

# What's new in *Nicotine & Tobacco Research*?

**Edited by Richard Hébert**

## Commentary

### *Reflections on Five Decades of Research*

An *SRNT Newsletter* writer once called him a 'lone ranger,' but Edward Lichtenstein of Oregon Research Institute (p. 139) says he always considered himself 'a good collaborator.' His reflections on his five decades of research trace the advance of that research from the first Surgeon General's report on smoking in 1964, the year Lichtenstein conducted his own first cessation study – a physician advice intervention, in which he found that a physician's smoking during the intervention had no effect on the outcome. 'I quickly abandoned this line of work for over 20 years,' he says, but 'what goes around comes around, and healthcare setting interventions are now my primary focus.'

During those 20 years he researched rapid smoking, then abandoned that for trials of small group interventions, then added training spouses and partners as facilitators. When one effort appeared to 'reach its limits,' he moved to the next. Today, meta-analyses show rapid smoking can be effective, and social support is now known to help tobacco users quit.

A year at the National Cancer Institute shifted his focus to population-based research, an NCI funding priority, and over time the population that drew his attention was that of smokers in healthcare settings – 'at the intersection of the clinical and public health approaches' – because 'most smokers will pass through a healthcare setting at least yearly,' offering a window of opportunity (see also Smith, p. 213). A major research challenge now, he states, is to develop and evaluate ways of disseminating such interventions to the larger population. Whatever the focus, he writes, 'our ultimate endpoints are reductions in morbidity and mortality. Tobacco use becomes an endpoint because of its documented association with morbidity and mortality. Now that we have validated interventions for tobacco cessation, implementation of these interventions becomes a legitimate endpoint.'

## Review Article

### *Biomarkers: When to Verify Abstinence?*

Should studies independently verify, through biochemical testing, self-reports by smokers that they have quit? A Society for Research on Nicotine and Tobacco subcommittee, chaired by Neal L. Benowitz of the University of California, San Francisco, has reviewed the scientific literature to determine the need for and relative merits of testing for biological markers to verify abstinence from smoking. The 'most striking finding,' the panel reports (p. 149), is that only 18% of the studies it identified included both self-report and biochemical data sufficient to allow comparisons. 'Reporting of both outcomes (in future studies) . . . would contribute to our understanding of when biochemical verification is useful,' they write. The panel also concludes, among other things:

1. Because of nicotine's short half-life and the technical difficulty and expense of collecting and measuring it, it is not recommended for general use as a biomarker.
2. Expired carbon monoxide is the least expensive (once the instrument to measure it has been bought) and the easiest to measure, providing feedback within seconds, but its half-life is brief.
3. Measuring cotinine, nicotine's major metabolite, in plasma, urine or saliva appears best. Cotinine is highly specific and sensitive for tobacco use (except for those on nicotine replacement therapy), it has a fairly long half-life, and it involves only moderate cost.
4. In field studies where baseline data are not readily available to estimate when non-smoker levels of cotinine would be reached, a 7-day window of self-reported abstinence probably will accurately capture almost all non-smokers.
5. Some (but not all) relevant studies show that cotinine can also predict treatment outcomes: smokers with

higher levels of cotinine have poorer results from nicotine dependence treatments.

6. In large population, low-intensity intervention trials, biochemical verification is neither feasible nor necessary, but in small population clinical trials of new interventions, where accurate estimates of quit rates are needed, it is 'feasible and strongly encouraged.'
7. Testing is also urged for special populations that have an incentive to deceive, such as adolescents, pregnant women, and patients with smoking-related diseases.
8. Biochemical information is 'mandatory' to evaluate novel nicotine delivery products, such as devices now being test-marketed that heat rather than burn tobacco, or for harm reduction studies in which the level of exposure to nicotine and other toxins is an essential endpoint.

