

New Variety of Street Drugs Poses Growing Problem

Designer drugs—analogs of compounds with proven pharmacological activity made by underground chemists—present novel challenges to law enforcement officials, legislators, and scientists

Rudy M. Baum, C&EN San Francisco

A breed of underground chemists, most of them in California, are playing a deadly cat-and-mouse game with law enforcement authorities. They are the manufacturers of what have become known as designer drugs. Their customers range from heroin addicts on the streets of Oakland, San Francisco, and Los Angeles to upscale young professionals in Marin County. Until recently, many of their products were perfectly legal. Until laws dealing with drugs of abuse are changed, it is likely that new products from their clandestine laboratories also will, for a time, be legal.

Designer drugs: It's a catchy sobriquet. It's also an imprecise one. Under its broad umbrella have been grouped compounds possessing enormously different pharmacological properties—and enormously different levels of danger to the people who consume them. One class of such drugs has been associated with more than 100 overdose deaths in California. An impurity in another designer drug has caused several cases of irreversible Parkinson's disease among the addicts who

used it. Yet another has been condemned by some as a damaging hallucinogen and championed by others as an important new therapeutic agent.

The phenomenon of designer drugs presents law enforcement and drug treatment officials, legislators, and scientists with novel challenges. For example, how does one design a law to make illegal a compound that has not yet been synthesized? Or for another example, is it possible to design a simple, relatively inexpensive analytical procedure to detect a compound present in body fluids at 1 ng per mL? Ironically, the phenomenon also has opened up an exciting new avenue into the study of neurological disease, one that could never have been ethically pursued in the absence of several hundred young heroin addicts who poisoned themselves with a tainted designer drug.

Designer drugs are analogs of compounds with proven pharmacological activity manufactured by underground chemists for sale on the street. For instance, the compound fentanyl is a powerful narcotic marketed under the tradename Sublimaze by Janssen Pharma-

Doonesbury

BY GARRY TRUDEAU



Copyright, 1985, G. B. Trudeau. Reprinted with permission of Universal Press Syndicate. All rights reserved.

ceutica of Belgium. Fentanyl is about 100 times as potent as morphine. It is very short-acting. Those properties have made it an extremely important drug in medicine—used as an anesthetic in, by one estimate, up to 70% of all surgical procedures in the U.S. Fentanyl is also just as addictive as heroin or morphine, and the "high" associated with it, though short-lived, appears to be very similar to that associated with heroin.

Fentanyl is not a simple molecule, and it turns out that a vast number of relatively minor modifications of its molecular structure result in compounds that also act as potent narcotics—in some cases, many times as potent as fentanyl itself. Tinker with a side chain here, add a halogen there, and the result is still probably a chemical that packs a powerful wallop, a chemical that can be sold on the street as heroin, and a chemical that might very well be as legal as sugar. It would still be legal because the traditional method of controlling drugs of abuse has been to classify specific chemical compounds as illegal. Until a compound is classified—a process known as scheduling—no laws apply to it.

The fentanyl analogs make up one of three classes of drugs that generally have been lumped together as designer drugs. Analogs of another, chemically distinct narcotic—meperidine—make up a second class. The third class contains a single member, 3,4-methylenedioxyamphetamine (MDMA), which, for a number of reasons, probably should not be designated a designer drug.

The underground chemists who make these drugs—some of whom apparently are quite sophisticated, many others pure hacks—have borrowed a technique from medicinal chemistry. In the search for new pharmaceuticals, whether they be pain killers, antitumor drugs, or antihypertensive agents, medicinal chemists synthesize large numbers of analogs of known drugs and determine their properties. Sometimes the goal is greater potency, sometimes it is to find an antagonist, sometimes it is to find a drug with fewer negative side effects, and sometimes it is simply to beat a competitor's patent.

The motives and methods of the designer drug manufacturers, however, are different from those of the medicinal chemist. With a few intriguing exceptions, the quality control exercised by the illicit drug manufacturers is often lousy. Terms like "bucket chemists" and "biker labs" are used by drug enforcement officials and scientists to describe the majority of these producers and their facilities.

Another crucial difference between the underground entrepreneurs and their medicinal chemist counterparts is that the designer drug manufacturers are not fastidious about determining the pharmacology and toxicology of their products in test animals before marketing them. Food & Drug Administration approval is not a matter of concern to them. New compounds and concoctions of drugs and reaction contaminants are tested first in the humans they are sold to, which will lead, inevitably, to a "designer drug disaster," according to Robert J. Robertson, chief of the

Division of Drug Programs of California's Department of Alcohol & Drug Programs. The first such disaster has already occurred. Robertson predicts that other such disasters will occur.

One motivation of underground analog chemists is to circumvent the laws governing illegal drugs—or controlled substances, as they are often called. Conviction for production or distribution of a drug that has been classified by the U.S. Drug Enforcement Administration as a Schedule I controlled substance—one with no medical uses and high abuse potential—carries a stiff fine and prison sentence. In a number of cases, analog chemists arrested by DEA or local law enforcement agents have simply been released because the compound being manufactured, although clearly a drug intended for sale, had not specifically been scheduled.

