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# Effects of Sidestream Smoke on Reproduction and Development of Two Inbred Murine Strains

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## Introduction

Since publication of the classical paper by Simpson in 1957 (47), many studies have examined the effects of smoking on maternal, fetal, and neonatal health. Infants born to women who smoke have a higher prevalence of signs suggesting intrauterine growth retardation (22). On average, the offspring of smoking mothers are 200 g or more lighter at term than those of nonsmoking mothers (47, 2). Women who smoke also have a higher prevalence of bleeding during pregnancy and delivery complications such as abruptio placentae, placenta previa, premature and prolonged rupture of membranes, spontaneous abortion, and perinatal mortality (34, 25, 55). Decreased placental blood flow (26), improper development of fetal coronary arteries (29), congenital heart disease (18), childhood respiratory ailments (9, 20, 8), and behavioral abnormalities of offspring (35) are other effects associated with maternal smoking.

Various animal studies have shown many of the same effects observed in humans. These include reduced birth weight (14, 41, 6), and increased perinatal morality (14).

There is growing evidence of health risks due to sidestream smoke (passive smoking), especially in infancy and early childhood (27, 16, 56). The issue of passive smoking is perhaps most cogent in children who are constantly subjected to smoke at home (8).

Most animal smoke-exposure studies have involved smoking machines that release either mainstream smoke (6, 32) or a combination of mainstream and sidestream smoke (24) in regulated, periodic puffs, or have exposed animals to different components of cigarette smoke (5, 39, 13, 48, 52). However, a few animal studies have involved sidestream smoke exclusively, and various harmful fetal and neonatal effects have been noted (54, 33). This study uses the same procedure and animal model used in a previous investigation (33) in an attempt to reproduce the reported effects of sidestream smoke exposure, and to determine whether or not strain variation occurs regarding these effects.

## Materials and Methods

Adult female mice of the BALB/cAnNHsd and C57BL/6NHsd strains (Harlan-Sprague Dawley, Indianapolis, IN) were randomly assigned to experimental and control groups and mated overnight with males of the same strain. The day a copulation plug was found was designated as gestation day 1. Pregnant mice were maintained in separate cages under environmental conditions controlled with respect to room temperature (20-25 C), humidity (55-60%), and photoperiod (12 hr light, 12 hr dark). They were fed Lab Blox pellets (Wayne Feed Division, Continental Grain Co.) and water *ad libitum* between trials.

The experimental procedure used in this study is similar to that used in a previous study (33). Experimental mice were placed in a plexiglas smoking chamber (25.5 cm $\times$ 30.5 cm $\times$ 21.0 cm) containing 6 airholes 6.5 mm in diameter on two opposite sides, and exposed each day of gestation (21 days) to the sidestream smoke from one filter-tip cigarette. The duration of each smoking session was 40 minutes. This provided a standard time period and insured that the cigarette had burned completely. Control mice were divided into two groups: sham controls and shelf controls. Sham

controls were placed in similar smoking chambers each day for 40 min, but were exposed to an unlit rather than a lit cigarette. Shelf controls remained in their respective cages throughout the gestation and weaning periods.

At the end of each treatment period, dams were returned to their respective cages. Treatment was terminated at parturition, and the dams (P generation) were allowed to nurture their litters (F1 generation) until they were weaned on postnatal day 21. On postnatal day 1 (within 16 hr of birth) all litters were sexed, weighed, and dead fetuses removed. Cages were observed daily and offspring deaths recorded. At the end of the 21-day weaning period, the pups were again sexed.

Upon reaching sexual maturity, control and experimental F1 females of both strains were mated with males of their own strain and exposed to the same treatment format as their mothers. Both parental and F1 litters of the two strains were observed for intrastrain and interstrain effects of sidestream smoke exposure.

In a parallel study, carboxyhemoglobin (COHb) concentrations of peripheral blood (vena cava) of female P and F1 generation (gen) mice, subjected to the same conditions described above, were determined using a Model 282 CO-Oximeter (Instrumentation Laboratories, Lexington, MA) and taken as an index of the amount of smoke inhaled. Since there was no significant difference in COHb values between P gen and F1 gen mice of either strain, results are reported as pooled means ± S.E. Chi-square analysis was used to evaluate percent mortality data. Differences between means were evaluated using Student's *t* test and a P value of less than 0.05 was considered to be significant. Sham mice are the controls of reference. Statistical analysis indicated no significant difference between shelf and sham control groups.

