Learning About Drugs and Alcohol Through Biotechnology

Drug and alcohol use starts as a voluntary choice. However, substance abuse causes changes in the brain that can lead to compulsive behaviors: addiction and alcoholism.
Your teenage years are the best and worst of times. Pimples pop, hairs sprout, legs lengthen, hormones rage, feelings reel. Freedom beckons; responsibilities press. Friends change, and parents frown. It’s a winding, rocky road to adulthood.

Despite these obvious changes, until recently scientists thought your brain was already fully grown. They knew the brain goes through great changes in your first three years of life. It grows in size and complexity. It decreases the number of neurons (nerve cells) but increases the number of connections among them. Those connections “wire” your brain into complex, interconnected circuits. Scientists say the brain is plastic because it adapts and changes. It is sculpted by your thoughts, experiences, and social interactions.

Nevertheless, they thought your brain was pretty well molded by grade school. Now, scientists realize that it keeps growing and making extra connections, like a tree growing new branches. Growth in some areas of your brain reaches a peak around puberty. As a teenager, you continue to prune those branches, choosing ones that help you flourish: Piano? Soccer? Math? Poetry? MTV?

Just like the rest of your body, different brain regions develop at different rates. One of the slower parts to develop is the frontal lobe, located behind your forehead. This section was the last to evolve in our species, and its complexity separates humans from other animals. It also takes the longest to develop in an individual, separating a child from an adult. It is the “seat of reason,” where you make decisions, plan for the future, and control your impulses. This “executive” section continues developing until you are about 21.

Until your brain matures, you behave differently from adults. You tend to use a brain section associated with emotions and gut reactions when adults use their frontal lobe. You take more chances, try more new things, and weigh cated behind your forehead. This section was the last to evolve in our species, and its complexity separates humans from other animals. It also takes the longest to develop in an individual, separating a child from an adult. It is the “seat of reason,” where you make decisions, plan for the future, and control your impulses. This “executive” section continues developing until you are about 21.

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Dear Readers,

The Biotechnology Institute is pleased to present the fall 2002 issue of Your World: “Learning About Drugs and Alcohol Through Biotechnology.” Drug and alcohol abuse is a worldwide problem that causes serious, costly, and sometimes deadly health problems. It affects all races, economic classes, and ages, including many students.

Advances in biotechnology now allow scientists to see how the brain of an abuser is different from a healthy brain, and how genetics may play a role in a person becoming addicted. This understanding promises to open new doors for treatment and prevention. Medications for helping people overcome substance abuse have often been essentially “hit or miss.” If they work, the physician and patient may not really know why. Biotechnology is enabling scientists to design medicines that target the precise brain function involved in a specific drug, eventually leading to tailored medications for people with differing genetic make-ups.

To keep this research moving forward, we need young, creative minds that are open to discovering the latest findings on these fascinating topics. Please let us know what you think about this issue of Your World and the problem of substance abuse among teenagers. I also want to thank our advisors, Frank Vocci of the National Institute on Drug Abuse and Raye Litten of the National Institute on Alcohol Abuse and Alcoholism, for helping us explore the latest findings on these fascinating topics.

Sincerely,

Paul Hanle, President

The Biotechnology Institute is a national non-profit entity based in Arlington, VA, and dedicated to education and research about biotechnology. Our mission is to engage, excite, and educate people about biotechnology’s potential to solve human health and environmental problems. Your World focuses on biotechnology issues and brings scientific discoveries to life for 7th to 12th grade students. We publish issues on different topics each fall and spring. Please contact Jeff Alan Davidson, Publisher, for information on subscriptions (individual, teacher, or library sets). Some back issues are available.

The Biotechnology Institute would like to thank the Pennsylvania Biotechnology Association, which originally developed Your World.

Teenagers are big risk takers! It’s fun to discover new things and have exciting experiences. However, using drugs and alcohol can prevent your brain from giving you pleasure in normal activities.

fewer consequences. This risk taking can help you do wonderful, courageous things. It can also put you in danger. Before you graduate from high school, you will probably face a choice about whether to smoke, drink, or try drugs. Your brain has a harder time controlling the impulse to just do it, even though you know you shouldn’t. By a cruel quirk of nature, your changing teenage brain also makes you more easily addicted to those substances than adults. It is also more easily—and more permanently—damaged by them. Your life choices can literally change your brain’s final form.

Why are some substances addictive? What happens in the brain to cause addiction? Why are some people more drawn to drugs and alcohol? Why is addiction so hard to kick? Until recently, these questions seemed impossible to answer. Advances in biotechnology now make it possible to study these questions scientifically. Biotechnology includes molecular biology and chemistry, genetic engineering, and the study of DNA, genes, proteins, brain chemicals, hormones, and other molecules in the body. However, studying the brain can’t just focus on biology. Our social environment, behavior, and personal choices also influence our brain.