Although that factor has received much attention, it tends to overlook the fact that many drugs, from heroin to the notorious phencyclidine (PCP), have been controlled for many years and continue to be produced. And with legislation currently before Congress to control production and distribution of drug analogs in general and legislation before the California legislature to control fentanyl analogs specifically, the motivation of their technical legality may soon be obviated. Yet no one expects the analogs to disappear, because, like heroin and PCP, there is a market for them whether they are legal or not.

The biggest motivation is pure profit. According to Frank Sapienza, a chemist at DEA headquarters in Washington, D.C., in rough numbers a \$2000 investment will yield about a kilogram of heroin worth about \$1 million on the street. A similar \$2000 investment in glassware and chemicals can be turned into a kilogram of 3-methyl fentanyl, currently the most common fentanyl analog being sold, worth about \$1 billion (yes, billion!) on the street. Although producers of the fentanyl analog must worry about distribution, they do not have to contend with buying opium in foreign countries or smuggling their products into the U.S.

Analogs of controlled substances are not new. As Sapienza points out, "Analogues have been around at least since the 1960s. When we controlled LSD, mescaline, and some of the substituted amphetamines, underground chemists produced new analogs of them. When we controlled PCP, new analogs were formulated."

Most of the concern about designer drugs centers on the fentanyl and meperidine analogs. Even its strong detractors admit that MDMA is a different sort of drug altogether.

A number of features make the fentanyl and meperidine analogs different from previous analogs that have appeared on the street. One is that "for the first time, we are dealing with potent narcotic drugs that can take the place of heroin," Sapienza says. "The manufacturers do not have to go across the border to obtain their opium or refined morphine or heroin. They can make everything in a clandestine lab. To our knowledge, that has never been done before. It makes



Henderson (left): single chemist is responsible. Langston (center): synthetic heroin was behind disaster. Robertson: stepped-up education, prevention efforts

for a scary situation. The way things stand, we have no indication that organized crime is involved. We have no indication that it is a nationwide problem. However, in terms of the potential threat, there are half a million heroin addicts across the country primed to be supplied with these synthetic drugs."

Another feature is that, at least in the case of fentanyl analogs, the level of sophistication required to make even a sloppy batch and not kill oneself is greater than for past analogs. "Making these fentanyl compounds is not the same as making PCP or methamphetamine," Sapienza says. "I don't think that the average bucket chemist would be able to follow a set of instructions to make 3-methyl fentanyl."

The fentanyl and meperidine analogs tend to be linked together in discussions of designer drugs because both classes of compounds are narcotics and are intended for sale to heroin addicts, but they are quite distinct chemically. The evolution of the two as designer drugs also is different, as are the implications of their continued use on the street.

"Fentanyl has been in use medically in Europe since the late 1960s and in the U.S. since the early 1970s, and no one thought it had abuse potential because it is so short-acting. Addicts wouldn't use it if the high lasted only 30 minutes," says Gary L. Henderson, a pharmacologist and toxicologist at the University of California, Davis, who has been studying fentanyl and its analogs since 1972. However, Henderson points out, the fentanyls are unique in that the entire class of compounds is so potent, and analogs can be designed, as they have been by researchers at Janssen, to be either shorter acting or much longer acting than fentanyl itself.

Henderson's involvement with fentanyl began when he was asked to develop an analytical assay for the drug in body fluids for use in clinical monitoring. Because the compound is such a potent narcotic, it is

present in very low concentrations in blood and urine of users, and development of such an assay is technically complex. The radioimmunoassay that Henderson and his coworkers fashioned has been improved to the point where it can now detect fentanyl or fentanyl analogs at concentrations as low as 1 ng per mL. Henderson's laboratory is the only one in California, and one of the few in the U.S., that can analyze for fentanyl analogs in body fluids.

Although fentanyl abuse by medical personnel is not uncommon, Henderson says, the first illicit use of the drug his laboratory was called on to investigate was in doping racehorses. "Racehorse underground chemists generally are years ahead of the chemists producing for street abuse," Henderson observes. The effects of narcotics are quite species specific, and in several species, including horses, they act as stimulants. "There is evidence that in ancient times opium extracts were used to stimulate horses. People were using methadone to dope racehorses before anyone in this country knew what methadone was," he says.

In 1981, Robertson contacted Henderson because fentanyl analogs had begun showing up in what were supposedly heroin samples seized by police. That contact has led to an ongoing contract between Henderson's lab and the Division of Drug Programs by which drug and body fluid samples from unexplained overdose deaths and from drug treatment centers can be sent to Henderson for analysis.

Over the past six years, several fentanyl analogs, as well as fentanyl itself, have shown up on the street, Henderson says. The analogs have appeared in a roughly sequential order with some overlap from one to the next. First came α -methyl fentanyl, then p -fluoro fentanyl, α -methyl acetyl fentanyl, and, in early 1984, 3-methyl fentanyl. At least two other analogs were found in samples but were probably synthetic by-products, Henderson says. The α -methyl, p -fluoro, and

3-methyl analogs are now Schedule I controlled substances. To date, fentanyl analogs, primarily 3-methyl fentanyl, have been responsible for more than 100 overdose deaths in California.

