What’s new in *Nicotine & Tobacco Research*?

By Richard Hébert

“*It’s time to regulate smoke’s toxin levels*”

Short of getting smokers to quit—or to never start—the harm that cigarettes do can be lessened in two ways: Reducing how much smoke is inhaled, and reducing the toxins in the smoke. Unfortunately, the checkered past of both strategies—from filters to “ultra-lights”—is littered with unintended consequences. The results of a half century of harm reduction attempts by the tobacco industry “can only be described as disastrous,” write Allen and colleagues (p. 777), and Gray and Henningfield (p. 789). “Today’s cigarette is highly addictive, misleadingly labeled, facilitates compensation, is easy to learn to smoke, delivers unnecessarily high levels of carcinogens and toxins, and its manufacture is not subject to meaningful regulation of its toxicant delivery.” Tests that show wide variability in the levels of specific toxins and carcinogens in today’s cigarettes clearly demonstrate that cigarettes can be made and marketed with substantially lower levels than most now deliver. The authors argue that it is time for comprehensive regulation of the chemical nature of tobacco products, and they applaud beginning efforts in that direction in the United States and Europe, and by the World Health Organization.

Where should the standard be set? For openers, the maximum allowed levels of major carcinogens and toxins should be the minimum levels currently on the market, they argue. Indeed, “A regulator could well be accused of negligence if higher levels were allowed.” Further, regulation should be accompanied by vigorous monitoring of the effects of regulation and public health messages. Both are needed to ensure that “safer” cigarettes do not undermine prevention and quitting efforts or subvert their own harm-reduction intent by inviting smokers to smoke more of them because of their presumed “safety.” As the authors note, “The difficulties of developing consensus around nicotine regulation are not an excuse for accepting the status quo. Control of toxicants is possible and is urgent.”

*Patches: Battle of the sexes*

It is thought that nicotine replacement works better for men than for women, but few studies have examined that hypothesis, and those that have studied it have arrived at different conclusions. To sort out what’s known, Munafò and his colleagues (p. 769) performed meta-analysis of 31 nicotine patch trials. They were able to get sex-specific data from only 11 of them, however. They conclude that patches are just as effective for women as for men at 6 months and a year after quitting. Unaided quit rates for both sexes were about 10% at 6 months and 8% at 12 months; adding patches improved the 12-month quit rates by 4.2% for women and 6.2% for men. That small difference, the authors conclude, “is unlikely to be of clinical significance.” They urge caution in interpreting results based on such limited data.

Perkins (p. 765) says that even greater caution is warranted, noting that the meta-analysis did not include three trials that found large differences between men and women in patches’ effectiveness. Further, he points out that many variables may account for or modify the differences, including genotypes. For example, the patch may be more effective for men because a common genotype associated with better nicotine replacement efficacy in men, but not in women, is more prevalent in the population. Instead of comparing the patch to a placebo, as in the studies analyzed by Munafò and his co-authors, Perkins recommends examining sex differences in outcomes between different medications, such as patches vs. nicotine inhalers or bupropion.

In response, Munafò and his associates (p. 865) write that including the three additional data sets would not have changed anything significantly. “[I]t is
worthwhile to take from this study the message that sex alone does not appear to have a dramatic effect on nicotine replacement (NRT) patch efficacy, that women do derive substantial benefit from NRT patch treatment… and that the elucidation of the mechanisms underlying perhaps modest differences in efficacy need to be explored using more complex data sets.”

Perkins and Munafo do agree on two overriding themes:

- Large studies are needed to examine differences in responses to treatments, particularly adequately powered studies of group–treatment interactions.
- A large body of data must be built up and centrally archived to permit such analyses.

After menopause: Can HRT boost NRT’s effects?