## Results

A 40 min exposure to sidestream smoke from one filter-tip cigarette produced a significant increase in the levels of carboxyhemoglobin (COHb) over background levels. BALB smoke-exposed dams had a mean COHb value of 28.33% (±3.39; N=24). Control dams had a COHb concentration of 2.15% (±0.33; N=14). Experimental C57 dams had a mean value of 30.68% (±2.32; N=24) and control dams had a mean value of 3.81% (±0.25; N=15). COHb levels of experimental dams of both strains returned to control range values within a 24 hr period (Table 1).

Table 1. Carboxyhemoglobin extinction data for BALB/c and C57BL mice following 40 min (0.7 hr) exposure to sidestream cigarette smoke.

| Strain | N | Time (hr) | COHb (%)[1] |
|---|---|---|---|
| BALB/c | 14 | 0.0 | 2.2 (±0.33) |
| | 24 | 0.7 | 28.3 (±3.39) |
| | 5 | 1.7 | 9.0 (±0.84) |
| | 5 | 2.7 | 3.1 (±0.12) |
| | 4 | 24.7 | 2.4 (±0.23) |
| C57BL | 15 | 0.0 | 3.8 (±0.25) |
| | 24 | 0.7 | 30.7 (±2.32) |
| | 5 | 1.7 | 9.7 (±1.05) |
| | 4 | 2.7 | 3.6 (±0.18) |
| | 5 | 24.7 | 3.1 (±0.25) |

1. Mean ± S.E.

Sidestream smoke produced significant but varied effects on both strains (Table 2). It reduced litter size, lowered off-spring birth weight, and increased offspring mortality of BALB parental generation (P gen) mice. A decrease in litter size and an increase in offspring mortality were observed in both C57 P gen and F1 gen mice.

Table 2. Effects of sidestream smoke on mouse litter size[1], birth weight (g), and survivorship to postnatal day 21. Number of litters given in parentheses.

| | | | | | Survivorship | | | |
|---|---|---|---|---|---|---|---|---|
| Strain | Gen | Group | Litter Size | Birth Weight | Surv/ Total | % | M21/M1 (%) | F21/F1 (%) |
| BALB/c | P | Con | 7.2 + 0.50 | 1.58 ± 0.02 | 180/210 | 89.1 | 85/101 | 95/101 |
| | | (28) | | | | | (84.2) | (94.1) |
| | | Exp | 5.6 ± 0.56[2] | 1.50 ± 0.03[2] | 111/146 | 76.0[3] | 47/65 | 64/81 |
| | | (26) | | | | | (72.3) | (79.0) |
| | F1 | Con | 7.3 ± 0.42 | 1.58 ± 0.03 | 235/263 | 89.0 | 106/124 | 129/138 |
| | | (36) | | | | | (84.8) | (98.5) |
| | | Exp | 6.8 ± 0.52 | 1.55 ± 0.02 | 161/197 | 81.4[4] | 71/96 | 90/101 |
| | | (29) | | | | | (74.0) | (89.1) |
| C57BL | P | Con | 7.4 ± 0.26 | 1.23 ± 0.21 | 295/463 | 63.7 | 140/237 | 155/226 |
| | | (63) | | | | | (59.2) | (68.6) |
| | | Exp | 6.3 ± 0.40[2] | 1.18 ± 0.02 | 82/170 | 48.0[3] | 45/86 | 37/84 |
| | | (27) | | | | | (52.3) | (44.1) |
| | F1 | Con | 7.4 ± 0.36 | 1.23 ± 0.04 | 146/221 | 66.1 | 66/110 | 80/111 |
| | | (30) | | | | | (60.0) | (72.1) |
| | | Exp | 6.2 ± 0.32[2] | 1.23 ± 0.02 | 61/181 | 33.7[3,5] | 28/92 | 33/84 |
| | | (29) | | | | | (30.4) | (39.3) |

1. Within 16 hr of parturition; equivalent to postnatal day 1.
2. Significantly different from control group, $P < 0.05$.
3. Significantly different from control group, $P < 0.01$.
4. Significantly different from control group, $P < 0.02$.
5. Significantly different from P gen exp group, $P < 0.01$.

Control and experimental mice of both BALB P and F1 generations had significantly higher ($P<0.01$) rates of survival than did respective C57 mice. The 47.4% difference between BALB P gen experimentals (81.4%) and C57 F1 gen experimentals (33.7%) was the greatest interstrain difference in survivorship. The fact that BALB mice are larger than C57 mice and that there is a 22-25% difference in survivorship among controls are interstrain variations unrelated to smoke exposure.