## Original Articles

### *Nursing Homes: Smoking's Special Risks*

Most healthcare facilities are smoke-free in recognition of the need to encourage good health behaviors, but there's one glaring exception: nursing homes. This, despite copious evidence that smoking presents special health, treatment and safety concerns for the elderly – as a risk factor for seven of the 14 major causes of chronic disease and death among them, as one of the most universally recognized barriers to health maintenance, affecting the metabolism of many medications used to treat seniors' conditions, and because it more than doubles the risk of severe burns resulting from many nursing home residents' falls and other accidents caused by physical and cognitive difficulties. Further, contrary to the common belief that quitting offers the elderly little benefit, evidence indicates that benefits may accrue even *more* rapidly for them.

Carosella *et al.* (p. 161) report on the first assessment of smoking attitudes and knowledge, readiness to change, and interventions in a nursing home population. They interviewed 25 smokers and 70 non-smokers aged 51–97 living in nursing home units. The smokers were less likely to agree that smoking is harmful to health or that quitting would benefit them, and only slightly more than half of both smokers *and* non-smokers knew about the dangers of passive smoke – significantly fewer than in the general population. Most smokers said they had no interest in quitting within the next 6 months, no in-house cessation programs were available, and fewer than half of the smokers said they had ever been advised to quit by either a physician or nurse. 'Recent encouraging findings suggest this may be changing,' the authors write. They also caution that 'it is not possible to make broad generalizations from the reported results . . . (but) the findings may serve as a springboard for research at other sites, and the beginning of the development of an evidence base from the perspective of the resident that may be useful in guiding decision-making regarding smoking intervention and policy in long-term care.'

### **Bangladeshi Women and Chewing Tobacco**

About half the men – but only about 4% of the women – are smokers among the Bangladeshi of London, UK. Instead, the women are much more likely to chew tobacco, mixing it with the traditional South Asian paan quid, made of betel leaf, lime and areca nut. Croucher *et al.* (p. 171) interviewed and took saliva and expired carbon monoxide samples from 229 Bangladeshi women in one London housing community where about a fourth of the city's Bangladeshis live. The community is characterized by strong family structures, low socioeconomic status, dependence on public housing, high unemployment, and little formal employment among women. The researchers calculated that almost half – 48.5% – of the women chew tobacco-laced paan. Those with above average cotinine concentrations in their saliva were four times more likely to have their first paan quid with tobacco within an hour of waking and just under four times more likely to use leaf tobacco in their quid instead of processed tobacco. As the investigators note, the 'validated estimate of the prevalence of chewing tobacco use and the levels of dependence this creates in Bangladeshi women can inform appropriate policy and program development, both nationally and locally.'

### *Kids' Beliefs: Shifting with Age*

Preadolescent and younger children hold quite negative attitudes about smoking and smokers, yet many begin smoking themselves in adolescence. To track how the attitude shift occurs, Gillmore *et al.* (p. 177) questioned 1161 children in grades 4–7 about how good or bad they thought smoking was, whether others approved of it or not, and whose norms they would be most influenced by.

Not surprisingly, the older children's attitudes about the benefits and long-term consequences of smoking were more favorable than those of their younger counterparts, but beliefs about the immediate negative effects of smoking (yellow teeth, bad breath, etc.) were not significantly different. Boys were more favorable toward smoking's likely positive outcomes than girls, and Caucasians were less worried about immediate negative consequences than African Americans, but no other significant gender or racial differences were found. Also, compared to the younger children, the older ones considered their friends as less disapproving of smoking and were significantly more motivated to comply with friends than with their own parents.

Why do the older children view smoking more favorably? The authors speculate that it may be because, as they age, they tend to stop thinking in 'all or nothing' terms they did when younger and may come to believe smoking can be both dangerous *and* desirable. Moreover, as they become older they are exposed to more cigarette advertising and more smokers, including among peers, and may notice that many seem to get pleasure from

smoking and show no evidence of harmful consequences. The investigators note that their research does not reveal whether the beliefs precede smoking or not, but ‘whether a cause or consequence of smoking . . . (the beliefs) suggest one avenue of intervention – changing beliefs that foster smoking. The beliefs most strongly related to smoking (that it hurts others, tastes good, makes you feel relaxed, and may cause a serious illness) are prime candidates for intervention.’

