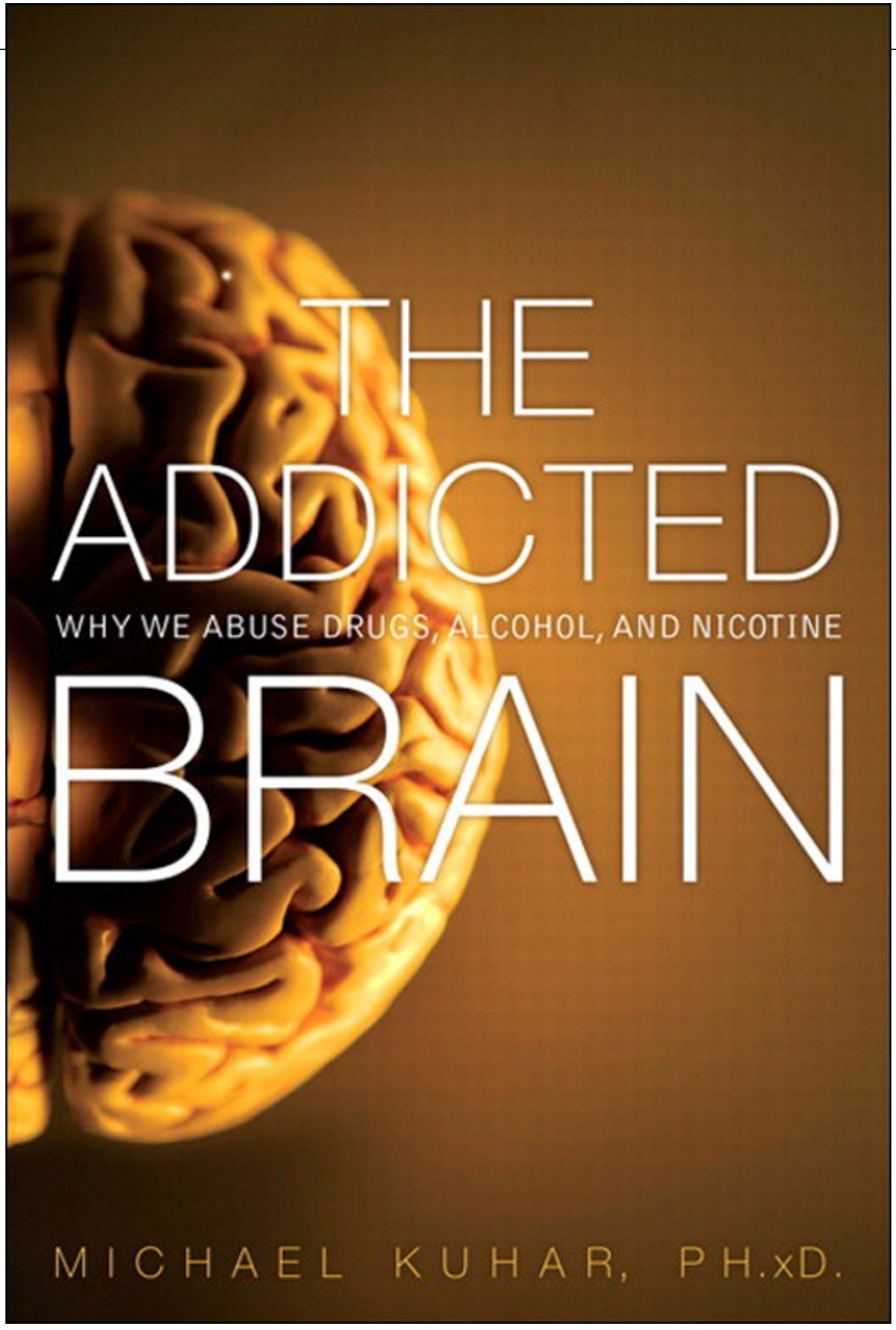
THE
ADDICTED
WHY WE ABUSE DRUGS, ALCOHOL, AND NICOTINE
BRAIN
MICHAEL KUHAR, PH.xD.

The Addicted Brain

Why We Abuse Drugs, Alcohol, and Nicotine

Michael Kuhar

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Printed in the United States of America

First Printing December 2011

ISBN-10: 0-13-254250-1
ISBN-13: 978-0-13-254250-0

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The Library of Congress cataloging-in-publication data is on file.

This book is dedicated to those afflicted with brain disease,
to their caregivers and supporters, and to the researchers
who hope for a better future.

Contents

Acknowledgments

Several individuals made important contributions to this book. I thank Dr. JoAnna Perry, who edite
contributed to several chapters, and obtained permissions for reproducing data; Sylvia Wrobel, wh
contributed to the first three chapters; Jordan Licata, who compiled the glossary; and Janie Langfor
who helped obtain permissions.

I also thank others who contributed to the book in various ways: Jo Tunstall, Pat Harris, Brenda Lloy
Susan Marshall, Dr. David Gorelick, Dr. Eliot Gardner, Dr. Roy Wise, Dr. Leonard Howell, Dr
Heather Kimmel, and Dr. Darryl Neill.

The editors, Russ Hall and Kirk Jensen, provided much needed advice and assistance every step of th
way.

I am very grateful for my mentors, colleagues, and trainees, who, for more than four decades helpe
develop my skills and knowledge so that this book was possible. Support from the National Institut
of Health (NIH) was essential.

Finally, I thank the Fulbright program and colleagues at the Catholic University in Santiago, Chil
especially Dr. Katya Gysling, who helped shape this book in my mind.

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Eddy lifetime achievement award from the College on Problems of Drug Dependence.

Introduction

Robert's friends convinced him to try crack cocaine at a senior party when he was still 17 years old. took his head places he could only imagine, and he wanted more, more, more. Three years later, h could no longer hold a job. His teeth were loose and two had fallen out. He stole. He sold his body. H did anything for more! He had been to rehab twice and was back on the street again, and all he wante was more.

This is a book about seduction, amazing pleasure, and a world inside your head that is both fantas and real. This fantasy world is not easy to give up, and, like all fantasies, it can be trouble if you can get back into the real world where you need to live, work, pay bills, and take care of loved one Drugs, the brain, and addiction create this dreamland of fantasy, but it can quickly turn into a hell, an it often does.

Research has taught us how drugs and other pleasures affect the brain. It turns out that drug gambling, Internet use, and chocolate all affect the brain in similar ways. The importance of th discovery extends well beyond knowing about drug abuse and pleasure; it impacts on ethics an morality, the nature of the brain as a survival organ, the evolution of the brain, and the good, the ba and the ugly of human nature. Anything that reveals the vagaries and limitations of the human brain useful and a service to us all. Understanding the brain and human behavior is a basic requirement f setting realistic goals for personal and societal improvement.