This issue of Your World focuses on how drugs and alcohol work in the brain. It describes the normal functioning of the “reward pathway,” how addictive substances “hijack” it, and how biotechnology may lead to better prevention and treatment methods. Knowing a bit about how a bicycle works—and what makes it crash—can help you keep control as you go through turns and patches of sand. Similarly, knowing how substances affect your brain—and what makes it malfunction—can help keep you safe as you travel the unpredictable path toward adulthood.

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The Reward Pathway: Why We All Scream for Ice Cream

Jamal* is 18 months old when he has his first bite of ice cream. His eyes (and mouth) open wide with astonished delight. He has two thoughts. “That tastes GREAT!” and “I want MORE!”

Born to Love It

What is not to love? Ice cream is made of substances we are “programmed” to seek out as a species: fat, sugar, and milk. We don’t need to be taught to like these things. Our brain is already wired to tell us they are good. Once we experience something good, our brain rewires itself to want to find more of it and remember how to find it in the future. For centuries, no one could explain why we like the things we do. Now, new biotechnology methods are unraveling mysteries such as why we love ice cream at first bite. (See box.) Here’s a glimpse inside Jamal’s brain.

As ice cream coats Jamal’s tongue, nerve cells (neurons) relay the wonderful taste to the “first responder” at the base of his brain (the ventral tegmental area, VTA). Those neurons pick up the taste message and release a message of their own, packaged as a brain chemical. (See diagram.) Brain chemicals are called neurotransmitters because they send or “transmit” messages to neurons. The pleasant taste releases the brain chemical dopamine, which makes people pay attention to new and pleasant things. The dopamine passes into a gap (synapse) between its home neuron and the next neuron. (Synapse comes from a Greek word meaning “joining together.”) While dopamine collects in the gap, it bumps into receptors on its neighboring neuron. A receptor is a structure that receives messages. It is like a lock that only a certain key can fit. The neurons in this region have receptors for dopamine. When dopamine locks into them, they get excited and pass the message “Yum, that’s good!” to several different brain sections that also have dopamine neurons.

One dopamine-rich section is the pleasure center (nucleus accumbens). The pleasure center rewards us for doing the things needed to survive, like eating and drinking. It also rewards us for learning! (Learning exposes us to new situations and shows us how to survive.) All animals, even insects and worms, have a similar reward system.

Sometimes, it’s hard to meet our survival needs. Imagine what it was like for early humans to hunt or gather enough berries to feed a family. Notice how ants struggle to carry crumbs. What motivates animals to work so hard? Dopamine! The same messenger that gives us pleasure also motivates us to get up and go find more of it. It changes our future behavior.

Learning to Find More

Other regions of Jamal’s brain containing dopamine are involved in learning and memory (including the hippocampus). As pleasure signals pass through these regions, they etch patterns that help him remember how to find ice cream again. His neurons undergo physical and chemical changes. Those changes strengthen existing connections and add new ones, imprinting a new memory track in the reward pathway. In that way, eating ice cream literally changes Jamal’s brain. (Similar things happen when his mother holds him on her lap to read a story.)

Think about it!

Why does hunger feel unpleasant? Why do we feel pleasure when we eat? How are these feelings fundamental to our survival? What would happen if we didn’t have them?

*The characters in these articles are composites and do not represent specific individuals.

How do motivation and learning influence our behavior?

1) The taste of ice cream sends the message “This tastes great!” to the brain.
2) A neuron has dendrites that reach out to pick up signals from other neurons.
3) An electrical pulse shoots through the cell body and down the long axon, which branches out to other neurons.
4) It reaches vesicles containing dopamine at the terminal of the axon.
5) The dopamine passes into a synapse between its home pre-synaptic neuron and a neighboring post-synaptic one.
6) In the synapse, the dopamine stimulates a receptor on its neighbor.
After a few scoops, other brain chemicals begin to override the pleasure messages. They slow down the neurons’ response to dopamine. At some point, Jamal thinks, “No more! I’ve had enough,” and stops eating. (Some eating disorders may be linked to imbalances in this override system.)

**Bundles of Anticipation**

From then on, Jamal’s reward pathway is fine-tuned for ice cream. His brain associates ice cream with pleasure. Ice cream will never again cause such an intense surprise. However, he never has to think about whether ice cream is good. He just knows it.

With return visits to the ice cream parlor, one part of Jamal’s reward pathway (basal ganglia) packages a whole range of cues along with the taste of ice cream, such as the smell of chocolate and the colorful bins in the display case. That bundling of many sensations is why a certain song can conjure up memories of an entire summer. When he is 18 years old, just one of those cues may make Jamal crave ice cream – and then head to his freezer.

