Will the Next Generation of "Safer" Cigarettes Be Safer?

Kenneth E. Warner, PhD

Summary: There are three basic means of avoiding smoking-related diseases: never starting to smoke, quitting, and avoiding smoke-filled environments. Recently, a fourth possibility has emerged: use of new, ostensibly less toxic products by smokers who cannot or will not quit, including "reduced toxin" cigarettes and novel smokeless tobacco products. To their purveyors, these new "tobacco harm reduction" (THR) products represent an opportunity for inveterate smokers to reduce their risk of lung cancer and other diseases. To health professionals, the new products pose a myriad of risks. This new generation of THR products is not the first to promise reduced risk, however. Both filtered cigarettes and low tar and nicotine cigarettes were marketed with explicit health themes, ultimately with disastrous results for public health. THR products enter the market subject to no product regulation whatsoever; thus, the opportunity for objective, independent scientific evaluation of their risks and benefits, and for regulation of advertising or sale as a result, is absent. This paper describes the new generation of THR products, discusses potential benefits and risks, examines lessons from the experience with filtered and low tar and nicotine cigarettes, and describes the principal challenges that confront the medical profession, government, and the public in determining what to do with this perplexing array of novel products.

Key Words: cigarette smoking, tobacco policy, harm reduction

(J Pediatr Hematol Oncol 2005;27:543-550)

ne of the greatest risks of death from adult-onset cancer confronted by the survivors of a pediatric malignancy is lung cancer, the leading cause of cancer mortality among all American men and women. Unlike many malignancies, lung cancer is virtually completely preventable, simply by avoiding cigarette smoking and living or working with smokers. Lung cancer is the leading cause of cancer death in both men and women, and 90% of lung cancers result from exposure to tobacco smoke, most by virtue of the patient's smoking.¹ Roughly 3,000 of the annual 164,000 lung cancer deaths in the United States are attributed to "second-hand" smoking,

Copyright © 2005 by Lippincott Williams & Wilkins

inhalation of the smoke of others.² A portion of second-hand smoking deaths may result from childhood exposure to parents' smoke, although the evidence is mixed.³

To this point in history, there have been only three means of avoiding smoking-related lung cancer: never starting to smoke, quitting, and avoiding smoky environments. Today, however, a fourth possibility has emerged, a highly controversial alternative supported primarily, but not exclusively, by the manufacturers of tobacco products^{3,4}: the use of new, ostensibly less toxic products by smokers who cannot or will not quit. These include a new generation of "reduced toxin" cigarettes as well as a range of novel smokeless tobacco products. To their purveyors, the new products represent an opportunity for inveterate smokers to reduce their risk of lung cancer and potentially other diseases. To health professionals, the new products pose a myriad of risks: encouraging smokers who would have quit smoking to switch to the ostensibly less hazardous product instead; causing some proportion of quitters to relapse in the belief that the risk they feared in ordinary cigarettes is eliminated in the new products; and introducing tobacco to some young people who never would have tried conventional cigarettes for fear of the dangers.⁴⁻⁶

The debate over "tobacco harm reduction" takes place in an environment devoid of any product regulation. Whereas manufactured food products and pharmaceuticals are regulated for safety, and other, hazardous products taken into the body are banned (eg, illicit drugs), tobacco products are subject to no product regulation whatsoever. Consider that the safest form of nicotine delivery ever developed-nicotine replacement therapy (NRT) pharmaceuticals—are subject to the full force of FDA regulatory authority. Before they can market NRT products, manufacturers must demonstrate that they are safe and efficacious. In striking and anomalous contrast, the manufacturers of the "dirtiest," most deadly form of nicotine delivery ever created-the cigarette-can market novel products whenever they wish, without subjecting them to any governmental review whatsoever. This grants the tobacco product manufacturers an enormous marketing advantage over the producers of NRT products: the former need not incur the burden of years of testing at a cost of tens or hundreds of millions of dollars, a burden borne by the pharmaceutical companies. Further, as is discussed below, the lack of safety regulation of tobacco products risks the introduction of novel disease risks.7

In 1996 the FDA announced baby steps toward regulating cigarette smoking.8 While acknowledging the lethality of tobacco products, the Supreme Court ruled that Congress had not granted FDA the authority to regulate them.⁹ Any such regulation, the Court said, would require new congressional action. The 108th Congress considered legislation granting

Received for publication August 23, 2005; accepted August 23, 2005.

From the School of Public Health, University of Michigan, Ann Arbor, MI. This is a revised version of the ASTRO/American Cancer Society Keynote Lecture, presented at the 46th Annual Meeting of the American Society of Therapeutic Radiological Oncology, Atlanta, Oct. 5, 2004.

Reprints: Kenneth Warner, Dean, Avedis Donabedian Distinguished University Professor of Public Health, Director, University of Michigan Tobacco Research Network, School of Public Health, University of Michigan, 109 S. Observatory, Ann Arbor, MI 48109-2029 (e-mail: kwarner@umich.edu).

