TOBACCO HARM REDUCTION and the Evolution of Nicotine Dependence

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In recent years, a renewed debate has developed around the potential for modified tobacco products to play a role in reducing tobacco-related harm. During the 1960s and 1970s medical experts recommended to smokers who could not quit that they switch to cigarettes with lower tar and nicotine content. At the time, survey data suggested that smokers who switched did not compensate for the reduction in nicotine by increasing their intake. However, public health scientists were hindered in their ability to evaluate the population impact of the reduced tar strategy by a limited understanding of nicotine addiction. Smoking dependence was seen as primarily psychological and social, rather than pharmacological or biological, until the late 1970s, when addiction researchers began to apply experimental techniques from other forms of drug abuse to study smoking behavior. This history has important lessons for current discussions about tobacco harm reduction and regulation of nicotine delivery. (*Am J Public Health*. 2011;101:632–641. doi:10.2105/AJPH.2009.189274)

OVER THE PAST 10 YEARS, the concept of tobacco harm reduction—reducing the morbidity and mortality from tobacco use without necessarily eliminating exposure to tobacco or nicotine—has drawn increasing attention and discussion among tobacco control scientists and public health professionals.[1] Proponents of harm reduction argue that cigarette smokers who are unable or unwilling to quit may benefit from harm-reduction strategies, similar to approaches used for other forms of drug abuse.[2] Additionally, the Family Smoking Prevention and Tobacco Control Act of 2009 (P.L. 111–131) granted the US Food and Drug Administration authority to regulate tobacco products, including establishing product standards for harmful constituents and nicotine content, with the aim of protecting public health. Internationally, there have been efforts to develop principles and guidelines for the regulation of tobacco products with the aim of reducing toxic exposures.[3]

However, the concept of tobacco harm reduction has also generated substantial controversy.[4] Skeptics warn that harm reduction interventions may have unintended adverse consequences, as perceptions that a product is less harmful or "safe" may lead to increased initiation and relapse or a decrease in cessation attempts.[5] Additionally, past efforts at tobacco harm reduction may have done more harm than good. During the 1960s and 1970s scientists and public health officials encouraged cigarette smokers to switch to cigarette brands with lower tar and nicotine content.[6] Decades later, "light" and "ultralight" brands still make up nearly 85% of the cigarettes sold in the United States.[7] But extensive epidemiological data have failed to show any benefit from changes in cigarette design over the past half century.[8]

So why did this failed harm-reduction strategy persist over more than two decades and how was it finally overturned? Previous research and investigations based on internal tobacco industry documents have shown how, beginning in the 1960s, cigarette manufacturers manipulated nicotine delivery in their products in ways that would not be detected by machine measurements and that they secretly conducted research demonstrating that smokers modified their nicotine intake when smoking low-tar cigarettes.[9] However, in this article I argue that public health scientists, who were not privy to internal tobacco industry research, were hindered in their ability to evaluate the impact of low-tar cigarettes by a lack of understanding of nicotine addiction and its impact on smoking behavior. Although early reports on the health effects of cigarette smoking

during the 1960s described the smoking "habit" and identified a range of psychological and social factors responsible for driving smoking behavior, there was little attention to or understanding of the biological basis of such behaviors. Indeed, the view that smoking dependence was primarily psychological and social prevailed well into the 1980s.[10] This history has important lessons for current tobacco harm-reduction efforts, which continue to focus primarily on product toxicity without sufficiently addressing changes to the addictiveness of the product or smoking behavior.

TOBACCO HABITUATION AND DEPENDENCE IN THE 1960S

As evidence accumulated regarding the health effects of cigarette smoking during the 1950s, the public health scientists studying smoking and health paid relatively little attention to the question of why people smoke. Nicotine had been studied in the laboratory as a central and pharmacologically active ingredient in tobacco since the 19th century, and for almost as long anti-tobacco forces had denounced cigarettes for their dependence-producing effects.[11] But, during the 1960s, health scientists continued to view the smoking "habit" as primarily psychological and social, rather than pharmacological or biological, as influential expert reports explained.