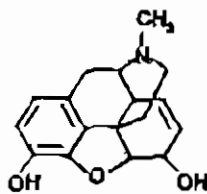
Henderson coined the term "designer drugs" specifically in reference to the fentanyl analogs he was analyzing. "I am probably going to be haunted by that until the day I die," he says. "It sounds like I am trivializing it, but I am not. We were getting samples that ranged from a pure white powder sold as China White to an off-white powder to a dark brown material that looked like Mexican Brown heroin. We got samples that were cut with heroin, and I wondered why someone would do that. It turns out that can help an addict get on a methadone program. The entire packaging and marketing concept to me was a designer phenomenon. Additionally, you could literally design the potency and duration of action into the molecule."

For a variety of reasons, Henderson believes that a single "world-class medicinal chemist" has been responsible for the various fentanyl analogs that have appeared. And the efforts of that anonymous chemist eerily paralleled those of reputable medicinal chemists seeking the ideal pharmaceutical. He or she found what was needed in 3-methyl fentanyl. It is extremely potent, about 3000 times more potent than morphine, and its duration of action and the high associated with it apparently are indistinguishable from heroin. "This gets misinterpreted, but 3-methyl fentanyl is actually a better drug than heroin," Henderson says. "It really is a designer drug. There is method to this madness. If someone said, 'Let's replace heroin,' this would be the way to do it."

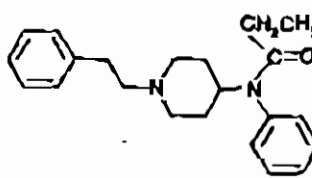
Henderson bases his assessment that a single, highly sophisticated chemist has been responsible for all the fentanyl analogs that have appeared on several factors. One is that, apparently, all of the syntheses were carried out using starting materials and a highly efficient reaction scheme not in the published literature.

Another factor was the appear-

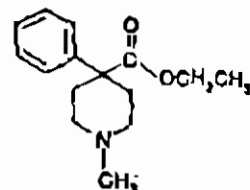
Morphine, fentanyl, and meperidine are useful narcotics...



Morphine

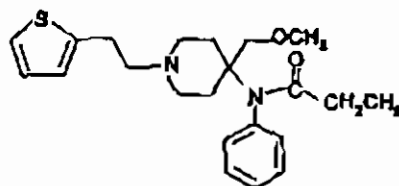


Fentanyl

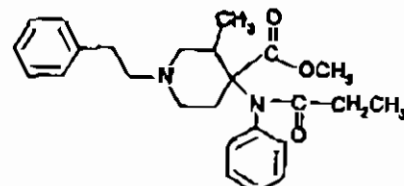


Meperidine

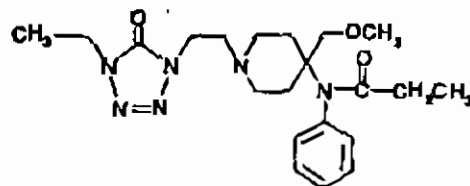
... and fentanyl derivatives are undergoing clinical trials...



Sulfentanyl

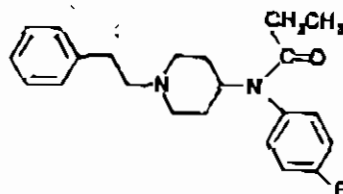


Lofentanyl

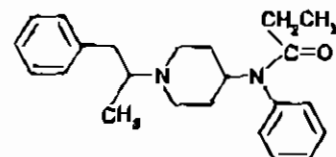


Alfentanyl

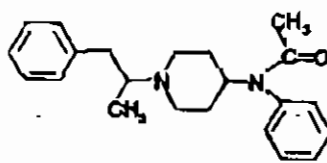
... while narcotic analogs are being sold on the street



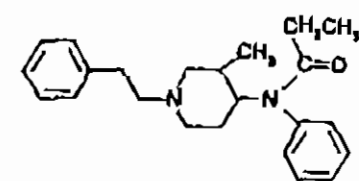
p-Fluoro fentanyl



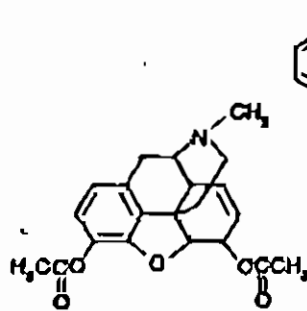
o-Methyl fentanyl



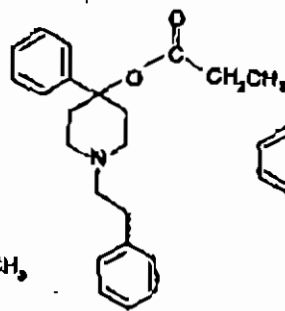
alpha-Methyl acetyl fentanyl



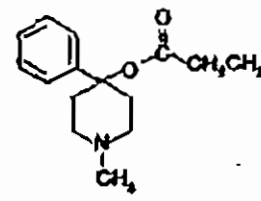
3-Methyl fentanyl



Heroin



PEPAOP



MPPP

ance of *p*-fluoro fentanyl. "That had not been described in the literature," Henderson says. "It is a straightforward thing to do, but unlike most underground chemists, he or she went to something that had never been published." A third factor is that "the quality control is really remarkable. These aren't garbage drugs. They are well made, with very few impurities, and the doses are uniform."