Aside from the amazing discoveries, a special glory of this book is the inclusion of wonderf techniques that help us examine the brains of drug users. For example, the development of bra imaging enables us to study how drugs affect the brain without any physical invasion of the head. Th is something not even imagined decades ago. There are many other striking techniques such as dru self-administration and biochemical analyses of tissues. When I say this is a glory, I realize th reveals something about me and my preferences, but you are invited to share in this. I'm lucky that have spent more than four decades doing this science, watching its progress, and seeing its impact o public health. Within these pages is a fascinating story of science in the service of men.

Different drugs, some legal and others illegal, release powerful demons in our brains. Surprisingly, th demons—the chemicals and nerve cells in our brains—are already there, working in an important b much smaller way that is essential for our functioning. Drugs create the demons by disrupting th chemicals and nerve cells so that they get out of control and wreak havoc in many people. Decades scientific research have revealed how this happens.

The demons behave as expected. Once unleashed and in power, they don't go away easily. Even afte we stop taking drugs, they influence our actions for a long time, for many months or even years. The want you to continue to feed them by taking more and more drugs. Part of the power of the demons that they reside in powerful brain systems. These brain systems *have* to be powerful because they hav a big job, such as keeping us fit and surviving. The long life and the power of the demons make the formidable enemies, but we are not alone or helpless. Treatment and rehab centers help us regai control of our lives. The same demons seem to apply to other addictions—gambling, carbohydrate sex, and the Internet. Studying one addiction—drugs—helps us understand other addictions.

Knowing the demons is helpful. Because we can understand them and what they do, we can develo medications and other treatments to thwart them and help drug users. In fact, the search f medications, although not yet complete, has been quite successful. We gain ground every day. Also changing our behaviors and habits in constructive ways thwarts the demons.

Some of us are lucky and we either have no interest in drugs or can walk away from them at any tim
Everybody's brains are different, at least to some degree, and have different vulnerabilities to dru
use. Surprisingly, women and men respond differently to drugs, and so do adolescents and adult
Teens are a special concern because of their youth and increased sensitivity to drugs. Many studi
have revealed why this is so and why some of us are more likely to get into trouble with drugs tha
others. Stress, involved in so many health problems, also feeds the demons of drug abuse. O
genetics also play a role, but not an overwhelming one; we can still fight back.

Drug abuse and addiction are costly, not the least because of the misery they bring. Because of th
cost, society has invested in science to combat drug use. It is paying off. We have found the demon
and we can fight. But if you are new to the war itself, because of the addiction of a loved one,
patient, or yourself, then prepare to arm yourself to fight.

1. What's in This Book, and Why Should I Read It?

"I'm only 14 years old and I'm in a drug counselor's office. I've been stealing, missing school, ar failing most of my subjects. It seemed to start when I got involved with drugs. We got dope fro older brothers and sisters, from parents' medicine cabinets, and on the streets. We never thought of as 'doing drugs.' We were just having fun and hanging out, and we thought we could stop anytim But we fooled ourselves. It caught up to us big time. Now I need to find out about what happened ar what I can do to turn my life around. I need to know everything!"

Getting hooked on drugs is a sequence of attraction, seduction, compulsion, and pain. Drugs a dangerous and widespread, and dealing with them requires knowledge and help. This book is abo alcohol, nicotine, and illegal drugs—how they work, what they do to the brain, and what can be do to stop using them. The book is especially about what happens inside the brain and why the brain ju happens to be set up for drugs. Yes, the brain is set up for drugs; the brain is a co-conspirator, albeit a unwitting one!

When is someone a drug abuser or an addict?[1] If someone uses drugs casually and infrequent without significant problems and can take them or leave them, that person might best be called a *use* which is still a dangerous situation. If taking drugs causes significant distress and problems in th person's life, then *abuser* might be the best descriptor. If drugs are in control of a person's life, or they can't stop, or if they do drugs in spite of personal distress and negative consequences, then the might be drug *dependent* or *addicted*. Even people who are not users, abusers, or addicts are ve likely to gain from reading this book.

The text box that follows provides definitions of specific levels of drug use. Addiction is the mo serious form of the disorder[2] and it can develop when drugs are taken repeatedly over a long period time. Taking larger quantities of drugs more frequently is likely to result in addiction more quickl However, there is no mathematical equation describing this process. It is not exact. Moreover, th process varies depending on the individual and his or her circumstances.

Definitions

DSM IV TR is the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* that is published through t American Psychiatric Association. It is the official manual for defining and diagnosing the spectrum of disorders that involve dr use. It is used by professionals to more precisely define the degree of drug abuse. Please see this manual for the offic definitions.[3]

- **Drug use** can refer to any use of a drug, but more often, it refers to an occasional or recreational use of drugs. In this ca acute or immediate effects and toxicities can be significant. If the drug used is an illegal one, then there is the leg transgression to be concerned with, too. Also, there is the danger of continued use of drugs to where they become a mo serious problem.
- **Drug abuse** is a more serious problem where there is a greater degree of drug use and a distressing or negative impact on t drug user's life. It can get further out of control.
- **Addiction** or **dependence** is yet more serious and includes more of a loss of control over drug seeking and drug taking in sp of distress and/or negative consequences. Note that both loss of control over behavior and distress or negative consequenc are emphasized. But, there are additional characteristics of drug addiction that are well known. Considerable time may spent getting and using the drug. More drug is taken than intended. Efforts to stop taking the drug often fail. Tolerance, whi is the need to take larger quantities of the drug to get the same effect, develops. Also, perhaps there are withdrawal sympto when the effect of the drug wears off. Thus, an individual might have a problem with drugs even though there are distressing feelings or negative consequences that are evident. The words addiction or dependence are used to refer to mo severe cases of drug seeking and taking.

The use of drugs is not simply a passing fad or the latest, cool thing. Drugs of one type or another hav
been with us for a long time, literally thousands of years. Opium has been used in China for centurie
and cocaine use in early Indian cultures goes back centuries. There is even a reference in the Bib
about getting drunk on wine. There are things about both the nature of drugs and the human brain th
make drug use enduring over the ages, and this reveals a special vulnerability in humans. For exampl
in 2006-2007 in the United States, there were more than 22 million people, 12 years of age and olde
who were classified with drug abuse or drug dependence on illicit drugs[4] or alcohol.

What is it about addiction that grips certain individuals so firmly that they lose at least some contr
over their drug taking and sometimes over their lives? This book attempts to answer this question b
examining research discoveries from the previous couple of decades. Extraordinary progress has bee
made in drug abuse research.

What Is a Drug?

