With names such as ecstasy, clarity, roofies, bidis, yellow sunshine and pina colada, they sound intoxicating and exotic. And they are. To many people, drugs seem to offer possibilities of making life better, more interesting, more exciting, more varied, less painful. Sometimes they do, for a while anyway. No one would take them if they didn't make people feel, if not good, at least very different.

But we now know that their short- and long-term effects are more dangerous than experts had thought even 10 years ago.

As scientists continue to unravel the mysteries of the brain, one thing is becoming crystal clear: Merely dabbling in drugs can cause severe, and often irreversible, damage to brain cells and the nervous system in general.

Thanks to sophisticated new imaging techniques such as functional magnetic resonance (fMRI) and positron emission tomography (PET scans), scientists can view the brain today in real time. Genetics research has enabled researchers to identify and clone the tiny sections of brain cells, called receptors, that respond to virtually every drug of abuse.

On the eve of a new millennium, scientists "know more about how drugs act in the brain than we do about anything else in the brain," says Alan Leshner, director of the National Institute on Drug Abuse (NIDA).

Most of the picture isn't pretty. Despite widely varying chemical structures, drugs of abuse typically ignite a biochemical cascade in the brain that almost always lights up reward or pleasure circuits, often by affecting the messenger chemicals, called neurotransmitters, that help transmit signals from one brain cell to another.

"Some of these changes may well be benign," Leshner says. "Some are not. But you use a drug, and you have changed your brain in big or little ways."
Nerve cells, like all cells, are equipped with several kinds of entry gates, called receptors, most of which protrude out of the cell's outer skin, or membrane.

Each receptor is designed to respond when it comes in contact with a neurotransmitter molecule of a certain shape, which fits the receptor's structure like a key in a lock. Drugs work because they fit those locks in nearly the same way that natural neurotransmitters do.

Many receptors trigger a channel to open and cause a brief rush of chemicals into the cell. If they're the right kind of chemicals, they can prompt the cell to "fire" -- that is, make it more likely to send a signal to its neighbor.

Those are called excitatory responses. Other compounds make cells less prone to fire; they are called inhibitory. Depressant drugs such as alcohol cause that kind of response.

Some receptors are inside the cell. When activated, they cause changes in the way a cell does its internal housekeeping.

Just as a key may fit in a lock but still not turn, some drugs merely plug a receptor, preventing the natural neurotransmitter from docking there. Other drugs act almost exactly like the natural compound, commanding the receptor channel to open and flood the cell's interior with various kinds of chemicals from outside.

So if drugs don't actually do much that isn't already done by naturally occurring compounds, why is everybody so worried about them? There are several answers, all rather grim.

For one thing, drugs can hit your brain in concentrations far greater than neurotransmitters ever would. Moreover, drugs can change the chemistry of your brain cells in temporary and permanent ways.

Some of them kill neurons outright or maim them so that they'll never work correctly. Others alter the nerve cells for days or weeks at a time -- long after the user may desperately wish to be straight -- often producing extremely painful withdrawal symptoms.

Why, then, do we do it? Attraction to drugs sort of runs in the family. It's surprisingly common in the animal world.
Many species will go out of their way to get intoxicated. House cats love to get high on catnip. Elephants in the wild will stop what they're doing to get drunk on fermented fruits. Some birds delight in eating berries that make them so stoned they can't fly straight.

But we are the only species that can understand what we're doing to ourselves.

For information, see NIDA's web site at http://www.nida.nih.gov.

Club Drugs

Typically found at all-night "raves" and "trances," so-called "club drugs" also are popular at some dance clubs and bars. Although they have benign-sounding names, many contain a potent and dangerous mix of compounds. They often come from home laboratories and frequently are laced with chemical contaminants that increase the risk of overdose.

Because many of these drugs are colorless, tasteless and odorless, they have been slipped into beverages and taken by unsuspecting individuals. In recent years, their use has been linked with an increasing number of date rapes and other sexual assaults.

Although they share the common informal designation as "club drugs," these compounds belong to at least three distinct categories.

