



The Great Nicotine Debate

Are cigarette recipes 'cooked' to keep smokers hooked?

By JANET RALOFF

First in a two-part series

Food and Drug Administration Commissioner David A. Kessler issued what amounted to a battle cry in February when he reported indications that cigarette manufacturers fortify low-tar brands with nicotine. Why would they do this? To ensure that all the nation's 50 million smokers maintain their addiction to tobacco, he said.

If true, it means that the tobacco industry is deliberately fostering a physical need for a product that kills 434,000 Americans each year, according to the U.S. Surgeon General's latest estimates.

Indeed, smoking-related illnesses accounted for nearly one in five U.S. deaths in 1990—most of them from heart disease and cancer—states a report in the March 31 *NEW ENGLAND JOURNAL OF MEDICINE* (NEJM). An April 7 follow-up on cigarettes' economic toll by the same University of Colorado School of Medicine team estimated that a smoker's average lifetime medical costs exceed a nonsmoker's by \$6,000.

In response, the House Subcommittee on Health and the Environment convened a trio of hearings in March and April, and more are planned. Kessler and several congressmen also have renewed calls for greater regulation of tobacco—perhaps as a drug—or for nicotinefree cigarettes.

Arguing that it does not *add* nicotine to cigarettes, the tobacco industry maintains that these recent salvos constitute nothing less than a move to prohibit the sale and use of cigarettes.

Make no mistake, says James W. Johnston, chief executive officer (CEO) of RJ Reynolds Tobacco in Winston-Salem, N.C., "Forcing manufacturers to produce products that smokers find unsatisfying and unacceptable [such as nicotinefree cigarettes] is backdoor prohibition." Similarly, he says, "Advocating that the FDA regulate cigarettes as a drug—which would effectively ban cigarettes from the market—is clearly backdoor prohibition."

If cigarettes are so dangerous, argues Johnston, then Congress should "vote for

prohibition—and be prepared for the consequences."

However, Henry Waxman (D-Calif.), chairman of the subcommittee, denies that prohibition is at issue. In fact, the exsmoker supports a bill by Mike Synar (D-Okla.), a member of the subcommittee, that would give FDA regulatory authority over cigarettes—something it does not now have—but would prohibit the agency from banning them.

Those who sell aspirin, cars, and soda "are all held to strict standards when [those products] cause harm," Waxman charges. "We don't allow them to suppress evidence of dangers . . . We don't allow them to ignore science and good sense. And we demand that when problems occur, corporations and their senior executives be accountable to Congress and the public."

From a regulatory perspective, tobacco remains unique. "Imagine our nation's outrage if two fully loaded jumbo jets crashed each day, killing all aboard. Yet that's the same number of Americans that cigarettes kill every 24 hours," Waxman says.

He warned that the decades-long exemption Congress has offered cigarettes from most consumer-protection and health laws must end. It's time to begin "a new relationship between Congress and the tobacco companies," he said. "The old rules are out. The standards that apply to every other company are in."

Part of that new relationship involves a face-off with tobacco executives testifying under oath and access to their in-house research.

The major U.S. cigarette makers initially declined the subcommittee's invitation to discuss the role and amounts of nicotine in their products. But that was before March 25, when Kessler laid out for the subcommittee compelling, if circumstantial, evidence of manipulated nicotine concentrations in cigarettes.

The tobacco industry has repeatedly reported that as it reduces a cigarette's

production of tar—the sooty particulates linked to adverse health effects—nicotine automatically falls by roughly equivalent amounts. To test that, FDA analyzed nicotine quantities in the tobacco found in three types of one brand.

"What surprised us," Kessler testified, "was that the lowest [tar] one in fact had the highest concentration of nicotine." Indeed, FDA's data showed an inverse relationship between a cigarette's tar rating and its nicotine content, with the "regular" tar variety containing 1.46 percent nicotine, the "low-tar" variety containing 1.67 percent, and the "ultra-low-tar" variety containing 1.99 percent nicotine.

If tobacco companies are not manipulating nicotine amounts, Kessler asked, why would the lowest-tar cigarettes have the highest percentage? Advertising and industry statements lead one to expect the opposite, he pointed out.

Moreover, Kessler testified, FDA analyses of annual federal measurements of smoke from each variety of cigarettes marketed over the 10 years beginning in 1982 "suggest that the amount of tar over this time period has remained relatively flat, while the proportional amount of nicotine has not." In fact, Kessler noted, nicotine concentrations in smoke appear to have *increased* over the last decade.