Expert Reports

The 1962 Royal College of Physicians report on *Smoking and Health*, the most comprehensive review of the evidence on the effects of cigarette smoking up to that point, concluded that "[s]mokers may be addicted to nicotine," but that "[i]t appears that social factors play a bigger part in determining smoking habits than internal drives or needs."[12(p86)] The report cited the variability of smoking habits across different populations and subgroups (e.g., ethnic groups, gender) as evidence that cultural factors play a large part in smoking behavior. They also described survey evidence of differences in personality and constitution between smokers and nonsmokers that could help explain patterns of smoking behavior: smokers change jobs more often, move more frequently, enter the hospital more frequently, participate in more sports, and exhibit more neurotic qualities. In other words, a heavy smoker's incessant puffing may be attributable to nervous constitution rather than to a physiological need.

The 1964 report of the advisory committee to the US Surgeon General on *Smoking and Health* similarly concluded that

> [t]he habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacological actions of nicotine.[13(p354)]

The report's chapter on the pharmacology and toxicology of nicotine focused solely on evidence of chronic toxicity from nicotine exposure, concluding that the risk of such effects among smokers was low, and did not address the question of addiction. A separate chapter titled "Characterization of the Tobacco Habit and Beneficial Effects of Tobacco" concluded that tobacco dependence should be characterized as a form of "habituation" rather than "addiction."

The report appealed to a 1957 World Health Organization document that differentiated habituation from addiction. The latter was characterized by "an overpowering desire" to continue taking the drug and obtain it "by any means," a tendency to increase the dose over time, a demonstrated physical dependence on the drug, and detrimental effects on the individual and society.[14] Additionally, the 1964 report cited a lack of evidence for a genuine abstinence syndrome, as some heavy smokers were able to quit spontaneously and others reported only a range of nonspecific symptoms, such as restlessness or anxiety. Some influential experts considered an opiate-style abstinence syndrome to be an essential element of addiction. As the only pharmacologist on the surgeon general's committee, Maurice Seevers held sway over the rest of the group on the question of addiction.[15] Seevers had previously served on the World Health Organization's expert committee that produced the 1957 definition of addiction, and was also a longtime proponent of the view that an observable physical abstinence syndrome was a crucial defining feature of addiction.[16] Moreover, Seevers had undisclosed ties to the tobacco industry at the time, which may have reinforced his rejection of nicotine addiction.[17]

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A subsequent World Health Organization definition, released in 1964 after the report of the surgeon general, replaced the earlier dichotomy of addiction versus habituation with a single broad category of "dependence."[18] Nevertheless, other expert reviews over the next few years also stopped short of claiming a biological basis for smoking dependence.[19] A working group at the first World Conference on Smoking and Health, held in 1967, recognized two different types of dependent smokers—those who experienced little difficulty in quitting and few withdrawal symptoms versus those who displayed severe reactions to withdrawal. For the latter type, the working group acknowledged that there might be a pharmacological element involved but cautioned about the "scanty existing knowledge of tobacco dependence."[20]

Minority Views

There were individual scientists at the conference who went further in their analysis of nicotine as the key and dependence-producing ingredient in tobacco. Murray E. Jarvik, then assistant professor of psychopharmacology at the Albert Einstein College of Medicine, warned that an addiction must have a chemical basis and that nicotine was clearly the active chemical agent in tobacco. Thus, efforts to reduce nicotine content in cigarettes might have the effect of "forcing the nicotine addict to smoke more cigarettes in order to reach his daily quota of the drug."[21(p142)] Ernst Wynder also

urged that nicotine must be central in smoking behavior based on the behavior of tobacco companies. At the time, tobacco manufacturers in the United Kingdom were proposing to reduce tar but maintain or increase nicotine levels in cigarettes. "Now, surely they know as much about smoking as we do," Wynder reasoned, and if they want to increase nicotine it must be because they know that "the higher the nicotine content the more people will become dependent upon the product."[22(p256)]

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Yet, despite the call for more research and the warnings of scientists such as Jarvik and Wynder, it would be another decade before federal research funders and public health scientists created an organized research program around smoking dependence and nicotine addiction. And there was no further discussion of tobacco or nicotine dependence or addiction in any subsequent reports of the surgeon general until 1979.