Older women who smoke face special barriers to quitting, such as menopausal symptoms, hormonal changes, and changes in their social roles. In the United States, 20.5 million women are 65 or older, and 1.9 million of them smoke, yet researchers have mostly overlooked the challenges they face, despite the substantial benefits of quitting, specifically, slower decline of lung function and reduced risks of osteoporosis, many cancers, and heart disease. Evidence that the nicotine patch affects women differently depending on their menstrual cycle phase suggests an interaction between nicotine and ovarian hormone fluctuations. Might nicotine replacement therapy (NRT) benefits be boosted for women who are also receiving hormone replacement therapy (HRT)?

To find out, Allen and co-authors (p. 777) studied 94 postmenopausal smokers instructed not to smoke for 2 weeks. Half were taking HRT, half not. In each group, subsets were randomized to active nicotine or placebo patches. Contrary to expectations, however, no interactions were found between HRT and the nicotine patch. The nicotine patch was effective in reducing withdrawal symptoms and craving during the first week of abstinence, regardless of whether the women were receiving HRT or not. Similarly, the women receiving HRT had significantly better mood and less depression, whether they were using nicotine patches or not.

“[I]t should be emphasized that NRT is effective only in the short-term,” the authors caution, pointing out also that recent trials indicate that the risks of using HRT might outweigh its benefits. “We are not suggesting that HRT be used as a treatment during a smoking quit attempt,” they write, “but it does appear that HRT is not detrimental and may even be beneficial in alleviating the mood disturbances that can be experienced during smoking cessation… Although HRT use may not be prudent at this time…, our study demonstrates that ovarian hormones might influence women’s responses to smoking cessation and thus should be considered in developing effective strategies for women to quit smoking.”

Infants’ hair: “Canaries in the coal mine”?

Secondhand smoke is associated with respiratory infections, asthma, ear and sinus infections, and Sudden Infant Death Syndrome, especially in children under 3. One of the best ways to measure such exposure is through hair cotinine, because it does not reflect direct contact with ambient smoke but rather with environmental smoke that is inhaled and absorbed into the bloodstream over several months, by children and adults alike. When Groner and colleagues (p. 789) examined hair samples from 104 pairs of mothers and their children under 3 years old, they found:

- Hair samples from the children of nonsmoking mothers who had minimal or no contact with smokers had “surprisingly high” cotinine levels, significantly more than even their mothers, suggesting more rapid absorption.
- Children of smokers had levels in the same range as their mothers, regardless of the number of smokers to whom they were exposed.
- Hair cotinine levels of African American children were significantly higher than those of Whites, even though the African American children were exposed to less smoking.

The higher absorption rate among African Americans supports findings from animal studies that suggest that more highly pigmented hair absorbs nicotine and cotinine faster, as well as studies reporting greater intake of nicotine and slower clearance of cotinine by African American smokers.

Importantly, most environmental smoke is sidestream smoke coming directly from the burning end of the cigarette, not smoke exhaled by a smoker. Sidestream smoke releases greater concentrations of both nicotine and other toxic and carcinogenic substances than what a smoker exhales. Because of this, the investigators warn, hair cotinine “is not only a marker for nicotine, but for all of these toxins. Young children may be the proverbial canaries in the coal mine, …who experience the effects of tobacco smoke well before their mothers do.”

“Lights” can be more toxic than “Regulars”

Reducing cigarettes’ tar and nicotine levels has not reduced cigarette-related health risks. One frequently offered explanation: Smokers of “lights” and “ultralights” compensate by blocking filter vents, puffing harder and faster, and holding smoke in longer and deeper. Industry defenders argue that such smokers still get less nicotine and tar than they would from...
In all three brand pairs, 23 toxicants had yields from various types of cigarettes. Analyses of the actual human dosages of toxicants critical degree of compensation. Needed next are author points out, "these calculations overstate the yield cigarettes raises toxicant-to-nicotine ratios," the cigarette. Doesn't raise the toxicant-to-nicotine ratio of a given "lights," even assuming that intensive smoking and 73% of the nicotine absent in normal smoking compensation at all was needed for three toxicants) would have to compensate only for between 0% (no these toxic compounds from "lights," smokers have to compensate only for between 0% (no compensation at all was needed for three toxicants) and 73% of the nicotine absent in normal smoking of "lights," even assuming that intensive smoking doesn't raise the toxicant-to-nicotine ratio of a given cigarette. "To the extent that more intense smoking of lower yield cigarettes raises toxicant-to-nicotine ratios," the author points out, "these calculations overstate the critical degree of compensation." Needed next are analyses of the actual human dosages of toxicants from various types of cigarettes.

