Environmental Tobacco Smoke, Cardiovascular Disease, and the Nonlinear Dose-Response Hypothesis

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Two recent government reports have focused attention on the hypothesis that environmental tobacco smoke (ETS) exposure increases the risk of cardiovascular disease (CVD) in nonsmokers. The first report was published by the California Environmental Protection Agency (CAEPA) in 1997. The second report was issued in 1998 by the Scientific Committee on Tobacco and Health (SCOTH) in the United Kingdom. A meta-analysis of five large prospective epidemiology studies reports that the relative risk for actively smoking 20 cigarettes per day is 1.78. Active smoking exposes the smoker to approximately 16 times the ETS concentration, and 100- to 300-fold the total smoke dose experienced by a nonsmoker (Smith and Ogden, 1998, JAMA 280, 32–33.). Despite the much lower smoke exposure, these government reports estimate the relative risk for ischemic heart disease in ETS-exposed nonsmokers at 1.30 (CAEPA) and 1.23 (SCOTH). As an explanation for this nonlinear dose-response anomaly, platelet aggregation is proposed to be a plausible and quantitatively consistent mechanism. Herein, evidence is presented suggesting that this low-dose hypothesis is inconsistent with the biochemistry and physiology of platelets and with the literature on the cardiovascular pathology of active smoking. In addition, several important biases and confounders are ignored. These epidemiologic biases and confounders include the following: misclassification of smokers as nonsmokers; improper use of death certificates as surrogates for mortality statistics; underreporting of diabetes and hypertension in the relatives of smokers; and additional atherogenic risk factors in smoking households. Future field studies on ETS and CVD should emphasize proximal markers of risk for thrombosis in exposed nonsmokers. Proximal thrombogenic risk markers identified in field studies should be mechanistically examined under controlled exposure conditions.

Key Words: environmental tobacco smoke; cardiovascular disease; active smoking; platelet aggregation; dose response; thrombogenesis; atherosclerotic plaque formation.

Two recent government reports and a meta-analysis (He et al., 1999) have focused attention on the hypothesis that environmental tobacco smoke (ETS) exposure increases the risk of cardiovascular disease (CVD) in nonsmokers. The first report was published in September, 1997 by the California Environmental Protection Agency (CAEPA, 1997). The second report was issued the following year by the Scientific Committee on Tobacco and Health (SCOTH) in the United Kingdom (SCOTH, 1998). CAEPA and SCOTH have estimated the relative risk of CVD in nonsmokers exposed to ETS at 1.30 and 1.23, respectively. The meta-analysis of ten cohort and eight case-control studies reports overall findings (relative risk 1.25) similar to these government publications, and reports a surprisingly high relative risk of 1.51 (95% confidence interval, 1.26 to 1.81) for the subgroup of eight case-control studies.

As compared with these relative risks, the relative risk for actively smoking 20 cigarettes per day is estimated by meta-analysis of five large prospective epidemiology studies at 1.78 (Fig. 1) (Law et al., 1997). The prospective epidemiology studies included in the meta-analysis by Law et al. (1997) are the following: American Cancer Society Nine State (Hammond and Dorn, 1958); British Doctors (Doll and Hill, 1964, 1966); U.S. Veterans (Kahn, 1966); American Cancer Society 25 State (Hammond, 1966); and the Pooling Project (Pooling Project Research Group, 1978). Law et al. (1997) analyzed each of the five studies separately. In each study, smokers were divided into three or four categories by the number of cigarettes smoked. In 10-year age groups, logistic linear regressions of the risk of ischemic heart disease relative to nonsmokers were fitted on the adjusted average number of cigarettes smoked per day in each consumption category. From each regression, the risk of ischemic heart disease associated with smoking one cigarette per day was linearly extrapolated. The average risk for the five studies was determined via weighting by the inverse variance. Because ETS exposure represents only approximately 0.3–1% of the dose of active smoking (Law et al., 1997; Smith and Ogden, 1998), accounting for the disproportionately high CVD risks reported for ETS exposure is problematic.