If nicotine wasn't needed for maintaining addiction, why would companies want to control its amount, Kessler asks, especially in low-tar cigarettes? As evidence that there are such efforts, he quoted from an ad in an international tobacco trade publication that began: "Nicotine levels are becoming a growing concern to the designers of modern cigarettes, particularly those with lower 'tar' deliveries."

It went on to describe a process that "permits adjustments of nicotine to your exact requirements." Kessler then cited a technical article describing how this particular process can triple the nicotine content of tobacco. Companies may also preferentially use tobaccos—or blends of tobacco—with naturally higher nicotine

content for the lower-tar brands.

Synar quoted from a 20-year-old "confidential" company memo that further supported Kessler's contention. Written by William L. Dunn of the Philip Morris Research Center in Richmond, Va., it said: "Without nicotine there would be no smoking, and strong evidence can be marshalled to support this argument. No one has ever become a cigarette smoker by smoking cigarettes without nicotine."

Three weeks later, the presidents and CEOs of the nation's seven largest tobacco companies — Philip Morris USA, RJ Reynolds, U.S. Tobacco, Lorillard Tobacco, Liggett Group, Brown and Williamson Tobacco, and American Tobacco — welcomed an opportunity to meet with Waxman's subcommittee and refute Kessler's charges.

Two subjects dominated the emotionally charged rhetoric of the 6-hour hearing on April 14: whether nicotine is addictive and whether tobacco companies tailor product recipes to control nicotine percentages.

Though each executive stated explicitly that nicotine does not cause addiction and that his company does not tinker with nicotine amounts in its products, these views appear to conflict both with research findings and with data on their own products.

Take the issue of addiction.

According to pharmacologist Kathy Ellis, director of research for the New York City-based Philip Morris, "the strict pharmacological definition of addiction" includes intoxication, physical dependence, and tolerance — different criteria from those used by Kessler or the U.S. Surgeon General. "Nicotine — and cigarette smoking — do not meet these criteria," she testified.

In fact, smoking's failure to intoxicate or to require an increase in dose in order to produce psychoactive effects justified, in part, the determination in the 1964 Surgeon General's report that smoking was habituating, not addictive, said Johnston of RJ Reynolds.

Though the 1988 Surgeon General's report did call smoking addictive, it merely "altered the definition [of addiction] to fit the existing data on smoking," Johnston contends. "In essence, the Surgeon General moved the goalposts after he located the ball on the field."

What's more, Johnston notes, nicotine fails even Kessler's definition of an addictive substance: something that fosters compulsive use, produces a psychoactive effect, causes a reinforcing behavior, and induces withdrawal symptoms when removed.

When it comes to compulsiveness, he said, "there is a world of difference between the irresistible need of the hard-drug addict and a 'strong urge' [of a smoker] to engage in a pleasurable behav-

ior." And defining psychoactive as producing changes in the brain, the Reynolds executive argued, makes sugar, warm milk, and watching sports psychoactive.

"Smoking is no more addictive than coffee, tea, or Twinkies," Johnston concluded.

But Johnston's arguments are "out of touch" with 3 decades of research on nicotine effects, says Jack E. Henningfield, chief of clinical pharmacology at the National Institute on Drug Abuse's (NIDA) Addiction Research Center in Baltimore.

For instance, he notes, even though they all have slightly different definitions of addiction, the Surgeon General, American Psychological Association, American Medical Association, World Health Organization (WHO), and American Psychiatric Association all describe the nicotine in cigarettes as an addictive substance. What's more, he adds, no major pharmacological society in the last 20 years has supported the criteria for addiction cited by Ellis.

"No one has ever become a cigarette smoker by smoking cigarettes without nicotine."

— Dunn

"Intoxication has not been a critical element used to identify drugs as addictive substances since before 1964," Henningfield notes. Cocaine and heroin — two powerfully addictive drugs — produce no intoxication at the doses typically used, he points out, yet at very high doses, they — and nicotine — can intoxicate.

Similarly, since 1964, the WHO expert committee on drug addiction has deemed physical dependence "neither necessary nor sufficient to define addiction." One reason, Henningfield explains, is that withdrawal symptoms can be hard to recognize. For example, someone sitting across the room from a smoker going through withdrawal may not pick up on the individual's distress, difficulty concentrating, or anxiety. However, Henningfield says, "I can tell by looking at electrical brain waves, motor functions, cognitive abilities — as well as their mood — that they are going through withdrawal."

