for 4 months, Zhang et al<sup>90</sup> noted an increase in interleukin-6, a proinflammatory cytokine.

The fine particulate matter in SHS probably plays an important role in mediating these effects. Particulate air pollution, which is quite similar to the particulate matter in SHS, evokes both pulmonary and systemic inflammatory responses in humans.<sup>21</sup> Four weeks of exposure to fine particulate matter ( $<10 \mu\text{m}$ ) led to an increase in polymorphonuclear leukocyte band cell counts (another type of inflammatory cell) in hypercholesterolemic rabbits and a corresponding progression in atherosclerotic lesions.<sup>91,92</sup>

Chronic infection has been proposed to contribute to the atherosclerotic process just as inflammation does.<sup>93</sup> An interaction between SHS and chronic infection (ie, chronic obstructive pulmonary disease, recurrent urinary tract infection, and chronic bronchitis) has been documented. In a community-based study, passive smokers had an increase in early (nonstenotic plaques; odds ratio [OR], 1.3; 95% CI, 1.0 to 1.8) and advanced (vessel stenosis  $>40\%$ ; OR, 1.5; 95% CI, 1.0 to 2.2) atherogenesis that was confined to subjects with chronic infection.<sup>94</sup>

Mouse experiments suggest that AIDS patients might be more susceptible to opportunistic infections if exposed to SHS. Using the murine AIDS model, Zhang et al<sup>95</sup> showed that SHS exposure for 12 weeks inhibited the proliferation of T cells, increased the release of tumor necrosis factor- $\alpha$ , interleukin-6 cytokines, and enhanced lipid peroxidation from the retrovirus-infected mice. These effects would make mice with murine AIDS more susceptible to opportunistic infections<sup>95</sup> and suggest that AIDS patients might be particularly at risk of opportunistic infections if exposed to SHS.

Human and animal data support the conclusion that SHS exposure increases inflammation, which is another potential mechanism by which SHS causes heart disease.

### Progression of Atherosclerosis

SHS contributes to the progression of atherosclerosis. Carotid IMT is a standard surrogate measurement of atherosclerosis.<sup>96</sup>

A study done in mice found that after 5 weeks of exposure to cigarette smoke (carboxyhemoglobin level of  $14.4 \pm 3.5\%$  [mean  $\pm$  SD] in exposed versus  $2.9 \pm 1.2\%$  in unexposed), carotid intimal area was significantly increased in the exposed compared with the unexposed group ( $0.05 \pm 0.034$  versus  $0.023 \pm 0.021 \text{ mm}^2$ ).<sup>97</sup> A population-based cohort study of middle-aged adults found that passive smokers (mean exposure, 10 h/wk) was associated with a 20% increase in the rate of IMT over a 3-year follow-up period (progression rate increased by  $5.9 \mu\text{m}/3 \text{ y}$ ) compared with nonexposed nonsmokers.<sup>98</sup> This increase in IMT persisted even after controlling for demographic characteristics, other cardiovascular risk factors, and lifestyle variables. In addition, the mean IMT increase in progression rate over the 3 years observed in passive smokers was 41% of that observed in current active smokers ( $14.3 \mu\text{m}/3 \text{ y}$ ) (Table 2).

Passive smokers have a higher number of stenotic coronary arteries than do nonpassive smokers. A case-control study from China found that the number of stenotic coronary arteries in women increased with exposure to SHS from their husbands' smoking. The number of stenotic arteries (left anterior descending artery, left circumflex artery, and right coronary artery) increased significantly with increasing number of years and cigarettes smoked by the subjects' husbands.<sup>99</sup>

Hepatic lipid peroxidation leads to the accumulation of cholesteryl esters in atherosclerotic plaque and a more rapid uptake of LDL cholesterol by human macrophages.<sup>100</sup> Macrophages then develop into foam cells, the predominant cells in an early atherosclerotic lesion.<sup>101,102</sup> Passive smoking increases lipid peroxidation in humans.<sup>103–106</sup> Just 30 minutes of exposure to SHS from 16 cigarettes leads to significant increases in the susceptibility of LDL to  $\text{Cu}^{2+}$ -initiated oxidation and serum end products of lipid peroxidation.<sup>106</sup>