THE PUBLIC HEALTH SERVICE AND THE TAR-REDUCTION STRATEGY

The surgeon general convened another group of experts on June 1, 1966, to review the evidence on the role of tar and nicotine content in cigarettes on health and smoking behavior. The group concluded that "[t]he preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the less harmful are the effects."[23(p16468)] They also specifically recommended that actions be encouraged to progressively reduce the tar and nicotine content of cigarette smoke.[23] The same year, the Federal Trade Commission reversed an earlier ruling to allow manufacturers to include statements about tar and nicotine content in advertising as long as they used a standardized machine testing method.[24] In 1970, the Federal Trade Commission entered into a voluntary agreement with the major cigarette manufacturers under which they agreed to disclose tar and nicotine content, measured according to the standardized Federal Trade Commission method, in all cigarette advertising.[25] Scientists and policymakers at the time believed that giving consumers access to tar and nicotine measurements would allow them to make informed decisions and to choose a less harmful product.[26] The Public Health Service produced a brochure for smokers explaining how they could reduce risk by switching to a brand with a lower tar and nicotine rating.[27]

A substantial research effort also developed around the potential for modifying cigarettes to make them less harmful, including leading public health scientists such as Wynder and the American Cancer Society's E. Cuyler Hammond.[28] Over a 10-year period, the National Cancer Institute (NCI) pursued a $50 million research program aimed at developing a "less hazardous cigarette."[29] New scientific findings during this period, including Oscar Auerbach's research with beagle dogs and Wynder's retrospective epidemiological studies, continued to provide support for the conclusion that lowering tar and nicotine levels reduces risk.[30] The findings were touted by NCI officials as evidence that the reduced-tar strategy was yielding public health benefits.[29] And reports of the surgeon general continued to endorse tar and nicotine reductions as the most promising avenue for harm reduction.[31]

However, these efforts focused exclusively on the potential benefits from reducing tar emissions from cigarettes; there was little discussion of smoking dependence, the role of nicotine, or what the impact of reduced nicotine might be. The NCI's "less hazardous cigarette" research program held a small meeting with tobacco scientists in 1976 to discuss the feasibility of developing a cigarette with reduced tar but moderate levels of nicotine.[32] The program sponsored one study of nicotine delivery and human smoking behavior, conducted by Gary Huber at Harvard University. Results suggested that smokers who switch to low tar and nicotine brands alter their inhalation patterns and increase their smoke intake. However, the findings were never published.[33]

During the 1970s, some consumer advocates and public health scientists also pushed for awarding an agency of the federal government authority to regulate tobacco products and establish limits for tar and nicotine. In 1973, the National Cancer Advisory Board, an external advisory group to the NCI, established an ad hoc committee to make recommendations regarding regulation of tar and nicotine levels. The committee, which included scientists and public

health officials from government and academia, agreed that decreasing tar and nicotine content was the most promising avenue for harm reduction, but they concluded that no "arbitrary 'safe' levels" could be established on the available evidence.[34] The following year, President Gerald Ford asked the National Cancer Advisory Board to provide an "assessment of the extent to which there exists a scientific basis for responsible regulation of cigarettes."[35] This time the board responded with 10 pages of references to scientific publications on smoking and health (though nothing on smoking behavior or dependence) and a resolution that:

> A government agency should be empowered to set maximum cigarette levels of tar and nicotine that will become progressively lower than the 1973 averages of 19.2 milligrams and 1.3 milligrams respectively.[36]

However, the basis for the threshold was more pragmatic than scientific, reflecting the sales-weighted average yield per cigarette as measured by the Federal Trade Commission in 1973. The board also cautioned that decreases in tar and nicotine content should occur "slowly enough to insure that no important increase in the number of cigarettes consumed does occur."[36] However, the recommendation was not followed by any new legislation or regulatory action.

MODIFIED SMOKING BEHAVIOR

The possibility that smokers who switched to a reduced tar and nicotine cigarette might compensate for the change by smoking more cigarettes had been considered by scientists outside the tobacco industry. Indeed, public health scientists raised the possibility early in the discussion. If a smoker switched to a reduced-yield cigarette but ended up smoking more cigarettes per day, this compensation effect would potentially cancel out any health gains made by the change in brand. Thus, some evidence was collected to determine whether such compensation occurred, but the early data suggested that there was no significant compensation problem.