FDA regulatory authority but failed to pass it. As of this writing, regulatory legislation is once again before the Congress.

The next section of this paper briefly summarizes the burden of smoking. The following section describes the nature of the new generation of ostensibly "reduced toxin" products now on the market and contemplates the potential health benefits, and risks, associated with them. Attention then turns to the history of tobacco industry introduction of purportedly less risky products, focusing on filtered cigarettes in the 1950s and low tar and nicotine cigarettes, first marketed in the late 1960s. Important lessons from those experiences are reviewed. The paper concludes with consideration of the issues and challenges that confront health professionals, and all Americans, in the new era of "tobacco harm reduction."

THE BURDEN OF SMOKING: HOW MUCH AND WHY

In addition to its lung cancer mortality, smoking is credited with causing deaths from coronary heart disease, stroke, chronic obstructive pulmonary disease, premature birth, and a myriad of other less commonly recognized conditions.^{1,10} All told, smoking causes nearly 450,000 deaths each year, a total put into perspective by realizing that cigarettes kill more Americans than all of the following combined: obesity, alcohol, motor vehicle injuries, AIDS, fires, homicide, suicide, heroin, and cocaine. The death toll of smoking exceeds the mortality caused by all forms of cancer other than cancer of the lung and bronchus. Approximately a sixth of all deaths of Americans are caused by smoking, including nearly a third of all deaths during middle age. The leading cause of avoidable premature death, smoking is also the leading cause of preventable morbidity and disability. For every death caused by smoking, approximately 20 living Americans-more than 8 million—suffer from smoking-produced illness and disability.1

The explanation of this extraordinary toll is, at one level, simple. About 45 million Americans smoke, most addicted. The smoke they suck into their lungs contains as many as 6,000 chemical compounds, over 50 of which are known human carcinogens. The list of chemicals inhaled by smokers every time they puff on a cigarette includes ammonia, arsenic, benzene, carbon monoxide, formaldehyde, hydrogen cyanide, radioactive polonium-210, and toluene. A typical pack-a-day smoker inhales these chemicals 10 or more times per cigarette, or more than 200 times per day. Over a year, pack-a-day smokers suck these chemicals into their lungs 73,000 times, having smoked 7,300 cigarettes. Over a 50-year smoking "career," commonly beginning around the age of 15, a smoker inhales these 6,000 chemicals 3.65 million times, having consumed more than a third of a million cigarettes. It is not surprising that smoking kills half of its life-long devotees.¹¹ What is perhaps more surprising is that it does not kill the other half. Indeed, one might consider the fact that half of lifelong smokers survive this remarkable chemical assault the most impressive testimony to the strength of the human organism imaginable.

Compounding the problem of the chemical assault is the addictiveness of smoking. Seventy percent of smokers claim that they want to quit. Fully 30% make a serious quit attempt

annually (defined as going without cigarettes for at least 24 hours with the intention of quitting). Yet only 2.5% succeed in quitting each year.⁷ The pervasiveness of smoking, its intensity in terms of daily exposure, the chemical composition of smoke, and the addictiveness of the behavior combine to make the situation a formula for disaster. Despite the impressive successes of the national antismoking campaign—one can argue that the campaign has been the single most successful public health effort of the past half century^{12,13}—the formula has persisted for decades, and the toll has mounted year after year.

A NEW GENERATION OF NOVEL NICOTINE AND TOBACCO PRODUCTS

Although public health authorities accept that total conquest of smoking will not occur in the foreseeable future, they concur that perseverance in the battle against smoking will continue to score victories, albeit of the small and gradual sort.¹⁴ It is that "small and gradual" character that evokes frustration, however, among both health professionals and inveterate smokers. Confronted with a "quit or die" message, many smokers who find themselves unable to quit, or unwilling to do so, resign themselves to the huge risk of the latter.

It is this sense of resignation that has spurred the development of the "tobacco harm reduction" (THR) movement.⁶ Put simply, proponents of THR answer the following question affirmatively: Is there an alternative to quitting for smokers who fear the health effects of smoking but cannot or will not quit? Particularly now that the major tobacco companies have publicly acknowledged the dangers of smoking,^{15–17} some 40 to 50 years after privately acknowledging them,¹⁸ they have the "liberty," if not self-perceived responsibility, to create ostensibly less hazardous products. Motivated by fear of losing even more customers to quitting, they are engaged in a frenzy of research and experimentation on new products. New product development is spurred as well by competition among the major cigarette producers and with both the smokeless tobacco industry and the pharmaceutical industry. The latter two perceive a potentially large market in competing with the cigarette manufacturers for the hearts and minds (and especially wallets) of America's smokers.¹⁹

The result is three major categories of products. (There are other categories as well that include such anomaloussounding products as nicotine water and juices, nicotine-laced lollipops, tobacco toothpaste, and some highly unorthodox pseudo-cigarettes.²⁰ Space will not permit their inclusion in this article.) One of the major categories, the most established and best known, consists of NRT and other pharmaceutical products, with substantial further innovation in the works at present. The second is a series of novel smokeless tobacco products, featuring both low-nitrosamine conventional smokeless tobacco and new compressed tobacco tablets (or tobacco "candies" as opponents have referred to them). The latter give users a jolt of nicotine while exposing them to relatively few of the toxins found in combusted tobacco products and conventional smokeless products. As well, they permit users to consume the entire product, avoiding the socially undesirable spitting associated with use of standard smokeless tobacco.