Animal studies support these clinical findings. LDL accumulation in the arterial wall is increased by SHS exposure.<sup>53,55,107</sup> Plasma containing fluorescently labeled LDL from rats exposed once to SHS for 4 hours was perfused into carotid arteries from unexposed rats. Compared with controls, LDL accumulation was significantly increased in the arteries perfused with SHS-exposed plasma ( $1.6 \pm 0.4$  and  $6.9 \pm 1.8 \text{ mV}/\text{min}$  [mean  $\pm$  SE], respectively).<sup>107</sup> Another study in mice found increased LDL accumulation in the 3 sections of the aorta (arch, thoracic, and abdominal) that depended on the dose of SHS.<sup>108</sup> Mice breathed SHS for 6 hours a day for 7, 10, and 14 weeks. Compared with unexposed controls, atherosclerotic lesions were greater in the exposed mice even at 7 weeks of exposure. In the thoracic aorta, at week 14,  $33 \pm 11\%$  of the intima was covered by grossly discernible lesions compared with  $10 \pm 8\%$  in controls.<sup>108</sup> Knight-Lozano et al<sup>109</sup> exposed mice to SHS from 2 cigarettes for just 15 min/d for 21 and 42 days; arteriosclerotic lesion size increased 76% and 156%, respectively compared with unexposed mice. Similar increases in atherosclerotic lesion after breathing SHS has been described in cockerels (22 weeks, 0.4% of projected lifespan)<sup>70,71</sup> and rabbits (10 weeks of exposure).<sup>33</sup> Nicotine does not appear to be required for SHS to increase arterial lipid lesions, because there were similar effects from SHS from nicotine-free cigarettes.<sup>72</sup> Other com-

ponents of the tobacco smoke appear to be important in terms of promoting atherosclerosis.

SHS also contributes to atherosclerotic plaque instability, which triggers thrombosis, the cause of occlusion and most acute vascular events. Matrix metalloproteinases, degrading enzymes secreted by endothelial and smooth muscle cells, are thought to weaken the arterial wall, thus contributing to destabilization and rupture of atherosclerotic plaques.<sup>110,111</sup> Nicotine, at concentrations found in passive smokers ( $10^{-8}$  mol/L), upregulates collagenase I, a type of matrix metalloproteinase, in human artery smooth muscle cells.<sup>112</sup> After 18 hours of incubation with nicotine, there was a 4.5-fold increase in collagenase I. Other matrix metalloproteinases were also upregulated by nicotine.

SHS leads to atherosclerosis through various mechanisms, including abnormal lipid profile (low HDL and high LDL), increased susceptibility to lipid peroxidation leading to increase lipid uptake by macrophages, stenosis of coronary arteries, and plaque instability. None of these events occurs alone; their effects are cumulative—perhaps even multiplicative—and are all affected by SHS.

### Infarct Size

SHS exposure increases experimentally induced infarct size in animals in a dose-dependent manner.<sup>35</sup> Zhu et al<sup>35</sup> exposed rats to 6 weeks of SHS (6 h/d, 5 d/wk) at levels observed in bars, then induced infarcts by tying off and releasing the left coronary artery. At the longest duration of exposure (180 hours total), infarcts were nearly twice as large as those in the unexposed group.<sup>35</sup> In another study to evaluate the effects of SHS on infarct size in the neonatal and adolescent period, pregnant rats received cumulative SHS exposures for 3 weeks; neonatal rats, for 4 weeks after birth; and adolescent rats, from weeks 6 to 12 after birth. Results showed that exposure to SHS in the neonatal to adolescent period for 12 weeks significantly increased experimentally induced infarct size, especially in female rats. In utero exposure for 3 weeks tended to increase infarct size ( $P=0.08$ ), especially in female rats.<sup>113</sup>

As a consequence of myocardial infarction, the left ventricle changes in size, shape, and thickness in the infarcted and noninfarcted segments of the ventricle through a process known as ventricular remodeling. Remodeling, which results from a combination of changes in left ventricular dilation and hypertrophy of residual noninfarcted myocardium, influences ventricular function.<sup>114</sup> Left ventricular hypertrophy, which leads to ventricular remodeling and increases the risk of a cardiovascular event and mortality,<sup>115</sup> has also been observed in 6-month-old rabbits exposed to SHS from 3 cigarettes for 30 minutes twice daily for 21 days.<sup>116</sup> After exposure, left ventricle weight and the ratio of left ventricle to body weight were significantly higher in the exposed group ( $2.99 \pm 0.12$  g and  $0.95 \pm 0.05$  g/kg (mean  $\pm$  SEM), respectively) compared with the control group ( $2.48 \pm 0.07$  g and  $0.77 \pm 0.02$  g/kg, respectively).