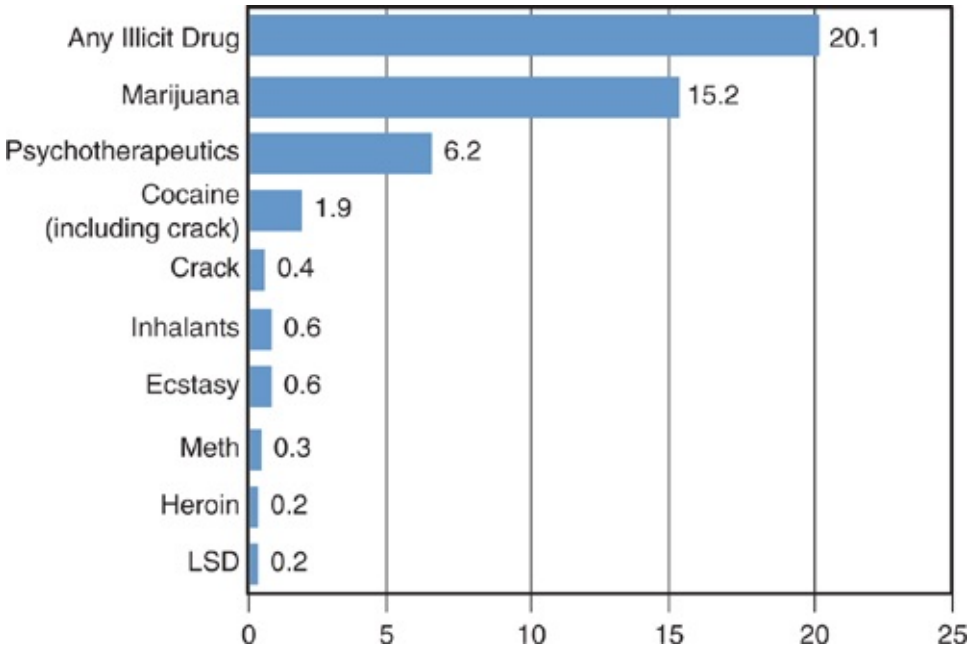
When talking about drugs that can be abused, there are about seven different groups of substance
These are nicotine; sedatives such as alcohol, barbiturates, benzodiazepines, and inhalants such
fumes from glue; opiates such as heroin and morphine; psychostimulants such as cocain
amphetamine, and methamphetamine; marijuana; hallucinogens; and caffeine. Prescription drugs th
are abused comprise many of the previous classes and are shown in the following list:

- Club drugs, which includes:
  - GHB (Also known as Goop)
  - Ketamine (Also known as K)
  - MDMA (Also known as E)
  - Rohypnol (Also known as Roofies)
- Cocaine, which is also known as nose candy, C, and blow
- Crack (another form of cocaine, and also known as Freebase, Rooster, and Tornado)
- Hallucinogens, which includes:
  - LSD
  - Mescaline (cactus)
  - Psilocybin (Mexican mushrooms)
- Heroin (Also known as Big H, China White, and Smack)
- Inhalants, which include:
  - Air blast
  - Huffing
  - Moon gas
- Marijuana
- Methamphetamine (Also known as Crank, Ice, and Stove top)
- Prescription drugs, which include:
  - Methaqualone (Also known as Ludes)
  - Oxycontin (Also known as Hillbilly heroin)
  - Ritalin (Also known as Vitamin R)
- Steroids (Also known as Juice, Pumpers, and Weight trainers)

This list is composed of illicit drugs and doesn't include alcohol or nicotine. A much more detaile list of abused drugs can be found on the ONDCP (Office of National Control Drug Policy) website http://www.whitehousedrugpolicy.gov/drugfact/crack/index.html.

Why are *these* groups of chemicals addicting? It is striking how they can have such different effec and uses; for example, opiates relieve pain, and sedatives produce sleep, yet both have the danger addiction. What is it about these chemicals, and not others, that give them such power? A reasonab answer is that it is an *accident* that all these particular compounds are addicting. There are, perhap millions of chemical compounds on this earth, and it is, perhaps, just unfortunate that some of the chemicals can hook into the brain in such a way that they become addicting. Of course, some of the drugs are used more than others (see Figure 1-1).

Figure 1-1. The number of individuals, ages 12 or older, who have used the indicated drug withi the past 12 months (in millions). Psychotherapeutics refers to prescription drugs that were abused; these drugs include Oxycontin, Vicodin, amphetamines, Ritalin, and sedatives. These numbers of users, which range from 200,000 to over 15 million, are small compared to the number of individuals using the legal drugs, like alcohol and nicotine. More than 50 million people smoke, and an even larger number take alcohol regularly. The relatively larger use of alcohol and nicotine are probably due to the legality of these drugs and their greater availabilit Legal drugs are used probably ten times more than illicit ones. (Source: SAMSHA, 2008, National Survey on Drug Use and Health, September 2009).



It is useful and can eliminate confusion to make a distinction between the words *drugs* a *medications*. The word *drug* is used in this book to refer to a substance with the potential to cau harm, abuse, and addiction. Of course, there are other drugs that are therapeutic, cure diseases, and a employed by doctors to treat specific maladies. These latter substances are referred to herein *medications*. Drugs of abuse can also have legitimate uses in medicine and be medications. Cocaine a powerful vasoconstrictor in that it closes off blood vessels and can be used to reduce bleeding surgery. Amphetamine is a stimulant and can be used to treat Attention Deficit Hyperactivity Disord (ADHD). Opiates are indispensable in the treatment of pain, but they can cause addiction nonetheles Depending on how and why they are used, many of the substances can be both drugs *and* medication *Prescription drugs* are another example of this; they are medications that can be abused and therefo are also drugs.

Why People Take Drugs

People take drugs for many reasons. They can produce a so-called rush of pleasurable sensation which is a dramatic and memorable experience. Sometimes drugs are taken because of peer pressu or stress. Related to the latter, drugs are sometimes used to self-medicate unpleasant feelings such a pain, anxiety, or depression. When addicted, users may take drugs to avoid the negative symptoms o withdrawal. Withdrawal is a series of distressing feelings and physiologic reactions that occur whe drug taking is stopped.

The Drug Experience

The drug experience usually fits a pattern among users. The first use of a drug, a critical occurrence, often influenced by various factors that include curiosity, friends who may apply pressure to try drug, availability of a drug, or even a permissive home where parents and siblings are users. Reaction to a drug can vary among individuals. Some people enjoy them and some don't. Perhaps someon begins taking a medication for a medical problem such as pain and then continues using.

The next phase is persistent drug use, in which there is more individual initiative and drive to find an take drugs. This can result in problems such as chronic intoxication, missing work or school, an perhaps stealing. There might be other missed obligations, arrests, or irresponsible behaviors such a unprotected sex. If drug taking continues, a state of addiction can result. Also, more and more of drug may be taken to get the same effect, and efforts to stop drug use may fail. Other drug-relate problems can occur in life, and good health can be threatened. Although some people can stop usin drugs, others drift in and out of drug use for decades or for a lifetime. Someone might someday fin that his or her life is gone, wasted by a brain disorder that he or she failed to understand and cop with.

Some drug abusers are lucky; they can quit by themselves or find a family member, friend, c counselor who can help them stop. They might get into treatment on their own or they might be force into treatment by a judge. However it happens, treatment is effective, even for people forced into Sadly, because of ignorance, poverty, denial, or fear of the stigma of being labeled an addict, som never find treatment.

