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Chapter 15

PUBLIC HEALTH AND LEVELS OF NICOTINE: SHOULD NICOTINE LEVELS IN CIGARETTES BE MINIMIZED OR MAXIMIZED?

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Smoking prevalence continues its decline in those developed countries that have longstanding and increasingly vigorous smoking control programs, but there are still many smokers who fail to stop before it is too late. For these smokers, it is important that the risks are minimized by the development of safer cigarettes.

In the early 1970s, it was already evident that nicotine dependence was the major factor underlying the maintenance of smoking (1); it was also clear that smokers unconsciously regulate their nicotine intake by reducing puff rate when smoking a high-nicotine cigarette and by increasing it to compensate for the drop in yield when smoking a low-nicotine cigarette (2-5). Confirmation of this self-regulation of nicotine intake, using carboxyhemoglobin (COHb) as a marker of inhalation, exposed the limitations of low-tar, low-nicotine cigarettes, as recommended in official national policies, and led us to suggest that the least harmful cigarettes for heavy smokers might be those with low tar and CO yields but a high, rather than low, nicotine yield (6,7). But, since it is also desirable to keep nicotine intake as low as possible, this was later modified to a "low-tar medium-nicotine" (LTMN) approach to safer smoking (8,9).

Every reader will be aware of the highly informed and well-argued strategy for reducing nicotine content of cigarettes to a subaddictive threshold, which Benowitz and Henningfield outlined with great clarity in the *New England Journal of Medicine* in 1994 (10). It is certainly an unambiguous proposal that nicotine levels in cigarettes be minimized. Its scope is also wider than that of the LTMN approach. It is designed to prevent the development of dependent smoking, especially in teenagers, and gradually to reduce levels of dependence in smokers to facilitate cessation. The LTMN approach is limited to reducing the health risks of smoking. Benowitz and Henningfield regard the two approaches as diametrically opposed. However, there may be some scope for overlap in the early stages of implementation. The crucial question is, which is more feasible, the LTMN or the "Benningfield" approach?

The Low-Tar, Medium-Nicotine Approach

The LTMN approach is based on a "nicotine regulation" model of smoking behavior (ie, that smokers alter their pattern of puffing and inhalation and thereby regulate their nicotine intake to maintain their individually preferred levels, which are kept fairly constant from one day to the next). The rationale for LTMN cigarettes is that it is unrealistic to expect addicted smokers, who cannot stop, to smoke cigarettes that deliver too little nicotine to provide reasonable satisfaction or relief of withdrawal, or, if they do smoke them, to expect that they will do so without compensatory increases in inhalation. It is, therefore, more logical to lower tar yields as much as possible, while maintaining nicotine yields at levels that are both acceptable to smokers and sufficient to prevent excessive compensation.

In essence, this approach is concerned with reducing the ratio of tar yield to nicotine yield to enable the selection of brands that deliver the lowest amount of tar per unit of nicotine, across a range of nicotine levels to suit the needs of individual smokers. In other words, the purpose of this approach is not so much to maximize nicotine deliveries, but rather to minimize intake of tar and harmful gases. A table was proposed of brands ranked by standard machine-smoked nicotine yields and tar/nicotine yield ratios (8). Such a table could be used by smokers to select as low a nicotine yield as possible (for this too is desirable) and then choose the least harmful cigarette at that level in terms of the tar/nicotine yield ratio.

In this post-Kessler era, it will be readily recognized that the LTMN approach is a crude beginning of what is essentially a "cleaning strategy" for the modern cigarette as a nicotine delivery system. Since people smoke for nicotine, but die mainly from the tar and harmful gases, the obvious strategy is to identify those constituents of the smoke that are harmful, and then to eliminate them as far as possible without seriously impairing acceptability or causing appreciable compensatory self-regulation. Nitrogen oxides, which damage the lungs and contribute to emphysema, are one example of a gas-phase component, present in concentrations that vary widely between brands, that could be eliminated with little effect on acceptability (11).