**The Addiction Highway**

The reward pathway is not just traveled by natural pleasures. It can’t tell the difference between substances that are good or bad for you, as long as they stimulate dopamine. Alcohol and drugs race along the same reward pathway, turning it into a highway to addiction. (For some people, gambling and other addictive behaviors also excite the dopamine system.) Mind-altering drugs are brain-changing substances. They override the brain’s reward pathway in ways that can cause an out-of-control, compulsive behavior. That rewiring makes the brain diseased, the way clogged arteries make a heart diseased.

**How Do We Know?**

Biotechnology allows scientists to peek inside the living brain and see brain chemicals at work. One technology, the PET Scan (positron emission tomography), uses a radioactive compound combined with chemicals that target different structures on neurons. It produces live images that track brain activity at the molecular level. For instance, they show dopamine receptors “lighting up” with activity when they receive a pleasure signal or respond to a drug. In addition, scientists can create molecules that make neurons release or remove a neurotransmitter, or bind to a receptor and either activate or deactivate it. Scientists also study the effects of drugs on cells grown in laboratories and then in animals. They breed animals that seek out drugs or alcohol and compare their brain activity with animals that avoid those substances. (See pages 8 and 9.) Other biotechnology techniques identify genes that control the activity of brain chemicals. To learn the function of a gene, scientists create “knock out” animals by deleting that gene to see the effect on behavior. The research discussed in this magazine results from the power of these biotechnology methods. These studies may lead to better medicines for fighting addiction – and other brain disorders like depression and schizophrenia.

**Career Center: Neuroscientist**

Develop new technologies to study how the brain responds to drugs.
People never plan to become addicted. But one day, oops, they are. No one knows when casual use might switch to a compulsive, out-of-control craving.

I’ll Just Try It Once!

Amber and her friend Jess just want to see what cocaine is like. "What could one time hurt?" Cocaine is one of the oldest drugs used by humans. People chewed coca leaves to get a mild pleasure – or to treat some illnesses. Today, cocaine comes in purified forms that produce very strong effects. Here’s what happens to Amber.

The cocaine enters her bloodstream and speeds to her brain, spreading through the dopamine pathway. (See previous article.) By an accident of nature, the cocaine molecule is similar to dopamine, so dopamine neurons attract cocaine like a magnet. Cocaine fits into the transporter pump, which normally pumps dopamine out of the gap between neurons and quiets down the firing. With cocaine clogging the pump, dopamine overcrowds the gap. It floods the dopamine receptors with “This is great!” messages that surge through the reward circuit.

Amber experiences a euphoria that makes a mark on her brain – and her memory.

Indeed, biotechnology research shows that using cocaine just one time changes the brain almost immediately. A week later, Amber’s brain still bears the tracks of cocaine. Cocaine also affects the body in other, sometimes deadly, ways.

Oops! I’m Doing It Again, and Again, and…

Cocaine wears off quickly, so Amber soon feels back to normal. Her brain, though, is not quite normal anymore. Cocaine carved such a deep groove in the reward pathway that her brain confuses the high with an important survival need. Her misguided brain urges her to find more of what seems so good.

The next time Amber tries cocaine, she doesn’t get the same rush. Imagine that people have a pleasure setting on a scale of 1 to 100. Before using cocaine, Amber’s setting was about 75 for normal pleasures. Her first use of cocaine raised her pleasure setting to 100. Her second use may only raise it to 95. To get a similar high, Amber needs to take more cocaine than before. A vicious cycle intensifies. She develops tolerance for the drug, meaning the same dose has less effect. Her dopamine neurons don’t react as intensely once they “know” cocaine. Brain images comparing long-term cocaine users to normal brains show fewer dopamine receptors. With repeated use, her normal pleasure setting drops from 75 to 50. As a result, Amber’s natural rewards (food, family, hobbies) no longer give her pleasure. She needs cocaine just to get her pleasure level up to 75. Without the drug, she feels bad.

Amber continues to use cocaine, and she craves it when she doesn’t have it. Finding more becomes her overriding motivation. At some point, Amber no longer uses drugs by choice. She is addicted. Cocaine has overwritten her normal brain circuits in ways that drive her compulsive behavior.