1. Tranquilizers and sedatives. Rohypnol -- also known as roofies, rophies, roche and forget-me pill -- is a member of the same well-known class of tranquilizers that includes Valium, Halcion and Xanax. All principally affect GABA receptors, with results ranging from sedation to coma.

Rohypnol usually is produced in pill form but sometimes is ground up and snorted. It is legal in many countries as a treatment for insomnia and as a sedative or presurgery anesthetic but has not been approved for prescription use by the Food and Drug Administration for use in the United States.

Rohypnol affects areas of the brain involved in memory processing and produces a condition called "retrograde amnesia" that is similar to a blackout -- users often can't remember events that occurred while under the drug's influence. The drug also lowers blood pressure and can produce
A similarly abused drug is GHB (gamma-hydroxybutyrate), variously known as grievous bodily harm, G, Georgia home boy and liquid ecstasy. It can be a clear liquid or a white powder and produced in tablet or capsule form.

GHB is an extremely powerful and fast-acting central nervous system depressant. For reasons not well understood, it once had a reputation on the steroid black market as a muscle-builder, fat-reducer and antidepressant. It hasn't been shown to do any of those things.

It does produce sedative effects 10 to 30 minutes after being taken. At low doses, it can relieve anxiety and cause drowsiness, sometimes accompanied by nausea, vomiting and headache. But at higher doses, GHB produces sleep and sometimes coma.

Like any broadly active sedative, it can slow breathing and heart rate to dangerously low levels, especially if combined with alcohol. Like Rohypnol, GHB frequently produces amnesia and often is implicated in date rape.

2. Psychedelic stimulants. Ecstasy -- also called clarity, XTC, adam or lover's speed -- contains MDMA, a compound very similar to methamphetamines [see article at lower left]. But it also can cause hallucinations equivalent to those induced by mescaline, the active ingredient in peyote mushrooms.

The parent compound of MDMA destroys serotonin-producing brain cells, and MDMA may do the same, at the long-term expense of thought and memory. MDMA itself damages neurons that respond to dopamine.

MDMA typically results in sweating, anxiety, increased heart rate and blood pressure. Muscle seizures are not uncommon, and users may employ an infant pacifier or other device to lessen the effects of involuntary jaw clenching.

3. Psychedelic anesthetics. Ketamine, sold legally to veterinarians for anesthesia, often is called special K, K, vitamin K and cat valiums.

It is chemically similar to PCP (phencyclidine), originally developed as an anesthetic but abandoned when it was seen to cause hallucinations and
psychotic states.

Taken in liquid form or as a powder often snorted or smoked with marijuana or tobacco -- and in some places injected into muscle tissue -- Ketamine and PCP bind to a kind of receptor that was not identified until the 1990s.

They affect the function of several neurotransmitters, particularly one called NMDA, and produce a characteristic stupor similar to extreme drunkenness. Panic, rage and paranoia are typical.

Ketamine increases blood pressure and can cause potentially fatal breathing problems.

At low doses, it impairs attention, learning ability and memory. At higher doses, it can cause degraded motor function, delirium and amnesia.

Methamphetamines

Also known as speed, uppers, meth, copilots, crank, crystal meth, fire, chalk and ice, these drugs are powerful stimulants that cause the heart to race, increase blood pressure and boost the body's metabolism.

People taking methamphetamines often become talkative, feel anxious and may experience a sense of exhilaration or euphoria. But this so-called "rush" or "flash" lasts only a few minutes. These powerful stimulants are highly addictive and have been showing up in recent years as part of the club scene.

Brain changes. Methamphetamines work in the brain on the so-called "pleasure circuit." They are chemically similar to two powerful neurotransmitters, dopamine and norepinephrine, causing their release in key areas of the brain, including the nucleus accumbens, which affects emotions; the prefrontal cortex, which plays a critical role in working memory; and the striatum, an area of the brain involved in movement.