Measurement of yields of some of the more important components relevant to health hazards of smoking show significant variation between brands (12). These included measures of benzo[a]pyrene and other polyaromatic hydrocarbons, tobacco-specific nitrosamines, acrolein, formaldehyde, acetaldehyde, nitrogen oxides, and hydrogen cyanide. They could be reduced by setting limits for all brands similar to those of the brands with the lowest levels. Many of these components are present in the tar, indicating the potential scope for beneficial qualitative changes in the future. This paper, however, is focused primarily on the quantitative reduction of tar intake. The ultimate potential of this strategy depends very much on the relative safety or harmfulness of nicotine, which is discussed elsewhere (Benowitz, this volume). Overall, a cigarette that burns tobacco is such a "dirty" delivery system that it seems more realistic to hope that cigarettes will one day be replaced by pure nicotine products (13, 14), with the Eclipse tobacco heating cigarette (15, 16) or a similar device as a possible intermediary (Rickert, Slade, this volume). All this is a logical extension of the LTMN approach and its rationale.

The U.K. Independent Scientific Committee on Smoking and Health cautiously supported the LTMN approach. It recommended in its Third Report (17), that "there should be available to the public some brands with tar yields below those of the principal low tar brands (ie, below about 8 mg/cigarette), but with proportionately higher nicotine yields (up to about 1 mg)." In the U.K., since 1976, tar/nicotine yield ratios of low-tar brands have been consistently lower than those of other brands, with official approval. This contrasts with the situation in the United States, where the efforts of the tobacco industry to make low tar cigarettes less harmful and more acceptable have been criticized.

Acceptability and Intake Regulation

Self-regulation of nicotine intake, or nicotine titration as it is sometimes called, is the model on which the LTMN strategy for reducing tar intake is based. Its success, however, would also depend on other factors. Taste, aroma, sensory impact, ease of puffing, and other characteristics subject to conditioning and habituation are important determinants of acceptability and satisfaction. An important question to consider is when and whether intake regulation is driven by the need for minimal nicotine levels to relieve or avoid withdrawal as opposed to the need for sharp peaks and boli for full satisfaction, and how precise the regulation has to be. Another crucial issue is how much and in which direction the nominal tar/nicotine yield ratio is affected by how the cigarette is smoked.

Various studies involving brand switching or comparisons within samples smoking their own brands, using measures of puffing patterns or biochemical measures of smoke intake, were a major interest throughout the 1970s and 1980s. Relatively few were directed specifically at the role of nicotine, as is evidenced in several reviews (18-22). Several studies of fairly large samples of 200-800 smokers, smoking their usual brands in their usual way, all show a strikingly wide range in the blood nicotine and/or cotinine levels of individual smokers (eg, from less than 10 ng/ml to more than 80 ng/ml, around a mean of about 35 ng/ml for peak nicotine levels just after smoking a cigarette), but an equally strikingly low correlation between the blood levels in the smokers and the nicotine yields of their cigarettes (23-27). Correlations with FTC nicotine yield among the different studies ranged from 0.15 with blood cotinine (25) to 0.37 with blood nicotine (27). Studies of this kind clearly show that smokers can easily and comfortably obtain two or three times more nicotine from their cigarettes than the standard machine-smoked ratings shown on their cigarette packs. The same is so for carbon monoxide and, no doubt, for tar. It is also evident that high-yield brands are often "under-smoked."

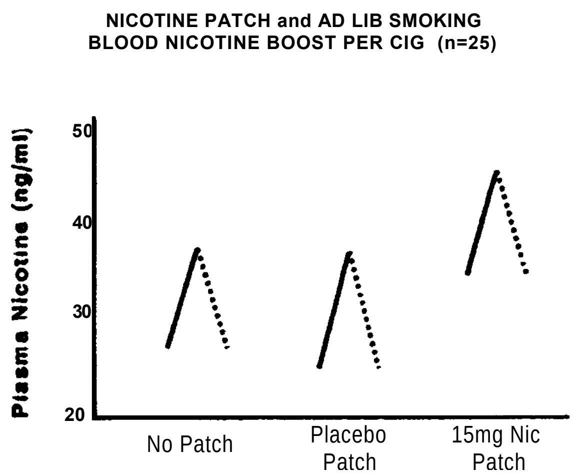
Brand-switching studies (see reviews cited above) were the first to show that on switching to higher or lower yield brands, smokers altered their pattern of smoking to maintain a constant intake. Similarly, it has been shown that if smokers cut down to smoking fewer cigarettes, they compensate by increasing their intake per cigarette (28, 29). Overall, these studies show that down-regulation to avoid excessive intake is fairly precise, whereas up-regulation to maintain former intake is only partial. Smokers appear to be able to tolerate a drop in peak blood nicotine to about two-thirds of their former level with only transient loss of satisfaction, no worse than switching to an unfamiliar brand with similar tar and nicotine yields (30). Most switching studies have been short-term. Two long-term studies showed that the drop in intake occurs immediately and persists over time for 10 weeks or more, without tendency to revert to preswitch levels (30,31).