Drug Use Is Costly in Many Ways

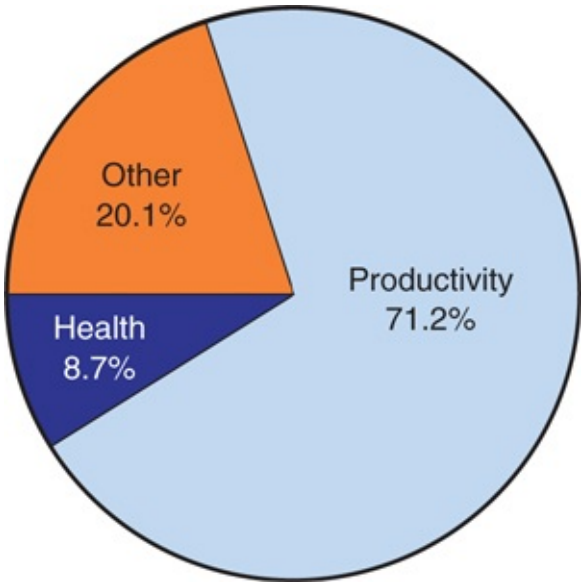
Many individuals and families know from first-hand experience how hurtful addiction can be, not on to the drug users, but also to individuals around them. The consequences of drug use include damagin families, relationships, or communities, and perhaps increasing the risks for serious illness or crim Often, the drug user has vowed to stop and has tried to stop many times only to fall back and relap into further drug use or dependence. The resulting feelings of helplessness, impotence, and failure ca engulf and doom someone's entire world.

The personal and societal costs of drugs can be seen around us and in the media. Robert Downey Jr., well known actor, producer, and singer, had a serious problem with drugs. He described to a judge ho he couldn't stop using them even though he knew he was in trouble. He also said that while starring o the television series Ally McBeal, he was at a low point and didn't care if his acting career was ove But after five years of drug abuse, arrests, stints in rehab, and many relapses, he settled down to wo on his problem. Ray Charles, the legendary performer, was addicted to heroin, but after his third dru bust, he went into rehab and gave up the drug. Fortunately, there are individuals who generously com forward, tell us their stories, and warn us about drugs. But not all drug users accept treatment or sto taking drugs, and that group generates great concern. There is even greater concern when our peers

the media glamorize drug use, which is quite dangerous.

Drug abuse is expensive. When we include additional health care costs, productivity losses, costs crime, and so on, the dollar amount is great.[5] In 2002, for example, overall costs exceeded 180 billio dollars, and loss of productivity accounted for a large portion of that (see Figure 1-2). Costs increase more than 5 percent annually since 1992, with the most rapid increase in costs related to the crimin justice system. These dollar figures are comparable to those for heart disease, cancer, and ment illness. They reflect a major drain on society's resources. Of course, dollar amounts do not begin reflect the *misery* that drug use can create for the individual, his or her friends, and family.

Figure 1-2. Distribution of illicit drug costs in 2002 by major components. The largest fraction the cost of drug abuse is due to loss of productivity. "Other" costs primarily reflect the costs o the criminal justice system (incarceration, court costs, and so on) costs to victims of related crimes, and costs for social welfare. From source cited in note 5.



While the problems are great, they are not hopeless. Perhaps determination is wanting. Dr. Berth Madras, a Harvard researcher in drug addiction and a former White House official, says, "Who viewed from a national perspective, the drug abuse problem in this country is staggering. Yet I ar certain that we can develop effective solutions and strategies if we overcome our biggest challenge- finding resolve."

Other Addictions

Although this is a book about drugs and how people become hooked on drugs, it is also about *all* our appetites; therefore, it can help us understand other potential addictions such as eating ar gambling. For example, if someone overeats, craves carbohydrates every day, and has withdraw symptoms when he stops cold turkey, then he may have a problem with carbohydrates. If such person seeks help, then this book can help with understanding the problem and the needs f treatment. More is said later about food, gambling, and sexual drives.

Other Medications

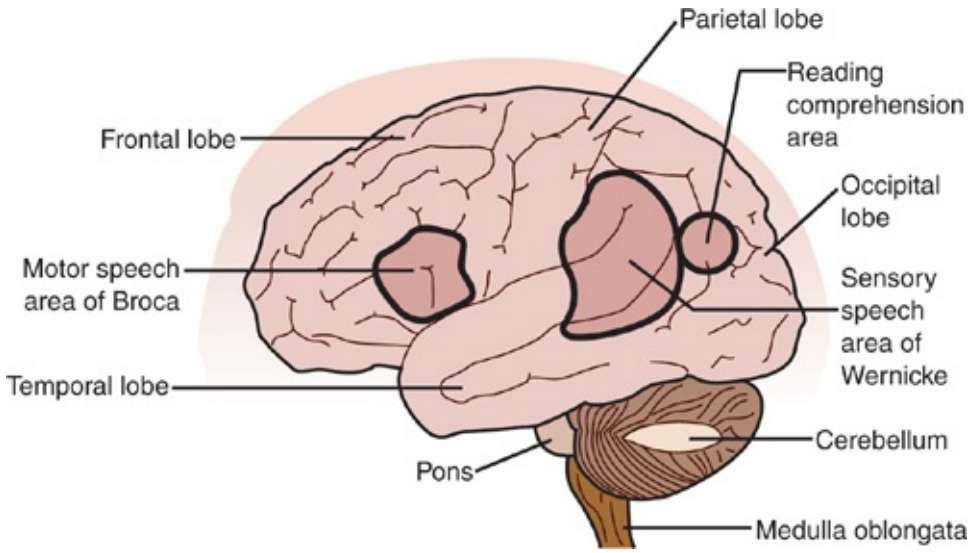
Another point is that some therapeutically useful medicines (not addicting drugs), such antidepressants, need to be taken over long periods of time and should not be stopped abruptly becau of the danger of recurring disease. Studies of abused drugs, which also involve taking drugs over long period of time, can inform us not only about how the useful medications produce their benefici

actions in the brain, but also about the problems in abruptly stopping their use.

Brain Structure and Functions

Before embarking on a study of the addicted brain, it is necessary to be aware of the brain and i organization. Different parts of the brain have different functions. Seventy-five percent of the huma brain is made up of the wrinkled outer covering referred to as the cerebral cortex, which has differe functional areas. Strokes or lesions of the motor cortex result in paralysis, the extent of which dependent on the extent of the motor area involved. Patients with strokes in the association corte have deficits of perception and attention. When the temporal lobe is damaged, the ability to recogni or name objects is impaired. Lesions or strokes of the frontal lobe result in personality change planning deficits, and inabilities to carry out complex behaviors. Strokes or tumors in other parts the brain have many other effects as well (see Figure 1-3).