Impulsivity: What's a nicotine "fix" worth?

Drug users deprived of their drugs behave more impulsively, choosing smaller, immediate rewards over larger, delayed rewards, or those that are uncertain or require them to make an effort. To find out if smokers deprived of their "nicotine fix" would behave similarly, Mitchell (p. 819) tested 11 smokers twice, once after 24 hr of abstinence and once without abstinence.

Both times, the smokers were asked to choose between immediately receiving a specified number of cigarettes, from zero to 60, and US$10 (the approximate price of three packs) with three scenarios: A delay of up to a year before they would get the money, the risk of not getting the money at all (by picking a "no" rather than a "yes" token from a bowl), and by squeezing a dynamometer for 5 s at a specified force level. Then they were asked the same choices, this time replacing the immediate cigarettes with an immediate sum of cash. The results:

- When deprived of nicotine, they more often chose immediate cigarettes than when not abstaining—reflecting increased impulsiveness.
- The number of such choices, however, was only modestly related to their withdrawal scores.
- Unexpectedly, when the choice was between immediate money and delayed, uncertain, or effortful money, depriving smokers of nicotine had no effect.

That the abstaining smokers preferred immediate cigarettes but not immediate cash, the author concludes, indicates that "the increase in impulsive responding was driven solely by increases in the value of the drug and was not accompanied by a heightened aversion to delayed rewards." That heightened impulsivity during withdrawal probably contributes to relapses from quit attempts. The findings also suggest that smokers experiencing withdrawal will not be more likely to be impulsive unless the behavior is smoking-related. For example, they're unlikely to make an expensive impulse purchase but might pick up a discarded cigarette butt to smoke, regardless of the health risks.

Smoking during pregnancy affects daughters more

It's known that children whose mothers smoked while they were pregnant are more likely to experiment with smoking, but does in utero exposure to tobacco smoke components also lead to more rapid progression to daily smoking? Does it impact nicotine dependence later in life? And are there gender differences at play? To seek answers, Oncken et al. (p. 829) surveyed 298 treatment-seeking smokers who said they knew whether they had been exposed to their mother's smoking before they were born. Women who had been exposed before birth said they had progressed from experimenting to daily smoking more rapidly than their unexposed counterparts; the opposite was true for men, possibly because they had started experimenting earlier. Men exposed in utero had started smoking on average 2.5 years earlier than those not exposed, but exposure did not appear to affect when women started smoking. In utero exposure also was associated with signs of greater nicotine dependence as adults, including more severe withdrawal symptoms and, for girls, fewer past attempts to quit.

"This work extends the notion that females exposed in utero may be especially vulnerable to nicotine addiction," the investigators report. Noting that the onset of withdrawal symptoms typically begins with daily smoking, they warn that "[t]he opportunity for
intervention between smoking initiation and established smoking at least half a year shorter for females exposed in utero compared with unexposed females.”

**Nicotine slows smoke’s effect on platelets**

Smoking is a primary risk factor for cardiovascular disease because it causes high activation of platelets; the consequent clotting obstructs blood vessels. Secondhand smoke does the same, but in neither case does it appear that nicotine is the culprit, because nicotine replacement products don’t have the same effect on platelet activation. To examine nicotine’s role, Ramachandran and colleagues (p. 835) exposed platelets to both mainstream and secondhand smoke extracts from high-, low- and zero-nicotine cigarettes under conditions that mimicked normal vascular blood flow.