Surveys and Compensatory Smoking

As part of its mandate to collect information on tobacco use in the United States, the Clearinghouse on Smoking and Health conducted the Use of Tobacco Survey, which included a wide range of questions on smoking patterns and attitudes about smoking. A national sample of 4700 participants was surveyed in 1964, including about 2000 cigarette smokers, and a subsample was reinterviewed in 1966. Questions included the number of cigarettes smoked per day and the name of the brand. Daniel Horn and Selwyn Waingrow in the clearinghouse office used tar-rating tables published by brand in the *Reader's Digest* and *Consumer Reports* to divide the cigarette brands into five categories from low to high tar. They then looked at people who had changed brands between the two surveys in 1964 and 1966 to see whether they changed the number of cigarettes they smoked. They found no significant difference in the number of cigarettes smoked among those who changed to a cigarette with a different tar rating score. "Of particular interest," they noted, "is the observation that of those who were categorized as having shown a reduction in their tar-rating score, exactly the same number (27.3%) were classified as smoking more cigarettes as were classified as smoking fewer cigarettes than previously, with 45.3% showing no change."[37(p30)] The 1967 clearinghouse educational brochure reassured smokers considering switching to a lower tar cigarette:

> Will such a switch result in your smoking more? Probably not. Most smokers who make such a change either continue to smoke at their previous rate or even smoke less.[38]

In June 1970, the Public Health Service convened another expert panel to discuss the scientific evidence on specific harmful constituents in tobacco smoke and how they might be reduced. The group discussed nicotine content, acknowledging that it was not the primary source of harm in cigarette smoke but could not be assumed to be innocuous either. One participant raised the issue of whether smokers might increase their cigarette consumption as a result of reduced nicotine content. Horn responded, referring to his survey analysis, that available evidence suggested smokers did not generally increase the number of cigarettes they smoked when switching to a lower-tar brand. Horn then went a step further and claimed that he had evidence that the addictive portion of the cigarette was not in fact nicotine, but was some substance or combination of substances in the tar, which he did not specify.[39]

During the same discussion, Wynder argued, as he had previously done, that the tobacco industry's actions indicated that nicotine was a central component in smoking behavior. But instead of making an argument for maintaining nicotine levels in cigarettes to prevent compensation, Wynder used this observation to argue for the reduction of nicotine in cigarettes as a means to help smokers quit:

> The tobacco industry knows the reason it likes to opt for nicotine. The industry likes to reduce 'tar' and up the nicotine. We know the higher the nicotine, the more difficult it is for people to give up smoking. Therefore, the reduction of nicotine in my view leads to making it easier for people to give up smoking.[39(p979)]

The claims of both Horn and Wynder were highly speculative and based on very limited data. The research to support recommendations regarding manipulation of nicotine levels in cigarettes simply had not been done yet, at least not outside the tobacco industry. A working group at the 1975 World Conference on Smoking and Health offered cautious support for nicotine reduction, warning that such action could have adverse effects:

> While reduction in nicotine content is desirable, such reduction in a pleasure giving constituent may increase inhalation of other toxic substances in cigarette smoke, for example, carbon monoxide. Nevertheless, we recommend lowering the nicotine level in tobacco products gradually—as much as consumer acceptability will allow.[40(p5)]

Experimental Studies of Smoking Behavior

At the same time, Jarvik, then a professor of psychopharmacology at Albert Einstein College of Medicine, was studying monkeys exposed to cigarette smoke in the laboratory to see whether they would learn to

smoke voluntarily. In 1970, he published an article titled "The Role of Nicotine in the Smoking Habit," in which he reviewed the scientific literature to date and argued that smoking was addictive and that nicotine was the driving factor. But experimental data on modified nicotine exposure in human smokers was extremely limited. One study had been conducted to measure changes in smoking patterns in smokers who were using reduced-nicotine cigarettes and found no evidence that smokers were titrating their nicotine intake by smoking more cigarettes; however, Jarvik noted that the study was limited in only measuring the number of cigarettes smoked. "[T]here are other ways in which subjects might adjust the amount of nicotine they take in," he explained, "by varying the depth of inhalation and the length of the cigarette that they actually smoke."[41(p173)] Studies using intravenous nicotine in humans and studies using animals provided limited evidence for nicotine regulation in dependent users, though not as clearly as for drugs traditionally considered addicting, such as opiates.[42]

