REGULATORY POLICY

Nicotine Scrutinized as FDA Seeks to Regulate Cigarettes

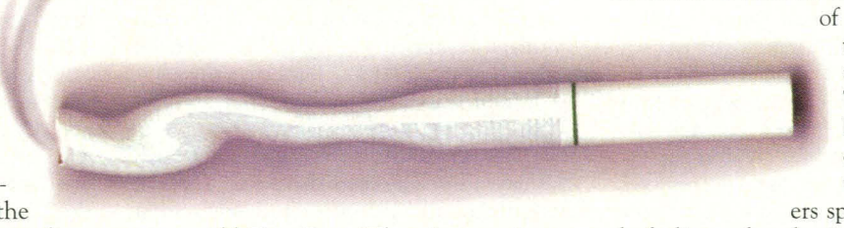

ILLUSTRATION: C. FABER SMITH

To cigarette smokers, the desire to smoke tobacco appears to be irresistible—so irresistible that about half will continue to smoke even after having a cancerous lung removed. Faced with any lesser incentive than imminent death, the chances that a smoker will stop are slim: About 80% of smokers say they want to kick the habit, but, each year, fewer than one in 10 actually succeeds.

To those trying to quit cigarettes, it may seem obvious that nicotine is an addictive drug. But over the next few months, the scientific evidence for that proposition is likely to be at the center of a major public health debate. The reason: Food and Drug Administration (FDA) commissioner David Kessler said in a letter to an antismoking coalition that the agency has evidence that tobacco companies intend cigarettes to provide nicotine to satisfy an addiction. And if that intention can be proved, the FDA gets to regulate cigarettes under the Federal Food, Drug, and Cosmetic Act, which considers a product a drug if the vendor intends it to be one. Kessler will discuss that proposition on 25 March at a hearing before a House of Representatives subcommittee on Health and the Environment, chaired by Henry Waxman (D–CA).

Until now, the FDA has always given tobacco companies the benefit of the doubt when they claim they sell cigarettes to provide sensory pleasure, not to satisfy an addiction. What's changed the FDA's attitude are allegations, detailed by ABC's *Day One*, that tobacco companies tailor the manufacture of cigarettes to deliver precise doses of nicotine in order to maximize addiction and minimize consumer attrition. Industry spokesperson Thomas Lauria of the Tobacco Institute says that those charges are "completely false." But if the FDA can show them to be true, then the door is open for regulation—a move that could ultimately result in a prohibition on cigarettes.

To make his case, however, Kessler will need proof that nicotine is addictive. At next week's hearing, he is expected to cite studies showing just how nicotine keeps smokers hooked, including recent research that suggests nicotine creates addicts by activating the same neural "reward" mechanisms that drive the primordial urges to eat, drink, or have sex. As Jack Henningfield, an expert on nicotine addiction at the National Institute of Drug Abuse (NIDA) in Baltimore, told *Day One*: "The cigarette is essentially the crack cocaine form of nicotine delivery."

But is nicotine as addictive as Henningfield's quote implies? With the exception of the Tobacco Institute's Lauria, the experts consulted by *Science* universally said yes. They cite the Surgeon General's 1988 report on the health consequences of smoking as showing conclusively that smoking, far from being a simple social habit as had once been postulated, results in a chemical dependency on nicotine that is similar to addiction to heroin or cocaine. For example, smokers show the three classic signs of addiction, says Henningfield. They become dependent; smokers who want to quit can't. They become tolerant; although a plateau is eventually reached, smokers initially have to take larger and larger doses to gain the same benefits. And finally, humans who do quit suffer clear symptoms of physical withdrawal, including headaches, constipation, insomnia, depression, an inability to concentrate, and anxiety.

That nicotine—or the lack of it—can have such powerful effects is dramatically illustrated by one study cited in the Surgeon General's report. It suggests that, on a gram-for-gram basis, nicotine is five to 10 times more effective at producing positive mood changes than amphetamines, which, pharmacologically, have very similar actions to cocaine. In practice, says Henningfield, who contributed to the work, "people take much higher doses [of heroin and cocaine than nicotine] because they have to, to get the effects."