Driving interest in low-nitrosamine smokeless tobacco products are two basic facts. First, they are clearly dramatically less hazardous to health than cigarette smoking.²¹ Second, to many observers, the first of their breed, snus, a product used by about 30% of Swedish males, serves as the world's only major natural experiment in tobacco harm reduction. Thanks primarily to a substantial tax-driven price differential (ie, cigarettes are heavily taxed; snus is not), snus has come to dominate smoking in male tobacco use in Sweden. As a consequence, Sweden has the lowest rate of male smoking in Europe, and the lowest rate of male lung cancer.²²

The third major category-products possessing the greatest potential for market success and posing the greatest source of concern to public health authorities-consists of reasonably conventional cigarettes that have been treated to reduce the yields of toxicants in cigarette smoke, most notably including several carcinogens. Several brands on the market today produce substantially lower yields of tobacco-specific nitrosamines, whereas at least one brand-Omni, produced by Vector Tobacco-claims substantial reductions in two other carcinogenic compounds as well. Advertising for Omni reads, "Reduced carcinogens. Premium taste. Introducing the first premium cigarette created to significantly reduce carcinogenic PAHs, nitrosamines, and catechols, which are the major causes of lung cancer in smokers." A voluntary warning label included in the corner of the ad, in print smaller than that required for the mandatory warning, then seemingly contradicts this encouraging claim, informing readers that "Reductions in carcinogens (PAHs, nitrosamines, and catechols) have NOT been proven to result in a safer cigarette."

To date, none of the modified cigarettes, nor any of the smokeless tobacco products, has captured a significant share of the market. Both the tobacco industry and the public health community are watching a contemporary development with interest, however: Philip Morris, the nation's largest and wealthiest cigarette manufacturer, has recently introduced into test markets a reduced-exposure addition to its Marlboro line, called Marlboro Ultrasmooth. The difference between Ultrasmooth and the other brands introduced to date is that Philip Morris has the marketing savvy and muscle to capture the attention of smokers, should it choose to do so.

Do the novel products represent a boon to health? No one knows. One might assume that reduced exposure to known toxins would reduce harm to smokers. However, as noted previously, cigarette smoke contains thousands of chemicals, with possibly hundreds of them hazardous to health. No one knows which chemicals, or which combinations, pose the greatest danger. Further, the novel products achieve their exposure reduction through a variety of techniques that may themselves pose risks, possibly new risks, to the health of their consumers. For example, one reduced-exposure brand of cigarettes uses palladium to achieve its objective. Is inhaling combusted palladium dangerous? No one knows.

A second instance relates to a pseudo-cigarette, Eclipse, produced by R.J. Reynolds. This device, the exterior of which looks like a cigarette, heats but does not burn tobacco, creating reduced levels of tars while producing nicotine yields comparable to low tar and nicotine cigarettes (and, interestingly, higher-than-average levels of carbon monoxide). Several years

ago, when Eclipse first entered test marketing, a scientist at Roswell Park Cancer Center in Buffalo, NY, discovered that particles of a fiberglass shield surrounding the product's heating element (to keep the element from burning users' fingers) broke off and adhered to the barrel of the cigarette, including clinging to the filter. As a consequence, consumers of Eclipse were inhaling glass particles.²³ When the scientist's findings were published, R.J. Reynolds acknowledged its awareness of this phenomenon but insisted that it posed no additional risks to health. Their explanation was, in part, that the glass filaments were structured to be sufficiently large that they "are unlikely to reach the pulmonary region of the respiratory tract."24 Whether or not one wishes to accept the assurances of a major cigarette manufacturer-and history would recommend strongly against doing so^{18,25,26}—the fact remains that because tobacco products are subject to no product regulation, there is no governmental body to assess and protect against new risks produced by novel products.