Law et al. (1997) hypothesize a platelet-aggregation mechanism to explain this highly nonlinear dose-response anomaly (Fig. 2). This hypothesis underlies the conclusions reached in both the CAEPA (1997) and SCOTH (1998) reports, influences He et al. (1999), and can be synthesized as follows:
Hypothesis: Platelet aggregation provides a plausible and quantitatively consistent mechanism for the low dose effect. The increase in platelet aggregation produced experimentally by exposure to environmental tobacco smoke would be expected to have acute effects increasing the risk of ischemic heart disease by 34%.

The purpose of this review is to evaluate this hypothesis in light of what is known about the cardiovascular effects of both active smoking and ETS. This analysis will also briefly consider differences in cardiovascular risk factors related to lifestyle and socioeconomics, which are more common in smokers and their spouses. An implicit assumption in this analysis is that any direct cardiotoxic effect of ETS exposure in nonsmokers would be expected to be seen in active smokers. This assumption is based on the approximately 16-fold increase in ETS exposure experienced by active smokers compared with nonsmokers (Ogden, 1996). In addition, despite significant physical and chemical differences, ETS and mainstream smoke possess many of the same compounds (Smith et al., 1992), with the active smoker receiving a much higher dose.

In order to analyze mechanistically the ETS/CVD nonlinear dose-response hypothesis, the following questions must be addressed:

**Active Smoking**
- What role does thrombus formation play in the pathogenesis of a myocardial infarction?
- What role does platelet aggregation play in thrombus formation?

**Environmental Tobacco Smoke**
- Is platelet aggregation induced by real-world ETS levels?
- Is clinically significant thrombus formation induced by real-world ETS levels?
- Does ETS exposure initiate the formation or exacerbate the growth of atherosclerotic plaques in the coronary arteries?
- Is plaque stability adversely affected by real-world ETS exposure?
- Does ETS exposure increase the risk of myocardial infarction and unstable angina?

By addressing the first six questions, it will be shown that real-world levels of ETS probably do not directly increase the risk of myocardial infarction and unstable angina in exposed nonsmokers. The possible role of sensory-mediated physiologic stress effects on the cardiovascular system of ETS-exposed nonsmokers is briefly addressed.

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**FIG. 1.** Nonlinear dose response. The nonlinear relationship between RR and exposure is demonstrated by the failure of these points to lie on a straight line that includes RR = 1 at 0 exposure. The 1.78 and 1.39 RRs are metaanalytic values derived from five large prospective active smoking epidemiology studies (see introductory section of paper). The 1.3 RR is the metaanalytic value for ETS exposure reported by Law et al. (1997). Exposure to ETS is expressed in terms of cigarette equivalents (CE) to allow a comparison with the two active-smoking points. The basis of the CE estimate is the exposed nonsmoker plasma-cotinine estimate proposed by Law et al. (1997): 1% of 20 cigarettes/day = 0.2 CE/day. Estimates from two recent, very large, demographically representative surveys not cited by Law (Pirkle et al., 1996; Health Survey for England, 1994) suggest that Law’s value is an overestimate. In particular, the serum cotinine data presented in these two studies predict nonsmoker exposures of approximately 0.2% to 0.4% (approximately 0.04 to 0.08 CE). Incorporation of either value in the figure would exacerbate the nonlinearity of the relationship. In general, CEs are used as approximate indicators of exposure to ETS. CEs based on markers other than cotinine may be higher or lower. See Phillips et al. (1999) and references therein.

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**FIG. 2.** Sensory-mediated responses to large, acute ETS doses.
Pathophysiology of Cardiovascular Disease

As a prelude to understanding the unresolved questions surrounding ETS and CVD, a brief summary of current concepts regarding the pathogenesis of myocardial infarction and the sometimes paradoxical cardiovascular pathology of active smoking may be illustrative.