Finally, "the real kicker to me was the appearance of 3-methyl fentanyl," Henderson says. "It is hard to synthesize. There is a lot of steric hindrance at the 3-position. Plus, to make this, you stand a good chance of killing yourself. It is so potent in its pure form that you just can't work with it in a normal underground laboratory."

Overall, Henderson concludes, "the thinking behind this is an order of magnitude over your classic amphetamine or PCP chemist who works from a cookbook recipe." However, if the thinking behind the fentanyl analogs is world class, the facilities required to make it are not. "The equipment required is about what you would find in an introductory organic chemistry laboratory," Henderson says.

Henderson's speculation that a single chemist has been behind the fentanyl analogs that have appeared thus far may well be correct. The identity of that chemist likely will never be determined, because, Henderson believes, he or she no longer needs to synthesize product.

"That is one problem with the law enforcement end of this," Henderson says. "The police are oriented toward biker labs. They think they are going to be riding around and see a 50-gal drum of acetone sitting next to a garage. They go inside, and sure enough, some guy has boxes of 3-methyl fentanyl sitting around. That is not going to happen. You make 3-methyl fentanyl once and you have a lifetime supply; 200 g is 200 million doses."

Even if the scenario of a single chemist culprit is correct, it seems likely that other, less sophisticated chemists are being drawn to the synthesis of fentanyl analogs by the potential profits involved. Sapienza says that in June, DEA agents raided two independent clandestine laboratories in the Los Angeles area that were attempting to make some sort of fentanyl analog. Which analog, Sapienza says, is not yet clear. What is clear from the material that was seized is that the chemists involved were not of the caliber of the one who made the material Henderson has analyzed. "What we are seeing from both laboratories are complex mixtures of a number of active ingredients along with many by-product intermediates and impurities," Sapienza says.

The technical sophistication involved in analyzing for fentanyl analogs in blood and urine is causing headaches for drug treatment centers and parole and probation departments. Henderson is working to develop an assay for other laboratories, but he says, "I think it is a quantum jump in technology to make it routine." In addition to the low concentrations involved, different fentanyl analogs may require different immunoreagents.

Robertson outlines the kinds of problems the fentanyl analogs pose. "Say I am a parole officer. I have a man on parole who is required to give a urine sample on demand. He walks into my office one day and I can see that he is high as a kite. I say to him, 'You've been using,' and he responds, 'I haven't used in months.' So we get a urine sample, it goes into the lab, and it tests negative because he has not been using heroin, he has been using 3-methyl fentanyl. There is nothing I can do. It is a perfect drug for people on parole or on probation. People in drug treatment programs can use it, and it will not show up in the routine tests."

One company that does such routine testing is PharmChem Laboratories Inc., Menlo Park, Calif., which specializes in screening for illicit drugs, primarily in urine samples. The company analyzes about 50,000 samples per month from a variety of clients. Among PharmChem's largest clients, in terms of number of samples, are methadone treatment centers and parole and probation departments.

The type of analysis done depends on the client, says Brian Sedgwick, director of research and development of the company. For a typical sample from a drug treatment center, PharmChem carries out a relatively simple, two-plate, thin-layer-chromatography analysis, which can detect seven classes of drugs, including opiates, methadone, amphetamines, barbiturates, and cocaine. The cost of such an analysis is \$3.00 to \$4.00 per sample.

Samples from another client, the Los Angeles County probation department, undergo a three-test system. The sample is first screened by a two-plate TLC analysis. Samples testing positive are confirmed by an enzyme-linked immunoassay and then by gas chromatography. Only samples testing positive in all three procedures are reported as positive. Some industrial clients require gas chromatography/mass spectroscopy confirmation of positive samples, which adds about \$45 to the cost of analysis, Sedgwick points out.

"The fentanyl series of compounds pose major analytical problems," Sedgwick says. For routine screening, the concentrations involved "are well below the range of TLC." That automatically means that immunoassay screening, which can be more expensive, will be required. Currently, an immunoreagent for fentanyl is not yet commercially available, Sedgwick says. And since GC/MS confirmation likely would be required for fentanyl analogs, the cost of analysis probably would be well beyond the budgets of most drug treatment centers and many parole and probation departments.

"If designer drugs do become a major part of the drug abuse scene, and if the trend is toward compounds with increasing potency, the implication for analytical laboratories such as PharmChem is that detection sensitivity will have to increase, and therefore our methodology will have to become more sophisticated, more precise, and possibly more expensive," Sedgwick says. Such trends would require a significant research and development effort.

The designer drugs that are analogs of meperidine

MDMA: A psychoactive drug with a schizophrenic reputation

Unlike the analogs of fentanyl and meperidine, the drug most commonly called MDMA has both its supporters and detractors.