Even if a novel product truly poses less risk to smokers than do conventional cigarettes, the aggregate, or population, impact might be negative. This would occur if a reduced risk to the individual who consumes the product instead of smoking conventional cigarettes is outweighed by increased use of tobacco products, including the novel product, in the aggregate. That is, use might increase, possibly substantially, because the perceived relative "safety" of the new product might lead some smokers to switch to the new product in lieu of quitting altogether. Similarly, former smokers who quit due to a concern about the relationship between smoking and lung cancer might relapse to a cigarette that promised "reduced carcinogens." Finally, some children who never would have smoked conventional cigarettes, for fear of their dangers, might experiment with the novel products, thereby joining the ranks of tobacco consumers. A subset of them, possibly quite large, might "graduate" from the new products to "better-tasting" conventional cigarettes. Kozlowski et al demonstrate the tradeoff between reduced risk for individual smokers and increased population use with a heuristic called the risk-use equilibrium.²⁷

Independent scientists concur that the task of evaluating the risk reduction of novel products, if it can be done at all, is enormously challenging.⁴ Although selected research groups, both inside and outside the tobacco industry, are engaging in harm reduction research,^{28–30} determination of the best methods to evaluate exposure and risk reduction remains a largely hypothetical exercise, the result of the complete absence of any requirement that it be done.

TOBACCO "HARM REDUCTION": A HISTORY

Keen observers have questioned the safety of tobacco smoking for literally centuries, at least four of them to be precise. In 1604, King James I of England declared smoking "a custome Lothsome to the eye, hatefull to the Nose, harmfull to the braine, [and] dangerous to the Lungs."³¹

In more contemporary times, "coffin nails," as cigarettes were called in the early and middle part of the past century, raised concerns shortly after cigarette advertising began in 1913.³² Within a couple of decades, cigarette brands competed for market share with claims that they were milder on the throat, less likely to produce coughs, and so forth.³³

The real "safer cigarette" era began in the early 1950s, shortly after an article in *Reader's Digest*, entitled "Cancer by the Carton," was published in December 1952.³⁴ The article brought to vivid public attention the findings from the first major epidemiologic research indicting cigarette smoking as a cause of lung cancer.^{35–37} The public reaction was dramatic. In 1953 and 1954, per capita cigarette consumption dropped for the first 2-year period in the century, with the exception of a 2-year decline during the Great Depression. The cigarette industry responded quickly, mass-producing filtered cigarettes for the first time and marketing filters as trapping the dangerous "stuff" in cigarette smoke and letting the flavor through. The smoking public bought the message with a great sense of relief. Per capita consumption resumed its steady upward climb, the period of 1953-54 now looking merely like an inadvertent blip (Fig. 1). During the 1950s, filtered cigarettes, virtually nonexistent at the decade's beginning, rose to become the dominant product.³⁸

We now know that the filter-tip "solution" was a public relations coup for the tobacco industry, not a public health triumph. Filter cigarette smokers acquired lung cancer at rates comparable to their unfiltered smoker predecessors. Evidence eventually emerged that because filters blocked the inhalation of smoke, manufacturers employed stronger tobaccos to counteract the filtering effect. Ironically, the brand of filtered cigarettes most widely adopted at the beginning of the era—Kent—had a filter made of asbestos.³⁹

The next significant venture into "less hazardous cigarettes" followed debate about the importance of tar and nicotine deliveries in cigarettes. The "tar wars" of the late 1960s and early 1970s broke out. Low tar and nicotine (t/n) cigarettes were marketed as an alternative to quitting for the health-concerned smoker. (For example, copy for a then-contemporary ad for True cigarettes showed an intelligent-looking professional woman saying, "All the fuss about smoking got me thinking I'd either quit or smoke True.

I smoke True.") As a consequence, low t/n cigarettes overtook "full-flavored" cigarettes in the span of a decade, much the way filtered cigarettes had come to dominate the market two decades earlier. In the early 1980s, textbooks of internal medicine instructed physicians to recommend low t/n cigarettes to their patients who would not quit.^{40,41} Only fairly recently has evidence emerged that the industry had designed low t/n cigarettes as public relations devices, much as was the case with filtered cigarettes a generation earlier. The PR tactic worked, extraordinarily well. Even today, smokers of low t/n cigarettes believe that their disease risks are substantially below those of smokers of "full-flavor" cigarettes.⁴² Yet the empirical evidence is quite clear that there is little to no health advantage to smoking low t/n cigarettes.⁴³ And the decision to switch to low t/n cigarettes rather than guit smoking, a decision likely made by millions of Americans, may well have increased the aggregate death toll associated with smoking.

Low t/n cigarettes offered a technological solution to the smoking "problem." Although different blends of tobaccos were used and cigarette papers were treated with different chemicals, the principal mechanism by which low t/n cigarettes reduced yields consisted of a series of miniscule vent holes placed midway down the filter.⁴⁴ More often than not (and now nearly always), the vent holes were invisible to the naked eye. They reduced yields, measured by the Federal Trade Commission, by allowing air to be sucked into the filter through the vent holes, thereby diluting the smoke that was also drawn in.