#### *Attention and Alertness: Nicotine’s Mixed Bag*

Nicotinic receptors are found in parts of the brain believed to carry out cognitive functions, such as attentional orienting, and on projections from brainstem nuclei considered critical for alertness. But does nicotine really improve both spatial attention and alertness? Several studies have suggested as much, but many were flawed: they studied smokers who had abstained, so the effects could easily have been caused by the relief of nicotine-withdrawal symptoms, and few of the studies examined blood plasma to determine whether subjects were receiving consistent levels of nicotine. Griesar *et al.* (p. 187) corrected for both flaws when they tested 12 non-smokers, comparing their spatial attention and alertness levels under each of three conditions: wearing two nicotine patches, wearing one plus a placebo patch, and wearing two placebo patches. The subjects were instructed to watch the center of a monitor and respond as rapidly and accurately as possible to a left- or right-pointing arrow or neutral crosshairs indicating – sometimes incorrectly – where a circle or square would next appear. The subjects were to press a button whenever a circle appeared, but not a square, thus requiring them to pre-emptively shift their spatial attention away from center-screen in order to discriminate the target. Nicotine did not improve their accuracy, the investigators report. Nicotine did, however, improve reaction times, although that increase was not dose-dependent. Rather, it was about the same whether the subjects wore one nicotine patch or two. To measure alertness, the investigators used both EEG recordings and self-reports on questionnaires; both showed that nicotine did indeed increase alertness.

#### *Non-Nicotine ‘Chew’ Can Ease Withdrawal*

During the past 30 years, smoking has declined but the use of smokeless tobacco, particularly ‘chew,’ has risen sharply, most dramatically among white males 18–35 years old. Still more alarming evidence suggests that more and more adolescents and children, even many boys under 12 years old, are experimenting with it and progressing toward regular use, adding to the urgency that effective ways be found to mitigate withdrawal symptoms and, hopefully, help them quit early. Research results on the use of non-nicotine substitutes to help users quit have been inconsistent, however. McChargue *et al.* (p. 197) have now tested two trademarked non-

nicotine substitutes against placebos on 19 users of chewing tobacco instructed to use the substitutes while abstaining for 48 h. BACCOFF, a non-nicotine chew, is composed of tea leaves, USP glycerine, sugar, salt, natural and artificial flavors and sodium benzoate, and DIPSTOP is a liquid containing the alkaloid, lobeline, which partly mimics peripheral nicotinic effects. The tests showed that, compared to DIPSTOP and the placebos, BACCOFF significantly reduced withdrawal symptoms, but not craving.

Of special significance was that users said BACCOFF most closely approximated their own preferred brand of chewing tobacco, suggesting that the product’s influence on withdrawal may result from its ability to imitate the preferred brand. Historically, researchers have postulated that withdrawal symptoms were primarily triggered by the physiological removal of nicotine from the body. ‘Our data, however,’ write McChargue *et al.*, ‘demonstrate that approximating similar sensory features of smokeless tobacco behavior substantially buffers certain aversive effects believed to derive from nicotine’s removal.’

#### *Kids Speak Out: Focusing on Addiction*

Scientists can measure nicotine dependence in adults, but they have no accepted, sound tools for doing so with adolescent smokers. Developing effective cessation programs for kids requires a much better understanding of how they become addicted and how they experience that dependence. O’Loughlin *et al.* (p. 203) asked teenagers themselves for input in six focus groups with students at three high schools, exploring their experience of nicotine addiction and, more specifically, assessing the 10-item Hooked on Nicotine Checklist (HONC), which measures the loss of autonomy over nicotine as manifested by loss of control, feelings of addiction, and withdrawal symptoms. The researchers validated all HONC items except the withdrawal symptom of feeling sad or depressed. Also, the teens considered smoking an appetite similar to eating, and said they felt an urge to smoke when they were angry or stressed, usually about interpersonal issues – items not on the HONC list.

The researchers also found other important differences between teen and adult smokers. For example, the notion of a ‘pack a day’ habit was not relevant for the young, who typically share a pack among themselves, a communal approach consistent with their peer-driven social orientation. And, ‘situational’ smoking is more pronounced among the young, who often are where they are not allowed to smoke and so are cued to smoke when and where it’s allowed.