Through endothelial dysfunction, platelet adhesion, and plaque instability, SHS is a trigger for myocardial infarction. After the infarction has occurred, SHS renders the myocardium more susceptible to a larger area of infarction and

greater risk of ventricular hypertrophy. These events make recovery of the myocardium more difficult and the myocardium more susceptible to a second event or heart failure.

### Oxidative Stress

Free oxygen radicals, also known as reactive oxygen species, lead to oxidative stress, blood vessel injury, and oxidized LDL. Free radicals are produced in cells as a result of the respiratory process that uses oxygen.<sup>117</sup> Under normal conditions, endogenous antioxidants protect the vascular system from oxidative stress damage. In addition to free radicals produced in the body, SHS is a source of free radicals that lead to oxidative stress and antioxidant depletion.<sup>118</sup> The oxidants in SHS act directly to depress NO production by the endothelium independently of any effect on mitochondrial respiration.<sup>60</sup> The oxidative stress from passive smoking influences the cardiovascular system in 2 ways: by directly delivering free radicals to the vascular system and by consuming antioxidants that would normally be available to protect against endogenous free radicals resulting from the respiratory process.

Various surrogate measures have been used to document the oxidative stress generated by SHS, including a decrease in antioxidant levels (eg, vitamin C and carotene) and an increase in oxidative stress biomarkers. In addition, it has been noted that these surrogate markers return to baseline levels after dietary supplementation with antioxidants in the presence of SHS, although such supplementation does not appear to affect the long-term risk of heart disease.<sup>119</sup>

### Decreased Antioxidant Levels

Antioxidant depletion as a marker of oxidative stress has been analyzed after exposure to SHS. The assumption is that antioxidants are being consumed under conditions of oxidative stress and that the depletion of endogenous antioxidants would be an indirect reflection of oxidative stress resulting from passive smoking. SHS has been shown to decrease levels of individual and total plasma antioxidants. Vitamin C (ascorbic acid) levels are lower in passive ( $53 \mu\text{mol/L}$ ; interquartile range, 41 to 79  $\mu\text{mol/L}$ ) and active ( $40 \mu\text{mol/L}$ ; interquartile range, 25 to 58  $\mu\text{mol/L}$ ) smokers compared with nonsmokers ( $70 \mu\text{mol/L}$ ; interquartile range, 56 to 82  $\mu\text{mol/L}$ ) (significant differences between the 3), with SHS having about two thirds the effect of active smoking (Table 2).<sup>120</sup> Hypovitaminosis was diagnosed in passive (12%) and active (24%) smokers but in none of the unexposed nonsmokers (Table 2). Exposure to SHS was on average 35 h/wk, and no significant differences were found in vitamin C intake among the 3 groups.<sup>120,121</sup>

Acute exposure to SHS (30 minutes from 16 cigarettes) led to an immediate one-third decrease in serum ascorbic acid (the reduced form of vitamin C) in healthy adults.<sup>106</sup> Ascorbic acid has an antioxidant effect; its oxidized form, dehydroascorbic acid (DHAA), is a marker of oxidative stress. In chronically exposed passive smokers ( $> 10$  h/wk of SHS exposure for  $> 6$  months), the proportion of DHAA to total ascorbic acid resembles levels in smokers ( $10.3 \pm 7.00\%$  [mean  $\pm$  SD] and  $11.2 \pm 6.9\%$ , respectively) and is significantly higher than levels in nonsmokers ( $7.07 \pm 6.24\%$ ) (Ta-

ble 2).<sup>122</sup> With ascorbic acid used as a marker of oxidative stress, passive smoking leads to oxidative stress in both long- and short-term exposures.

