NEW CONCEPTS

- New research has overturned the dogma that cigarette addiction takes years to develop. Studies of adolescent smokers show that symptoms of addiction, such as withdrawal, craving for cigarettes and failed attempts at quitting, can appear within the first weeks of smoking.
- To account for these findings, scientists have developed a new theory positing that the brain quickly develops adaptations that counter the effects of nicotine. These adaptations lead to withdrawal symptoms when the effects of nicotine wear off.
- The results highlight the importance of boosting government funding for antismoking campaigns, particularly those aimed at youngsters.

—The Editors

HOOKE FROM THE FIRST CIGARETTE

New findings reveal that cigarette addiction can arise astonishingly fast. But the research could lead to therapies that make quitting easier

By Joseph R. DiFranza

While I was training to become a family doctor, I learned the conventional wisdom about nicotine addiction. Physicians have long believed that people smoke primarily for pleasure and become psychologically dependent on that pleasure. Tolerance to the effects of nicotine prompts more frequent smoking; when the habit reaches a critical frequency—about five cigarettes per day—and nicotine is constantly present in the blood, physical dependence may begin, usually after thousands of cigarettes and years of smoking. Within hours of the last cigarette, the addicted smoker experiences the symptoms of nicotine withdrawal: restlessness, irritability, inability to concentrate, and so on. According to this understanding, those who smoke fewer than five cigarettes per day are not addicted.

I was armed with this knowledge when I encountered the proverbial patient who had not read the textbook. During a routine physical, an adolescent girl told me she was unable to quit smoking despite having started only two months before. I thought this patient must be an outlier, a rare exception to the rule that addiction takes years to develop. But my curiosity was piqued, so I went to the local high school to interview students about their smoking. There a 14-year-old girl told me that she had made two serious attempts to quit, failing both times. This was eye-opening because she had smoked only a few cigarettes a week for two months. When she described her withdrawal symptoms, her story sounded like the lament of one of my two-pack-a-day patients. The rapid onset of these symptoms in the absence of daily smoking contradicted most of what I thought I knew about nicotine addiction. And when I tracked that received wisdom back to its source, I found that everything I had learned was just a poor educated guess.

With funding from the National Cancer Institute and the National Institute on Drug Abuse (NIDA), I have spent the past decade exploring how nicotine addiction develops in novice smokers. I now know that the model of addiction described in the opening paragraph is fiction. My research supports a new hypothesis asserting that limited exposure to nicotine—as little as one cigarette—can change the brain, modifying its neurons in a way that stimulates the craving to smoke. This understanding, if proved correct, may someday provide researchers with promising avenues for developing new drugs and other therapies that could help people kick the habit.

A Loss of Autonomy

When I started this investigation in 1997 with my colleagues at the University of Massachusetts Medical School in Worcester, our first challenge was to develop a reliable tool to detect the first symptoms of addiction as they emerged. In my view, the defining feature of addiction is
the loss of autonomy, when the smoker finds that quitting cigarettes requires an effort or involves discomfort. To detect this loss, I devised the Hooked on Nicotine Checklist (HONC); an answer of “yes” to any of the questions on the list indicates that addiction has begun [see side bar on page 86]. Now in use in 13 languages, the HONC is the most thoroughly validated measure of nicotine addiction. (And the checklist could easily be adapted to the study of other drugs.)

We administered the HONC to hundreds of adolescents repeatedly over three years. It turned out that the rapid onset of addiction was quite common. The month after the first cigarette was by far the most likely time for addiction to begin; any of the HONC symptoms, including cravings for cigarettes and failed attempts at quitting, could appear within the first weeks of smoking. On average, the adolescents were smoking only two cigarettes a week when the first symptoms appeared. The data shattered the conventional wisdom and provided a wealth of insight into how addiction starts. But when I presented these
findings in February 2000 and proclaimed that some youths had symptoms of addiction after smoking just one or two cigarettes, I was widely regarded as the professor who had not read his textbook correctly.

Many laypeople told me that they knew from experience that I was on the right track. But if any scientists believed me, they were not willing to risk their reputations by admitting it publicly. Skepticism was widespread. How could addiction start so quickly? How could withdrawal symptoms be present in smokers who do not maintain constant blood levels of nicotine?