Role of Thrombus Formation in the Pathogenesis of a Myocardial Infarction

Over the last decade, understanding of the mechanistic basis underlying acute myocardial infarction and unstable angina has been revolutionized. Despite this conceptual revolution, much of the basis of clinical cardiology and cardiac surgery rests on an outdated axiom: the greater the stenosis, the greater the risk of an adverse clinical event (Libby, 1995). This axiom is outdated because of the emergence of the following concepts:

- Mechanically and biochemically stable atherosclerotic plaques may narrow the arterial lumen and cause stable angina pectoris but are relatively harmless (Schroeder and Falk, 1995).
- Even in partially unstable plaques, small plaque defects usually do not cause clinical events. Examples of small defects would include plaque erosions (superficial intimal injury) and modest fissures with overlying microscopic mural thrombosis (Fishbein and Siegel, 1996).
- Due to compensatory enlargement of arteries with atherosclerosis, luminal inner diameter of the vessel remains normal until approximately 40% of the arterial cross-section is occupied by plaque. This occurrence is referred to as the Glagov phenomenon (Glagov et al., 1987).
- It is large unstable plaques, which do not produce significant stenosis because of remodeling, that rupture and form occlusive thrombosis, resulting in myocardial infarction and unstable angina (Fishbein and Siegel, 1996).
- Vulnerable plaques prone to rupture are characterized by a thin, fibrous cap infiltrated by macrophages (Burke et al., 1998).
- During an acute myocardial infarction, blood flow to the myocardium can be intermittent due to the competing processes of thrombosis and thrombolysis (Schroeder and Falk, 1995).
- Inflammatory processes are important in the pathogenesis of an acute myocardial infarction. Accumulations of mast cells (200-fold more than in the unaffected coronary intima) develop at the site of occlusive atheromatous erosion or rupture (Kov- anen et al., 1995). In addition, interleukin-1β is present in luminal and adventitial vessel endothelial cells and macrophages in coronary arteries from patients with ischemic heart disease (Galea et al., 1996).

Implications of myocardial infarction mechanisms vis-à-vis ETS. Given what is currently known about the causes of a myocardial infarction, what effects would ETS exposure need to elicit to increase risk? The answer to this question requires the separation of two issues. The first issue is whether ETS can initiate cardiovascular disease, i.e., cause plaque formation. The second issue is whether ETS exposure could exacerbate preexisting cardiovascular disease. Exacerbation could take several forms, including but not limited to the following: growth enhancement of dietary-, hemodynamic-, or otherwise-induced plaque; destabilization of preexisting plaque, e.g., increase in inflammatory infiltrate; increased tendency to develop thrombus; decrease in thrombolysis; or increase in vaso-ospasm of an atherosclerotic vessel (Meredith et al., 1993).

Role of Platelet Aggregation in Thrombus Formation

Central to the hypothesis stated in the first section is the role of the platelet in thrombosis. Coronary thrombi are rich in platelets. These platelets can be activated either directly by shear forces on exposed plaque components, or indirectly through thrombin generation (Schroeder and Falk, 1995). In patients with acute coronary syndromes, the data suggest that thrombin is generated via the intrinsic (contact activation) coagulation pathway (Hoffmeister et al., 1995; Merlini et al., 1994). If this suggestion is correct, then monocyte tissue factor may be important in initiating thrombosis after plaque disruption (Fernandez-Ortiz et al., 1994). Mechanical forces may also contribute, as the greater the stenosis and coarser the arterial surface, the more platelets tend to aggregate and deposit (Falk, 1983; Fernandez-Ortiz et al., 1994; Folts, 1991).

Under nonpathologic circumstances, in vivo coagulation and platelet activation are normal physiologic processes essential for maintaining homeostasis. Platelets are affected by activating agents in a dose-dependent manner with reversible responses at lower doses and irreversible activation occurring at higher agonist concentrations (Winslow et al., 1987). Both reversible and irreversible platelet activation occur in normal individuals without cardiovascular diseases.