To a number of psychiatrists scattered across the country, MDMA is a useful therapeutic tool. Those psychiatrists have been using MDMA quietly since the mid-1970s in counseling sessions as an adjunct to psychotherapy. They report that, when used under controlled conditions, MDMA has few negative side effects and can act to ease psychic trauma and break down barriers to communication.

To recreational users, whose numbers vary widely depending on the source of the estimate, MDMA is a pleasant way of getting in touch with oneself, of raising one's consciousness. To many such users, MDMA possesses the positive features of LSD without LSD's hallucinatory properties.

The National Institute on Drug Abuse (NIDA) maintains that MDMA is a "nationwide problem as well as a serious health threat." According to a NIDA publication, MDMA users experience problems similar to those associated with use of amphetamines and cocaine. The publication cites specifically "psychological difficulties, including confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia—during and sometimes weeks after taking MDMA."

The Drug Enforcement Administration believes that MDMA is a drug with high

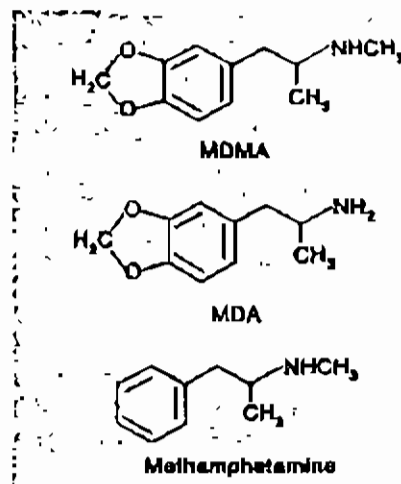
abuse potential and no medical uses. As such, DEA recently invoked its emergency scheduling procedures to classify MDMA as a Schedule I controlled substance.

MDMA is an abbreviation derived from 3,4-methylenedioxymethamphetamine. Popular accounts of the designer drug phenomenon often cite the compound as an example of a designer drug. That classification has resulted largely because MDMA and designer drugs achieved notoriety simultaneously. MDMA's history and pharmacology, however, bear almost no resemblance to the analogs of fentanyl and meperidine.

MDMA was first synthesized and patented by E. Merck & Co., Germany, in 1914 as an appetite suppressant. The compound was never marketed, however, and the patent on it has long since expired. Until the DEA emergency scheduling, MDMA was not a controlled substance nor had it been approved by the Food & Drug Administration for medical use.

The compound goes by as many names as there are opinions regarding it. It has been referred to by at least half a dozen names in the scientific literature. Its currently accepted *Chemical Abstracts* designation is *N,α*-dimethyl-1,3-benzodioxole-5-ethanamine. On the street, it is sold as MDMA, MDM, Adam, Ecstasy, or XTC.

Chemically, MDMA is related both to methamphetamine and 3,4-methylenedioxymethamphetamine (MDA). According to a



number of research workers, however, it bears little pharmacological relationship to those drugs. "It stands out unique in its constellation of properties," says one.

As is usually the case with psychoactive drugs, describing those properties in precise scientific language is difficult. Unlike MDA, MDMA appears to have almost no hallucinogenic properties. Nor is its effect primarily that of a stimulant such as methamphetamine. Instead, MDMA seems to break down barriers to communication between people, ease psychic trauma, and allow individuals access to repressed psychological information.

Because of those properties, some psychiatrists believe it is a useful drug in psychotherapy. George Greer, a psychiatrist in private practice in Santa F

have followed a strikingly different path from that of the fentanyl analogs. Meperidine is a narcotic that was synthesized and patented in 1939 by Winthrop Laboratories and sold under the tradename Demerol.

The principal meperidine analog that has appeared on the street is 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP). It often is referred to as the "reverse ester" of meperidine. A synthesis and pharmacological evaluation of MPPP was first reported in 1947 by Albert Ziering and coworkers at Hoffmann-La Roche. The compound is about three times as potent as morphine and about 25 times as potent as meperidine. It was taken to clinical trials but never commercialized and never scheduled as a controlled substance.

Superficially, at least, MPPP is a simple molecule to synthesize. That, and its lack of a legal status, led to its discovery by one or more designer drug chemists. The reaction sequence, though simple, must be carried out

under the proper conditions. If the reaction is carried out at too high a temperature or too low a pH, much of the product will be another compound altogether: 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP).

Apparently working from a set of instructions derived from Ziering's journal article, an underground chemist managed to produce a drug batch that contained primarily MPTP. Sold on the street in 1982 in areas near San Jose, Calif., as "synthetic heroin," the MPPP/MPTP mixture caused the first designer drug disaster.

The key figure in unraveling that disaster was William Langston, chairman of the department of neurology at Santa Clara Valley Medical Center in San Jose. Langston was called in to examine a 42-year-old male heroin addict who was "literally frozen." "I couldn't move at all. He couldn't talk," Langston said. "There were some findings that suggested that he had

N.M., has published one of the few studies of such MDMA therapy. Greer administered MDMA to 29 subjects, 14 of whom were experiencing relatively minor psychological problems, such as dissatisfaction with themselves and minor depression. Although admitting that the study lacked rigorous scientific controls, Greer found that all 29 subjects reported some benefit from MDMA during the session.