The problem was that people never smoked low t/n cigarettes the way testing machines did. The testing machines held cigarettes at the very end, exposing the vent holes to the air. The machine took a specified number of "drags" per minute with a fixed intensity; hence, the air flowing through the filter vents diluted the smoke delivery substantially. Humans, however, often blocked some or all of the holes. The holes were located strategically so that a smoker holding a cigarette between two fingers was covering up half or more of the holes. Smokers with large lips blocked all of the holes when placing cigarettes in their mouths. (Such smokers have



FIGURE 1. Adult per capita cigarette consumption and major smoking and health events, United States, 1900–2001.

been referred to as "congenital hole-blockers.") The net effect was to block the dilution of the smoke and increase the effective yield of tar and nicotine.⁴⁵

Smokers who didn't naturally block most of the holes found other ways to compensate for the reduced yield of nicotine—and compensate is exactly what smokers do when confronted with a cigarette that gives them less nicotine than they are accustomed to.⁴⁶ Such smokers have been documented to smoke more cigarettes, suck harder on the cigarette, smoke it further down the butt, and so forth. One consequence, discovered only fairly recently, is that long-term smokers of low t/n cigarettes are developing lung cancers further down into their lungs than do "full-flavor" smokers.⁴⁷ Independent observers have concluded that low t/n cigarettes are a fraud perpetrated on a smoking public eager to avoid risk but at least equally eager to persist in smoking.⁴⁸

Although the counterfactual cannot be proven, there is a consensus among tobacco control experts that since the middle of the 20th century, smoking prevalence would have been significantly lower than the levels actually achieved had the tobacco industry never introduced filtered and low t/n cigarettes and marketed them as "safer cigarettes." The consequence of the industry's successful experiments with an illusory "harm reduction" has been a higher body count—a larger toll of death, illness, and disability—than would have existed in the absence of filters and low t/n cigarettes. The lesson for the current generation is clear: The industry is never to be trusted. Messages, implicit or explicit, that novel products will reduce risk should never be accepted at face value.

The fact remains, however, that some of the novel products may actually reduce exposure and possibly risk. (Compared with smoking cigarettes, some clearly do, most notably all of the pharmaceuticals and the low-nitrosamine smokeless tobacco products.²¹) The crucial lesson here is that we cannot know without proper, objective analysis produced by scientists working solely in the interests of the health of the public. Such analysis must be mandated by federal law.⁷

ISSUES AND CHALLENGES

Despite the certitude with which the public health community has accepted the necessity of government regulation of novel tobacco products, the fact remains that determining *how* to regulate such products is no easy task. And it is only one of several challenges that confront a health community that does not want to cede control over tobacco product innovation to the tobacco industry. Four such issues are readily identified.

First is the question of how one can ascertain risk reduction potential at the level of the individual consumer. In its study, an Institute of Medicine committee concluded that it may not be possible to assess risk reduction potential for many products and for many diseases. For example, determination of the carcinogenicity of new products cannot await the passage of decades, as happened with conventional cigarettes. Given the multitude of products likely to be on the market and the multitude of mixed product use patterns, it might not be possible to assess cancer risk reduction even with the passage of decades. Some disease effects might be determined through real-time observation, such as impacts on pregnancy outcomes. Overall, however, the IOM committee concluded that more productive evaluation would focus on toxin exposure reduction. Hence, the committee referred to such novel tobacco products as PREPs (potential reduced-exposure products).⁷

Essential to evaluating either risk or exposure reduction is determination of alternative use patterns: that is, for example, are PREP consumers using the new products instead of quitting or instead of continuing to smoke conventional cigarettes? In the latter instance, a true reduced-exposure product might reduce disease risk; in the case of the former, reduced, but not eliminated, exposures would *increase* disease risk.

Second is the problem of assessing population effects. Even if exposure or risk reduction can be evaluated for an individual user (compared with smoking conventional cigarettes), the "balancing act" between benefits to the individual and costs to the broader population needs to be evaluated. How many more people will use tobacco products, given the availability of PREPs, than would in a regimen of only conventional products? According to the risk-use equilibrium,²⁷ a graph that shows the population risk trade-off, if a PREP reduces disease risk by 20%, an increase in population use of the PREP of 25% will negate any aggregate benefit to the public health. If a still larger percentage of the population uses the product, compared with not consuming any tobacco products, population health will actually suffer. What are the surveillance methods, if any, that would permit determination of the trade-off between individual benefit and population cost? Keep in mind the difficulty of assessing potential benefit to the individual in the first place.⁷

Third is the question of how both health professionals and the public can be educated about the use of PREPs in a manner that will enhance their risk-reduction potential and discourage their substitution for non-use of tobacco products. Proper resolution of this question is essential, as improper education may well lead to misuse of PREPS by a wide variety of people, including both current smokers and non-tobacco users. Short of possessing sound knowledge of the exposureand risk-reduction potential of PREPs, however, it is hard to imagine how to begin to address this challenge. Keep in mind how poorly we educated health professionals about the use of the first true risk-reduction product, nicotine polacrilex (nicotine "gum"), and hence how poorly they, in turn, instructed their patients. The instruction message is simple: users should bite into the product a few times until they experience a "tingling" or peppery taste; then they should "park" the product between the cheek and gum until the tingling ceases; then they repeat the process until they no longer generate the tingling sensation. The instructions clearly emphasize that users should not chew the product, like regular gum. Yet many health professionals either wrongly told their patients to chew the product or left it to the patients' imagination, with chewing being the logical response to "gum." If the pharmaceutical industry (with its economic interest) and the public health community failed to educate health professionals and consumers about the proper use of "gum," with the simple instruction involved, how can public health professionals convey a meaningful message about PREPs when no one understands their individual or population effects?