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By the mid-1970s a handful of innovative experimental studies were being conducted to determine whether varying the nicotine content of cigarettes would cause changes in human smoking behavior. Because one of the traditional characteristics of addiction is drug tolerance and a tendency to maintain or increase dose, researchers were interested in studying whether smokers regulate their nicotine intake. These early studies were conducted largely by addiction researchers, not the public health scientists who had been studying the effects of smoking on health. Most of these studies used relatively small numbers of participants (n=10–23) and employed a variety of creative techniques to attempt to modify the smokers' exposure to nicotine, including cutting cigarettes in half and using alternative smoking materials. A 1970 study by Jarvik et al. used cigarettes containing lettuce to which nicotine was added at different levels; no effect was found on smoking behavior by varying nicotine levels, but this finding may have been confounded by the fact that participants smoked fewer cigarettes overall because they objected to the taste of the lettuce cigarettes.[43] Another study from the same team found no significant difference in the number of cigarettes smoked when smokers switched to cigarettes that had been cut in half.[44] Other studies found some evidence that smokers took more time to smoke a cigarette with higher nicotine content and took more frequent puffs with low-nicotine cigarettes.[45] Overall, results in these studies were mixed, though they did provide some limited evidence that smokers modify their behavior in response to changes in nicotine exposure.

At the same time in the United Kingdom, Michael Russell was studying nicotine manipulation and smoking behavior.[46] Russell pioneered the view that research and policy efforts should focus on developing and encouraging use of cigarettes with low tar but medium levels of nicotine as an alternative to the standard low tar–low nicotine approach.[47]

A NEW RESEARCH AGENDA IN THE MID-1970S

By the mid-1970s, scientists began to compare tobacco smoking with other forms of drug dependence. A working group at the 1975 World Conference on Smoking and Health concluded that cigarette smoking should "be viewed as a form of drug dependence, most appropriately termed, in heavy smokers, compulsive drug use or drug addiction."[48(p5)] Jerome Jaffe, who had promoted methadone treatment of heroin addicts as President Richard Nixon's "drug czar" from 1971 to 1973, commented at the conference that

> The major difference between tobacco dependence and other drug addictions is tobacco's social acceptability.[49(p627)]

An organized research effort on smoking behavior began to develop momentum. This avenue of research was led by researchers, such as Jarvik, who applied methods from studying other forms of drug addiction to tobacco.[50] In 1977, the National Institute on Drug Abuse began to support studies of cigarette smoking as a "dependence process" and as a possible gateway to other drugs, which marked the beginning of sustained support for research on nicotine and smoking behavior that had previously been lacking.[51] These developments also coincided with a dramatic expansion of addiction

research during the 1970s, fueled largely by the recently created National Institute on Drug Abuse.[52]

Changes in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, the authoritative reference textbook of US pharmacology, help illustrate the shift occurring in the understanding of nicotine and tobacco dependence. In the 1965 and 1975 editions, nicotine was primarily discussed within a chapter on ganglionic agents, focusing on its pharmacologic effects on the nervous system without any discussion of dependence.[53] However, in the 1975 edition, the chapter on drug addiction and abuse, authored by Jaffe, included a brief half-page entry on nicotine for the first time. Jaffe acknowledged that "[t]he question of nicotine physical dependence is somewhat controversial" and noted conflicting reports on the existence of an abstinence syndrome.[54(p305)] The 1980 edition treated nicotine very differently. Now the ganglionic chapter contained only a brief discussion of nicotine, covering its acute pharmacologic effects. The primary discussion of nicotine and tobacco now took three pages in Jaffe's "Drug Addiction and Drug Abuse" chapter. The text described studies of tolerance to nicotine in smokers, evidence of a withdrawal syndrome, and nicotine titration behavior in smokers, and highlighted the significance of these findings for understanding of the effects of low-tar cigarettes.[55]

A substantial portion of the 1979 surgeon general's report was devoted to behavioral aspects of smoking for the first time since 1964, emphasizing the need for research on smoking dependence. In a chapter authored by Jarvik, the report described accumulated evidence of a tobacco-withdrawal syndrome, but noted that its symptoms vary; studies had failed to show that heavier smokers consistently exhibit greater withdrawal symptoms, but the report noted that daily cigarette consumption might be a poor measure of dose because smokers may modify their smoking in other ways.[56] Authors of the report avoided using the term "addiction." It was not until the 1988 report that the surgeon general declared that cigarettes are addicting and that nicotine is the primary agent of addiction.[57]