Of the numerous studies of smoke intake regulation, very few have examined the effect on smoking of manipulating nicotine independently of other smoke components. Various approaches have been used to show that puffing patterns and inhalation are changed to regulate nicotine. These include down-regulation of intake from smoking when nicotine is administered from another source (32-34), its up-regulation by more intensive puffing (35) and inhalation to give higher CO and blood nicotine levels when the effects are blocked by mecamylamine (36, 37), and its regulation either way to correct for alterations in urinary excretion induced by manipulation of urinary pH (38). These more direct studies were also consistent with the view that down-regulation to avoid exceeding usual peak blood nicotine levels was fairly precise, whereas up-regulation to maintain peak blood levels was usually only partial (22), or such was the position until 1990.

This position appeared to be challenged by the findings of two more recent studies. The first, by Benowitz and Jacob, showed that although prolonged intravenous nicotine infusion suppressed nicotine intake from smoking, down regulation was imprecise (39). The other, by Foulds et al. using a nicotine patch during *ad libitum* smoking, reached the same conclusions (40). However, if the Foulds et al. data are reexamined, it is evident that, although the peak level following a cigarette and the trough level preceding it are substantially higher when wearing a nicotine patch, the blood nicotine boost per cigarette is kept constant and does not differ between the normal smoking, placebo patch, and active patch conditions (Figure 1). It is evident that the subjects tolerated substantially higher trough and peak nicotine levels and some loss of satisfaction to maintain a constant boost per cigarette (41).

It is not surprising that smokers adjust their smoking patterns to maintain their nicotine boosts.

Figure 1. Blood nicotine boost per cigarette (means in 25 subjects) during *ad libitum* smoking with and without a nicotine skin patch. The peaks as shown are mainly schematic. The only components based on real data are the vertical dimensions of the solid lines.



Source: Reprinted with permission from Russell et al. (41)

The typical venous blood nicotine profile of smokers who inhale is characterized by a series of sharp peaks coinciding with each cigarette. The boost per cigarette, during steady-state, averages about 10-12 ng/ml and reflects the average "smoking dose" of 1.0 mg/cigarette of systemically available nicotine (42, 43). This 1.0 mg dose is taken typically as about ten 0.1 mg puff-by-puff doses absorbed sufficiently rapidly through the lungs to deliver transient high nicotine boli in arterial blood within 10 seconds of each inhaled puff (44). Postpuff arterial blood nicotine concentrations average 100-150 ng/ml (45-48), but are difficult to catch at their peak and may be much higher. Peak levels in venous blood average about 30-40 ng/ml, but it is the size of the boost per cigarette, rather than peak level just after the cigarette, that would correlate best with the concentration in arterial boli. A very small venous blood boost would indicate insignificant arterial blood boli.

Since some 50% of smokers smoke at least once every hour and start within 30 minutes of waking, most of their nicotinic receptors may be desensitized to agonist effects at venous blood trough levels. It is possible that, in those with prominent boosts and sharp peaks after each cigarette, the boli may activate some nondesensitized receptors and obtain positive effects, whereas those with less prominent peaks and boli may be motivated more by a need for chronic desensitization to which they have become accustomed throughout the day and most of the night. It is noteworthy that nicotine gum and patches provide significant relief of withdrawal at steady-state levels around 10-15 ng/ml. Absorption from the patch is so slow that a significant agonist effect is unlikely. This suggests that its clinical efficacy must lie in maintaining nicotinic receptor desensitization—a likely mechanism underlying relief of withdrawal. Lack of space and limited relevance to the case for or against the LTMN approach preclude discussion of the pharmacokinetic-pharmacodynamic interactions involved in dose-response effects of nicotine that have been described elsewhere (22, 49).