Fourth is the issue with which this section opened. Although there is widespread agreement about the need for government regulation-some elements of the tobacco industry even support regulation^{4,15}—there is little consensus about what form such regulation should take. The IOM committee proposed regulation of claims.⁷ IOM called for the requirement that no company be permitted to make any product claim, explicit or implicit, regarding exposure or risk reduction unless they had submitted scientific evidence backing up the claim sufficient to convince a designated regulatory authority of the validity of the claim. Note that, as is the case with FDA regulation of pharmaceuticals, this form of regulation ignores population effects, although in concept it need not. (That is, the regulatory authority could require convincing scientific evidence that any exposure or risk reduction realized by a cigarette smoker switching to the PREP would not be offset by exposure-or risk-increasing population use.) Note, as well, that with the limited science available today, it is not clear what sort of scientific evidence a tobacco company would have to submit, especially with regard to harm-reduction claims. (Exposure-reduction claims would be easier to document, although here, too, important challenges remain.⁶) Finally, the IOM committee stopped short of recommending regulation of the marketing of novel products.

As an example of a more stringent regulatory environment, the designated regulatory body might mandate performance standards for cigarettes and PREPs. For example, now that several manufacturers have demonstrated the ability to remove most of the nitrosamines from cigarette smoke, the regulatory authority could require that all cigarettes meet some maximum allowable nitrosamine standard. Similarly, with firesafe cigarettes now being marketed in response to legal requirements in specific jurisdictions (eg, New York state requires that cigarettes meet a fire safety standard), a national regulatory authority could require that all cigarettes meet the same (or conceivably more stringent) fire safety standard. Under such a regimen, manufacturers could be rewarded for achieving various exposure-reduction (if not measurable harm-reduction) improvements by regulations requiring similar attainment by other producers, with the original producers of the innovation deriving income by licensing their novel technology.

A myriad of alternative approaches to regulation of both conventional tobacco products and PREPs exists. These two illustrate their range. The critical point is that there is little agreement as to what constitutes the optimal approach, reflecting the scientific complexity of establishing exposure and risk reduction and the political, economic (who pays and how?), and enforcement problems associated with demanding regulation.

CONCLUSIONS

I have been a student of tobacco policy for three decades. I have studied such issues as tobacco taxation, advertising and countermarketing, and clean indoor air laws and have struggled to correct the many myths about the economics of tobacco that pervade the debate on tobacco policy.⁴⁹ During these 30 years, I have *never* encountered a tobacco policy issue that I have found more perplexing and fundamentally unsolvable than what to do about "harm reduction." In the first

major article on the subject, published less than a decade ago,¹⁹ two colleagues and I identified the inevitable emergence of the issue and urged our colleagues to confront it head on. That has happened. Many of the leaders of the tobacco control community, both national and global, perceive harm reduction as one of the preeminent tobacco control issues of the day.⁴ They meet to discuss the issue in multiple forums both at home and around the world. Yet to date, it is safe to say that there is no prescriptive consensus as to how to address the issue, save for the widespread agreement on the need for (some ill-defined form of) government regulation.^{4,7}

Agreement exists on two basic issues. The tobacco control community appears to be close to unanimous in the opinion that the risks associated with all novel combusted tobacco products, including their potential attractiveness to children and former cigarette smokers, make combusted products a poor choice for harm reduction.^{4,5} In contrast, medicinal nicotine, even if used on a sustained basis over a lifetime, is likely an excellent candidate for harm reduction. Indeed, many experts believe that physicians should encourage their inveterate smokers to try to depend instead on nicotine replacement products, even using multiple products (eg, patch and gum) at the same time. The risk-use equilibrium²⁷ brings both the undesirability of combusted products and the attractiveness of medicinal nicotine into vivid relief.

Despite this consensus within the health community, most of the big-money innovation in new products resides within cigarette manufacturing, the domain of the tobacco industry with the most at stake and the most to invest in novel products. In contrast with independent scientists, scientists within the industry believe that combusted products, and particularly reduced-yield cigarettes, are necessary to achieve harm reduction because, they assert, they are the only products to which committed cigarette smokers might switch.⁴

The source of much debate within the tobacco control community is whether low-nitrosamine smokeless tobacco products should be promoted for harm-reduction purposes.^{5,22,50} There is no question that low-nitrosamine smokeless products are dramatically less dangerous than cigarette smoking,²¹ but it is not certain that promoting them as such would necessarily benefit population health. In some contexts, with some forms of promotion, they could actually be increasing harm. For example, their manufacturers advertise them today as being for "those times when you cannot smoke." If smokers start using smokeless to tide themselves over during the daytime hours, when they're not permitted to smoke at work, smoking rates could actually be higher than they would be in the absence of the smokeless products. This would result because, as has been well demonstrated in research, prohibitions against smoking at work increase smoking cessation rates.⁵¹ If smokeless permits smokers to maintain their nicotine "buzz" between smoking periods (at home, mornings and nights), it may thus exacerbate the aggregate damage produced by tobacco, even if the smokeless products themselves are relatively low risk.