Figure 1-3. A lateral (sideways) surface view of the brain shows some of the more obvious regions, and each region has its own function. The specific functions of the various brain region have become known after centuries of studies of patients with strokes, injuries, and tumors. Dru addiction also involves certain regions. (Adapted from http://medicalimages.allrefer.com/large/brain.jpg, accessed on December 20, 2010.)



The brain is also the organ of awareness. When general anesthetics are administered, the electric activity of the brain is reduced, and we lose awareness or go to sleep. If we stimulate the visual corte we might have visual images pop into our awareness. If the olfactory cortex is stimulated, then v might perceive odors. If we stimulate other parts of the brain, other events or sensations enter o awareness. Emotional behavior is also based in the brain. A group of brain regions collectively know as the limbic system controls emotional behavior and is partly responsible for feeling good. Th following chapters link certain brain regions with feeling good and with drugs.

The Tool Box

Science, like everything else in our lives, has become technology-driven, and there are marvelous ne approaches and instruments that allow us to examine the tiniest parts of our chromosomes or peer in the depths of our brains without surgical invasion of the skull. These tools are powerful an interesting in and of themselves.

The science of genetics has advanced, and it is now possible, with a small sample of blood, to examin our genes. Because genes are the basis of heredity, and some aspects of drug addiction are heritabl studies of genes can be informative. The target of these studies is DNA, which is made up of fo

different chemicals called bases, and it is *the order of these chemicals in our DNA* that specifies o genes. These chemicals—abbreviated as the letters A, T, G, and C—are lined up in two parall strands that comprise the structure of DNA. Again, it is the sequence of these bases, in groups of thre that constitutes our genetic code, and certain parts of our genetic code can contribute to the likeliho of our becoming a drug user.

For looking inside our brains, noninvasive brain imaging techniques can be astonishing. Magnet resonance imaging (or MRI) describes the structure of our brains, such that changes in the size parts of our brains can be measured. Functional magnetic resonance imaging (fMRI) tells us about t functional activity of various brain regions. Positron emission tomography (PET) scanning versatile. It can be used to reveal the activity of different brain regions or even the levels of certa brain chemicals and proteins. Overall, genetic and imaging studies are but two of the new tools th have become available over the past 25 to 35 years. These tools are out in front in the attack on drugs

Questions to Be Answered

This book addresses many questions about drugs and the brain, including:

- Why is it said that addiction is a brain disorder rather than perhaps a moral failing?
- What happens in the brain of someone who uses drugs repeatedly?
- Can better medications for addicted individuals be expected in the future?
- Why is drug abuse chronic and relapsing, which is part of the essence of this disorder?
- Why are drugs so powerful that they can gain control of our behaviors, but we can't give u responsibility for our actions?
- Will *I* become drug dependent?
- Are there differences among, men, women, adolescents, and older adults in how they respond and experience drugs?
- Can one recover from drug addiction and be cured?
- The stigma of being a drug abuser is a problem in that it often prevents searching for treatme or dealing with the problem openly.

Endnotes

[1] Throughout this book, we tend to refer to addiction as a disorder, but it is also often called disease. The definition of addiction that is used in this book focuses on continued drug use in spi of distress and negative consequences. However, the official description is given in the Diagnost and Statistical Manual of Mental Disorders produced by the American Psychiatric Associatio and it includes more elements. The DSM IV TR is the current edition used by medic professionals for official diagnoses. The DSM is an evolving document and DSM V is due in th near future. Currently, the diagnosis of drug dependence requires the presence of three or more several symptoms, and it is possible to have a diagnosis of substance dependence without th presence of distress or negative consequences. The official list of symptoms and diagnost criteria for Substance Dependence and Substance Abuse can be found in an online version of th DSM IV TR. One possible site is http://www.psychiatryonline.com/content.aspx?aID=629, whic was accessed on June 28, 2011. Only a qualified professional can make a diagnosis.

[2] Ibid.

[3] Ibid.

[4] An illicit drug is one that is not legal to produce, not legal to use or possess, or a medically usef therapeutic drug that is used non-medically.

[5] Office of National Drug Control Policy (2004). "The Economic Costs of Drug Abuse in the Unite States," 1992–2002. Washington, DC: Executive Office of the President (Publication No. 207303

2. Hardwired: What Animals Tell Us About the Human Desire for Drugs

"I gotta get a hit. I steal money, leave work in the middle of the day to get high, and I can't sto What's happened to me?"

For many years, doctors and scientists have been trying to figure out how addiction works and ho addicts can be treated. The research has become sophisticated with elaborate laboratories for huma subjects in many of our best medical centers. Hundreds and hundreds of publications every ye describe new findings that promise a better understanding of and improved treatments for dru abusers.

Studies with animals, in addition to humans, have been helpful. In fact, using animals in research h a number of advantages over studying humans.[1] Importantly, the environment, nutrition, gener health, and drug use of an animal can be rigidly controlled since its birth, although this is not possib with humans. Because of this, animal experiments can be more carefully defined and more easi interpreted. Also, animals cannot refuse good medical care during periods of experimentatio whereas humans are not bound to follow medical advice. Animals are in controlled and protecte environments, whereas we have little control over humans' choices of environments. In additio animals can be given new treatments and medications, and indeed, the FDA requires that animals b used for proof of safety of new medications. Despite these advantages, the use of animals in researc is not taken without care or caution. Each and every experimental procedure must be described detail and approved by a learned committee before the experiments can be carried out.[2] Unexpecte problems are studied by committees to learn how we can better care for our animal subjects. Scientis are sensitive to these issues and often have beloved pets at home.

Going Back for More

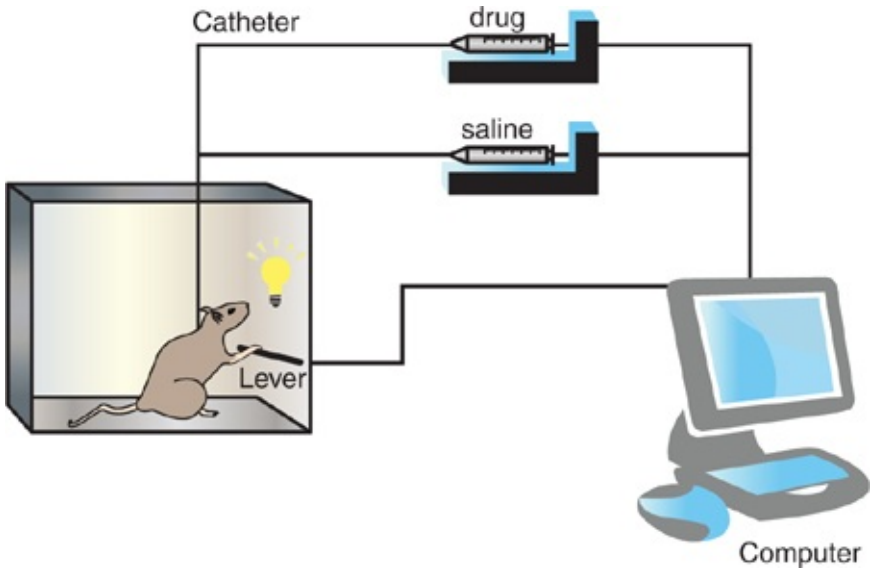
Although animals were part of addiction research during the 1920s, this earlier research focuse primarily on understanding how drugs affected the animal's physiology. Typically, drugs wer injected into animals that were held or immobilized; the animals were passive recipients. Then variety of tests and measurements were made on the animals, and a great deal was learned that is th basis of much work today. But in a new procedure developed in the 60s and 70s, the animals wer given control over their own drug injections. They actively and freely pressed a lever to get a dru injection. The rate of lever pressing reflected their desire for more of the drug and its effects. Th control over drug taking is more like the situation with humans who have control over drug taking an provides a better animal model of human drug taking.

