**Hooked From The First Cigarette**  
*Scientific American—May 2008*

**HOOKED 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 traced 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 sidebar 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


do not hallucinate
A NEW HYPOTHESIS

QUICK ADDICTION

Researchers have proposed a new theory to explain how withdrawal symptoms can develop so quickly in novice smokers. Although this model is controversial, it may someday lead to a better understanding of cigarette addiction.

A HEALTHY BALANCE

In nonsmokers, the brain's systems for generating and inhibiting cravings are in balance. The craving-generation system triggers appetitive behavior (such as eating), and the craving-inhibition system stops the behavior when the individual is sated (at the end of the meal).

THE FIRST CIGARETTE

Nicotine stimulates the craving-inhibition system until its activity far exceeds that of the craving-generation system. The brain attempts to restore its balance by rapidly developing adaptations that boost the activity of the craving-generation system. These changes are called withdrawal-related adaptations.

WITHDRAWAL

Once the effects of nicotine wear off, the craving-inhibition system no longer stimulates and returns to a lower level of activity. But the craving-generation system, enhanced by the withdrawal-related adaptations, now throws the brain off-balance again, producing an intense desire for the one thing that can inhibit the craving—another cigarette.

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 terms of investigators led by Jennifer O’Loughlin of McGill University, Denise Kandel of Columbia University, and Robert Schragg 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 nicotine 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 neural 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 was correct, shouldn’t the most addicted smokers enjoy it the most? Eric Moelcham 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...
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 ever have strong cravings to smoke?

Have you ever felt like you really needed a cigarette?

Is it hard to keep from smoking in places where you are not supposed to, like school?

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

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?

Did you feel nervous, restless or anxious because you couldn’t smoke?

vious rate, indicating that their LTW had lengthened. We believe the craving-free interval between cigarettes increases because the withdrawal-related adaptations disappear during the first few weeks of abstinence. With the resumption of smoking, however, the withdrawal-related adaptations quickly redevelop, and over the next few weeks relapsed smokers find they must smoke just as often as they used to.

We also discovered, however, that abstinence greater than three months had almost no additional impact on the length of the LTW. Even after years of abstinence, smoking resumed at about 40 percent of the prior rate, typically six or seven cigarettes a day. This finding suggests that increases in tolerance are permanent; a relapsing smoker will never get as much suppression of craving from a single cigarette as a novice smoker will. In other words, the brain of a smoker is never restored to its original state.

But if dependence-related tolerance stimulates the craving-generation system and never completely goes away, why don’t former smokers continue hungering for cigarettes forever? Our research subjects could not tell us why their craving for nicotine eventually lessened, so I looked at what the sensitization-homeostasis theory would predict. I reasoned that former smokers must develop abstinence-related adaptations that mimic the action of nicotine, inhibiting the craving-generation system and restoring homeostasis. Smoking cessation would not result in a quiet return to normal brain function; rather it would trigger a dynamic period of neuroplasticity during which new adaptations would appear in the former smoker’s brain. Because of these adaptations, the ex-smoker’s brain would resemble neither that of the smoker nor of the nonsmoker.

To test this prediction, Slorokin and his colleagues examined the brains of rats before nicotine exposure, during exposure, during withdrawal and long after withdrawal. They found clear-cut evidence of changes in the functioning of neurons in the brain’s cortex that employ acetylcholine and serotonin to transmit signals—changes that appeared only after the acute withdrawal period. As predicted, the brains of the “ex-smoker” rats showed unique adaptations that were not present in the “smokers” or “nonsmokers.” And at the College of Medicine at the Catholic University of Korea, HeeJin Lim and colleagues found evidence of brain remodeling in humans who quit smoking by studying brain-derived neurotrophic factor, a stimulant of neuroplasticity. Levels of this factor in ex-
smokers tripled after two months of abstinence.

Thus, abstinence-related adaptations seem to
counter the tolerance-related adaptations by in-
hibiting 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 sit-
uation worse. Because these adaptations mimic
the effect of nicotine, they would need to be re-
moved to restore homeostasis; when the effect
of nicotine wears off, the tolerance-related ad-
aptations would be left unopposed in stimulat-
ing 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.

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 remod-
eling of the brain. Although some may argue
about what criteria should be used to render a

--- MORE TO EXPLORE ---

Measuring the Loss of Autonomy over Nicotine Use in Adolescents


1. How was the conventional idea of addiction challenged at the beginning of this article?

_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________

2. What is the biochemical link that is shown by chronic exposure to nicotine?

_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________


_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________

4. Explain sensitization, common to all addictive compounds.

_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________
_____________________________________________________________________________
5. What was significant about the information learned from fMRI studies?

_____________________________________________________________________________

_____________________________________________________________________________

_____________________________________________________________________________

6. What is unfortunate about once you start smoking (that is, once you introduce nicotine to the brain)?

_____________________________________________________________________________

_____________________________________________________________________________

_____________________________________________________________________________