Vindication has come with time as teams of investigators led by Jennifer O’Loughlin of McGill University, Denise Kandel of Columbia University and Robert Scragg of the University of Auckland in New Zealand replicated all of my discoveries. A dozen studies have now established that nicotine withdrawal is common among novice smokers. Of those who experience symptoms of addiction, 10 percent do so within two days of their first cigarette and 25 to 35 percent do so within a month. In a very large study of New Zealand youths, 25 percent had symptoms after smoking one to four cigarettes. And the early appearance of HONC symptoms increased the odds that the youths would progress to daily smoking by nearly 200-fold.

These results raise the question of how the nicotine from a single cigarette could alter the brain enough to trigger the onset of addiction. Earlier research with laboratory animals has found that chronic high-dose exposure to nicotine—the equivalent of one to three packs a day—stimulates an increase in the number of neuron receptors that have a high affinity for nicotine. Autopsies of human smokers reveal 50 to 100 percent increases in the brain’s frontal lobe, hippocampus and cerebellum.

I persuaded Theodore Slotkin of Duke University to determine the minimum nicotine exposure needed to provoke this so-called up-regulation of receptors. On consecutive days his team administered small amounts of nicotine (equivalent to one to two cigarettes) to rats and found up-regulation in the hippocampus—which is involved in long-term memory—by the second day. Subsequently, Arthur Brody and his colleagues at the University of California, Los Angeles, discovered that the nicotine from one cigarette was sufficient to occupy 88 percent of the brain’s nicotinic receptors. Although the role of receptor up-regulation in addiction
is unknown, these studies make it physiologically plausible that adolescents could have withdrawal symptoms just two days after their first cigarette.

According to addiction researchers, withdrawal symptoms result from drug-induced homeostatic adaptations—the body’s attempts to keep its functions and chemicals in balance. For example, certain addictive drugs increase the production of neurotransmitters—chemicals that transmit signals among neurons—and in response the body develops adaptations that inhibit these chemicals. When the user stops taking the drug, however, the inhibition becomes excessive and withdrawal symptoms appear. We know that these withdrawal-related adaptations could develop rapidly after the first cigarette, because other addictive drugs such as morphine produce similar changes very quickly. But most longtime smokers find they can forgo cigarettes for only an hour or two before craving another, whereas novice smokers can go weeks without lighting up. Amazingly, in the early stages of addiction a single cigarette can suppress withdrawal symptoms for weeks, even though the nicotine is gone from the body within a day.

The explanation for this remarkable fact is that the consequences of flooding the brain with nicotine linger long after the event itself. Nicotine triggers brain circuits involving biochemical compounds such as acetylcholine, dopamine, GABA, glutamate, noradrenaline, opioid peptides and serotonin. In rats, a single dose of nicotine increases noradrenaline synthesis in the hippocampus for at least one month, and nicotine’s effects on certain neurological and cognitive functions also persist for weeks. Although it is not known if any of these phenomena are related to withdrawal, they establish that the impact of nicotine far outlasts its presence in the brain.

The symptom-free interval between the last cigarette and the onset of withdrawal is called the latency to withdrawal (LTW). For novice smokers the LTW is long, and a cigarette every few weeks keeps withdrawal in check. With repeated use, however, tolerance develops and the impact of each cigarette diminishes; the LTW shortens, and cigarettes must be spaced at ever closer intervals to stave off withdrawal. This phenomenon of diminishing LTW is called dependence-related tolerance. Compared with the withdrawal-related adaptations that may appear overnight, dependence-related tolerance typically develops at a glacial pace. It may take years for the LTW to shrink enough to require someone to smoke five cigarettes a day. In reality, then, withdrawal symptoms are the cause of long-term heavy use, not the other way around as we had previously thought.

Time for a New Theory

I had always been skeptical of the notion that smokers were addicted to the pleasure of smoking, because some of my most addicted patients hated the habit. If the conventional thinking were correct, shouldn’t the most addicted smokers enjoy it the most? Eric Moolchan of the NIDA demonstrated that although adolescents showed increasing levels of addiction over time, they reported decreasing pleasure from smoking. A new theory was needed to explain these discoveries.