It has been mentioned that smokers compensate only partially on switching to lower-yield brands and adjust with little difficulty to a drop in peak blood nicotine levels to about two-thirds of their usual levels. Despite the lower peak levels it is likely that they preserve an adequate blood nicotine boost, from trough levels at or just over a 10-15 ng/ml withdrawal threshold. However, on switching to ultralow-yield cigarettes (tar 1.0 mg, nicotine 0.1 mg), adequate compensation becomes impossible (without covering vent holes or removing the filter). Blood nicotine levels drop 50-60% to levels around 10 ng/ml, with subjects suffering partial withdrawal (50). Other studies find that smokers compensate completely on switching to low-yield cigarettes (tar 5 mg, nicotine 0.4 mg/cig) (51,52), but agree that compensation is only partial on the ultralow cigarettes (tar 0.8 mg, nicotine 0.1 mg), tar and nicotine intake being reduced by 50% and 56%, respectively, compared with the high- and low-yield test cigarettes. The ultralow brand was also rated poorly and devoid of satisfaction (52).

These findings are consistent with the theoretical hyperbolic relationship between the volume of diluted, less strong smoke it is necessary to inhale to compensate for a given degree of smoke dilution (53). To illustrate the problem, consider the case of a smoker who takes in 1 mg of nicotine from a cigarette that delivers this in 400 ml of smoke inhaled from ten 40-ml puffs. On switching to brands measured with the same machine setting to give the following yields: 0.8, 0.6, 0.5, 0.4, 0.2 mg, to obtain 1 mg of nicotine, the smoker would have to inhale 500, 668, 800, 1000, 2000 ml, respectively, of smoke per cigarette. Puff volumes of 70 ml or more are difficult to take. The kind of intake many smokers obtain, even from cigarettes with only moderately low nominal yields of 0.5 or 0.4 mg, seems rather more than compensatory increases in intensity of smoking might explain (eg, shorter butts and reduced filter efficiency). Ultralows would be totally unacceptable, as they for many years in the U.K., without a major defeat of the design, such as hole-blocking, which Kozlowski et al. identified and have emphasized and demonstrated over many years (54,55).

A somewhat surprising finding of the two brand-switching studies discussed above was that tar, nicotine, and CO intake were substantially higher from the usual brand than from the high-tar test cigarette, although the yields were similar (51,52). This is clearly not attributable to nicotine but is likely to be due to habituation and conditioning to the flavor, draw, and other sensory characteristics, mainly in the tar. In a study of the relationship between cigarette yields and blood nicotine levels of smokers smoking their usual brands, regression analysis found some evidence of compensation for tar. When nicotine yield was controlled for, smokers of lower tar cigarettes had higher blood nicotine levels than smokers of high-tar cigarettes (56).

Investigating the Low-Tar, Medium-Nicotine Approach

For some years, we have used a rough index of tar intake for comparative purposes. It is derived from the measured intake of a marker and the ratio of tar to marker yields of the cigarette. For example, the index of tar intake using plasma nicotine concentrations as the marker is the simple product: TI(Nic) = plasma nicotine X T/N yield ratio. As an attempt at validation, we used the nicotine/CO yield ratio to test the accuracy of COHb as a marker of nicotine intake. Predicted vs measured nicotine levels were 31.9 and 31.8 ng/ml, respectively, with 316 and 333 ng/ml for cotinine (27).

Few studies have used experimental cigarettes with low tar/nicotine ratios. Stepney studied 19 middle-tar smokers who smoked their own brands for 3 weeks (mean yields 19 mg tar, 1.55 mg nicotine, 18 mg CO) and switched to an LTMN cigarette (10 mg tar, 1.1 mg nicotine, 6 mg CO) and a control low-tar low-nicotine cigarette (11 mg tar, 0.7 mg nicotine, 13 mg CO) for 3 weeks (57). Mainly because mouth-level tar exposure was similar, the author concluded that the LTMN cigarette had no advantage over the control low-tar product. However, 24-hour urine nicotine and cotinine were measured. Using a tar intake index based on these measures and the nominal tar/nicotine ratios, one can calculate that reductions in tar intake compared with usual brand averaged 25% on the LTMN cigarette and 14% for the control LT cigarette (based on nicotine), and 21% and 4%, respectively, based on cotinine levels. Using the same indices for comparison, tar intake from the LTMN cigarette averaged 13% and 17% less than the control LT cigarette, based on the measured nicotine and cotinine levels, respectively. After subtracting the nonsmoker level of 6ppm, as recommended by Stephen et al. (58), expired-air CO on the LTMN cigarette was 51% less than on the usual brand and 23% less than the control low-tar cigarette. The LTMN cigarette was also more satisfying than the control cigarette. A tar-intake index based on nominal yields must be viewed with caution, but in this study, the tar/nicotine ratio was lowered in all three types of cigarette when the smoking machine was set on the conditions of the human smokers.