* Alcohol and drug abuse is a worldwide problem, but worldwide statistics are difficult to gather. Sources for these data are the U.S. Dept. of Health and Human Services Fact Sheet, NIDA Monitoring the Future, National Center for Health Statistics, and World Health Organization.
**Blocking the High**

What if Amber could take a medication that robs her of the cocaine high? Perhaps her brain would stop linking cocaine with an intense, important pleasure. Researchers are exploring ways to block cocaine’s access to the reward pathway. One approach is to use a molecule that “competes” with cocaine for a spot on the dopamine transporter, so dopamine won’t collect in the synapse and create intense firing. The trick is to still allow dopamine’s normal functions to continue. To accomplish this feat, scientists are using computer models of the three-dimensional dopamine transporter, as well as the cocaine and dopamine molecules. On the computer, they design an “ideal” molecule that will slip into the transporter in a way that will block cocaine but not dopamine. Once they have that design, they go to the chemistry lab to create a molecule to match that design. Then they test that molecule in animals that have been trained to seek out cocaine to see if it keeps them from responding to cocaine. If it does, they will test the therapy among volunteer cocaine addicts. Scientists hope to eventually use computer-designed molecules to treat many forms of addiction and alcoholism.

**Career Center:** Drug researcher – Use new insights into the biological, genetic, and social factors of addiction to develop new treatments.

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**Cravings and Relapses**

“Okay,” Amber resolves. “I’ll never do it again.” She seeks professional help, yet there are still no medications that can restore the normal wiring of her brain. (See box.) Instead, she must control her behavior. However, her brain works against her. Her repeated experiences bundled all the aspects of drug use together in her memory. Years later, she may see, hear, or smell something that reminds her of a time or place she used cocaine. That sensation triggers a craving for cocaine. Brain scans of former addicts show that merely seeing a needle or the word “cocaine” can stimulate dopamine neurons in the pleasure center. That’s why recovering addicts face a lifelong struggle with cravings and risk of relapse.

Now that scientists understand more about how addiction affects the brain, they hope to develop ways to help addicts free themselves of its grip. First, scientists must identify the many different types of receptors, transporters, and other neuron features in the brain’s intertwined pathways. Then they can use those features as targets for medications that block the effects of drugs and restore normal brain functions.

**Not All Equal**

Why did Amber become addicted, while her friend Jess never tried it a second time? Drugs affect people in different ways because of their individual biology. (See next article.) For reasons not yet understood, each of us has different “settings” for those neuron features. You may have more receptors in a certain brain region than your friend has. Your sister’s receptors may be more sensitive to stimulation than yours are. Figuring out why and how is one of the important scientific quests of the 21st century.
Alcohol: Rats, Genes, and Teens

Animals help us learn all kinds of things about humans, including how we respond to alcohol. They are even teaching us why only some people abuse it or become alcoholics.

People have long observed that alcoholism can "run in families." Does a son drink because his parent used alcohol to deal with problems or because his life is stressful and unhappy? Maybe. He might also have genes that make him more prone to heavy drinking.

To separate environmental from genetic influences, scientists use several strategies. They study twins separated at birth, because they share genes but not environment. They study adopted siblings, because they share environment but not genes. Such studies suggest that genes account for about fifty percent of the risk of alcohol abuse. Still, there is no way to determine the genetic risk for any one person.

To isolate biological and genetic differences, scientists study rats, fruit flies, and other animals. For example, they selected rats that drank alcohol and selectively bred them to create a line of rats that became heavy drinkers when given unlimited alcohol. They also bred "teetotalling" rats that avoided alcohol. Then they studied the differences in the two breeds to get a picture of possible genetic factors at play. That exploration is part of a field called pharmacogenetics, which explores how variations in genes (genetics) cause different responses to drugs ("pharma" in ancient Greek).

These studies reveal that a whole "cocktail" of neurotransmitters interact with alcohol and disrupt interconnected pathways in the brain. These brain chemicals govern pleasure seeking, physical and mental sedation, depression, memory, stress, and pain. Dozens of genes are involved in producing and regulating each of these chemicals.

Happy Hour

When some of these neurotransmitters are off-balance, they can tip the scale toward alcohol abuse. One part of this complex picture involves the brain chemical serotonin, which controls a sense of emotional well-being and happiness. People with low serotonin levels are often depressed and anxious. Drinking rats and teetotalling rats have different levels of serotonin. The drinker rats are naturally more anxious than the teetotallers, and they have both low serotonin and fewer tools, called axons, for releasing it. Maybe rats – and some people – with low serotonin levels drink to reduce anxiety and depression.

Interestingly, some "early onset" alcoholics (people who begin abusing alcohol as teens) often have fewer receptors for serotonin. Scientists are searching for genetic variations that cause this scarcity. Finding them might help explain how genes influence some types of alcoholism.

To complicate matters, drinking also influences the activity of genes. Alcohol turns the "dial" up, down, on, or off for different genes. For example, heavy drinking reduces the number of serotonin receptors from previous levels, which may make the drinker more depressed and lead to a craving for more alcohol. Thus, behavior influences the activity level of genes that, in turn, influence behavior again!

Heavy Drinking Genes?