Although there were no significant intrastrain or interstrain differences in sex ratios, female pups of both strains tended to have a higher survival rate than males (Table 2). The only indication that one sex might be negatively affected more than the other is shown by the large decrease in survivorship of P gen experimental females of both strains. This is particularly evident for C57 P gen experimental females, which declined by 14.5% (68.6% to 44.1%) while corresponding males declined by only 7% (59.2% to 52.3%).

The effects of sidestream smoke on perinatal and postnatal mortality are recorded in Table 3. Perinatal mortality represents the dead mice on postnatal day 1 (within 16 hr of parturition). These mice include stillbirths and neonatal deaths, and were

TABLE 3. Effects of sidestream smoke on perinatal (D1) and postnatal (D2-D21) mortality[1].

| Strain | Gen | Group | N | Mortality | |
|---|---|---|---|---|---|
| | | | | Perinatal (%) | Postnatal (%) |
| BALB/c | P | Con | 28 | 1/202 (0.5) | 21/201 (10.5) |
| | | Exp | 26 | 10/146 (6.9) | 25/111 (22.5) |
| | F1 | Con | 36 | 1/263 (0.4) | 27/235 (11.5) |
| | | Exp | 29 | 20/197 (10.2) | 16/177 (9.0) |
| C57BL | P | Con | 63 | 3/463 (0.7) | 165/460 (35.9) |
| | | Exp | 27 | 3/170 (1.8) | 85/167 (50.9) |
| | F1 | Con | 30 | 1/221 (0.5) | 74/220 (33.6) |
| | | Exp | 29 | 29/181 (16.0) | 91/512 (59.9) |

1. Postnatal mortality is significantly higher ($P<0.01$) than perinatal mortality in all cases except that no signif-cant difference occurs between BALB experimetnal F1 gen peri- and postnatal values.

included in the litter size counts. Postnatal mortality represents those mice that died from postnatal day 2 to postnatal day 21 (weaning). Postnatal mortality is significantly higher than perinatal mortality in all but one case. BALB experimental F1 gen mice showed no difference between early and late death.

A decrease in food intake by smoke-exposed dams resulting in undernutrition is a potential variable that could interfere with the results of this study. However, no discernible differences between control and experimental dams were observed regarding their food intake or state of nutrition.

## Discussion

More than 2000 compounds have been identified in cigarette smoke, many of which are established carcinogens, irritants, and asphyxiants (49). Currently, the most

widely accepted hypothesis relating maternal smoking and effects on the fetus and newborn is that smoking affects the fetus by way of intrauterine hypoxia. Such hypoxia could occur as a result of one or a number of factors associated with smoking (1).

Carbon monoxide and nicotine are the two substances that have received the most attention (42). Both carbon monoxide and nicotine that women absorb from cigarettes reduce the delivery of oxygen to fetal tissues (28). In the blood, carbon monoxide has a higher affinity for hemoglobin than does oxygen, and it combines with hemoglobin to form carboxyhemoglobin (COHb), thereby producing as much as a 12% reduction of the oxygen-carrying capacity of the blood, resulting in fetal hypoxia (1).

COHb levels in pregnant nonsmokers vary from 0.4 to 4.4%, whereas in chronic smokers, levels may very from 2 to 14%. At birth, these levels in infants of nonsmokers are 0.2 to 3.6% compared to 1.1 to 9.2% for infants of smokers and are close to those which have independently been shown to reduce birth weights, increase perinatal mortality and adversely affect subsequent behavior in animals (1).

It has also been contended that nicotine causes fetal hypoxia by vasoconstriction of uterine blood vessels (40) and decreased perfusion of intervillous spaces (28). The umbilical, placental, and fetal circulation could also be affected by catecholamine release induced by nicotine crossing the placental barrier (12).

The chemical composition of sidestream smoke (smoke emitted into the environment by a smoker between puffs) is qualitatively similar to the mainstream smoke inhaled by the smoker (36). Analytical studies indicate that sidestream smoke contains a larger proportion than mainstream smoke of many of the compounds present in smoke on a per cigarette basis (44). Among the gas phase constituents of cigarette smoke that result in high sidestream (SS)/mainstream (MS) ratios are carbon monoxide (2.5), carbon dioxide (8.1), and ammonia (73.0). Two important particulate phase components with high SS/MS ratio are nicotine (2.7), and "tar" (1.7) (23).