Greer concluded that "the single best use of MDMA is to facilitate more direct communication between people involved in a significant emotional relationship. Not only is communication enhanced during the session, but afterward as well. Once a therapeutically motivated person has experienced the lack of true risk involved in direct and open communication, it can be practiced without the assistance of MDMA." Greer also observed that "MDMA's use as an adjunct to insight-oriented psychotherapy was specifically recommended by six subjects. Many felt that MDMA enhanced self-understanding and was useful in their personal and spiritual growth."

The psychiatrists who have used MDMA in therapy also believe that it has relatively low abuse potential because its beneficial or pleasant effects diminish rapidly with regular use.

By contrast, DEA's Frank Sapienza says that MDMA's abuse potential has been demonstrated by the simple fact that a lot of the drug is being synthesized, sold by dealers on the street, and

used by recreational drug users. Based on that evidence and the fact that MDMA is chemically similar to other drugs of abuse, DEA proposed in July 1984 that MDMA be classified as a Schedule I controlled substance. The Schedule I classification was proposed because the Food & Drug Administration had never approved MDMA for medical use. "That is the definition we use," Sapienza says.

DEA was surprised when several psychiatrists and psychologists objected to the proposed scheduling. "We didn't know that it was being used in therapy sessions," Sapienza says.

In hearings on the scheduling, psychiatrists who have used MDMA in therapy argued that the drug should certainly be controlled, but that it should be classified as a Schedule III controlled substance, which is defined as one with moderate abuse potential and accepted medical uses. DEA's emergency scheduling action, coming in the midst of the permanent scheduling procedure, caught those physicians off guard.

Sapienza defends DEA's action on the grounds that research conducted at the University of Chicago demonstrated that MDA is selectively neurotoxic to serotonergic neurons in the brain. Although MDMA's mechanism of action remains unknown, research has shown that its action involves serotonergic neurons. By extrapolation, MDMA also might be neurotoxic to such neurons. DEA's emergency scheduling was based on

that possible neurotoxicity and the increasing availability of the drug on the street.

"I think the different views of MDMA are compatible," Sapienza says. In terms of MDMA's abuse potential, he points out that the law does not equate abuse with harmful side effects. It equates abuse with how many people want to use a drug. And there appear to be a significant number of people who want to use MDMA. "They might not call that abuse," he says. "They might call it recreational use." However, the law does not differentiate between the two.

The same sort of dichotomy applies to what is meant by medically accepted uses. The law clearly states that a drug "must go through accepted procedures to prove that it is safe, that it can be produced in pure form, and that it treats some condition," Sapienza says. "MDMA may be able to fit into that category, but the studies have not been done to show that. Therefore, we have to say that it has no accepted medical use, and it has to go into Schedule I."

Such a classification, however, creates a catch-22 situation for the proponents of MDMA as a useful therapeutic drug. The laws applying to Schedule I controlled substances make it quite difficult to obtain approval to conduct clinical trials of a drug. Because it is impossible to obtain patent protection on MDMA, it is unlikely that a pharmaceutical firm will undertake the costly effort to obtain FDA approval for its use.

suffered neurological damage, but I had never seen anything like it before."

Langston and his colleagues found out that the patient's girlfriend, also a heroin addict, was in the same condition. She was admitted to the medical center. Although Langston was convinced that their condition was caused by some environmental source, he was not sure enough that it was the heroin to issue a public alarm. Then through what Langston calls a "remarkable series of coincidences," he learned of two similar cases in Santa Cruz, a town about 30 miles from San Jose on the California coast. Two brothers had used a synthetic heroin and both began to freeze up. They continued to use the drug until both were unable to move. Both probably would have starved had their mother not stopped by their apartment to check on them.

The link to the synthetic heroin had been estab-

lished in Langston's mind, and he put out a public warning. The publicity surrounding the announcement brought to light three more cases and samples of the synthetic heroin. Ian Irwin, a chemist working with Langston, analyzed the samples by GC/MS, but found no matches against a library of 40,000 mass spectra.

The publicity resulted in yet another clue. Halle Weingarten, a toxicologist with the Santa Clara County Crime Laboratory, called Langston to tell him that she recalled reading about a student who had synthesized his own narcotics and been stricken with symptoms resembling Parkinson's disease. The case had been described by Glenn C. Davis, then an associate professor of psychiatry at the University of Tennessee's Center for the Health Sciences, and several co-workers in a 1979 issue of *Psychiatry Research*. After reading the article, Langston and Irwin concluded

that MPTP had been responsible for the student's condition. They then verified that the major constituent of the synthetic heroin samples sold in the San Jose area was, in fact, MPTP.

"That set off a real explosion of activity," Langston says. Once convinced that the condition of his patients was irreversible and strikingly similar to classic Parkinson's disease, Langston put them on L-dopa therapy. Parkinson's disease is caused by the death of dopaminergic neurons in an area of the brain called the substantia nigra. Dopamine is a neurotransmitter produced by the neurons of the substantia nigra, as well as by neurons in many other areas of the brain, and supplied to neurons of the striatum. It is necessary for normal muscle control. Dopamine cannot be administered orally, however, whereas L-dopa can. In patients with Parkinson's disease, L-dopa is converted by the remaining cells of the substantia nigra to dopamine. The response of his patients to L-dopa, Langston says, was dramatic.