A similar study by Fagerstrom was also moderately encouraging for the LTMN approach (59). After 3 weeks of monitoring on their usual brand (mean tar 14 mg, nicotine 1.1 mg, CO 12 mg) 12 middle-tar smokers switched to an LTMN (tar 5.8 mg, nicotine 1.1 mg, CO 4.1 mg) and a conventional low-tar control cigarette (tar 4.8 mg, nicotine 0.5 mg, CO 4.0 mg) for 4 weeks in a balanced crossover design. Reductions in expired-air CO, compared with usual brand, averaged 36% on the LTMN cigarette and 31% on the control, after correcting for background nonsmoking levels by subtracting 6 ppm from the measured values. CO intake from the LTMN cigarette was only 8% less than the control. Since blood nicotine and cotinine were not measured on the usual brand, comparison of indices of tar intake is possible only between the control cigarettes. Blood nicotine levels averaging 17.4 and 16.5 ng/ml on the low-tar control and LTMN cigarettes, respectively, with respective mean cotinine levels of 270 and 319 ng/ml, were not significantly different. This indicates a substantial compensatory increase in inhalation when smoking the control cigarette. Use of the tar-intake index, based on nominal tar/nicotine yield ratios, indicates that tar intake from the LTMN cigarettes was 48% lower (using blood nicotine) and 35% lower (using blood cotinine) than when smoking the low tar control cigarette.

Another major study by Armitage et al. involved 21 middle-tar smokers, who smoked each of three experimental cigarettes for 2 weeks (60). Numerous biochemical and puffing pattern measures were made, but the overall results are difficult to assess. Test cigarettes included a middle-tar type (tar 16.9 mg, nicotine 1.7 mg, CO 15.1 mg), a low-tar type (tar 9.1 mg, nicotine 0.8 mg, CO 8.5 mg), and an LTMN cigarette (tar 11.2 mg, nicotine 1.4 mg, CO 9.9 mg). Blood nicotine data were given only as the boost from a single cigarette. Using the tar-intake index based on nominal tar/nicotine ratios, and averaging the estimates based on blood nicotine boost, blood cotinine, and saliva cotinine, tar intake from the LTMN cigarette and the conventional low-tar cigarette was reduced by 17.2% and 13.5%, respectively, compared with the middle-tar cigarette. The authors used a complex index of tar intake derived from various ratios of tar, nicotine, and CO deliveries obtained under human smoking conditions, compared with those obtained under standard smoking conditions. They estimated a 23% to 28% reduction in tar intake from the LTMN type cigarette compared with the middle-tar cigarette but, due to incomplete data, were unable to derive an estimate for the low-tar cigarette.

Urinary nicotine metabolites were used as a measure of nicotine intake in a sample of 296 smokers, who were part of a larger long-term study to assess the effect on pulmonary symptoms and functions of switching to lower yield cigarettes (61). The subjects, all male middle-tar smokers, were randomly assigned to one of three test cigarettes: a middle-tar medium nicotine (tar 13.8 mg, nicotine 1.24 mg), a low-tar low nicotine (tar 9.7 mg, nicotine 1.04 mg), or an LTMN cigarette (tar 9.5 mg, nicotine 1.16 mg) which they continued smoking for 24 weeks. No carbon monoxide measures were used, but the urinary nicotine metabolites were measured on six occasions during the study with no significant change from baseline levels for their previous usual brands throughout the study, and no significant differences between the three study groups. Applying the nominal tar/nicotine yield ratios to estimate tar intake shows no change in the middle-tar medium nicotine group, but reductions of 14% in the low tar low nicotine group and 18% in the LTMN group. This rather small difference between the two low-tar cigarettes may be attributable to the atypically high nicotine yield (1.04 mg) of the low-tar control cigarette.