Reversible platelet activation (or priming) can be elicited by epinephrine or norepinephrine (Larsson et al., 1989; Larsson et al., 1990; Siess, 1989) and occurs in response to routine daily stresses. For example, the psychological pressure associated with performing mental arithmetic (Grignani et al., 1991), taking an examination (Mest et al., 1982), giving a presentation (Arkel, 1977), hearing a loud sound (Andres et al., 1993), being confused (Larsson et al., 1989), and receiving bad news (Rostrup et al., 1990) have all been reported to potentiate platelet activation. In addition, exercise has also been reported to enhance platelet activation (Burghuber et al., 1981; Wang et al., 1994).

Evidence for irreversible platelet activation in normal individuals is provided by the observation that a fraction of platelets circulate as microaggregates (Amodeo et al., 1980) and display the P-selectin marker for degranulation (Tanoue et al., 1992). Although the in vivo cause of irreversible platelet activation is unknown, it may occur in response to endothelial stress from rheological shear forces and/or inflammatory processes.
Active smoking and cardiovascular disease. A voluminous literature suggests that the major clinical cardiovascular risk factor associated with active smoking is an increased tendency toward thrombosis (Barbash et al., 1993; Mueller et al., 1992). This tendency may increase the risk of both myocardial infarction and ischemic stroke, due to occlusion of the carotid arteries (American Heart Association, 1998). Myocardial infarction will be discussed here because it is responsible for the majority of cardiovascular deaths (American Heart Association, 1998) and has been the focus of concerns by regulatory bodies.

The following points summarize the active smoking literature:

- In hyperlipidemic populations, e.g., the United States, smoking is associated with increased atherosclerosis (Roberts, 1989).
- The abdominal aorta and the carotid arteries are reportedly affected more than the coronary arteries (McGill, 1988; McGill et al., 1997). The average increase in coronary artery atherosclerosis in smokers is approximately 25% (McGill, 1988). In fact, a recent publication from the Pathologic Determinants of Atherosclerosis in Youth (PDAy) study (McGill et al., 1997) reports no effect of smoking on the extent of either fatty streaks or raised coronary lesions in the right coronary artery. This result was determined from autopsies of 1079 men and 364 women in the 25- to 34-year age group.
- Other results from the PDAy study (1990) suggest that the increase in smoking-associated atherosclerosis may be related to inflammatory processes. This suggestion is based on the observation that young smokers with the same blood serum cholesterol levels as age-matched nonsmokers display increases in abdominal atherosclerosis. The possible role of inflammation is an important point that will be separately discussed in the subsequent text.
- The relatively small increase in coronary atherosclerosis is not sufficient to account for the approximately 2-fold increase in myocardial infarction seen in heavy smokers (McGill, 1988).
- Smokers display increases in blood coagulability (McKarns et al., 1995).
- In summary, the combination of modest increases in coronary artery atherosclerosis and increased tendency toward thrombosis is believed to underlie the increased myocardial infarction risk reported in smokers (Molstad, 1991).

Plausibility of ETS-Induced Platelet Aggregation

Returning to the main topic, we ask whether it is plausible that real-world ETS exposures could, by a mechanism of platelet aggregation, increase the risk of myocardial infarction in nonsmokers by an amount similar to that found in active smokers. If it is not plausible, then there is an alternative explanation for the similarity in reported relative risks for CVD across such a wide range of smoke dose exposures? To this end we first investigate whether very small concentrations of ETS would be expected to elicit platelet aggregation to approximately the same degree seen in active smokers, who experience 100- to 300-fold more smoke exposure (Smith and Ogden, 1998). At least two reasons suggest that a similar degree of platelet response would not be expected.

Dose-response behavior in platelets. First, there is a significant literature that reports monotonic increasing (often sigmoidal) dose-response curves for the aggregation of platelets. This holds for stimulation by a variety of agonists across a wide range of concentrations. For example, Winslow et al. (1987) report a sigmoidal dose-response curve for the aggregation of platelets in the presence of platelet-activating factor (PAF), measured at agonist concentrations across a 100,000-fold range. Schmaier (1987) has observed sigmoidal dose response of platelets following stimulation by both collagen and ionophore A23187. Moreover, Feinstein et al. (1985) have reported increases in platelet aggregation as a function of increasing concentration of thrombin. In summary, aggregating platelets behave like many other cell types in displaying increased biologic activity with increasing stimulation by agonists (Ross, 1995). Therefore, the much lower smoke exposure associated with ETS as compared with active smoking would be expected to elicit significantly less platelet activation.