Children and adolescents who are passive and active smokers also have lower levels of vitamin C.<sup>123</sup> After adjustment for age, gender, vitamin C intake, and multivitamin use, cotinine levels were significantly associated with lower levels of vitamin C in children exposed at home to low and high levels of SHS and active smokers (serum cotinine levels <2, 2 to 15, and >15 ng/mL, respectively).<sup>123</sup> After controlling for age, gender, vitamin C intake, and multivitamin use, children exposed to high levels of SHS had about the same reduction in serum ascorbic acid levels observed in children who were active smokers (Table 2). Preston et al<sup>124</sup> found plasma vitamin C levels to be on average 3.2  $\mu\text{mol/L}$  lower in children exposed to SHS compared with unexposed children (both groups had similar dietary intake of vitamin C).

Carotenoids, another group of antioxidants, are also decreased by SHS. These plant pigments include  $\beta$ - and  $\alpha$ -carotene, lycopene, and cryptoxanthin. Alberg et al<sup>125</sup> and van der Vliet<sup>126</sup> used serum collected in a private census in 1975 as part of another study to assess the relationship between breathing SHS (assessed as living with a smoking spouse) and several micronutrients. Nonsmokers who lived with smokers had lower serum total carotenoid (significant for men),  $\alpha$ -carotene (significant for women),  $\beta$ -carotene (significant for men), and cryptoxanthin (significant for both genders) concentrations than nonsmokers who lived in households with no smokers. (The nonsignificant changes were in the same direction as the significant changes. The failure to reach significance may reflect, in part, the high background levels of SHS exposure that was present when the data were collected in 1975.) These carotenoid measures were also decreased in active smokers (Table 2).<sup>125</sup>

Dietrich et al<sup>127</sup> evaluated plasma samples from 83 smokers, 40 passive smokers, and 36 nonsmokers. Passive smokers had been exposed to SHS from >1 cigarette per day at least 5 d/wk for  $\geq 1$  years. Smoke exposure status was assessed by cotinine levels, and dietary history was collected with a self-administered questionnaire.  $\beta$ -Carotene levels in passive smokers (0.15  $\mu\text{mol/L}$ ) were significantly lower than in nonsmokers (0.24  $\mu\text{mol/L}$ ) but were not significantly different from the levels in smokers (0.17  $\mu\text{mol/L}$ ) (Table 2).  $\beta$ -Carotene was also decreased in Italian women married to smoking husbands.<sup>128</sup> Levels were lower among women in the 2 highest exposure categories (11 to 20 and >20 cigarettes per day), with a dose-response relationship. After dietary intake, vitamin supplementation, alcohol consumption, and BMI were controlled for, the association persisted. The decrease was highest (27%) in those with the highest level of exposure ( $\geq 21$  cigarettes per day). This study was done in Italy where most of the population is exposed to SHS outside the home; therefore, even those women who reported no exposure at home had elevated cotinine levels (mean, 7.95 ng/mL), leading to an underestimate of the effects of SHS exposure at home.

Folate, a vitamin emerging as a potential tool for preventing heart disease, probably by decreasing homocysteine levels,<sup>129</sup> is decreased by SHS. Data from NHANES III

revealed that passive and active smokers have dose-dependent decreased folate levels.<sup>130</sup> After adjustment for covariates (age, sex, race, socioeconomic status, daily folate intake from 24-hour recall, vitamin use, and alcohol use), the odds of having low red blood cell folate (<340 nmol/L) were 1.3 (95% CI, 1.1 to 1.5), 1.5 (95% CI, 1.3 to 1.9), and 2.4 (95% CI, 2.0 to 2.8) for moderate- and high-exposure passive smokers and active smokers compared with low-exposure passive smokers, respectively. This same trend was observed for serum folate level. Among those with heavy exposure (serum cotinine 0.4 to <15 ng/mL), serum and red blood cell folate levels were  $\approx 60\%$  of those seen in smokers (Table 2).

Passive smoking adults and children have lower levels of antioxidant vitamins, about two thirds of the effect observed in active smokers. SHS leads to depletion of endogenous antioxidants, leaving the cardiovascular system without its natural barrier against oxidative stress.