Nicotine's psychoactivity produces powerful, recognizable changes in the brain — changes characteristic of addictive drugs. For instance, almost all such drugs affect parts of the brain important to emotion and motivation, Kessler notes. "Specifically, they affect regulation of the

brain chemical dopamine, which produces psychoactive sensations and reinforces drug-use behavior." Though studies of dopamine's role in addiction initially focused on cocaine, Henningfield says, by the late 1980s "this was starting to get nailed down for nicotine as well."

And what of Johnston's charge that nicotine users don't exhibit the compulsive behavior of hard-drug users?

Even after surgery for lung cancer, nearly 50 percent of smokers return to cigarettes. Some 38 percent of smokers will light up even before they leave the hospital following a heart attack. And among smokers who have had a cancerous larynx removed, 40 percent will attempt to smoke again, reported Kessler.

One needn't depend on statistics and anecdotes for evidence of compulsion, however. Henningfield says animal research has reproducibly and quantifiably demonstrated nicotine-induced compulsive — indeed, addictive — behavior, beginning decades ago. Ironically, some of the first really strong evidence emerged in Philip Morris research conducted during the early 1980s. Two company papers — ultimately withdrawn from the journals to which they were submitted for publication — showed that rats will self-administer nicotine.

While declining to explain why his firm had the papers pulled — or why in 1984 it abruptly shut down the research on which they had been based (SN: 5/7/94, p.294) — Philip Morris President William I. Campbell said it was not because they showed nicotine is addictive. The studies' lead author, Victor J. DeNoble, eventually concluded that nicotine is weakly reinforcing and "in the class of nonaddictive chemical compounds such as saccharin and water," Campbell testified.

But at the March 25 subcommittee hearing, Henningfield described talking to DeNoble shortly after the papers had been pulled. And he recalled DeNoble saying that Philip Morris officials had rightly interpreted the suppressed studies as showing that, in terms of potential addictiveness, "nicotine looked like heroin."

The subcommittee decided that the only way to resolve the contradictory testimony was to question DeNoble directly. However, a "confidentiality agreement" between Philip Morris and DeNoble and his coworkers forbade the behavioral psychologist from discussing any of his nicotine research.

So at the April 14 hearing, Synar asked Campbell to release DeNoble from this gag order. After more than a little hesitation, the Philip Morris president agreed.

Two weeks later, DeNoble and Paul

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Mele, a coinvestigator at Philip Morris' short-lived behavioral pharmacology laboratory in Richmond, Va., appeared before the subcommittee to discuss their nicotine studies.

While saccharin and water can set up reinforcing behavior, DeNoble said, they do so only if an animal can taste the saccharin or is thirsty for water. What sets addictive drugs apart is that brain chemistry drives the reinforcing behavior. Thus, intravenous injections of an addictive substance — which can't be tasted or felt in the tactile sense — will satisfy the brain's craving.

DeNoble said his work demonstrated that, like heroin and cocaine, intravenous nicotine satisfies such a craving. Moreover, he and Mele used a series of chemicals that block certain drug receptors in the brain "to show that it was the brain activity of nicotine . . . that determined its reinforcing effects." That's what makes intravenous self-administration of nicotine by animals — as demonstrated by DeNoble and Mele — "a hallmark" of addiction, observed NIDA Director Alan Leshner in an April 13 letter to Waxman.

And what of the tobacco companies' claim that DeNoble's work indicated nicotine is not addictive?

"When you talk about addiction, you're talking about a human condition," DeNoble says. Animal studies, especially the preliminary ones his lab conducted in the early 1980s, could not establish whether a substance would prove addictive, he says. Indeed, his lab was unable to establish that discontinuing nicotine could induce withdrawal symptoms. Those findings would come later, DeNoble testified, from labs that used more sensitive screening techniques.

However, he pointed out, his lab's groundbreaking work on self-administration by rodents "clearly shows that nicotine is an intravenously delivered reinforcer." And that, he emphasized, "is a

characteristic of a drug of abuse." As such, he testified, his work indicated the potential for nicotine to be addictive in humans. And work since 1984, DeNoble said, has established "an overwhelming body of evidence that nicotine does produce an addiction in the human."

How much of this did company officials know, Waxman and others asked? "Senior research management in Richmond, Va., as well as top officials at the Philip Morris Co. in New York continually reviewed our research and approved our research," DeNoble said.