Mechanism of platelet aggregation in active smoking. The second reason that platelets would probably not be induced to aggregate at the low ETS concentrations usually encountered by exposed nonsmokers is based on the mechanism by which active smoking is believed to accentuate acute platelet activation. Most likely, the mechanism is related to sensitization of the platelet by nicotine-induced release of epinephrine. Exposure of the platelet to epinephrine increases the tendency toward aggregation in the presence of agonists, e.g., ADP, collagen, thrombin, PAF, etc. (Smith et al., 1998).

How much exposure to nicotine do nonsmokers receive from ETS? Serum nicotine concentrations between 0.9 and 2.8 ng/ml have been reported following ETS exposure (Biber et al., 1987; Davis et al., 1989; Jarvis et al., 1983; Scherer et al., 1990). Baseline serum nicotine concentration for controls not exposed to ETS is approximately 1 ng/ml. These concentrations are below the threshold of 3 ng/ml for measurable hemodynamic effects (Andersson et al., 1993; Benowitz et al., 1982; Goldsmith et al., 1989; Netscher et al., 1995) (Fig. 3).

It should be noted that there are at least three problems associated with measuring low levels of serum nicotine. First, the gas chromatographic methods utilized are near the level of detection, i.e., 1–2 ng/ml. Biber et al. (1987) compared serum nicotine levels measured by gas chromatograph from five laboratories in both ETS-exposed and control subjects. Reported values for a single subject ranged from 0.2 to 9.6 ng/ml with an average of 2.8 ng/ml. Secondly, ETS exposure based on self-reporting can be skewed by misclassified subjects who can have mainstream exposure nicotine levels from 10 to 30 ng/ml.
Finally, nicotine naturally occurring in foods can contribute to baseline values (Davis et al., 1991).

In summary, smoking-related acute platelet aggregation probably results from sensitization of platelets by epinephrine released by the adrenals following nicotine binding to specific receptors (Cryer et al., 1976; Smith et al., 1998). The serum nicotine levels in nonsmokers following ETS exposure are probably not sufficient to stimulate the release of hemodynamically or biochemically significant amounts of epinephrine.

**Inflammation and Antioxidants**

**Atherogenic lifestyle.** Cigarette smokers as a group have lifestyles in addition to their smoking that put them at greater risk for chronic disease than nonsmokers (Blair et al., 1980; Cress et al., 1994; Edington, 1988; Lazarus et al., 1989; Shibata et al., 1989; Thompson and Warburton, 1993; Whichelow et al., 1988). Smokers reportedly differ from nonsmokers in many aspects including the following: less educated; attend church less frequently; more likely to have spouses who smoke; more physically active on the job; less likely to eat breakfast and desserts; consume more soft drinks, alcoholic beverages and coffee; sleep less; and have higher pulse rates (men only) and thicker skinfolds. Smokers comprise those occupational groups and social strata with increased exposure to hazards in the workplace, including dust, fumes, and toxic substances (Sterling and Weinkam, 1990).

Many studies have examined smokers’ diets. Smokers consume more calories from saturated fat, fewer grams of fiber, fewer fruits and vegetables, and fewer daily micronutrients including vitamin A, vitamin C, retinol, α-tocopherol and iron (Emmons, et al., 1995; Hirayama, 1984; Midgette, et al., 1993). This dietary pattern increases risk for atherosclerosis and coronary heart disease. In addition, Oliver (1989) has suggested that smokers have a reduced intake of the polyunsaturated fatty acid linoleic acid. Low levels of linoleic acid in fat tissue are associated with increased coronary risk at both population and individual levels (Oliver, 1989). Finally, smokers exercise significantly less than nonsmokers (Lazarus et al., 1989).