Methamphetamines elicit pleasure through a complex chain reaction around and inside nerve cells. The drugs pass easily through nerve cell membranes, taken up by transporter molecules that normally would carry dopamine or norepinephrine through the cell wall.

Inside the nerve cell, methamphetamine then enters holding tanks called
vesicles that contain dopamine and norepinephrine. This, in turn, prompts release of more dopamine and norepinephrine. Normally, enzymes would break down the overflow of neurotransmitters, but methamphetamine blocks this reaction.

Transporter molecules then remove the excess dopamine and norepinephrine, dumping them into the synapse, or space between nerve cells. As the levels of dopamine increase, so do feelings of pleasure and euphoria. Norepinephrine appears to be responsible for feelings of alertness and thwarts fatigue.

Other physical effects. Methamphetamines raise blood pressure and can cause dangerous irregular heartbeats, chest pain, shortness of breath, nausea, vomiting and diarrhea. They also can increase body temperature to fatal levels, particularly during overdoses.

Biggest risks. Brain hemorrhage can cause permanent paralysis and speech loss or be fatal. Laboratory research in animals also suggests that even a single, high dose of methamphetamine can destroy as much as one-half of nerve cells producing dopamine in the brain. A similar destruction, not caused by drugs, is involved in Parkinson's disease, a progressive, debilitating neurological condition.

Inhalants

The name says it all: Inhalants are chemical fumes that are sniffed or inhaled. They provide one of the swiftest ways for drugs to reach the brain because they enter the bloodstream directly through the lungs.

Also known as chemical vapors, these substances are found in a wide range of common products. They have been used at least once by an estimated 21 percent of eighth-graders, according to the National Institute on Drug Abuse.

The chemicals found in inhalants are as varied as their use. Cigarette lighters and refills contain the gas butane.

Paint thinner may have toluene, turpentine, ethyl acetate or mineral spirits. Fingernail polish remover contains acetone, as does rubber cement.

Pressurized cans of hair spray, computer cleaner and whipped cream contain fluorinated hydrocarbons.
Medical anesthetic gases contain ether, chloroform, halothane and nitrous oxide, also known as laughing gas.

Brain changes. Some inhalants act somewhat like surgical anesthetics, suppressing nerve action in a way not clearly understood and causing various degrees of stupor. Some produce structural changes in brain cells.

These often affect the cerebral cortex, the cerebellum and the brain stem. As a result, chronic inhalant users often move slowly and clumsily because of loss of coordination.

The frontal cortex, a region of the brain that helps to solve complex problems, also is affected by inhalants, as is the hippocampus, a part of the brain involved in memory retention. Inhalants rob the brain of oxygen, reducing nerve cell activity and killing some cells. That, in turn, can affect thinking, memory and ability to learn.

Other physical effects. Permanent hearing loss, especially from inhaling toluene found in paint sprays, glues and dewaxers, is a big risk for inhalant users. Irreversible damage to nerves throughout the body, a condition called polyneuropathy, is common. Among the most vulnerable nerves are those in the back and legs.

Inhalants chemically attach to fatty tissues, especially the white myelin sheaths that protectively coat nerve axons, somewhat like the insulation on electrical wires, and speed nerve conduction. Inhalants damage the myelin and destroy it. Some of these changes are temporary, but others can produce long-lasting damage.

Elsewhere in the body, inhalants can cause a chemically induced hepatitis (inflammation of the liver), liver failure and muscle weakness.

They also sometimes interfere with blood cell production, which can result in the life-threatening condition known as aplastic anemia.

Biggest risks. "Sudden sniffing death" occurs when inhaled vapors replace oxygen in the lungs and the brain. Inhalants also can interfere with the normal heart rhythm and lead to cardiac arrest.
Pot, weed, grass, ganja, M.J. or whatever -- it's the most commonly used illicit drug in the United States. Marijuana is the dried leaves and flowers of the hemp plant, also known as Cannabis sativa. Delta-9 tetrahydrocannabinol (THC) is the leading active ingredient in marijuana, but it includes more than 400 other compounds.