### Effects of Antioxidant Supplementation on Oxidative Stress Biomarkers

Antioxidant supplementation might protect against the deleterious effects of SHS by providing additional antioxidant capacity to the body.<sup>90,105,131,132</sup> Experiments have been conducted in humans and animals supplemented either with a single vitamin or a multivitamin. Vitamin E supplementation (100 mg  $\alpha$ -tocopherol for 14 days) in children breathing SHS lowered thiobarbituric acid-reactive substances (TBARS) (plasma and erythrocyte) and erythrocyte-oxidized glutathione, both indexes of lipid peroxidation.<sup>131</sup> TBARS lead to increase lipid uptake by macrophages that give rise to the atherosclerotic plaque. In another experiment, mice were exposed to SHS for 5 h/d and fed a vitamin E supplemented diet for 10 days. Vitamin E prevented the lipid peroxidation observed in the exposed and nonsupplemented controls.<sup>133</sup>

Vitamin C has been shown to mitigate the increase in oxidative stress biomarkers as a result of SHS exposure. In passive smokers, the lipid peroxidation biomarker  $F_2$ -isoprostane ( $F_2$ -IsoP) decreased by 17.2 pmol/L or 11.4% in those supplemented with vitamin C for 2 months compared with those receiving placebo.<sup>134</sup> In another experiment, nonsmoking human subjects breathed SHS from 16 cigarettes for 30 minutes on 2 different days. One day, they received a normal diet; on the other day, they were given a vitamin C supplement (3 g ascorbic acid) before breathing SHS. Measurements of total plasma antioxidant trapping potential (TRAP) and TBARS were taken 1.5 hours after the breathing session. When subjects breathed SHS with no vitamin C supplementation, they had a significant decrease in TRAP and an increase in TBARS. When they were given the vitamin C supplement, SHS failed to decrease TRAP and the formation of TBARS was significantly lower than in the day without the supplement, leading the authors to conclude that total plasma antioxidant potential and oxidative stress produced by SHS can be prevented with vitamin C supplementation.<sup>105</sup>

A combination of antioxidants has also been shown to protect against the oxidative stress resulting from passive smoking. This has been confirmed in human and animal studies. Giving passive smokers (exposure to  $\geq 1$  cigarette per

day for  $\geq 5$  d/wk indoors) antioxidant supplements (vitamin C,  $\alpha$ -lipoic acid, and vitamin E) for 2 months resulted in lower F<sub>2</sub>-IsoP levels than in a control group (adjusted for baseline F<sub>2</sub>-IsoP, BMI, sex, alcohol intake, number of years exposed to SHS, average number of cigarettes exposed per day, hours since last exposure to SHS before to blood draw, baseline plasma antioxidants, and lipids).<sup>134</sup> Mice exposed to SHS for 30 min/d, 2 cigarettes every 10 minutes, for 4 months showed a significant increase in lipid peroxidation.<sup>90</sup> Lipid peroxidation was significantly decreased in both SHS-exposed and -nonexposed mice that received antioxidant supplementation (including  $\beta$ -carotene, bioflavonoids, coenzyme Q10, D- $\alpha$ -tocopherol, L-ascorbic acid, magnesium, N-acetylcysteine, retinol, selenium, and zinc). In the exposed mice, lipid peroxidation decreased almost to the level observed in the unexposed mice that received the supplement.

In another study, mice were supplemented with an antioxidant-rich byproduct of olive oil, olive mill wastewater, for 2 days and then exposed to SHS (1 cigarette for 20 minutes) for 4 days. The urinary excretion of the oxidative stress marker 8-iso-prostaglandin F<sub>2 $\alpha$</sub>  (8-iso-PGF<sub>2 $\alpha$</sub> ) was measured daily. Compared with the group not receiving supplement, in the supplemented group, 8-iso-PGF<sub>2 $\alpha$</sub>  did not increase at 48 hours ( $44 \pm 4.2\%$  increment in the group not supplemented), and there was a smaller increase in 8-iso-PGF<sub>2 $\alpha$</sub>  at 96 hours ( $34 \pm 18\%$  versus  $55 \pm 10\%$  increases in the supplemented and not supplemented groups, respectively).<sup>132</sup> The authors of this study concluded that the antioxidant-rich byproduct of olive oil can mitigate the increase in oxidative stress resulting from passive smoking.