The lifestyle and socioeconomic risk factors found in smokers are also prevalent in nonsmoking spouses of smokers. For example, familial aggregation in physical fitness (Perusse et al., 1987) and increased concordance of physical activity for married versus surrogate pairs (Venters et al., 1984) have been observed, suggesting that the spouses of smokers may exercise less than spouses of nonsmokers. There are also significant dietary differences between the spouses of smokers and the spouses of nonsmokers (Knutsen and Knutsen, 1989; Koo et al., 1988; Rylander, 1999). Intakes of β-carotene, a good marker for vegetable consumption, were reported to be inversely related to ETS exposure (Marchand et al., 1991). Likewise, self-reported mean dietary intake of β-carotene is lower in nonsmokers exposed to ETS at home than in non-smokers not exposed to ETS at home (Sidney et al., 1989). The exposed subgroup in the Sidney study also had slightly higher mean body mass index despite its considerably lower average age. Diets of nonsmokers living with smokers were also found to include more calories from fat, fewer grams of fiber, more alcohol, fewer fruits and vegetables, fewer vitamin supplements, and fewer daily micronutrients (Emmons et al., 1995; Matanoski et al., 1995). The dietary differences between the spouses of smokers and the spouses of nonsmokers are to be expected considering the concordance of husband-wife dietary practices (Lindsted and Kuzma, 1990). Therefore, smokers and their nonsmoking spouses share an increased risk for CVD compared with the nonsmoking population because of concordant lifestyle-associated risk factors.

**Free radicals.** In addition to a reduced intake of dietary antioxidants, smokers are also exposed to free radicals from both cigarette smoke and increased pulmonary inflammation (Pittilo and Woolf, 1994). The possible importance of free radicals in cardiovascular health was demonstrated by improvement in endothelium-dependent vasomotion with cholesterol-lowering antioxidant therapy (Anderson et al., 1995).

**Possible influence of lifestyle on thrombogenesis.** Lifestyle is usually considered in regard to atherosclerosis because of potential effects on cholesterol metabolism. However, we have...
collected preliminary evidence that suggests lifestyle may also influence the tendency toward thrombogenesis. In an intensive hematologic study on healthy subjects following lifestyles with minimal cardiovascular risk factors other than smoking, thrombogenic risk was less than that previously reported for smokers (McKarns et al., 1995). Although some cardiovascular risk factor increases in the smokers were noted, they were smaller than previously reported. Among males, the following differences between smokers and nonsmokers were noted: white blood cell counts, +26%; fibrinogen levels, +17%; mean corpuscular hemoglobin, +5%; mean corpuscular volume, +4%. In addition, prothrombin time was decreased by 5%. Among females, the only thrombogenic risk factor that differed significantly was the white blood cell count (+43% in the smokers). In this study no atherogenic risk factor differed between smokers and nonsmokers, including cholesterol, low-density lipoprotein, very low-density lipoprotein, triglycerides, and glucose.

**Clinically Significant Thrombus Formation and ETS Levels**

In an environmental chamber study using fresh diluted sidestream cigarette smoke (FDSS) at a concentration of 179 \(\mu g/m^3\) respirable particulate matter (RSP) for 7.33 hours (Smith et al., 1996), several measurements related to blood clotting and viscosity were unchanged by exposure. These measurements included fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hematocrit, hemoglobin, number of red blood cells (RBC), and number of white blood cells (WBC). The only potentially thrombotic measurement that changed in an exposure-related manner was the platelet count, which decreased significantly on the exposure day.

**Possible Indirect (Sensory) Effects of Large Acute ETS Exposures**

Elucidating the cardiovascular effects of odors may facilitate interpretation of results from ETS studies. In the environmental chamber study described above (Smith et al., 1996), several changes in blood lipid measurements were observed in both male and female subjects. Among male subjects, triglyceride levels increased by 15%, whereas high-density lipoprotein (HDL) levels decreased by 4.8%. Such lipoprotein changes are consistent with a stress-related catecholamine-induced mobilization of free fatty acids and concomitant decrease in HDL (Nikkila, 1984). This suggests that the observed cardiovascular alterations may have been affected by sensory-mediated stress reactions.