However, although L-dopa therapy is a boon to Parkinson's disease patients, and probably proved life-saving for three of Langston's patients, disabling side effects, including hallucinations and exaggerated movements known as dyskinesias, are associated with it. These side effects appeared rapidly in Langston's patients, and in three of them maintaining an effective dosage has now become very difficult.

From a scientific point of view, the discovery that MPTP selectively destroyed neurons in the substantia nigra set off a major burst of activity in the study of Parkinson's disease, a field that had been relatively quiescent since the advent of L-dopa therapy almost two decades ago. Through the efforts of Langston and his coworkers and a number of independent researchers, many pieces of data fell into place over the following three years.

The authors of the 1979 *Psychiatry Research* paper had never identified the compound responsible for their patient's condition because they had focused on MPPP, not MPTP, Langston says. Those researchers studied the compounds in rats and, in doing so, made a double mistake. Rats respond to narcotics in a way that no other species does: They become catatonic. Rats also appear to be very resistant to MPTP-induced neuronal damage.

"What is interesting about that," Langston says, "is that a huge amount of experimental data in medicine is generated in rats. This is a stunning example in which rats do not predict the primate at all. If you did MPTP toxicity screening in rats, you would miss this completely."

Researchers then demonstrated that MPTP was selectively toxic to substantia nigra neurons in rhesus monkeys, and Langston and coworkers found that it had the same effect in squirrel monkeys. When the animals that had been treated with MPTP were sacrificed, the damage to substantia nigra neurons appeared identical to that observed in the brains of deceased Parkinson's disease patients. MPTP had provided an animal model of Parkinson's disease, something that researchers had never before possessed.

"To the best of my knowledge, MPTP is the most selective neurotoxin ever discovered," Langston says. "These discoveries have set off a real scientific race to find out how it acts. There are really three major questions. One is: Why is MPTP so incredibly selective and how does it destroy just one type of dopaminergic cell in the brain? The second is: What is the cause of the species selectivity? Primates are much more sensitive than rodents. The third question is: Will understanding the mechanism of action by which MPTP causes cell death help us to understand why those same cells die in Parkinson's disease? There is a great deal of hope that that will be the case. It could actually unravel Parkinson's disease. That is a big one in medicine."

What has been discovered is that MPTP is rapidly converted somewhere in the brain to the 1-methyl-4-phenylpyridinium ion (MPP⁺). This conversion is catalyzed by the enzyme monoamine oxidase. Langston, Irwin, and coworkers have accumulated evidence that this conversion is necessary for MPTP to exert its toxic effects. They have shown that 1-methyl-4-phenylpiperidine, a compound lacking the double bond in the dehydropyridine ring of MPTP, cannot be converted to MPP⁺ by monoamine oxidase and does not exhibit the neurotoxicity of MPTP. Another finding dovetailing with this is that monoamine oxidase inhibitors block the neurotoxic effect of MPTP.

Another important piece of evidence is that MPP⁺, but not MPTP, is actively taken up by the dopamine uptake system at a rate similar to dopamine itself. "What probably happens is that some extraneuronal component, either neuronal support cells or cells somewhere else in the brain, converts MPTP to MPP⁺, and then the nigral neurons take up the MPP⁺," Langston says. Why the dopaminergic neurons of the substantia nigra are destroyed by the MPP⁺ whereas other dopaminergic neurons seem not to be affected by it remains a mystery.

Is MPTP the cause of classical Parkinson's disease? That, too, remains an open question. Langston, however, has become convinced that, if not MPTP, then some other environmental factor is responsible for a large percentage of the cases of the disease. He and Donald B. Calne, a neurologist at the University of British Columbia, Vancouver, have published a hypothesis to that effect.

Langston explains that studies of twins have pretty much ruled out a hereditary explanation for the disease. It has been known that 5 to 8% of nigral neurons die naturally with each decade of life. However, 80% of such neurons must die before the first symptoms of Parkinson's disease appear. That means that most people never exhaust their reserve of such neurons during their lifetimes.

Langston and Calne suggest that most cases of Parkinson's disease result from an environmental insult such as exposure to MPTP that causes the death of some fraction of the nigral neurons during midlife. If that insult destroyed, say, 50% of the nigral neurons, there would be no symptoms. However, the natural process of nigral cell death would move that person

below the 20% threshold for such symptoms much earlier in life than would normally occur.

The MPTP-contaminated synthetic heroin is going to provide a crucial test for that hypothesis over the next decade, Langston points out. In cooperation with the Centers for Disease Control, Langston has identified more than 400 other people who probably used the tainted synthetic heroin. In a sense, they have volunteered for a grim epidemiological study. If the hypothesis is correct, many of those people will develop symptoms of Parkinsonism in the coming years.