This evolving research emphasis had a substantial impact on the assumptions underlying the low-yield cigarette strategy. As more behavioral researchers began to study smoking, it became increasingly clear that smokers could unknowingly modify their behavior in subtle and effective ways to control nicotine intake (i.e., by increasing their depth of inhalation, taking more frequent puffs, holding smoke in the lungs longer, and blocking ventilation holes, as well as by smoking more cigarettes), thus overturning the reduced exposure assumption.[58] In the preface to the 1981 surgeon general's report *The Changing Cigarette*, Surgeon General Julius Richmond wrote:

> Overall, our judgment is unchanged from that of 1966 and 1979: smokers who are unwilling or as yet unable to quit are well advised to switch to cigarettes yielding less 'tar' and nicotine, provided they do not increase their smoking or change their smoking in other ways.[59(pv)]

He then went on to clarify that there is no safe level of smoking, that smokers may modify their behavior when they switch, and that switching to low-tar cigarettes may reduce lung cancer risk but "the benefits are minimal."[59(pvi)]

WHY DID THE STRATEGY PERSIST?

The 1979 surgeon general's report noted that although substantial data had been accumulated on the health effects of smoking, much less was known even then about the reasons why people smoke or have trouble quitting: "little is known for certain, and questions far outnumber answers."[60] Because regular smoking was so widespread and socially accepted during the 1960s and into the 1970s, scientists and public health leaders had been reluctant to portray smokers as "addicts" in need of medical attention. Additionally, the researchers who studied the health effects of smoking were epidemiologists, statisticians, and pathologists without experience in studying addictive behavior. Evidence was lacking (outside the tobacco industry) to sufficiently describe the role of nicotine and provide a physiological basis for smoking dependence. It was only once researchers experienced in studying other forms of drug abuse applied their methods to the study of cigarette smoking, under a broader definition of drug dependence, that a more in-depth research agenda developed around tobacco dependence. Meanwhile, scientists and public health leaders continued to promote the reduction of tar and nicotine levels in cigarettes as a harm-reduction measure. Finally, in the late 1970s and early 1980s, emerging experimental studies of human smoking behavior began to produce a body of evidence independent of the tobacco industry that challenged the assumptions behind the low tar–low nicotine strategy.

Understanding of nicotine addiction and smoking behavior was also hindered by the tobacco industry's efforts to suppress its own internal research. Previously secret internal documents show that, by the mid-1960s, around the time of the first surgeon general's report, some tobacco company scientists and executives already recognized nicotine as an addictive drug and cited internal animal studies to support their conclusion.[61] Philip Morris began using ammonia to increase the amount of free nicotine in cigarette smoke, a technique that other manufacturers soon followed. This development allowed the creation of low-yield cigarettes that still delivered a powerful nicotine kick.[62] Moreover, during the 1970s, tobacco manufacturers conducted numerous internal studies of nicotine dosing and smoking behavior, including studies that provided evidence of compensatory smoking behavior. This research was at least as advanced as work going on outside and was several years ahead of the general scientific community.[63] Industry representatives served on an advisory group to the NCI's smoking and health program during the 1970s, but failed to share relevant findings from their internal research and successfully sought to remove proposed funding for research on pharmacologic interventions for smoking cessation.[64]

The lack of attention to the underlying factors driving risky smoking behavior could also be seen as a symptom of a larger oversight in the field of cancer control. For much of the 20th century, cancer prevention was focused on early detection and

treatment, rather than on the environmental conditions or exposures that promote cancer. Prevention strategies focused largely on educating the public about the importance of early detection in an effort to encourage more frequent interactions with medical professionals.[65] It was not until the 1970s that scientific and popular attention grew toward environmental causes of cancer. The mandates of the 1971 National Cancer Act increased the profile of cancer prevention and control research.[66] Early critics of the war on cancer argued that these reforms did not go far enough and urged a more direct attack on commercial industries that produced or used suspected carcinogens.[67] Epidemiology textbooks of the 1960s and 1970s promoted a more complex model of disease causation that replaced the traditional concept of a necessary and sufficient cause of disease with a complex causal web that captured a range of biological and environmental factors.[68] This shift toward a broader concept of disease causation and growing concern over environmental causes of cancer, including the products of private industry, were also important steps in encouraging a focus on nicotine manipulation as a cause of smoking and, in turn, of cancer. In the 1980s, research on smoking and health had assumed an entirely new set of priorities focusing on large-scale smoking prevention and cessation programs, pharmacologic interventions, and secondhand smoke.[69]