Because many types of stressful stimuli can induce catecholamine release (Wilson and Foster, 1985), it is possible that the odor strength and/or sensory irritation of this acute exposure to a relatively high level of cigarette smoke (252 times the median U.S. smoking workplace ETS exposure level) (Jenkins et al., 1996) elicited norepinephrine release in these ETS-naïve individuals. Unfortunately, an odor only control, e.g., propionic acid, was not conducted in this environmental chamber study (Walker et al., 1999) to determine if dose-related cardiovascular alterations would result.

In a field study conducted on 19 ETS-exposed and 9 non-exposed waitresses, Moffatt et al. (1995) also observed decreases in HDL levels in the exposed group. These authors reported an overall decrease in HDL cholesterol of 14% in the ETS-exposed group as compared to the nonexposed group. Similarly, Valkonen and Kuusi (1998) have also reported changes in low-density lipoprotein in blood samples taken from 10 ETS-exposed nonsmokers. This group reported decreases in serum ascorbic acid and serum antioxidant defense, and a reduced capacity of LDL to resist oxidation. Although ETS-associated changes in cholesterol levels are mechanistically interesting, data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY Research group, 1990) multicenter study suggest that the small cholesterol level differences between active smokers and nonsmokers (Craig et al., 1989) are probably not clinically significant vis-à-vis coronary artery disease.

**ETS and Atherosclerotic Plaque Stability**

The data on plaque stability in relation to both active smoking and ETS are limited. The following discussion attempts to summarize and connect a body of poorly understood results. First, in our environmental chamber exposure study (Smith et al., 1996), serum levels of the inflammatory mediators leukotriene B\(_4\) (LBT) and prostaglandin E\(_1\) (PGE\(_1\)) increased 42% and 40%, respectively, on the exposure day. These levels returned to pre-exposure values on the next clean-air day. Interleukin-1, believed to be important in plaque inflammation (Galea et al., 1996), did not change as a result of ETS exposure. Basophils also did not appear to change with exposure. Whether this phenomenon is related to mast cell infiltration in plaque (Kovanen et al., 1995) is unknown.

The consistent observation that peripheral white blood cell count is elevated in active smokers is also difficult to directly relate to plaque stability. Budde and Schaefer (1989) examined the bone marrow of 32 cigarette smokers collected by trephine biopsies (performed because of mild peripheral leukocytosis). In all biopsy samples, they found a moderate to significant increase in granulopoietic cells and stimulation of phagocytic activity in macrophages, with neutrophils being the major target for phagocytosis. These authors interpreted this result as a smoking induced inhibition of locomotion in segmented neutrophils leading to an accumulation of mature polymorphs in the bone marrow, with consecutive breakdown and phagocytosis of senescent cells. The mechanism of this smoking-induced inhibition and the process by which granulopoietic cells increase are unknown.
The macrophage white blood cell population has been directly compared in the developing atherosclerotic lesions of young smokers and nonsmokers. Botti et al. (1996) have demonstrated greater macrophage foam cell populations in 216 quantitative measurements taken from 27 autopsied PDAY cases. The relationship between the peripheral white blood cell count and this observation is also unknown.

Potential physiologic stress effects may interfere with experiments on ETS and white blood cells. Specifically, a significant portion of the WBC population adheres to the blood vessel wall through a process termed margination. Epinephrine release initiates demargination, whereby the measured peripheral WBC count increases, whereas the actual total population remains unchanged (Brenner et al., 1998). Because epinephrine release may result from multiple stimuli, including fear of needles, fear of ETS, or an unpleasant sensory response to ETS, it is difficult to interpret ETS-associated changes in peripheral WBC count. In our chamber study we did not observe changes in peripheral WBC at 179 μg/m³ RSP for 7.33 hours (Smith et al., 1996).