Their results clearly demonstrated that platelet activation is inversely related to nicotine content: Nicotine-free smoke made the platelets more susceptible to increased activation than either the high- or low-nicotine brands. Also, the highly potent nature of the zero-nicotine extract was essentially the same for both mainstream and secondhand smoke extracts. To confirm that nicotine actually inhibits platelet activation, they then added nicotine to the nicotine-free smoke in a concentration equivalent to what smokers get from one “light” cigarette; platelet activation dropped 75%.

The experiments do not constitute definite proof, the authors acknowledge, because other components in the nicotine-free cigarettes may account for the accelerated platelet activity. They conclude, however, that “even though low- and zero-nicotine cigarettes may be useful in weaning smokers from cigarettes, they might also cause a significantly increased risk of thrombotic disease.”

**Mapping kids’ ascent toward being ‘hooked’**

Few studies have charted the important trajectories of how and at what rate adolescents go from early experimenting to heavy smoking, or to explore the predictors of which ones will follow that path. Stanton et al. (p. 839) did both by analyzing data on 306 New Zealand youths who smoked. Data were collected at ages 9, 11, 13, 15 and 18 years. They identified six classes of smokers:

- **Late rapid escalators**, the largest group, increased smoking somewhat after age 13, then accelerated after age 15 to more than 335 cigarettes a month by age 18;
- **Early rapid escalators** escalated smoking after age 11, accelerated after age 13 and again after age 15, also to more than 335 cigarettes a month;
- **Late moderate escalators** took only a couple of puffs a month early on, and escalated after age 15 to about 73 cigarettes a month;
- **Late slow escalators** took only a couple of puffs a month until age 15, then increased to an average of 7.74 cigarettes a month by age 18;
- **Late slow escalating puffers** did not increase smoking beyond .55 cigarettes a month;
- **Stable puffers** took only a few puffs occasionally throughout the study period.

Different predictors kicked in at different stages. By age 13, having friends who smoked predicted who would be early rapid escalators. Later, marijuana use and conforming to parental smoking predicted both early and late rapid escalators. Among mental health and sociodemographic factors, as early as age 9, maternal psychological symptoms predicted early rapid escalation; at ages 11–13, high Attention Deficit Disorder scores also predicted rapid escalation; at 15, behavior problems, depression scores, and frequent changes of address became important predictors; and at 18, poor school performance, not belonging to a club, and not having close friends were most predictive.

As the authors point out, the predictors combine push and pull mechanisms: “Early predictors can be seen to drive or determine the trajectory, which in turn leads to a drift toward other characteristics or outcomes identified as late predictors.” Two surprise findings: Alcohol use did not predict smoking trajectories, and intention to smoke at age 9 predicted “puffing,” not rapid escalation.

**Why kids smoke and get ‘hooked’**

Compared with what is known about adult smokers, little is known about the biological and behavioral reasons adolescents smoke. To address that knowledge gap, Wood and colleagues (p. 853) tested 50 Ohio smokers aged 13–18 years. In addition to taking a battery of other tests, the teenagers smoked a single cigarette of their usual brand through a device to measure puff frequency and volume. Testing indicated that, on average, the teenagers were moderately nicotine dependent, with few differences between young men and young women. Among the research team’s other findings:

- “[E]ven at a relatively young age, a relationship between length of smoking and strength of dependence was identified.”
- Exhaled carbon monoxide levels after smoking proved a significant predictor of dependence.
- Males puffed more often and took larger and longer puffs than females, producing higher exhaled carbon monoxide levels, but the two sexes “had similar smoke constituent exposure” based on their nicotine and cotinine levels, possibly related to differences in nicotine metabolism.
The most important motives for smoking were pleasure and relaxation and to reduce tension and craving. The same was true for both males and females.

Those who puffed more often on their cigarette had tried to quit less often.

The motivating factors—pleasure and relaxation, and reducing tension and craving—the authors suggest, “can be emphasized in developing smoking cessation interventions for youth with appropriate stress reduction and problem-solving techniques, as well as pharmacotherapy such as nicotine replacement and bupropion.”