These data suggest that a supplement with various antioxidants might also be effective in compensating for the depletion of antioxidants resulting from SHS exposure. Taking antioxidant supplements, however, probably will not prevent the damage associated with SHS because such supplements do not seem to reduce the risk of heart disease in general.<sup>119</sup>

### DNA Damage From Oxidative Stress

Enzymes used as markers of oxidative stress and DNA damage resulting from oxidative stress have been found to be elevated in passive smokers.<sup>135</sup> A cross-sectional study found that passive smokers ( $6.6 \pm 1.6$  [mean  $\pm$  SE] h/d of exposure at work) have higher levels of enzymes that increase with exposure to reactive oxygen species. Superoxide dismutase (SOD), glutathione peroxidase (GPOX), glutathione reductase (GR), and catalase were found to be elevated in the exposed (only GPOX [10% higher] and GR [4% higher] were significant) compared with the unexposed group.<sup>135</sup> In addition, the DNA adduct 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of DNA damage resulting from oxidative stress that has been shown to be elevated in smokers, was analyzed. Passive smokers had a significant 63% increase in 8-OHdG.<sup>135</sup> An antioxidant supplement (300  $\mu$ g  $\beta$ -carotene, 60 mg vitamin C, 30 IU  $\alpha$ -tocopherol, 40 mg zinc, 40  $\mu$ g selenium, and 2 mg copper) was then administered to these same subjects for 60 days (exposed and unexposed). Passive smokers who received the antioxidant supplement had SOD activity levels 18% and 8-OHdG levels 62% below those of the SHS-exposed subjects who did not receive the supple-

ment. The rest of the enzymes showed the same trend, although the decrease was not significant.<sup>136</sup>

### Mitochondrial Damage

Another global effect of SHS is inhibition of energy production by the mitochondria. Animal studies have shown that SHS impairs the ability of the heart muscle to convert oxygen into the energy molecule adenosine triphosphate.<sup>137-139</sup> The activity of one of the enzymes that mediates this process, cytochrome oxidase, fell 25% after a single 30-minute exposure to SHS, and the activity continued to decline with longer exposure.<sup>137</sup>

Mitochondrial damage in passive smokers includes decreased adenine nucleotide translocator (ANT) and mitochondrial superoxide dismutase (SOD2) activity and mitochondrial DNA (mtDNA) damage in aortic tissue. Low levels of ANT and SOD2 are markers of increased oxidative stress. Knight-Lozano et al<sup>109</sup> exposed mice with normal and high cholesterol to SHS from 2 cigarettes every 15 minutes, 6 h/d, 5 d/wk for 21 and 42 days. The 21-day group was exposed to filtered air for 21 days before the SHS exposure period. SHS was associated with a significant decrease in ANT and SOD2 in the high-cholesterol mice, with a significant interaction between SHS exposure and high cholesterol in decreasing the activity in both enzymes. This result suggests that SHS-induced oxidative stress reduces mitochondrial ANT and SOD2 activities. In addition, SHS exposure resulted in higher levels of aortic mtDNA damage regardless of diet compared with unexposed mice. Increased duration of exposure resulted in even higher levels of mtDNA damage, and high cholesterol accentuated the effects of SHS. In unexposed mice, mtDNA damage was higher in mice with high cholesterol compared with those with normal cholesterol, indicating that the deleterious effects of SHS on mtDNA damage are potentiated by high cholesterol levels. These data suggest that SHS leads to increased mtDNA damage in aortic tissue, possibly mediated by oxidative stress. High cholesterol levels accentuate the deleterious effects of SHS on aortic mitochondria.

Given the increased oxidative stress and DNA damage in the mitochondria resulting from passive smoking, other energy sources have to be used. The anaerobic pathway, another source of energy in the body, leads to an increase in lactate in venous blood. It has been noted that passive smokers have increased levels of lactate in venous blood.<sup>140</sup> This clinical finding is consistent with the conclusion that passive smoking leads to mitochondrial damage, affecting directly the body's ability to produce energy to sustain exercise.