But were they specifically told about nicotine's potential addictiveness, the subcommittee asked? Yes, DeNoble and Mele said — and that appeared to be why the company asked them to pull two manuscripts and a poster paper that had been approved for publication.

"It had to do with the fact that this would not look good in current litigation," DeNoble recalled — litigation in which admitting nicotine's addictiveness would undercut claims that people could voluntarily quit smoking any time they learned it might harm their health.

Indeed, DeNoble and Mele recalled that at least three attorneys descended on the lab for days, sifting through their research files, photocopying documents and data. Two months later — in November 1983 — the company's president-CEO and a lawyer from its New York office visited their lab. After DeNoble and Mele demonstrated a rat self-administering nicotine, the CEO asked if this indicated that the drug was addictive. DeNoble told him such behavior only suggested the drug's potential for addictiveness. That prompted the lawyer to ask if the test they had just witnessed was one a government agency would use to demonstrate addiction. DeNoble says he answered, "It's the exact procedure that NIDA would use to demonstrate abuse liability, yes."

At about this time, officials at the company's Richmond research facility began talking about shutting down the

nicotine pharmacology lab it had asked DeNoble to establish only 3 years earlier. But because the officials thought the nicotine work ought to continue, they considered having the pharmacologists set up as independent contractors in the Richmond area, the researchers testified. However, DeNoble recalled, "that really [wouldn't] remove [the studies] from the company as much as they would like, so they talked about sending us to Lausanne, Switzerland, to a contract facility"

Since cigarette companies have the technical know-how to eliminate nicotine, why don't they? It provides "an important flavor to me," explains Alexander W. Spears, chief operating officer of the New York City-based Lorillard.

But other, nonaddictive compounds could provide the same biting, acrid flavor, so why not use a substitute and "take the nicotine out of the product," Synar asked.

"Why should we take the nicotine out?" Spears responded. "It is integral to the product."

Waxman proposes either requiring manufacturers to take nicotine out or putting a label on cigarette packs warning against nicotine's addictive properties — something he says the industry has successfully lobbied against in the past.

New legislation would also step up policing of cigarette sales to minors. Figures from the Centers for Disease Control and Prevention indicate that about 75 percent of smokers become addicted by age 18 — before it is even legal for most of them to buy tobacco products.

Contending that cigarettes are "the single most dangerous consumer product ever sold," Waxman argues that such moves would constitute pretty tame medicine. □

Next: Chemicals That Manufacturers Add to Cigarettes

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The major emitters of mercury are soil and vegetation evapotranspiration, followed by all kinds of combustion (household fires, forest fires, slash-and-burn clearing of land, brick-making, and, last, power plants).

One ton of mercury emissions per day is nothing compared to over 100 tons per day from all global sources.

*Evaldo L. Kothny
Walnut Creek, Calif.*

Hidden risks of testicular cancer?

In the sidebar to the article about testicular cancer ("Manhood's Cancer," SN: 2/26/94, p.138), there was posed the question of why such cancers are occurring more frequently since the early 1940s. I suspect that the cause is related to the reduction in sperm counts observed in recent years.

I suggest that both phenomena are related to the switch during the past 40 years from loose (boxer) underwear to tight (jockey) underwear worn by men.

*Loy Wiese
Berkeley, Calif.*

Since professional and white-collar occupations tend to be sit-down occupations, I am moved to wonder whether the true risk factor for testicular cancer is not a period of elevated testicular temperature and to ask whether anyone has compared the incidence of testicular cancer in wearers of jockey and boxer shorts.

*Thomas A. Easton
Belfast, Maine*

No chance of bias

I would like to respond to Warner Clements' charge ("Questioning psi-ence," SN: 3/19/94,

p.179) that subjects' preferences for particular targets in the ganzfeld ESP experiments reviewed by Bem and Honorton would raise the probability of .25. This is impossible.

If a sender has a preference for one of the targets in a four-item target pool, the probability that that target will in fact prove to be the actual target is still .25 because the targets are selected randomly. The sender is not free to select whatever target he or she finds most appealing, as is implied in Clements' letter. Thus, any common bias the sender and receiver might have for a particular target cannot raise the probability of a hit above chance.

*Douglas M. Stokes
Wayne, Pa.*

CORRECTION

In "Radar paints land with colors of life" (SN: 4/23/94, p.263), the two radar images are reversed.