Marijuana is gaining popularity among youth after nearly a decade of decline, although rates still haven't reached levels seen in the 1970s and 1980s.

In 1999, 22 percent of eighth-graders had tried marijuana, compared with just 10 percent in 1991, according to the Monitoring the Future Study, sponsored by the National Institute on Drug Abuse (NIDA). Among high school seniors, Monitoring the Future found that nearly 50 percent had tried marijuana in 1999, compared with 37 percent in 1991.

The drug is mostly smoked in hand-rolled "joints" but also can be smoked from pipes, bongs or hollowed-out cigars. Some people also use marijuana to brew tea, or they include it in foods, such as brownies or cookies.

Brain changes. For a long time, nobody knew what THC was doing in the brain because there didn't seem to be a receptor for it. Only in the last 10 years did scientists finally find the receptor and isolate a naturally occurring brain chemical called anandamide that binds to it.

THC also binds to the anandamide receptor and suppresses activity in the hippocampus, an area of the brain pivotal for learning, memory and emotions. Studies show that learned behaviors deteriorate with marijuana use. That translates to problems with attention, memory and learning -- all of which are impaired among college students who use marijuana heavily, even after they have stopped using the drug for 24 hours.

On average, it takes at least 30 hours for the body to clear even half of the THC from a single use. Those who begin using marijuana before college show lower achievement and are more likely to engage in more delinquent behavior and aggressiveness than non-users.

There also are lots of anandamide receptors in the basal ganglia and cerebellum, both of which are involved in movement control, and in the cerebral cortex, where the "high" probably is generated.

Other physical effects. In the lung, marijuana produces many of the same
health effects as tobacco smoke -- daily coughs, phlegm, chronic bronchitis and increased susceptibility to chest colds. Long-term marijuana use damages lungs.

Since marijuana smokers inhale deeply and hold the smoke in their lungs for long periods of time, they also appear to be exposed to three to five times the levels of carbon monoxide as tobacco smokers. Marijuana increases heart rate and raises blood pressure.

Like nearly all drugs, marijuana doesn't mix with pregnancy. Use of marijuana by expectant mothers raises the risk of delivering a baby who has a low birth weight and is at increased risk for various health problems.

Nursing mothers who smoke marijuana pass THC to their babies through breast milk and risk damaging their infant's motor development. Children who breathe passive marijuana smoke display more temper tantrums, thumb sucking and anger than youngsters not exposed.

Biggest short-term risks. Marijuana users are as uncoordinated as drunks on standard driving tests, and more than 120,000 people seek treatment each year for marijuana addiction, according to NIDA.

Alcohol and Cigarettes

Often dismissed as "just alcohol" or "just cigarettes," these substances contain powerful drugs that are very harmful to brain and body.

Both are widely used. A 1999 survey conducted by the National Institute on Drug Abuse found that more than half of all eighth-graders and 80 percent of high school seniors had imbibed alcohol at least once, despite the legal drinking age of 21 years.

The same study showed that 44 percent of eighth-graders and two-thirds of high school seniors had smoked at least once. About 14 percent of eighth-graders and roughly one in four high school seniors also have used smokeless tobacco.

Brain changes. Some of the brain's messenger chemicals excite nerve cells; others dull or inhibit them. Among other activities, alcohol affects the most powerful of the inhibitory systems -- those involving the neurotransmitter GABA -- and that results in a general depression of many kinds of nerve response.
Too much alcohol floods neurons and changes gene function of the cells, which in turn appears to alter receptors and results in intoxication, brain-cell death and, if repeated, dependence and alcoholism.

Nicotine, the active ingredient in tobacco, reaches the brain just eight seconds after being inhaled and is both a stimulant and a sedative. Chemically similar to a powerful neurotransmitter called acetylcholine, nicotine activates areas of the brain in feeling pleasure and reward. It does so by boosting production of dopamine, another powerful neurotransmitter, in a part of the brain called the nucleus accumbens.

Chewed or smoked, nicotine is addictive, like heroin or cocaine -- one reason that those who begin smoking before age 21 have the hardest time quitting.