While struggling to understand the rapid onset of nicotine addiction, a paradox occurred to me. The only action of nicotine that is obvious to the casual observer is that it provides a temporary suppression of craving for itself, yet only people previously exposed to nicotine crave it. How can one drug both create craving and suppress it? I began to speculate that the direct immediate action of nicotine is to suppress craving and that this action could become magnified to an extreme because subsequent doses of nicotine provoke greater responses than the first dose. (This phenomenon, common to all addictive drugs, is known as sensitization.) The brain might then quickly develop withdrawal-related adaptations to counter the action of nicotine, thereby restoring the homeostatic balance. But when the action of nicotine wore off, these adaptations would stimulate craving for another cigarette.

Under this sensitization-homeostasis theory, nicotine is addictive not because it produces pleasure but simply because it suppresses craving. Because nicotine stimulates neurons, I envisioned it activating the nerve cells in a craving-inhibition system in the brain. Activation of this hypothesized system would then suppress the activity in a complementary system for generating cravings. The natural role of the craving-generation system would be to receive sensory cues (such as sights and smells), compare them with memories of rewarding objects (such as food), and produce craving to motivate and direct appetitive behavior (such as eating). The role of the craving-inhibition system would be to signal satisfaction so that the animal would

**GLOSSARY**

**Nicotine withdrawal:** A cluster of symptoms that include craving, restlessness, nervousness, irritability, difficulty concentrating and difficulty sleeping.

**Latency to withdrawal:** The symptom-free interval between the last cigarette and the onset of withdrawal symptoms. It can shrink from weeks to minutes over many years of tobacco use.

**Dependence-related tolerance:** The mechanism that causes the latency to withdrawal to shrink gradually over time.

**Abstinence-related adaptations:** A mechanism that mimics the action of nicotine by inhibiting craving. It develops in ex-smokers to counter the enduring effects of dependence-related tolerance.

**Joseph R. DiFranza** is a family physician practicing out of the University of Massachusetts Medical School in Worcester. A perennial thorn in the side of the tobacco industry for 25 years, DiFranza has been an advocate for efforts to prevent the tobacco industry from selling its products to children, and it was his research and complaint to the Federal Trade Commission that resulted in the demise of the notorious Joe Camel advertisements for Camel cigarettes. DiFranza has received a grant from Pfizer to determine whether his theory of cigarette addiction explains the effectiveness of smoking-cessation medications.
stop the appetitive behavior when it became appropriate to do so.

Because the body would try to keep these two systems in balance, the nicotine-induced suppression of the craving-generation system would trigger the development of withdrawal-related adaptations that would boost the system’s activity. During the withdrawal period, when the inhibitory effect of nicotine has worn off, the craving-generation system would be left in a state of excitement that would result in the excessive desire for another cigarette [see box on page 84]. These shifts in brain activity would come about through rapid changes in the configurations of neuron receptors, which would explain why adolescents could start to crave cigarettes after smoking just once.

The first support for this model has come from the many functional magnetic resonance imaging (fMRI) studies of humans showing that cue-induced craving for nicotine, alcohol, cocaine, opiates and chocolate increases metabolic activity in the anterior cingulate gyrus and other frontal-lobe areas of the brain. This finding suggests the existence of a craving-generation system. And Hyun-Kook Lim and his colleagues at the Korea College of Medicine recently found evidence that nicotine suppresses this system. The researchers demonstrated that prior administration of the drug can block the pattern of regional brain activation that accompanies cue-induced craving in humans.

The sensitization-homeostasis model can also explain dependence-related tolerance. Repeated suppression of activity in the craving-generation system triggers another homeostatic adaptation that stimulates craving by shortening the duration of nicotine’s inhibitory effects. As mentioned earlier, tolerance develops much more slowly than the withdrawal-related adaptations, but once it emerges tolerance becomes firmly entrenched. Although it usually takes two years or more before adolescents need to smoke five cigarettes a day, I noticed that when my patients quit smoking and then relapsed, it took them only a few days to return to their old frequency, even after a lengthy abstinence.