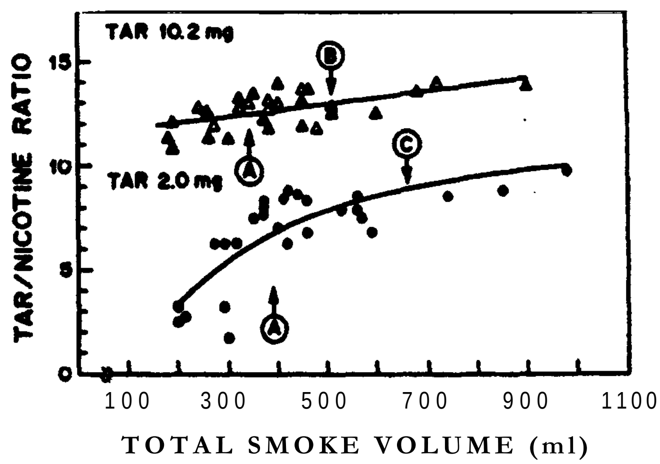
The results of these few studies are far from definitive but do provide some evidence that lowering tar/nicotine yield ratios appears to reduce compensatory smoking from low tar cigarettes, thereby reducing tar intake.

Tar to Nicotine Yield Ratios From Human Smoking

It is clear that the tar/nicotine yield ratio of a cigarette based on standard machine smoking may change under conditions of human smoking, especially with high-intensity smoking of lower yield cigarettes. Some studies have shown that more intensive smoking results in an increase in the tar/nicotine ratio (55, 62-64). This would obviously reduce or negate the potential benefits of selecting brands with low standard machine-based tar/nicotine ratios and undermine the validity of the index of tar intake derived from these ratios. However, other studies find that standard tar/nicotine yield ratios are unchanged or even slightly improved (i.e., reduced) by human smoking (57,65). It appears that this may depend in part on how the smoker compensates. For example, increasing puff rate to 30-sec intervals or puff volume to 45 or 55 ml can improve the ratio, while hole-blocking or increasing puff duration to 3 seconds can make it worse (66).

No others have investigated this issue more assiduously than Rickert et al. (67). Their work shows that a machine-smoked tar/nicotine ratio of 6.1 increases to 9.7 for the smoker of an ultralow cigarette (tar yield 2.0 mg) who is trying to compensate by smoking more intensively (Figure 2). However, despite undermining 50% of the potential benefits of the low-tar/nicotine ratio, the ultralow smoker retains an advantage over a typical middle-tar smoker (tar yield 10.2 mg).

Figure 2. Tar:nicotine ratio as a function of the total smoke volume taken for analysis. 'A' represents the volume under standard conditions, 'B' and 'C' the average total volume inhalation for a middle-tar and a low-tar cigarette, respectively.



Overall, although serious impairment (ie, increase) in the tar/nicotine yield ratio with high-intensity human smoking would reduce the potential benefits of an LTMN approach, it does not follow that the approach should be abandoned. It could be argued that this tendency should be counteracted by more strenuous application of the model by raising nicotine deliveries while continuing to reduce the levels of harmful products in the tar and among the gases. The value of tar-and harm-reduction policies for product modification in the U.K. has been encouraged by reliable evidence of declining lung cancer mortality rates in men under age 60, over and above that attributable to the decline in smoking. This trend, which started in 1965 in men, is now beginning to emerge in young women (68,69).