This procedure or model was developed by several scientists including Drs. James Weeks, C.E Schuster, and Tomoji Yanagita. When animals were allowed to administer drugs to themselves b pressing a lever, they did so, and with surprising gusto! In this drug self-administration model, catheter is placed surgically under anesthesia in an animal's jugular vein so that a measured quanti of a drug can be delivered (by a lever press) directly to the animal's bloodstream where it rapid circulates to the brain. The animals appear to quickly adapt to the presence of the catheter, goin about their activities probably with no more notice than a dog pays to his or her leash while out on walk.

There are small variations on how to do this, but the idea is that an animal is placed in a soun insulated chamber to avoid distraction and is then presented with two levers. One activates delivery

a saline solution, the other a saline solution containing a drug such as cocaine. Of course, the anim does not know it is receiving an injection, but it obviously learns that pressing the drug-related lev produces a different sensation than pressing the saline-related lever. Which lever it presses and ho often it does so are clear, quantifiable measures of which sensation it prefers (see Figure 2-1).

Figure 2-1. Animals will self-administer drugs. The figure shows a rat that has access to levers (only one is visible), and each lever is hooked to either saline (a saltwater solution) or a drug solution such as one with cocaine. The rat also has a catheter or drug delivery tube implanted i its blood vessels. The computer controls how often and how much of the drug is given when the lever is pressed. When the drug-related lever is pressed, the rat does not know it is getting an injection, but rather it has a sensation, and if it likes the sensation, it will press the lever again and again and again. Moreover, the rat learns to ignore the lever that results in an injection of drug-free solution. This animal model of drug self-administration is vitally important for research and understanding the how and why of addiction. (Modified from www.pharmaco.umontreal.ca/apropos/LaboFilep/images/Self-administrationEN_000.jpg, as accessed on February 24, 2009.)



When offered one of almost any of the drugs that humans abuse (exceptions being those that disto sensations and perceptions, such as hallucinogens like LSD), the animal almost always chooses th lever that results in drug delivery. The sensation brought about by the infusion of the drug is positiv and acts as a *reward* that positively *reinforces* the act of pressing the lever. Every lever pres followed by an infusion of the sensation-producing drug, further reinforces the lever-pressin behavior. The animal appears hooked, pressing the lever repeatedly. In the case of a rewarding dru such as cocaine, the animal might ignore food, water, or even a sexually available mate, and it presse the lever until it is too exhausted to continue. Although the animal controls the act of lever pressin the researcher controls the total amount of drug that is administered and prevents the animal fro taking enough to injure or kill itself accidentally, as sadly can happen with humans.

If the researcher suddenly reverses the levers so that the one delivering cocaine now delivers salin the animal soon discovers the drug-related lever and starts pressing it. If the drug is remove completely, the animal keeps lever pressing for some time, apparently in the hope that it wi reappear. It might require a large number of unsuccessful presses to “extinguish” the pressin behavior, meaning the animal no longer associates pressing the lever with the desirable sensation an stops.

In these controlled experiments described previously, the animals have access to a restricted amou

of drug over a restricted time. But the human situation doesn't always work that way. Sometimes dru users have access to a drug for a long, extended time. George Koob, his colleagues, and other studied this in animals. They allowed some animals to have longer access to the drug. For exampl rats were allowed to self-administer cocaine for either one hour or six hours per day. In the group wi one hour access, cocaine intake was lower and stable over days. But the group that had six hours access gradually *increased* its intake over days. Access and availability of a drug can make difference in the amount of drug that is taken. This is consistent with the behavior of heavy drug user

Because the drug self-administration paradigm has been so successful, it is a trusted model for huma addiction. It is used to determine if new drugs or medications are potentially addicting. For exampl if some compound X affects the brain, it is reasonable to see if it is self-administered. If it is, then has to be considered as a potentially dangerous and addicting substance.

Because of the robust self-administration of drugs in both animals and humans, there seems no oth explanation than the fact that animals and humans share some property in the brain that makes th sensation produced by these drugs desirable. In other words, there seems to be some hardwiring in th brain that is shared by both humans and animals that facilitates drug addiction. The danger addiction is a biological vulnerability that both humans and animals share. Some see this as evidenc that widespread drug-using behavior in humans cannot be simply explained as a moral weakne because a biological basis for it exists.

Darwin Saw It

Looking back, it shouldn't be surprising that at least some animals share an interest in drugs wi humans. In 1871, Darwin made some interesting observations that are humorous and enlightening.

On Booze, Men, and Monkeys

"Many kinds of monkeys have a strong taste for tea, coffee, and spirituous liquors: They will also, as I have myself seen, smo tobacco with pleasure. Brehm asserts that the natives of north-eastern Africa catch the wild baboons by exposing vessels wi strong beer, by which they are made drunk. He has seen some of these animals, which he kept in confinement in this state, and gives a laughable account of their behaviors and strange grimaces. On the following morning, they were cross and dismal; th held their aching heads with both hands and wore a most pitiable expression. When beer or wine was offered them, they turn away with disgust, but relished the juice of lemons. An American monkey, an Ateles, after getting drunk on brandy, would neve touch it again, and thus was wiser than many men." (From Charles Darwin's *On The Descent of Man*, Penguin Classics, pp. 23–2

Today Google, YouTube, and other websites permit all of us to see what our forefathers must hav noted in nature: wallabies munching opium-ripe poppies, tree shrews seeking out fermented pal nectar, and even more examples of animals taking advantage of human brews carelessly left sittin around. Unfortunately for modern man, however, the attraction to alcohol, like attraction to food, ca go awry in a world where both are easy to get.