Alternative Hypothesis: Influence of Biases and Confounders

Does ETS exposure increase the risk of myocardial infarction and unstable angina? Our recent pilot study (Smith et al., 1998) of 21 ETS-exposed nonsmokers suggests that real-world concentrations of ETS may not aggregate platelets. If this result holds in general, then the putative mechanism of increased CVD risk proposed by Law and others is spurious. The disproportionately high relative risk for CVD reported in Law’s meta-analysis of 18 epidemiologic studies must then have another explanation. A far more likely and far less speculative explanation lies in the numerous biases and confounders reported in the ETS/CVD literature. A selection of biases and confounders in CVD in epidemiology studies follows:

- Smokers incorrectly classified as nonsmokers.
- Large error rate introduced through use of death certificates as surrogates for mortality statistics.
- Fewer medical records and less medical care in smoker families.
- Underreporting of diabetes and hypertension in smokers and their relatives.
- Smokers and their families have more atherogenic risk factors.

Among those of particular relevance to this question are the following: misclassification bias, whereby smokers are incorrectly classified as nonsmokers (Ogden et al., 1997; Wagenknecht et al., 1992); underreporting of diabetes and hypertension (ADA, 1997; AHA, 1998; Connolly and Kesson, 1996; Duenas, 1998; Mackenbach et al., 1996); and diagnostic flaws.

Diagnostic flaws. There are at least two major diagnostic flaws that adversely affect the premises upon which the epidemiology studies on ETS and CVD are based: death certificate errors and smoker lifestyle confounding. First, causes of death listed on death certificates are used as surrogates for mortality statistics. A comprehensive review of the literature comparing the accuracy of death certificate data with autopsy and medical record–validated causes of death demonstrates a large error rate on the death certificates (Smith et al., 1998). This large death certificate error rate for CVD is propagated, without critique or compensation, throughout the calculation of a very small increase in relative risk associated with ETS. Second, these epidemiology studies ignore a diagnostic inaccuracy operating against smokers and their spouses. On a comparative basis, this smoker-lifestyle confounder tends to underestimate the incidence of CVD during the lifetime of the smoker and his/her spouse. Conversely, the incidence of CVD, particularly myocardial infarction, is overestimated at death in this group. A major influence underlying this diagnostic inaccuracy is the relative absence of information concerning CVD in smokers and their spouses as compared with nonsmokers, due to socioeconomic, geographic and psychological factors in smoking households (Smith et al., 1998).
ducibility, magnitude, directionality, potential for reversibility, and possibility of adaptation. Proper consideration of these factors can allow the results of a series of carefully controlled studies to suggest whether a change is likely to be a negative health effect, a risk factor for the future development of a negative health effect, a temporary adverse change to which the body will adapt, or an inconsequential change within the normal homeostatic range.

In general, changes likely to be more serious would necessarily have the following characteristics: occur at ETS exposure levels encountered in the real world, be reproducible either within an individual test subject or within a subject population, move baseline biochemical or physiologic values outside of the normal clinical range, move baseline values toward increased risk levels in a manner mechanistically consistent with biologically plausible alterations in cardiovascular pathology, display sensitization with increasing exposure, and not display adaptation or reversibility.

Several basic questions should be asked before accepting the conclusions of the CAEPA (1997) and SCOTH (1998) reports. These conclusions are based on the underlying assumptions of Law et al. (1997) and lead to the following relative risks in nonexposed individuals for ischemic heart disease: ETS exposure, 1.23; smoking one cigarette per day, 1.39; and actively smoking 20 cigarettes per day, 1.78 (Fig. 1). First, are these results consistent with the known cardiovascular pathology of cigarette smoking? Second, are they consistent with the biochemistry and physiology of platelets? Third, do they take into account the demographic, behavioral, and socioeconomic literature on smokers and their families? The current data suggests that the answer to all three questions is probably no. More definitive answers are likely to emerge as biochemical and epidemiologic understanding grows through carefully focused research. In particular, data on the cardiovascular effects of odors and irritants is rapidly expanding as the results of additional field and chamber studies become available.

REFERENCES


Minnesota BRFSS (Behavioral Risk Factor Surveillance Systems Survey).