HARM-REDUCTION RESEARCH AND POLICY

In recent years, a renewed debate has developed around the potential for modified tobacco products to play a role in reducing tobacco-related harm. Some public health scientists have offered a qualified endorsement of the concept of tobacco harm reduction.[70] Additionally, the World Health Organization's Study Group on Tobacco Product Regulation has recommended, as a precautionary measure, establishing maximum levels for certain toxic constituents in tobacco products.[71] However, these proposals have focused primarily on the potential for reducing exposure to harmful constituents in tobacco and smoke. Limited attention has been given to the potential effects (positive or negative) from changes that would impact the addictive properties of cigarettes.

However, based on historical analysis, I suggest that attention to the addictive properties of tobacco products is essential to evaluating any harm-reduction strategy. The hypothesis that reducing exposure to tobacco tar and nicotine would reduce harm was not entirely wrong; rather, the failure of the reduced tar–nicotine strategy was in the limitations of the machine testing protocol to account for how smokers actually smoked and, in turn, the actual exposures they received. But the reason that public health scientists (in contrast with tobacco industry scientists) were slow to recognize the limitations of the method was that they did not understand the complexity of actual smoking behavior and the role of nicotine in driving that behavior. Although nonindustry scientists acknowledged the potential for compensatory smoking even in the early 1960s, the available survey evidence suggested that this did not occur. It was not until the late 1970s that the tools for measuring more subtle forms of dose manipulation in smokers eventually came from drug researchers experienced in studying addictive behaviors. Moreover, although there had been substantial epidemiological and laboratory research supporting a dose–response relationship between exposure to tobacco tar and lung cancer risk, almost no research was publicly available until the late 1970s, apart from a few isolated small studies[72] regarding the impact of reducing nicotine in cigarettes. The conclusions of those, such as Wynder, who argued for reducing nicotine, were based on assumptions and beliefs about the actions of the tobacco industry rather than on a body of scientific knowledge.

To avoid repeating the same errors, current discussions of harm reduction should look beyond simply assessing exposure reduction and should include assessment of the product's abuse liability,[73] particularly its potential for promoting addiction. Evidence suggests that tobacco manufacturers have continued to manipulate nicotine delivery levels in cigarettes and smokeless tobacco products in recent years, although the impact of these changes on tobacco use is not well understood.[74] It is also important to understand the impact of a potentially reduced-harm product on other tobacco-use behaviors, such as initiation and cessation. For example, proponents of using smokeless tobacco for harm reduction in cigarette smokers point to substantially lower disease risks in smokeless tobacco users compared with smokers.[75] However, the overall population impact of such a strategy depends not only on the product's toxicity but also on how it is actually used.[76] Tobacco companies are increasingly marketing novel

smokeless tobacco products to smokers for situations in which they cannot smoke, and this trend may lead to an increase in dual product use rather than a decrease in cigarette smoking.[77]

Another avenue toward harm reduction that has been suggested involves the progressive reduction of nicotine content in cigarettes to nonaddicting levels. This strategy aims to reduce toxic exposures by targeting the underlying motivation for tobacco use. Benowitz and Henningfield first proposed this strategy in 1994 as a hypothesis for investigation.[78] Since then, additional research has been conducted on nicotine reduction, suggesting that smokers can progressively reduce nicotine intake and toxic exposures, without substantial compensation.[79] Recently, other tobacco control experts have urged further investigation of the potential for nicotine reduction.[80]

Additionally, the Family Smoking Prevention and Tobacco Control Act gives the Food and Drug Administration the authority to establish standards for nicotine yields in tobacco products (with the exception that the agency cannot require that nicotine content be reduced to zero). However, substantial research gaps remain, as no specific threshold has been identified yet below which nicotine is no longer reinforcing, and limited data are available to assess the potential impact of nicotine reduction at the population level.[81] The advent of Food and Drug Administration regulation provides substantial new tools for addressing the harm from tobacco products that could prevent repetition of the reduced-tar strategy, including industry information disclosure, premarket approval for new or modified products, and rules governing the introduction and marketing of potentially reduced-harm products. Yet history suggests that tobacco harm-reduction efforts should be approached with caution and require support from a diverse and robust body of scientific evidence. ■

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