One gap in the evidence cited in the Surgeon General's report, however, was a clear understanding of the biochemical pathways through which nicotine exerts its addictive effects. But that gap is gradually getting filled. For instance, over the past few years, researchers have found that nicotine activates certain neurons in a part of the brain called the mesolimbic system, the very pathway that creates the intense cravings to consume certain foods and drink, or to have sex.

Nicotine researchers first became interested in the mesolimbic system after David Roberts, then at the University of British Columbia in Vancouver, showed in the 1970s that this system is activated in rats addicted to cocaine. In an unaddicted animal, when the mesolimbic system is stimulated by an incoming signal—perhaps generated by eating pleasant-tasting food—certain of its neurons release dopamine, one of the chemicals that transmit signals between nerve cells. That dopamine release effectively produces a chemical reward that researchers speculate creates subtle feelings of euphoria, "conditioning" the animal into seeking out that food again. Cocaine, it turned out, blocks the re-uptake of the dopamine at the nerve endings, thus prolonging its action and enhancing its euphoric effects.

Nicotine works on those same dopamine-releasing neurons of the mesolimbic system, says John Dani, a nicotine receptor researcher at Baylor College of Medicine in Texas. "Nicotine [appears] to commandeer these normal pathways of reward," he says. "When you smoke a cigarette....It tells you to keep on smoking."

Nicotine's action is somewhat different from cocaine's, however. Rather than blocking cocaine uptake, nicotine stimulates its release. One indication of that came as early as 1986, when Assunta Imperato and Gaetano Di Chiara of the University of Cagliari in Italy showed that subcutaneous injections of nicotine more than double the levels of dopamine in a rat's mesolimbic system.

More direct evidence that nicotine acts through the mesolimbic system comes from studies of the receptors through which the drug exerts its action on nerve cells. These are the same receptors that respond to the neurotransmitter acetylcholine, whose actions nicotine mimics when it binds to the receptors. Since one type of these receptors is found on the dopamine-releasing mesolimbic neurons, nicotine activation of the receptor stimulates the neurons to release dopamine.

And over the past few years William Corrigall of the Addiction Research Foundation in Toronto and his colleagues, using rats that are trained to push a lever five times to get a dose of nicotine injected directly into their veins, have further established the importance of the mesolimbic system for nicotine addiction. In 1991 and 1992, the Corrigall team showed that the rats lose their appetite for nicotine, and stop pressing the levers, if they receive injections of chemicals that block the action of dopamine or if the nerve fibers in their mesolimbic systems are destroyed. And, in an upcoming issue of the journal *Brain*

Research, they will report that infusions into the mesolimbic system of tiny amounts of chemicals that block the binding of the nicotine to its receptors also cures rats of their nicotine addiction. "Its the same system that cocaine targets, except that cocaine binds at [receptors] at the ends of the nerves, [and nicotine binds to receptors] in the cell bodies," says Corrigall.

Nicotine's effects on the dopamine reward system may also explain why, despite the unremitting drive to smoke, many smokers find that only the first cigarette of the day truly satisfies. In the rat, at least, too much nicotine results in too little dopamine release, according to studies presented by David Balfour of the University of Dundee, Scotland, at a workshop held in February 1993 by the German Research Council on Smoking and Health in Titisee, Germany. When Balfour and his colleagues gave rats five or six daily subcutaneous injections of nicotine, they found that the animals secreted pulses of dopamine in response to each injection. If, however, the rats receive a constant subcutaneous infusion of nicotine for 10 days prior to, as well as during, the injections, dopamine secretion remains normal. Balfour says that this situation more closely resembles what happens with a human smoker.

"Plasma nicotine levels are rising through the day until it gets to the point where it desensitizes the receptor, and when that happens you no longer get the buzz, the pleasant sensation," says Balfour, a theory with which Dani and Corrigall both agree.

Of course the new studies on nicotine receptors and the mesolimbic system have yet to explain all facets of cigarette smoking. For example, why do people smoke in the first place despite feelings of nausea? And what accounts for the withdrawal symptoms?

Nonetheless, "all these studies will be critical to the FDA's case." predicts Edythe London of NIDA, who also studies nicotine's effects on the brain. "Since the 1980s," she says, "we've shown that when you give the nicotine, it gets into the brain, interacts with specific receptors in the brain, and has distinct effects on the brain. All cigarettes are, are a sophisticated system for delivering the drug." And that is exactly what the FDA wants to prove.