Conclusion

Finally, as mentioned in the introduction, there may be some scope for overlap with the Benowitz-Henningfield proposal in the early stages. Their suggestion to base nicotine yield ratings on nicotine content and maximal availability from cigarettes poses no problems for the LTMN approach. They recognize that compensatory smoking will pose a problem, necessitating some attempt to reduce deliveries of tar, CO, and other toxic components. This overlaps directly with the LTMN approach, but will in their case become increasingly difficult as nicotine reduction proceeds, probably causing increased health risks over several years. It is likely that dependent smokers would adjust to gradual reductions in nicotine over time, but unlikely that many will reduce their nicotine intake to 0.17 mg per cigarette, an amount present smokers get in one to two puffs. The expectation is that many will eventually decide to quit. Others may resort to pure nicotine products, both of which would be extremely good outcomes. Although they address the potential problem posed by smuggling, they have not considered that smokers, having adjusted to a low-nicotine dose, would be at high risk of rapid relapse to former levels of dependence after a brief binge on full-strength cigarettes obtained from a visiting friend or while away on holiday. In my view, the approach in its early stages would be as likely to increase the chances of novices getting hooked as it would be in preventing this in its later stages. Overall, it is a brilliant strategy, which would work well in rats, but, try as we may, I doubt whether the tightest of regulations could control humans in this way. My vote goes to working toward the development of better pure nicotine delivery systems and using taxation to encourage smokers to switch to them. However, scientific advances will likely provide an altogether different and completely effective solution. Indeed, during the time of writing, it seems the prospect of immunization against the pharmacologic effects of nicotine has appeared on the near horizon.

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Discussion

Nigel Gray: The idea of what constitutes a low-tar or low-nicotine cigarette has changed over time. The sales-weighted figures, and a good look at the number of brands that are on the market, show that 0.8 milligrams of nicotine by machine yield is the major part of the market in the United Kingdom, based on the 1995 figures. Now that's a very low-nicotine cigarette compared to some of the low-nicotine cigarettes that were being tested in the early 1980s. And we are now in an era when every cigarette is low tar. A high-tar cigarette according to my old-fashioned definition is between 13 milligrams and 16 milligrams, but the definitions do change over time. I no longer know what a low-tar cigarette is, given that the upper limit in Europe is now close to 12 milligrams.

Michael Russell: I take your point absolutely, which is why throughout my presentation I've shown the actual yields of all types of cigarette mentioned. In the U.K., from 1972, cigarettes were categorized as low-tar if the yield was 10 mg or less, high-tar if 29 mg or more. From 1985, below 10 mg for low-tar and 18 mg or more for high-tar. In 1992, the banding was phased out and actual yields were printed on all packets. To comply with European regulations, in 1991, the U.K. Government Laboratory changed their smoking machines and based all yields on a longer butt length. Nicotine yields in particular were switched from measuring "total nicotine alkaloids" to pure nicotine. These changes were followed by a sharp but spurious drop in sales-weighted yields of tar, nicotine, and CO; since then, all three declined more gradually to about 10.8, 0.84, and 12.3 mg for tar, nicotine, and CO, respectively, by 1994. It is inexcusable that the former methods of measurement weren't continued in parallel with the new for sufficient time to allow for more valid assessment of the changes in cigarettes consumed.

Greg Connolly: Hoffman (1) recently studied a group of smokers. Because of a switch to a higher-nicotine cigarette, there's more use of burl tobacco with higher nitrate content. There were also changes in the way that the smoking behavior occurred, which increases the burn temperature at the cone. In doing so, these changes probably knocked out benzopyrene and some of the polyhydrocarbons, but they sharply increased the levels of nitrosamines. Then, in their animal research, they could show that the nitrosamines were linked with adenocarcinomas in rats.

Michael Russell: I have limited myself to the purely quantitative aspect of tar, which is very limited. I think the real way ahead for the approach is to maintain nicotine, and then reduce the other harmful products as much as is possible without over-compromising acceptability or inducing compensation. So you could take away some harmful products that don't affect acceptability. Oxides of nitrogen is one; it can be reduced fairly easily and it doesn't touch acceptability. You might think benzopyrenes are important and want to focus on them. In fact, the English government chemist has got deliveries of some of these special noxi, and there are considerable differences between brands. Figures like those for benzopyrenes and other tobacco smoke constituents are something that should be available, not for all the public, but for people to look at on a regular basis. If one brand is able to get some toxic component down, you can set your standards and set limits with other brands, given time to do it. That needn't be expensive, because you could put the onus on the tobacco industry to measure these things accurately and supply you with the details of their brands every year. Then you occasionally do checks and, if they cheat, they have huge penalties. This would do much to "clean" cigarette smoke. What you have to keep up is the nicotine.

Warren Bickel: Dr. Benowitz, if the cigarette you proposed with the low-nicotine content is used, will it be sufficient to maintain self-administration? Because if it does not, then you're proposing a cigarette for which there will be no market.