Contemplating the complexity of the harm-reduction issue can lead to frustration and even despair. The subject is not going to disappear, however. The intensity of new product development—a new product is put into test markets approximately every 3 months—reflects the intensity of competition for what is arguably a significant slice of the money-saturated tobacco market pie. Cigarette history recommends caution and skepticism. We have been burned twice (as it were), first by filtered cigarettes and then by low t/n cigarettes. The toll of tobacco today almost certainly greatly exceeds what it would have been had smokers been restricted to the old "full-strength" unfiltered cigarettes of 1950, with no promises of lower yields and reduced toxicities. Yet we must acknowledge that today may be different. A new generation of consumer-acceptable less hazardous products may emerge and may reduce the enormous burden tobacco places on the health of the population.

The next essential step is to bring the contemporary creative chaos under sensible regulatory control. Precisely how that regulation should function is unclear; the need for the protective oversight of independent regulation is not. The "unlevel playing field," with pharmaceuticals heavily regulated, at high cost, and tobacco products regulated not at all, constitutes a situation that no one in their right mind ever would have created.

REFERENCES

- The Health Consequence of Smoking: A Report of the Surgeon General. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, US Department of Health and Human Services; 2004.
- Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. Washington, DC: U.S. Environmental Protection Agency; 1992. EPA/600/6-90/006F.
- Boffetta P, Trédaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. *Environ Health Perspect*. 2000;108:73–82.
- Martin EG, Warner KE, Lantz PM. Tobacco harm reduction: what do the experts think? *Tob Control*. 2004;13:123–128.
- Warner KE, Martin EG. The U.S. tobacco control community's view of the future of tobacco harm reduction. *Tob Control.* 2003;12:383–390.
- Warner KE. Tobacco harm reduction: promise and perils. *Nicotine Tob Res.* 2002;4(suppl 2):S61–S71.
- Stratton K, Shetty P, Wallace R, et al, eds. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: National Academy Press, 2001.
- Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents. U.S. Department of Health and Human Services, Food and Drug Administration; August 28, 1996. Final Rule. 21 CFR Part 801, et al.
- Gottlieb S. Supreme Court rules that FDA cannot regulate tobacco industry. Br Med J. 2000;320:894.
- Meister K, Ross GL, Schneider KL, et al, eds. *Cigarettes: What the Warning Label Doesn't Tell You*, 2nd ed. New York: American Council on Science and Health, 2003.
- Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *Br Med J.* 2004;328:1533.
- Department of Health and Human Services, Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900–1999. Morb Mortal Wkly Rep. 1999;48:241–243.
- 13. Warner KE. Effects of the antismoking campaign: an update. *Am J Public Health*. 1989;79:144–151.
- Mendez D, Warner KE. Adult cigarette smoking prevalence: declining as expected (if not as desired). Am J Public Health. 2004;94:251–252.
- Health issues [Philip Morris USA website]. Available at: http://www. philipmorrisusa.com/en/health_issues/?source=home_fca1. Accessed Aug. 9, 2005.
- Smoking & disease [R.J. Reynolds website]. Available at http://www. rjrt.com/smoking/diseaseCover.aspx. Accessed Aug. 9, 2005.
- Health risks of smoking [British American Tobacco website]. Available at: http://www.bat.com/OneWeb/sites/uk_3mnfen.nsf/vwPagesWebLive/

DE4F97D8B81E209480256BF400033188?opendocument&SID= 51A8B161712F4D9DD6A72B6DD5021265&DTC=20050809. Accessed Aug. 9, 2005.