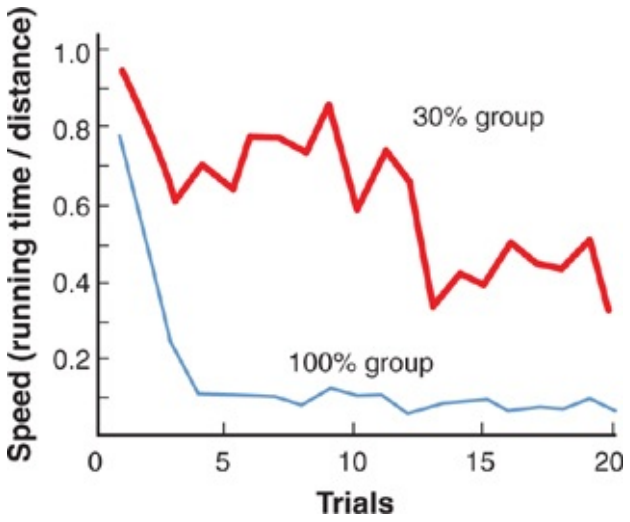
Uncertain or Nonregular Rewards Are More Addicting

What if every lever press doesn't result in a drug hit, but rather about every third? As psychologis have discovered, and as any gambler knows, an occasional payoff serves as a stronger reinforceme of a given behavior than does an entirely predictable payoff.

Experiments on food reinforced behavior in the 1950s showed this nicely. Rats traversed a runway get food as a reward. One group was given a food reward every time they moved down the runway. another group, there was a reward only about 30 percent of the time. Both groups learned to run dow the runway in expectation of a reward. Then the food reward was eliminated for both groups, but the were still allowed to run down the runway in search of it. Now you would expect that the rats wouldn

give up immediately. They would continue down the runway in subsequent trials even if they we disappointed the previous time, and that's just what they did. Now here's the interesting part. Th animals that received rewards only 30 percent of the time persisted in the runway behavior muc longer than the rats that were rewarded each and every time (see Figure 2-2). They tried for a long time. A nonregular reward was more reinforcing and shaped seeking behavior more strongly than th regular reward, whereas actually, the opposite might be expected. We seem to want rewards that hav been uncertain or not regular more than we do certain, regular ones!

Figure 2-2. Nonregular or uncertain rewards are more addicting or reinforcing. Rats were trained to run down a runway for food. One group was rewarded with food every time, and another group was rewarded only 30 percent of the time. Then the food reward was removed completely. The group of rats that had been rewarded each and every time (100 percent of group) gave up or extinguished their running behavior more readily than the rats receiving a reward only 30 percent of the time. The 30-percent group persisted in running down the runwa for longer times and more trials, even though there were no rewards. (Adapted from Figure 4.2 from *Psychology*, First Edition, by Henry Gleitman. Copyright © 1981 by W.W. Norton & Company, Inc. Used with permission of W. W. Norton & Company, Inc.)



This has important implications in our everyday life, where, for example, we may want to shape th behavior of a pet. Suppose a dog begs for table food, and you restrain yourself but nevertheless give every so often. Although you tell yourself that you don't do it all the time, and you think you are doi well, you are in fact making it harder for the dog to stop begging. We can easily think of simil scenarios with children, students, and so on. This should give us insight into our own behaviors. Is th why some of us find gambling such a persistent urge?

Animal Model Extended

The animal model of drug self-administration (see Figure 2-1) has been critically important f research in drug addiction. Interestingly, our appreciation of the model has continued to evolve. B extending and examining the model more closely, you can study additional aspects or phases of dru addiction. These include: the initiation of drug taking or the rate at which an animal learns to sel administer it; the maintenance of drug taking, which is the phase where the lever pressing has bec learned and is stable or relatively unchanging; the extinction of drug taking, which occurs when th lever pressing no longer produces a drug reward and the lever pressing gradually stops; and the relap to drug taking, which is either stress, cue (see the following sidebar), or drug-induced, and occu when an extinguished subject begins to seek drugs again. These four phases are different and can re

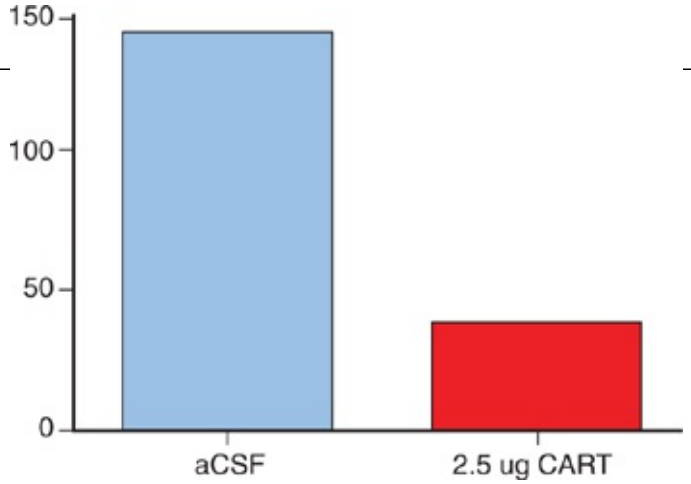
on different processes in the brain. Moreover, certain medications can be more effective in treatin one phase compared to the other phases. Thus, the tools for searching for medications and treatmen are becoming more sophisticated.

A "cue," in this context, is anything that reminds you of drugs or taking drugs. It can be the sight of a friend that you take dru with, the place where you have taken drugs, or even something like a white powder whether it is drug or not. The importance o cue is that it can precipitate a relapse. A cue can trigger a response in your brain that makes you want drugs. Someone who wan to stop taking drugs must learn his or her cues, or danger signs, that lead to craving and more drug taking, and he or she mu avoid them or neutralize them in his or her mind.

An Example of a New Idea

An example of how this model can be used to explore new ideas is an experiment with CART peptid that comes from the author's laboratory. CART peptide is a chemical found in brain regions that ar involved in drug abuse, and the effect of CART peptide on drug taking can be explored by using th animal model. If an animal has been allowed to learn the self-administration of cocaine, it can then b forced to give up or extinguish lever pressing by requiring a very large number of lever presses to g a reward. Instead of getting a drug injection for every lever press or for every other lever press, th number of lever presses required to get just one injection of cocaine can be made so great that th animal just gives up pressing. Now, here is the key part. The drugs that the animals like better elic more attempts to get the drug than other less desirable drugs. The number of presses that the anim makes for a drug before it gives up is a measure of how much the animal wants the drug. Suppo animals are allowed to lever press to get injections of cocaine, and they learn to expect this whenev they press the lever. By withholding the drug injection, the number of presses required before the give up lever pressing can be measured. An interesting experimental result is that if CART peptide injected into critical brain regions, the animal gives up lever pressing *sooner* (Figure 2-3). It appea that the animal is less interested in getting a cocaine reward when it has been given CART peptide.