### Heart Rate Variability

Acute exposure (2 periods of 2 hours during an 8-hour experiment in an airport smoking lounge) to SHS reduces heart rate variability.<sup>141</sup> Heart rate variability, the beat-to-beat variations in heart rate reflected in the R-R interval variation in the ECG, gives information about the propensity toward malignant ventricular arrhythmias and cardiac death.<sup>21,142</sup> Two hours of exposure was associated with a 12% reduction in heart rate variability. This reduction has been associated with an increased risk of ventricular fibrillation or ventricular

tachycardia in patients after a myocardial infarction or in those with chronic heart failure. During the subsequent 2 hours when the subjects were out of the smoking room, the heart rate variability returned to baseline. Similar reductions in heart rate variability have also been noted in response to air pollution (ambient particulate matter); after all, SHS is air pollution.<sup>21,92,143</sup> It is likely that the effects of SHS on heart rate variability are mediated by the fine particles in SHS. The reductions in heart rate variability reflect a decrease in the parasympathetic input to the heart, providing an important mechanistic link between SHS (and air pollution) and heart disease by promoting fatal tachyarrhythmias.<sup>21</sup>

### Insulin Resistance

Increased insulin resistance is now recognized as increasing the risk of heart disease.<sup>144</sup> The resulting compensatory hyperinsulinemia leads to a number of proatherogenic abnormalities known to as insulin resistance syndrome (hypertension, abdominal obesity, dyslipidemia, prothrombotic state, endothelial dysfunction, and chronic subclinical inflammation). Insulin resistance per se is inadequate for identifying people with the highest risk for heart disease; the entire syndrome best identifies these people.<sup>144</sup> Cross-sectional data from the Insulin Resistance Atherosclerosis Study (IRAS) showed that exposure to SHS can lead to an increase in insulin resistance, significantly in women (insulin sensitivity index in passive smokers,  $1.07 \pm 0.07$  [mean  $\pm$  SE]; in unexposed nonsmokers,  $1.19 \pm 0.04$ ;  $P=0.013$ ) even after controlling for potentially confounding demographic and physiological variables.<sup>145</sup> In smokers, data are not yet conclusive; there was no relationship with insulin sensitivity in IRAS, but another study did find an increase in insulin resistance.<sup>146</sup> SHS might also lead to an increase in heart disease by increasing insulin resistance.

### Conclusions

The evidence that SHS causes heart disease has continued to accumulate in terms of both the epidemiological evidence and our understanding of mechanisms. Most important, this evidence shows consistently and from many dimensions that passive smoking has much larger effects on the cardiovascular system than would be expected from a comparison of the doses of toxins delivered to active and passive smokers. Indeed, the effects of SHS are, on average, 80% to 90% as large as those from active smoking (Table 2). The mechanisms by which passive smoking increases the risk of heart disease are multiple and interact with each other (Table 1). These mechanisms include increase platelet aggregability, endothelial dysfunction, increased arterial stiffness, increased atherosclerosis, increased oxidative stress and decreased antioxidant defense, inflammation, decreased energy production in the heart muscle, and a decrease in the parasympathetic output to the heart. Like outdoor air pollution,<sup>21</sup> on a population basis, the effects of SHS are rapid and large.

Implementation of smoke-free policies for the 30% of Americans—and most of the world's population—who currently do not enjoy them would have substantial effects on heart disease morbidity and mortality through a combination of reducing SHS exposure and providing an environment that

makes it easier for people to stop smoking.<sup>9–11,147</sup> Furthermore, it has been estimated that if all US workplaces were to be smoke-free by law, in the first year after law was implemented, there would be  $\approx 1500$  myocardial infarctions prevented, yielding nearly \$49 million in savings in direct medical costs, because some people would stop smoking or consume fewer cigarettes.<sup>9</sup> These benefits would grow over time. While providing health benefits, smoke-free policies also reduce revenues and profits to tobacco companies; implementation of these policies in the remaining workplaces in the United States would reduce cigarette consumption by an estimated 950 million packs a year, worth \$2.3 billion to the tobacco industry in sales.<sup>9</sup> It is no surprise that the tobacco industry (often through surrogates<sup>148</sup>) continues contesting the evidence linking SHS with heart and other diseases and continues fighting smoke-free policies around the world.<sup>149–151</sup> Physicians, public health advocates, and policy makers can move forward in implementing these policies, secure in the knowledge that implementing smoke-free environments to rapidly and substantially improve cardiovascular health rests on a strong scientific foundation.

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