Variations in another gene pathway may allow some rats to drink more heavily than others. Those genes regulate a brain chemical called GABA (gamma-aminobutyric acid). GABA quiets down (inhibits) other neurons and makes them less sensitive to signals. At first, alcohol enhances this sedative effect, but long-term drinking has the opposite (excitatory) effect. Drinking rats have higher GABA levels than teetotallers, which may allow them to drink heavily without staggering. Scientists are exploring whether differences in GABA levels, or in the makeup of the GABA receptors, enable some humans to drink more heavily as well.

On the other hand, some genetic variations may discourage heavy drinking. For example, a mutation in one gene causes
The Teenage Difference

Adolescent (“teenage”) rats appear less drunk than adult rats on the same amount of alcohol. That may happen with human adolescents, too. Still, they suffer more impairment to parts of the brain involved in judgment and reasoning. Thus, a teen might be able to walk a straight line, but still be mentally unable to drive a car or make decisions about proper and safe behavior.

Another important difference comes in the area of learning and memory. The teenage brain is geared for learning, and this shows at the level of specialized receptors for an important neurotransmitter (glutamate) in a key brain region where memories are formed (the hippocampus). In young animals, those receptors (called NMDA for N-methyl-D-aspartate) stay open longer than they do in adults. The longer-opening receptors may help them learn faster and remember more. Alcohol blocks the NMDA receptors, and that blockage can shut down new memories, cause blackouts with heavy drinking, and could even kill brain cells. Research suggests that teenagers are more vulnerable to this memory loss because their more potent NMDA receptors react more strongly to alcohol’s blockage. That over-reaction may also explain why teenagers suffer more brain damage from long-term drinking. Studies show that teenagers who drink heavily have smaller hippocampi (the plural of hippocampus). The younger a teen begins to drink, the smaller the hippocampus.*

Checks and Balances

The interaction between alcohol and brain chemicals is so complex that treating alcoholism requires a many-sided approach. One study showed that alcohol-loving rats that receive extra serotonin begin to drink less. Increasing serotonin, however, doesn’t help all human alcoholics cut back on drinking. That’s probably because the human serotonin system is very complex, consisting of many different types of serotonin receptors, each with a specific role. Moreover, many other neurotransmitters interact with alcohol as well. Future therapies will evolve as we learn more about those complex interactions.

Get Help

Many teens use drugs and alcohol to escape problems in their schools, families, or neighborhoods. If you are depressed or can’t cope with a traumatic experience, find help with a counselor, religious leader, trusted friend or adult, call a crisis hotline, or contact:

- Alateen <http://www.alanon.Alateen.org>
- Find Treatment < http://findtreatment.samhsa.gov/facilitylocatordoc.htm>

Learn more about it:

- Alcohol and The Adolesant Brain <http://www.duke.edu/~amwhite/>
- Alcohol Quiz: <www.med.unc.edu/alcohol/prevention/quiz/quiz.html>

* Read more about this research in Discover: Getting Stupid (March 2001) and What You Can Learn from Drunk Monkeys (July 2002).
One drop of the pure stuff would kill you. It’s used as a pesticide. It’s as addictive as heroin and is the most heavily used drug in the world. It’s nicotine, an ingredient in tobacco leaves.

The First Cigarette
Sarah had heard all the warnings, but like 3,000 other U.S. teens each day, she had her first cigarette before getting her driver’s license. In general, teens get addicted to nicotine more quickly than adults. Some teenagers become addicted even before smoking becomes a daily habit. Like most other smokers, Sarah is trying to quit. After six years, though, the ritual of smoking has become second nature to her.

Physical Dependence
While Sarah smoked, she became physically dependent on the addictive ingredient in tobacco: nicotine. (Nicotine was named after Jean Nicot, who brought tobacco to France from the Americas in 1560.) Nicotine mimics the neurotransmitter acetylcholine, which is involved in movement, breathing, heart rate, learning, and memory. It also triggers the release of dopamine, which makes nicotine addictive. Sarah’s neurons responded to nicotine by increasing the number of receptors for it. Those extra receptors released even more dopamine with her next cigarette.

Another still-unidentified ingredient in cigarettes increased the impact of her dopamine release. It slowed the breakdown of dopamine in Sarah’s brain, making it last longer. Thus, cigarettes gave Sarah a double dopamine high. They increased both the amount and the staying power of the dopamine.

The nicotine altered the way her neurons functioned, so they could no longer work normally without it. When she went too long without a cigarette, she felt unpleasant withdrawal symptoms. Tobacco contains 4,000 other, often toxic, chemicals that cause more deaths and hospitalizations than all illegal drugs combined. Sarah knows that smoking is aging her skin and damaging her heart and lungs, so she steels herself to suffer through nicotine withdrawal.