In recent studies, passive smoking (inhalation of sidestream smoke) has been associated with many of the same outcomes as direct smoking (inhalation of mainstream smoke) such as low birth weight (31), aggravation of angina pectoris (4), lung cancer (21, 31), asthma (20), and other respiratory illnesses in children and infants (57, 53, 45). Animal studies have shown that sidestream smoke can result in a decrease in both cell viability and protein synthesis as well as the production of cell stress/heat shock-like polypeptides (24).

Exposure of pregnant animals to concentrations of carbon monoxide that produces COHb values of 11 to 28% lowers birth weight (37), decreases litter size (13), and increases perinatal mortality (30). A mean COHb concentration of 28.3% (BALB) and 30.7% (C57) immediately following smoke exposure under the conditions of this investigation barely exceed the upper end of this range. These concentrations are also consistent with those reported previously for a different mouse strain (33).

The fact that we observed a higher incidence of postnatal mortality than perinatal mortality might indicate that the cause of pup death is due to factors other than, or in addition to, in utero effects of smoke exposure. One possibility is that smoke inhibits lactation, which would effect pup growth and development. Injection of nicotine (7) and inhalation of tobacco smoke (17) inhibits prolactin secretion in rats. Andersen, et al. (3) showed that pregnant women who smoked had significantly lower levels of serum prolactin than nonsmoking pregnant women; whereas, Counsilman and Mackay (11) found that smokers tended to wean earlier than nonsmokers, and suggested that this was caused by tobacco smoke inhibition of milk production. However, since most of our pup mortality occurred early in the postnatal period (between D2 and D5), it appears that in utero effects are probably more significant

to pup mortality than decreased lactation, but further research is needed to substantiate this hypothesis.

A number of studies have shown that humans exposed to sidestream smoke exhibit lower COHb levels than were produced in our study. Russell, et al. (43) found that COHb levels increased from 1.6% to 2.6% in nonsmokers present in a smoke-polluted room with a carbon monoxide level of 38 ppm. Aronow (4) reported that exposure of 10 patients with coronary artery disease to the smoke from 15 cigarettes over a 2 hour period in a 30.8 $m^3$ room increased the COHb levels of nonsmokers from a baseline of 1.26% to 2.28% when the ventilation was turned off. However, carbon monoxide concentrations as high as 200 ppm in a closed environment have been reported (46). Carbon monoxide levels of 150 ppm and 300 ppm resulted in COHb concentrations of 18.5% and 26.8%, respectively, in rats (52).

Comparison of animal smoke-exposure studies is often difficult to make. There are several reasons for this. Differences in smoking procedures and the kinds of animals used account for much of the difficulty. For example, baseline levels of COHb, which is a major biochemical marker of smoke exposure, can vary significantly among different species. This in turn affects COHb levels produced upon exposure to smoke. One study on the effects of passive smoke exposure on sheep reported COHb baseline concentrations of 6.6% (50). This value compares to baseline COHb averages of 2.2% and 3.8% for the BALB and C57 mice used in this investigation. The differences (8-12 times) between baseline and experimental COHb levels attained in our study approximate those reported for heavy smokers (1). Although the mice in this investigation were exposed to somewhat higher concentrations of sidestream smoke than humans are in a smokefilled environment, the data support the growing number of studies that demonstrate the potential health hazards of sidestream smoke (19, 51). In addition, we have shown that animals of the same species, with similar COHb baseline values, can vary in their susceptibility to sidestream smoke. The strain variation to the sidestream smoke effects observed in this study does not appear to be caused by differences in smoke absorption since both the BALB and C57 mice had similar blood carboxyhemoglobin concentrations following the 40 min smoke exposure. In general, the effects of smoke exposure are more pronounced in the C57 strain. This may be due, in part, to the fact that the C57 mice are about 22% (0.3g) lighter than the BALB mice. However, it would seem that other factors are also involved. In spite of the size differential, C57 controls and BALB controls produced similar litter sizes (7.2-7.4) and sex ratios. In addition, pup weight was generally unaffected by smoke exposure in either strain. A 5.1% decline in the BALB P gen experimental group was the lone exception. A reduction in birth weight (31) would appear to be the most incriminating evidence to date that passive smoking has an affect on human reproduction and development.

## Summary

Our results indicate that sidestream smoke which produces COHb concentrations of 28-31% can produce deleterious effects on mouse reproduction and development. They also demonstrate that not all strains of a given type of animal are affected by sidestream smoke equally. We suggest that strain selection is an important variable and should be taken into consideration in future smoke-exposure studies. In conclusion, our results substantiate a recent study of the National Academy of Sciences (10) which stated in its report on indoor pollutants that: "Public policy should clearly articulate that involuntary exposure to tobacco smoke ought to be minimized or avoided where possible."

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