Neal Benowitz: Well, tobacco companies say people smoke cigarettes because they like to smoke. They like the taste. They like the smell. People can be free to smoke those cigarette for those reasons.

John Hughes: It seems to me that there are already some indirect tests of your proposal, Neal. For example, the proposal assumes that adolescents who start on lower-nicotine cigarettes would be less likely to progress to addiction than those who start on higher-nicotine cigarettes. We have several data sets of prevention studies in which we know the nicotine yields at point A and we know how the people turned out—whether they became regular smokers or not at point B. It seems that would be an indirect test of an assumption in your plan.

Neal Benowitz: That's not really what I would expect to happen. I don't think a nicotine-reduction strategy would work until you get down to very low nicotine-content levels. The only reason for the tapering is for the sake of existing addicted smokers. But until you get to the point where the nicotine delivery is not going to maintain addiction, the strategy is not going to work. If you compare current low-yield cigarettes, no matter what youth start at, it's not relevant.

John Hughes: But I thought a nicotine content of 0.4 and 0.5 was what you're recommending. Are there no cigarettes like that—Carlton, for example?

Neal Benowitz: No, they contain 9 to 10 milligrams nicotine. There's nothing like a low-nicotine content cigarette on the market at all.

John Hughes: So you're saying that, above that threshold, the dose of nicotine means nothing? So we have a relationship that jumps up and then there's a flat dose-response relationship after that?

Neal Benowitz: Right. Where that jump is, if it's 0.5 milligrams or 1 milligram, we don't know.

John Hughes: Just to be the devil's advocate: I don't know many physiological functions in which there is no dose-response relationship—where there's a set-point until which the phenomenon doesn't occur, and then when you get to that point, it occurs across a range of doses. That would be unusual.

Neal Benowitz: That may be true, but if we reduce nicotine content of cigarettes gradually over 15 years, it's going to take at least 10 years of those 15 before you get down to the point where those levels have been reached. As long as there is plenty of nicotine in the cigarette to get, people will get it.

Michael Russell: I think Neal's basis of estimating the available nicotine from the cigarette is very sound. People won't be able to compensate beyond a certain point. I showed you that increasing dilution curve, which is meaningless now because people can just cover the holes and defeat it very easily. But the strategy will really start to bite with cigarettes of the type that Neal is advocating. So they will find it very hard to smoke and get full satisfaction from a cigarette with a nicotine yield of say 0.4 milligram. They will have to learn to do with less nicotine, because they won't be able to compensate.

Ken Perkins: It stands to reason that the threshold per cigarette is probably not below the threshold for discrimination. We have some unpublished research on nicotine discrimination in nonsmokers, and that threshold tends to be about 0.14 milligrams. We correct for body weight; it works out to be about 2 micrograms per kilogram, which in a 70 kg person is 0.14 milligrams. If I understand your proposal, Neal, you're suggesting a maximum extraction of about 0.17 milligrams. That's right in the same ballpark that we're finding the threshold for discrimination of nicotine in nonsmokers. That's by nasal spray, so of course the comparisons are not going to be that direct, but at least it's in the same ballpark.

Neal Benowitz: That really is an area in which research could be done, to find out the threshold of discrimination for reinforcement from individual cigarettes.

John Hughes: Has anyone tried this with alcohol? In experience with alcohol, is there any analogy to Dr. Benowitz's proposal?

Robin Room: At the end of Prohibition in the United States, the original proposal was to legalize low-strength alcohol—beer and wine. The proposal eventually got overwhelmed by events. There was actually a short period before the actual repeal happened, in which beer below 3.2% was legal. But the answer is pretty well "no."

You can think of some analogies. Apple juice, for instance, sold in North America can have up to 0.5 percent alcohol in it. Plain old apple juice and many other products on your grocery shelves have a very small amount of alcohol in them. You may remember the old song about the man eating fruitcake until he gets tight. There are plenty of things that a heavily addicted drinker might try, from which he would have a difficult time getting a fix—things that are not typically thought of as alcoholic beverages. I don't know of any studies of what happens with respect to 0.9% alcohol—the really low-alcohol beer, which has a substantial market share in Australia, where people can drink pretty well as much as they like and still drive a car. I don't know what someone in withdrawal from alcohol would get out of a 1% alcoholic beverage. It's an interesting question that probably no one has ever looked at.

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