She finds she can’t stop “cold turkey,” so she tries to wean herself from nicotine slowly. She uses a nicotine replacement therapy: a skin patch, gum, spray, or inhaler. These therapies allow a small dose of nicotine to be absorbed through the skin, mouth, or lungs. That small dose can satisfy her physical dependency. Then, ever-smaller doses can help her body get past the dependency altogether.

Unfortunately for Sarah, such therapies don’t work as well for women as for men. Researchers don’t yet know why. Perhaps women smoke for different reasons than men. Perhaps their nicotine receptors are “tuned” differently. Researchers have discovered that biological differences among people can influence how fast and hard they become addicted. Some people have a super-efficient enzyme (a type of protein) that breaks down dopamine more quickly. They tend to be heavier smokers, because they use nicotine to keep their dopamine levels high. Researchers...
Marijuana, PCP, and the Monoclonal Antibody

Each year more than 200,000 people, mostly teens, seek treatment to control their use of marijuana. Unfortunately, marijuana is often doped with very dangerous substances. One of those is PCP (phencyclidine), which is toxic to neurons and can make people behave violently—toward themselves and others. The effort to counteract PCP is on the forefront of drug development. Normally, your body produces antibodies to destroy foreign invaders like viruses and bacteria. Most drugs, however, are too small for the body to recognize. Thus, drugs don't trigger an immune response, and your body doesn't produce antibodies against them. To get around this problem, scientists use biotechnology to produce antibodies against drugs in the lab. When these antibodies are injected into the body, they can fight the invader. To make the anti-PCP antibody, researchers joined PCP compounds to a foreign protein and immunized a mouse, which produced antibodies against PCP in its spleen. A spleen cell was then fused to a fast-growing cell (like a cancer cell) and grown in the lab. These fused cells all produce identical antibodies, which are called monoclonal antibodies because they are from copies (clones) of the same (mono) cell. They are being tested as a treatment for people with PCP overdoses. Scientists hope to create similar antibodies against cocaine and other drugs of abuse. Another way scientists are using the immune system to treat drug abuse is with vaccines that block the cocaine molecule from entering the brain.

Mental Dependence

Like most smokers who try to quit, Sarah can't kick her habit. It's not that she is weak. It's because of the role of memory in her reward pathway. As we saw with ice cream and cocaine, smoking is bundled with other actions and situations that are part of her everyday life, such as driving in a car, going out with friends, or sitting around after dinner. Her reward pathway links these activities to a pleasurable dopamine rush. Long after her body stops needing nicotine, her brain still craves it.

Sarah also has physical memories of smoking: tapping out a cigarette, sucking in the smoke, and rolling the cigarette in an ash tray. These rituals created a collection of automatic behaviors linked to her smoking cues. Sometimes she relapses because she can't stand having nothing to do with her hands!

Something To Do When Cued

Scientists are developing new ways of delivering medications to address how Sarah actually experiences her addiction. One method is a nicotine straw filled with tiny beads of nicotine. She could put it in a drink and sip it to increase her dopamine levels—and have something to fiddle with while she talks with friends. Sarah could use it to learn new behaviors and override the memories that nicotine ingrained in her brain.

Finding better ways to treat nicotine addiction may be a proving ground for other forms of addiction. New understandings about how addiction affects memory may lead to both better medications and better delivery methods that free addicts from relapses.

Career Center: Geneticist—Discover how different genes influence an individual's response to drugs.
Ecstasy (and Agony)

It seemed like a partygoer’s dream: A little designer pill that would give powerful feelings of peace, love, and understanding—and (supposedly) no side effects. In short, ecstasy. The trouble is, it is too good to be true!

Dance Party

The little pill contains a relative of amphetamine, a stimulant that revs you up. It made its debut as a “club drug” in Europe, where people used it for all-night dance parties or “raves.” Called Ecstasy and other nicknames, it contains the chemical MDMA (3,4-methylenedioxoy-N-methylamphetamine). Unlike the drugs discussed in previous articles, MDMA does not come from a plant. It is human-made and often comes mixed with impurities, by design or accident. Some of those are extremely dangerous. Even in its pure form, Ecstasy can ravage the mind and the body. Here’s what could happen to you.

When MDMA enters the brain, it primarily targets the neuron terminals (ends) that release the brain chemical serotonin. When you have a good serotonin level, you have a sense of well-being and happiness. If you have too little serotonin, you become depressed. In some cases, low serotonin levels make people aggressive, violent, and alcoholic. Serotonin connects many brain regions and helps regulate your body temperature and muscle activity.