- Cummings KM, Morley CP, Hyland A. Failed promises of the cigarette industry and its effect on consumer misperceptions about the health risks of smoking. *Tob Control*. 2002;11(suppl 1):i110–i117.
- Warner KE, Slade J, Sweanor D. The emerging market for long-term nicotine maintenance. JAMA. 1997;278:1087–1092.
- Shiffman S, Gitchell JG, Warner KE, et al. Tobacco harm reduction: conceptual structure and nomenclature for analysis and research. *Nicotine Tob Res.* 2002;4(suppl 2):S113–S129.
- Levy DT, Mumford EA, Cummings KM, et al. The relative risks of a lownitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol Biomarkers Prev.* 2004;13:2035–2042.
- Foulds J, Ramstrom L, Burke M, et al. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control.* 2003;12: 349–359.
- Pauly JL, Lee HJ, Hurley EL, et al. Glass fiber contamination of cigarette filters: an additional health risk to the smoker? *Cancer Epidemiol Bio*markers Prev. 1998;7:967–979.
- Swauger JE, Pauly JL, et al. Glass fiber contamination of cigarette filters: an additional health risk to the smoker? *Cancer Epidemiol Biomarkers Prev.* 1998;7:967–979.
- Warner KE. Tobacco industry scientific advisors: serving society or selling cigarettes? Am J Public Health. 1991;81:839–842.
- Bero L. Implications of the tobacco industry documents for public health and policy. *Annu Rev Public Health*. 2003;24:267–288.
- Kozlowski LT, Strasser AA, Giovino GA, et al. Applying the risk-use equilibrium: use medicinal nicotine now for harm reduction. *Tob Control.* 2001;10:201–203.
- Hatsukami DK, Henningfield JE, Kotlyar M. Harm reduction approaches to reducing tobacco-related mortality. *Annu Rev Public Health.* 2004;25: 377–395.
- Hatsukami D, Hecht S, Hennrikus D, et al. Biomarkers of tobacco exposure or harm: application to clinical and epidemiological studies. *Nicotine Tob Res.* 2003;5:387–396.
- Breland AB, Acosta MC, Eissenberg T. Tobacco specific nitrosamines and potential reduced exposure products for smokers: a preliminary evaluation of Advance. *Tob Control*. 2003;12:317–321.
- 31. King James I. A Counterblaste to Tobacco, 1604.
- Tate C. Cigarette Wars: The Triumph of "The Little White Slaver." New York: Oxford University Press, 1999.
- 33. Kozlowski LT. Some lessons from the history of American tobacco advertising and its regulations in the 20th century. In: Ferrence R, Slade J, Room R, et al., eds. *Nicotine and Public Health*. Washington: American Public Health Association, 2000:17–32.
- 34. Norr R. Cancer by the carton. Reader's Digest. December 1952:7-8.
- Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma: a study of 684 proved cases. *JAMA*. 1950; 143:329–396.
- Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report. *Br Med J.* 1954;1:1451–1455.
- Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking habits: a second report on the mortality of British doctors. *Br Med J.* 1956;2:1071–1081.
- Reducing the Health Consequences of Smoking. 25 Years of Progress. Washington, DC: Government Printing Office. U.S. Department of Health and Human Services, Public Health Service. A Report of the Surgeon General; 1989. Chapter 8. DHHS Pub. No. (CDC) 89-8411.
- Slade J. Nicotine delivery devices. In: Orleans CT, Slade J, eds. *Nicotine Addiction: Principles and Management*. New York: Oxford University Press, 1993:3–23.
- Holbrook J. Tobacco smoking. In: Petersdorf RG, ed. Harrison's Principles of Internal Medicine. New York: McGraw-Hill, 1983:1303–1305.
- Willner JS. Tobacco abuse and dependence. In: Taylor RB, ed. Family Medicine, 2nd ed. New York: Springer-Verlag, 1983:1662–1665.
- Shiffman S, Pillitteri JL, Burton SL, et al. Smokers' beliefs about 'light' and 'ultra light' cigarettes. *Tob Control*. 2001;10(suppl 1):i17–i23.
- Burns DM, Major JM, Shanks TG, et al. Smoking lower yield cigarettes and disease risks. *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. Department

of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, Smoking and Tobacco Control Monograph 13; October 2001:65–158. NIH Pub. No. 02-5074.

- Kozlowski LT, Pillitteri JL, Sweeney CT. Misuse of 'light' cigarettes by means of vent blocking. J Subst Abuse. 2004;6:333–336.
- 45. Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Smoking and Tobacco Control Monograph No. 13; October 2001. NIH Pub. No. 02-5074.
- 46. Benowitz NL. Compensatory smoking of low-yield cigarettes. *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, Smoking and Tobacco Control Monograph 13; October 2001:39–63. NIH Pub. No. 02-5074.
- Brooks DR, Austin JHM, Heelan RT, et al. Influence of type of cigarette on peripheral versus central lung cancer. *Cancer Epidemiol Biomarkers Prev.* 2005;14:576–581.
- 48. Pollay RW, Dewhirst T. Marketing cigarettes with low machine-measured yields. *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, Smoking and Tobacco Control Monograph 13; October 2001:199–235. NIH Pub. No. 02-5074.
- Warner KE. The economics of tobacco: myths and realities. *Tob Control.* 2000;9:78–89.
- Tomar SL, Connolly GN, Wilkenfeld J, et al. Declining smoking in Sweden: is Swedish match getting the credit for Swedish tobacco control's efforts? *Tob Control.* 2003;12:368–371.
- Fichtenberg CM, Glantz SA. Effect of smoke-free workplaces on smoking behaviour: systematic review. Br Med J. 2002;325:188–195.