Along with Robert Wellman of Fitchburg State College, I investigated this phenomenon in a study that asked 2,000 smokers how much they smoked before quitting, how long they had abstained and how much they smoked immediately after relapsing. Smokers who relapsed after an abstinence of three months renewed smoking at about 40 percent of their pre-

### THE HOOKED ON NICOTINE CHECKLIST

Researchers use the following questions to determine whether adolescent smokers are addicted. An answer of “yes” to any one of the questions indicates that addiction has begun:

- Have you ever tried to quit smoking, but couldn’t?
- Do you smoke now because it is really hard to quit?
- Have you ever felt like you were addicted to tobacco?
- Do you have ever strong cravings in places where you are not supposed to, like school?
- Have you ever felt like you really needed a cigarette?
- Is it hard to keep from smoking?
- Did you feel nervous, restless or anxious because you couldn’t smoke?
- Did you find it hard to concentrate because you couldn’t smoke?
- Did you feel more irritable because you couldn’t smoke?
- Did you feel a strong need or urge to smoke?

When you tried to stop smoking (or, when you haven’t used tobacco for a while):

- Did you think about smoking?
- Did you feel a need to smoke?
- Did you feel more nervous when you were out?
- Did you feel more irritable when you were out?
- Did you feel less able to concentrate when you were out?
- Did you feel less able to concentrate when you were out?
- Did you feel a strong need or urge to smoke? (Even if you couldn’t.)

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### ON NICOTINE

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- Do you smoke now because it is really hard to quit?
Recent studies have confirmed that nicotine evokes rapid changes in brain physiology. The author and Jean A. King of the Center for Comparative NeuroImaging at the University of Massachusetts Medical School used functional magnetic resonance imaging (fMRI) to measure levels of metabolic activity in the brains of rats given a dose of nicotine on five consecutive days. The response to the first dose was relatively limited (red areas in image on left), but brain activity was much more intense (yellow) and widespread after the fifth dose (image on right). These findings indicate that the brain quickly becomes sensitized to nicotine, enabling addiction to appear after just a few doses.

A better understanding of nicotine's deadly pull involves many symptoms of addiction very soon after they smoke their first cigarette. This finding underlines the importance of bolstering government funding for antismoking campaigns, which has fallen in recent years.

To fully test my theory, which has been simplified here, researchers need a reliable method to detect sensitization in humans. I have worked with Jean A. King and her colleagues at the Center for Comparative NeuroImaging to demonstrate nicotine sensitization in rats using fMRI. Images comparing brain responses to the first dose of nicotine and to the fifth dose given four days later illustrate the dramatic changes in brain function in areas such as the anterior cingulate gyrus and hippocampus. We have just received funding from the NIDA to use fMRI to visualize sensitization in smokers, with future plans to determine which brain regions are involved in the craving-inhibition and craving-generation systems.

Our long-term goal is to identify drugs that can manipulate these systems to treat or cure addiction. Although nicotine-replacement therapies may double the success rate for smoking cessation, failed attempts still far outnumber the successes. The sensitization-homeostasis theory suggests that what is needed is a therapy that will suppress craving without stimulating compensatory responses that only make the craving worse in the long run. A better understanding of the addiction process may help researchers develop new treatments that can safely liberate smokers from nicotine’s deadly pull.

New Hope for Smokers
This model of addiction by no means represents the prevailing opinion. In my view, addiction is an accident of physiology. Because so many careers have been built on the assumption that the roots of addiction lie in psychology rather than physiology, I did not expect my ideas to receive a warm welcome.

Whether or not the sensitization-homeostasis theory is correct, it is clear that the nicotine from the first cigarette is sufficient to trigger a remodeling of the brain. Although some may argue about what criteria should be used to render a proper diagnosis of addiction, it is now well established that adolescents have many symptoms of addiction very soon after they smoke their first cigarette. This finding underlines the importance of bolstering government funding for antismoking campaigns, which has fallen in recent years.

Thus, abstinence-related adaptations seem to counter the tolerance-related adaptations by inhibiting the craving-generation system so that it eventually stops compelling the former smoker to light up. Smoking cues in the environment might still provoke craving, however, and if the long-abstinent smoker were to surrender to an urge to smoke just once, nicotine would again produce a profound suppression of activity in the craving-generation system. The abstinence-related adaptations would then make a bad situation worse. Because these adaptations mimic the effect of nicotine, they would need to be removed to restore homeostasis; when the effect of nicotine wears off, the tolerance-related adaptations would be left unopposed in stimulating the craving-generation system. Struck with a strong craving, the relapsing smoker would need to puff six or seven cigarettes a day to keep it under control.

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