Avoiding Addiction and Alcoholism

- Do you ever do things because your friends do? Would you use drugs because they do?
- Does involvement in sports, music, hobbies, or other adventures make teens less likely to try drugs?
- Can thinking about your life goals and interests help you find a positive niche for yourself?
- Read what teenagers say about their experiences with drug abuse at In the Mix <http://www.pbs.org/inthemix/>
MDMA enters the transporters (vacuums) that normally pump serotonin out of the synapse (gap) between two neurons. It puts the vacuum in reverse, flushing serotonin out of the neuron. The serotonin rushes into the gap, flooding the receptors. A tidal wave of all the good things serotonin makes you feel washes over you. You feel enlightened. Your body also experiences a wave of motor stimulation. A dance rave!

This ecstatic high may last a few hours. While you feel great, you are actually at risk of suffering damage. MDMA makes your body’s thermostat malfunction. It can’t keep your body temperature at the normal level. Dancing makes you flushed and overheated. You’re in danger of heat stroke – a leading cause of death from Ecstasy.

Your thermostat may recover when Ecstasy wears off, but your serotonin system won’t be back to normal for some time. Serotonin is only made in certain neurons, and those cells dumped most of it out during the Ecstasy high. It takes time to make more. Until then, you feel the opposite of ecstasy: depression. Nothing seems good any more.

What’s the fix? Can you regain your happiness by taking more Ecstasy? Because MDMA also stimulates the dopamine system, you’re motivated to want more, anyway. It won’t work. If you take more too soon, your neurons have not replaced enough serotonin, so there’s not much to release. If you wait for serotonin to build up again, you may be in for another disappointment.

**Brain Damage**

In ways not yet fully understood, MDMA can destroy many of the serotonin neurons’ axons and terminals. The long axons do not grow back, so serotonin activity in much of the brain is lost. Short axons may eventually grow back in abnormally high numbers, but these do not appear to work properly. These changes are probably responsible for the problems with memory, “executive functioning” (reasoning), impulsivity, and other impairments that have been observed in long-term Ecstasy users.

Researchers have living proof of the long-term brain damage Ecstasy causes. They created molecules that attach to the ends of active serotonin neurons for use in PET scans. The scans show an eerily dark image for Ecstasy users, even weeks after using it. (See photo.) Research on monkeys confirms the serotonin system makes very little recovery seven long years after four days of MDMA use.

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**Inhalants**

Many everyday products contain chemicals that can be dangerous if inhaled. Too many young teens do just that, because the fumes make them high. Like all drugs of abuse, they alter your “mind” because they change your brain chemistry. They contain a mix of chemicals, so each inhalant alters your brain in a different way. Most affect not only your brain, but also nerves throughout your body. They are attracted to the fatty coating (myelin) that wraps your nerves. Like the rubber around an electrical wire, this coating insulates the electrical pulses in your nerves and speeds the connection. Inhaled chemicals degrade this covering, interrupting the flow of messages and even harming the nerves themselves. This damage is permanent. It interferes with your thinking and reasoning. It also creates motor difficulty, making it hard to control your legs or fingers. Some chemicals in inhalants replace oxygen in your lungs and elsewhere. You can suffocate. Other chemicals make your heart rhythm go haywire. You can die of a heart attack. These are high prices to pay for such a cheap high.
Huda Akil wondered why our brains produce a morphine-like chemical that makes us feel no pain. That question led to exploring the relationship between stress and addiction.

Huda Akil was born in Damascus, Syria, where she received a French and Arabic education. Although most girls in Syria were not encouraged to go to college, Huda studied psychology at the American University in Beirut, Lebanon. She was interested in how humans learn language and how language helps us think. She was so fascinated by the brain biology underlying complex behaviors that she moved to the U.S. for a Ph.D. in psychobiology from the University of California, Los Angeles. She continued her studies at Stanford University, focusing on the chemistry of the brain.

While at UCLA, she shifted gears from studying language to studying fundamental processes common to all animals – the pleasure and pain responses. “We didn’t yet have the biotechnology tools to understand the biology of highly complex brain functions. Then I read about studies in which rats would work really hard to press a lever that electrically stimulates a part of their brain that rewards them with pleasure. I was surprised that biologists could locate a part of the brain that controlled a specific behavior.”

Huda’s graduate research focused on how animals process pain. “By chance, we found that when we stimulated one part of their brain, they felt less pain,” she said. “The rats could happily sit in a bucket of ice. When we stopped stimulating that section, they jumped right out. That was evidence that the brain has natural ways to block pain.” The stimulation made the brain produce “endorphins,” which dull pain in the same way that opiates such as morphine, heroin, and opium do.

“We asked ourselves, why does the brain have receptors for opiates? Our research showed that the brain makes natural opiates to block pain. That’s why it recognizes morphine and other opiate drugs. Then we asked: why does the brain make that substance? We realized it has a natural biological function: to block pain when under extreme stress. If an animal’s survival is at stake, it doesn’t have time to worry about pain. It first needs to run or fight, and deal with the pain later.” Our basic biological need to sometimes block pain is what also makes our brains recognize opiate drugs.