Other physical effects. Heavy alcohol use delays puberty and can slow bone growth in laboratory animals, leading scientists to suspect that it could do the same in humans. Elsewhere in the body, alcohol can deplete B vitamins important for neurological function and optimal use of peripheral nerves in fingers and toes.

In the liver, chronic alcohol abuse over time causes degeneration, swelling and scarring of the liver (called cirrhosis) and can lead to liver failure. Light drinking may provide some moderate protection against heart disease, but the exact dose is dicey.

A recent study by researchers at the University of Pennsylvania found that even social drinking increased free radicals, harmful substances linked to development of premature heart disease, stroke, cirrhosis and many other disorders.

Nicotine increases heart rate and blood pressure. It also alters breathing patterns and damages the lungs. In very high concentrations, nicotine is a poison. In fact, just one drop of purified nicotine on the tongue is deadly.

Biggest short-term risks are addiction to alcohol and nicotine and death from binge drinking.

Long-term smokers are more likely than nonsmokers to develop lung cancer (caused by smoke, not nicotine) and other tumors. Emphysema, difficulty in breathing caused by destruction of air pockets in the lungs, also
is a major risk for smokers.

Women who smoke undergo menopause sooner than nonsmokers and suffer the effects of aging, including wrinkled skin, earlier than their nonsmoking counterparts. Alcoholics face a high risk of liver disease. Alcoholics who smoke are particularly vulnerable to cancer of the throat, mouth and esophagus.

IT'S ALL IN YOUR HEAD

Unlike many substances, drugs can seep through blood vessels in the brain and reach nerve cells, or neurons.

Brain areas most affected by drugs

Limbic system

1. Striatum

Nucleus accumbens

Caudate nucleus

Thalamus

Hippocampus

Ventral tegmental area

Cerebellum

Brain stem

Cerebral cortex

Frontal cortex

Prefrontal cortex

Fooling receptors
A receptor designed to respond to a natural neurotransmitter can be either blocked or activated by drug molecules that have a similar, but not identical, shape.

Anatomy of a neuron

Neurons gather incoming messages -- both excitatory and inhibitory -- from their neighbors across narrow gaps between cells called synapses. When a cell "fires," it sends a signal down its axon. Tiny pouches called vesicles spray neurotransmitters across the synapse, which then affect receptors on the receiving cell.

Five important neurotransmitters . . .

Serotonin

Widespread substance that affects mood, appetite, sexual activity, aggression, body temperature and sleep.

Norepinephrine

Regulates blood pressure and prompts extreme arousal, "fight or flight" response, mental focus and pain reduction.

Dopamine

A key compound that is an important part of the brain's "reward" system, causing feelings of wellbeing.

GABA

The brain's major inhibiting compound, involved in muscle relaxation, sleep, diminished emotional reaction and sedation.

Acetylcholine

Involved in muscle action all over the body; in the brain affects arousal, attention, learning, mood and sleep.
and drugs that interfere with them

Ecstasy (MDMA)

Damages or destroys serotonin neurons, alters balance and action of norepinephrine and dopamine.

Methamphetamines

Increase concentrations of norepinephrine and dopamine in nucleus accumbens, caudate nucleus and prefrontal cortex, among other structures.

Alcohol, Tranquilizers

Alcohol increases activity of GABA, inhibits release of acetylcholine and excites dopamine neurons in ventral tegmental area activity. Benzodiazepine tranquilizers, such as Rohypnol, boost GABA activity in cerebellum, brain stem and spinal cord.

Pschedelics

Activate some serotonin receptors on post-synaptic cells, change balance and action of norepinephrine and dopamine.

Ketamine

Affects special PCP receptors, inhibiting two key neurotransmitters (NMDA and glutamate) and stifling neural activity.

SOURCES: A Primer of Drug Action, 7th Edition by Robert M. Julien (W.H. Freeman, 1995); Drugs and the Brain by Solomon H. Snyder (Scientific American Library, 1996); NIDA

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