‘Cigarettes can serve both as personal and social supports,’ the authors write, ‘and thus can acquire newly positive meaning for adolescents,’ who say they find many aspects of smoking pleasurable: it increases complicity and solidarity with friends and relieves boredom, stress and social tension. ‘Stopping smoking,’ they write, ‘will leave a gaping hole in their lives, which

cessation programs must be able to redress.' In fact, they warn, 'failed quit attempts already characterize many of these young smokers' experience with smoking, and for some bring the first sinking realizations that they have become seriously addicted. Our observations suggest that unsuccessful quit attempts in this age group may have particularly devastating psychological consequences.'

#### *Success Story: Hospital Nurse-based Initiative*

Hospitalization offers an excellent window of opportunity for smoking-cessation efforts. Smokers are more likely to be hospitalized than non-smokers, and they are likely to be particularly receptive to quitting when they feel vulnerable to illness. Also, many hospital patients are too ill to smoke, they are removed from their daily cues to smoke, and smoking bans force them to quit at least temporarily. Randomized trials have demonstrated that intensive inpatient smoking-cessation programs have proven cost-effective for heart disease risk management, yet few such programs are ever introduced into standard practice, so it is unclear whether trial results generalize to standard practice once tight study controls are lifted. Smith *et al.* (p. 213) have now demonstrated that trial results can be generalized.

All smokers admitted to Stanford University Hospital between September 1993 and June 1996 were offered a free smoking-cessation program that included 45–60 min of in-hospital bedside counseling by a trained nurse; physician advice; a take-home workbook, 17-min video, and 18-min relaxation audio-tape; the offer of nicotine replacement therapy to counter severe withdrawal symptoms; and follow-up counseling calls 2, 7, 21, and 90 days after leaving the hospital. Almost half (49%) of the 509 contacted patients who had been enrolled at least a year said they had been smoke-free the previous 7 days, compared to 39% in an earlier randomized trial. Patients hospitalized for smoking-related illnesses (cancer, cardiovascular, or pulmonary diseases) reported the highest quit rates – 63, 57, and 46% respectively. As the researchers conclude, 'The program, relatively inexpensive to deliver, appears to be acceptable to the majority of smokers who are hospitalized, resulted in

high 1-year cessation rates, and can be extended to hospital employees and their families, work-sites, and communities on a cost-recovery basis.'

#### **Brief Report**

##### *Addiction-fighting Drug Could Raise Smoking*

Alcohol, stimulants and opioids are all linked to increased cigarette smoking. Buprenorphine, currently under Food and Drug Administration review for use in treating opioid addiction, similarly increased cigarette smoking among heroine addicts when administered subcutaneously, but sublingual buprenorphine has never before been studied. Mutschler *et al.* (p. 225) have now tested the drug sublingually on 23 male smokers with a history of both cocaine and opioid abuse. After detoxification using methadone, the men were kept drug-free for 6 days, then given gradually increasing daily sublingual doses of buprenorphine, peaking after 5 days at either 4 or 8 mg per day, randomly assigned, then maintained at that level for 12 days. They were allowed to smoke freely their favored brand, issued by an automatic dispenser that recorded the time and number of cigarettes each smoker acquired.

As expected, they smoked less – 18.5 cigarettes a day on average – during the drug-free phase than they said they'd smoked before. No significant differences were noted in smoking frequency between the two peak levels of buprenorphine dosage, but the number of cigarettes acquired did increase once drug dosages began, and increased daily thereafter to a peak. Cigarette acquisition levels then remained much the same throughout peak buprenorphine maintenance – at about 25.5 cigarettes a day, on average. This was the first such study to test the smoking effects of sublingual administration of the drug, to test those effects on abusers of both opioids and cocaine, and to automate the dispensing of cigarettes to remove any possible bias caused by staff distribution. As the authors note, 'The significant relationship between increases in buprenorphine doses and cigarette acquisition during the induction phase is consistent with the interpretation that buprenorphine, and not other variables, was the primary determinant of the changes in smoking behavior observed.'