Huda is now a professor at the University of Michigan, where she researches the relationship between stress and addiction. “Animals that react more strongly to stress may be more prone to addiction,” Huda explained. “Also, a more stressful environment can make an animal more likely to take drugs.” That relationship holds for humans as well.

“It’s a big unknown how your own body is going to react to stress and drugs. There are real genetic differences, and real differences among individual brains. You can’t go by statistics or by what happens to your friend. It’s a gamble, especially if there is vulnerability in your family.”

Career Center: Policy Maker – Apply new scientific understandings to decide how to adjust public funding of prevention and treatment programs.
You’re in a hurry to get to class. You round a corner and nearly collide with another student! As you pick up the books you dropped in fright, you feel your heart pounding.

**Rising Heart Rates**

Why does being startled cause your heart rate to speed up? When you are frightened, stressed, or upset, your brain releases the neurotransmitter acetylcholine, which in turn releases the hormone adrenaline (epinephrine). Adrenaline increases the number of heartbeats per minute. It helps you deal with potentially dangerous situations by increasing the amount of blood delivered to your organs. Many foods, medicines, and illegal drugs contain chemicals that also increase your heart rate, as well as your blood pressure and the force of your heart contractions. These chemicals belong to a class of substances called **stimulants**. Other chemicals, known as **depressants**, slow heart rate and decrease both blood pressure and the heart’s pumping force. Stimulants and depressants also influence many other systems in the body. However, since heart rate is easily measured, it is used to determine the effect of a particular chemical on the body.

In the laboratory, the effects of chemicals can be measured on organisms that “model” the effects of those chemicals on the human body. *Daphnia*, a small crustacean relative of shrimp, lobsters, and crabs, is a useful model organism for classifying chemicals as stimulants or depressants. Its outer body shell is transparent, so you can view its heart beating under a microscope.

**What To Do**


**Caution:**

Wear goggles and gloves, and do not touch or taste these chemicals. Wash hands after the experiment.

- Predict the effects of chemicals on the heart rate of *Daphnia*.
- Measure the heart rate of *Daphnia* under “control” and “variable” chemical conditions.
- Create a data table and calculate the percent change in heart rate for each chemical.
- Classify chemicals as depressants or stimulants after observing their effects on heart rate.

**Discussion and Exploration**

1. Based on your data, would you classify your experimental chemical as a stimulant or a depressant?
2. Why is it important to use average heart rates for each condition?
3. Why is it important to use a new *Daphnia* for each chemical tested?
4. How can too much of a stimulant or depressant (overdose) be fatal?
5. Design an experiment using *Daphnia* to study the effect of temperature on heart rate.
6. Amphetamine drugs contain stimulants. Research their effects on the brain and central nervous system.
7. As with all drugs, your individual biology probably influences the way stimulants and depressants affect you. Follow the latest research at [http://www.nida.nih.gov/](http://www.nida.nih.gov/)

**Caffeine Link**

Caffeine affects brain chemicals that influence your mood and behavior. If you drink caffeinated drinks, take your pulse before and after. Can you relate any changes to changes in how you feel or behave?
Keeping Safe

- Interview a parent or other adult about how drugs and alcohol affect their peers. Has substance abuse interfered with people’s plans and goals?
- Explain the newest scientific understanding about alcohol to an adult.
- Talk to younger children about the dangers of inhalants, drugs, and other substances. Encourage them to discover interesting activities to fill their free time.
- What messages and programs work for teens? Devise a prevention program to keep your peers off drugs.

Online Teacher’s Guide

Visit the Biotechnology Institute on-line at www.BiotechInstitute.org for:

- Teacher’s Guide.
- Activity Supplement: Student and Activity Guides.
- Overheads, links, and survey.
- Information on subscriptions and previous issues.
- Downloadable Teacher’s Guides from previous issues.

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Read More About It:


Web Sites to Explore

Becoming a Neuroscientist <http://faculty.washington.edu/chudler/sem.html>
Brain Facts <http://web.sfn.org/content/Publications/BrainFacts/index.html>
Dr. Drew <http://www.drdrew.com/>  
National Institute on Drug Abuse <http://www.nida.nih.gov/>
Check out the Mind Over Matter materials and links to specific drugs of abuse.
National Institute on Alcohol Abuse and Alcoholism <http://www.niaaa.nih.gov/>
Neuroscience for Kids <http://faculty.washington.edu/chudler/neurok.html>
Partnership for a Drug-Free America <http://www.drugfreeamerica.org/>
Teens Health <http://www.teenshealth.org/teen/drug_alcohol/>