Figure 2-3. Injections of CART peptide reduce cocaine reward and intake. Animals work to receive injections of cocaine by lever pressing because they find cocaine rewarding and they wan it. In fact, they press the lever many times to get a single injection of the drug. Now let's add another part to the experiment. If a drug-free solution (aCSF) is injected into the brain, the animals can still press for cocaine hoping to get some drug (the number of presses corresponds t the height of the bars in the figure). But if CART peptide (2.5 micrograms) is injected into a par of the brain associated with cocaine use (the nucleus accumbens), then the animal works much less for cocaine as indicated by the shorter bar on the right. You can think of the length of the bar as a measure of cocaine's desirability to the animal, and an injection of CART peptide reduces the desirability of cocaine and shortens the bar. More details about this kind of experiment are given in subsequent chapters. (Summarized from Jaworski et al.. "Injection of CART Peptide into the Nucleus Accumbens Reduces Cocaine Self-Administration in Rats." *Behavioral Brain Res* 191:266-271, 2008.)



The bottom line of the story is that CART peptide injected into the brain can function to make cocain less attractive. Perhaps CART peptide is part of a chemical reflex that tries to control the excess bra activity produced by cocaine, and more will be said about this in later chapters. But, wouldn't it l interesting if medications based on CART peptide could be developed to make cocaine less attracti to addicts? This last question is speculative because we need to learn much more about CART peptic before we think about treating humans, but you get the idea. There are many experiments like th using drug self-administration that generate many new ideas for additional treatments.

You can see how important this drug self-administration model is (and other models, too). By showi that drug addiction is a physiological process based in the brain, we can then search for ne medications and treatments for addiction that block or reverse the drug-induced processes in the brai It provides a rational and physiology-based search for new treatments. We can inject drugs direct into various brain regions or surgically alter those regions to define the parts of the brain that media addiction. Of course, it goes without saying, that experiments like this using human beings are gross unethical and impossible.[4] Thus, the animal models make significant progress possible.

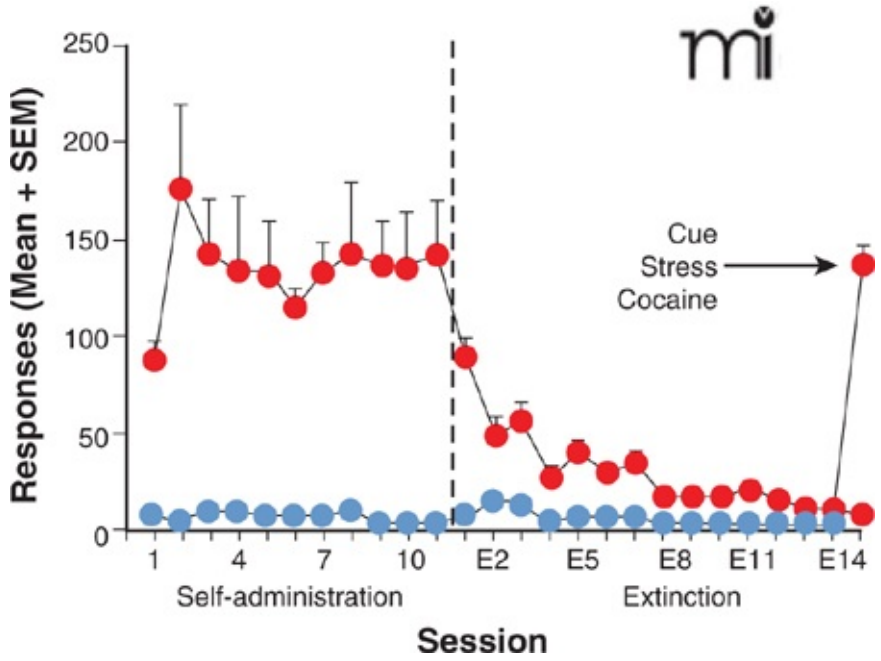
Relapse, Craving, and Reinstatement

Drug abuse is a relapsing disorder. In fact, most drug abusers and addicts have stopped or tried to sto taking drugs, only to eventually relapse. So at any given time, most drug abusers are in fact relapser Therefore, it is important to study relapse itself, and this is nicely done in a variant of the sel administration model, as mentioned previously. It works by allowing the animal to learn to sel administer a drug, such as cocaine, until the lever pressing is stable. Then, the drug is withdrawn, an as expected, the animal gradually tires of lever pressing without a reward and the lever pressi behavior is extinguished. This animal is now an experienced drug user, much like most humans wh have used drugs but have stopped. A human in this condition likely thinks about the drug, and whe stressed or reminded of the drug, perhaps by some cue, craves the drug and perhaps starts looking f a drug. The cue can be the sight of friends who use drugs, the crack house, or even some white powd that reminds him or her of the drug. Cues and their effects are very interesting and currently studie For example, Drs. Leslie Lundahl and Chris-Ellyn Johanson recently found that drug-related cues s off cravings in marijuana-dependent subjects.[5] Getting even a small amount of the drug (which is cue) might set off a binge of drug taking. So, as you can see, certain events can trigger craving, dru seeking, and relapse.

Now, let's return to the animal that has experienced a drug but is currently without it. If stress, such a a foot shock, is present or if the drug is injected, the animal remarkably starts to press the lever th previously resulted in a drug injection. The animal does this even if *no drug is given* by the lever pre (see Figure 2-4). Previous drug use has conditioned the animal to look for the drug in situations th

elicit cravings in humans.

Figure 2-4. Drug self-administration in animals provides a model for relapse in humans. Anima were presented with both a drug-related lever (darker dots) and a nondrug lever (lighter dots) The nondrug lever was rarely pressed as expected (shown on the vertical axis as "responses"). They were trained for 12 days to self-administer cocaine (left half of figure), and drug delivery was accompanied by a cue, which was typically a light and/or a tone. Drug self-administration was stable at about 140 responses (on the vertical axis), except for the first day when the anima were learning. In the second phase of the experiment (right half of figure), animals underwent "extinction training" during which no drug was administered in response to lever presses (E1-E14), and the rate of lever pressing dropped nearly to zero. At the end of this second phase, animals were presented with the cue that had accompanied each drug infusion during self-administration, a mild stressor (typically foot shock), or the drug itself. Each of these stimuli reliably overcame extinction training and the animals pressed the lever, even though no drug wa delivered. This reinstatement or reoccurrence of lever pressing is considered to be a bout of dru seeking or relapse. Although this is a complicated experiment, it is clear evidence that stress or single injection of a drug can stimulate drug seeking in an animal with previous drug-taking experience. This animal model can be used to study relapse. (Adapted from PW Kalivas, Jamie Peters, and Lori Knackstedt. "Animal Models and Brain Circuits in Drug Addiction." *Mol Interv.* December 2006: 6:339–344.)



In this animal model, it is possible to ask a variety of questions about relapse, and we can begin consider which medications are best for treating or preventing relapse.

Other Animal Models

Other models allow us to study additional properties of the brain and of drugs. These models, such "conditioned place preference" and "drug discrimination," are technical and sometimes complex b quite useful. These are mentioned only to inform you that the experimental repertoire in dru addiction research is quite rich. In the next chapter, we explore "electrical self-stimulation" and why is important for this discussion.

A Transformation in Thinking