–Rachel Nowak

With reporting by Richard Stone.

ARCHEOLOGY

Professor Slams MIT Over Center Closure

For Heather Lechtman, 1984 was a banner year. In recognition of her work as director of the Massachusetts Institute of Technology's (MIT) Center for Materials Research in Archeology and Ethnology (CMRAE)—a pioneering effort to integrate the usually separate worlds of the physical and social sciences—the MacArthur Foundation awarded her one of its prestigious fellowships: a so-called genius grant. A decade later, however, MIT is about to recognize Lechtman's work in a less auspicious way: It plans to close CMRAE down at the end of June, a move that has sparked a bitter feud on campus.

MIT's provost Mark Wrighton delivered CMRAE's sentence last August, even though all but one member of a seven-person review committee that he had convened to examine the center's future had recommended expanding it into an MIT graduate degree-granting entity. Now, Lechtman, a physicist, anthropologist, and art historian, has launched an unusually fierce and public counterattack. Her principal weapon: More than 400 copies of a 29-page pamphlet, titled *An Institute In Ruins*, that she distributed in the past few weeks to MIT colleagues and staff.

In the pamphlet and interviews with *Science*, Lechtman charges that Wrighton intended all along to shut down the center. The 1993 review was just a "sham," Lechtman contends. As just one piece of evidence, she cites his choice of MIT history professor Peter Perdue to chair the committee. Perdue, she claims, was visibly antagonistic to the center and deliberately ignored the positive consensus of the other six review members. Other MIT faculty, however, suggest the center's troubles result more from something pointedly ignored by the pamphlet: a long divisive battle, over issues such as teaching load and control of the center, between Lechtman and MIT's humanities department, which oversaw the center. After that battle, they say, the center with Lechtman as director was left with no viable home. The humanities department would not support it, no other school wanted to add to its budget, and the provost was reluctant to take CMRAE under his own wing.

"The administration has thrown away something unique."

—Heather Lechtman

For his part, Wrighton denies predetermining CMRAE's closure. While praising the center, he says that at a time when MIT is facing a budget deficit, it simply did not garner sufficient interest, compared to other projects, among the school's deans to warrant an expensive expansion that would include the hiring of at least two new faculty members. "I rest comfortable with the review process and the eventual outcome," he told *Science*. (Perdue declined to be interviewed for this story.)

That outcome apparently marks the end of a trailblazing effort in archeometry, the application of materials science techniques to the study of historical artifacts, that began in the 1960s in the lab of MIT metallurgist Cyril Stanley Smith. His interests led to the creation, in 1977, of CMRAE and the selection of Lechtman as its first and only director. Although run by MIT, the center is actually a consortium of eight local institutions, including Harvard, Boston University, Wellesley, and Boston's Museum of Fine Arts. In short, says Lechtman, the center's goal is "to read culture out of technological behavior." Pursuing that goal, CMRAE has held classes and summer symposia and, in general, served as a rigorous training ground for those pursuing the relatively new discipline of archeometry.

CMRAE wins high marks for those efforts from archeologists, who are particularly happy with the center's home at MIT, because it provides access to the school's wealth of lab equipment and materials scientists. It's that access, agreed all the members of the review except Perdue, that could have made MIT one of the top archeology graduate programs in the nation, if the university had decided to expand the center's faculty and resources. "I'm really saddened by the closing," says University of Chicago archeologist Jane Buikstra, who participated in the center's review. So are members of the consortium, who had even offered to help provide classes and faculty to MIT, if that was what was holding back the establishment of a graduate program. Wrighton simply ignored the proposal, says Lechtman.

While her treatise will apparently not change the center's fate, Lechtman says she has achieved some goals by taking the dispute public. One was to explain that "the administration has thrown away something unique in the truest sense of the word," a particularly ironic act, she says, since the school heavily promotes the idea of bridging the arts and sciences. The second goal was to prompt MIT to take a new look at how the school evaluates interdisciplinary centers and to develop better guidelines to ensure the integrity of such reviews. That may be happening: MIT president Charles Vest has already convened a small committee of faculty to review the process by which the school decided to close the center.

–John Travis