Another patient of Langston's developed symptoms that strongly resemble Huntington's chorea within an hour of using a synthetic heroin. Huntington's chorea is an inheritable disease involving the death of neurons in the basal ganglia, a region of the brain that connects with the substantia nigra. The patient was referred to Langston as a possible MPTP victim, but Huntington's chorea, Langston says, involves excessive uncontrollable movement, almost the opposite of Parkinson's disease. Langston was ready to dismiss the patient when he learned that the patient apparently had purchased his synthetic heroin from the same drug dealer that had sold the MPPP/MPTP concoction to the patients who developed Parkinson's disease.

Another meperidine analog, 1-(2-phenylethyl)-4-phenylacetoxypiperidine (PEPAOP), was identified in a sample of synthetic heroin in 1984, Langston says. Improper synthesis of PEPAOP can result in production of an MPTP analog, 1-(2-phenylethyl)-4-phenyl-1,2,3,6-tetrahydropyridine (PEPTP).

"We have been predicting a 'drug x' for about six

months," Langston says, based on the patient with symptoms resembling Huntington's chorea and certain other symptoms that have been showing up in patients who use narcotics. "The question is: Could PEPAOP or PEPTP be drug x?" Langston asks. He has initiated studies of the neurotoxicity of the compounds in an attempt to answer that question.

Designer drugs have proven to be a source of enormous frustration for drug enforcement authorities. Until 1984, scheduling a compound was a procedure that could take up to several years. The Comprehensive Crime Control Act of 1984 gave the Attorney General emergency scheduling authority, which bypasses hearings involved in permanent scheduling. Under the law, a drug can be designated as a controlled substance within 30 days of a determination that it represents a hazard to public safety. The emergency scheduling remains in effect for one year. Emergency scheduling provisions have been used to classify MPPP, PEPAOP, and 3-methyl fentanyl as Schedule I drugs.

The Justice Department and many others, however, believe that emergency scheduling is inadequate to deal with the designer drug phenomenon. Legislation supported by the Justice Department and DEA was introduced in the Senate in July to control the analogs, even if they do not yet exist, of controlled substances. Titled the "Designer Drug" Enforcement Act, the legislation imposes penalties for manufacturing, possessing, or distributing a designer drug for human consumption. The act exempts substances manufactured or distributed in conformance with an approved new drug application or an exemption for investiga-

MPTP, chemists, and Parkinson's disease

Whether classical Parkinson's disease is caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or some other environmental toxin remains an open question. That the disease can be caused by exposure to MPTP, however, has clearly been demonstrated. And that is a finding that chemists should take note of, says J. William Langston.

Shortly after Langston's first paper linking MPTP and Parkinson's disease appeared in *Science*, he received a letter from a pharmaceutical chemist who had worked with MPTP for eight years during his 30s. The chemist had been synthesizing MPTP and using it as a building block in the synthesis of benzomorphine derivatives.

"During the next to last year he was working with MPTP, he noticed that his tennis game was falling apart," Langston says. The chemist was 37.

Because of increasing problems with coordination, he visited a neurologist, who diagnosed the condition as early Parkinson's disease. Langston says that since then he has learned of five other chemists who developed Parkinson's disease while working with MPTP.

Unlike the heroin addicts Langston is treating for MPTP-induced Parkinson's disease, those chemists clearly did not inject themselves with the compound. "There is no question that MPTP exposure in a laboratory—either through inhalation or cutaneous contact—can cause the disease," Langston says, "and that should be of some concern to anybody working in a chemistry laboratory."

Langston points out that MPTP is a relatively simple pyridine that could be a trace by-product of a variety of chemical reactions. Langston and Donald B.

Calne, a neurologist at the University of British Columbia, Vancouver, have suggested that most cases of Parkinson's disease may be caused by some kind of environmental factor, such as exposure to a neurotoxin like MPTP, coupled with the normal process of aging. In such a scenario, the effect of exposure to a small amount of MPTP might not manifest itself until many years later.

"Chemists must wonder, when they get a disease, whether a compound they worked with caused it," Langston says. In the case of the chemists who worked with MPTP and developed Parkinson's disease, such a suspicion would have been justified. And Langston suggests that other progressive diseases of aging, such as Alzheimer's disease, might be explained by a similar model of early to midlife brain damage caused by an environmental factor that manifests itself only later in life.

tional use so as not to interfere with legitimate research and development of new pharmaceuticals.

The act defines a designer drug as "a substance other than a controlled substance that has a chemical structure substantially similar to that of a controlled substance in Schedules I or II or that was specifically designed to produce an effect substantially similar to that of a controlled substance in Schedules I or II."

The bill is now before the Judiciary Committee. No hearings on it have yet been scheduled.

Response to the bill has been cautious, and many involved in the effort to control designer drugs refuse to comment on it beyond saying that it probably will emerge from hearings in somewhat different form. Many pharmaceutical manufacturers have not yet taken a position on it, although there appears to be some consensus that because the intent of the legislation is not to interfere with legitimate research, it will not pose a problem for drug companies. A spokesman for the Pharmaceutical Manufacturers Association says that that organization is studying the bill but has not yet taken a position on it. A spokesman for Merck says that the company "welcomes the legislation to control this aspect of drug abuse" and that the company believes that the wording adequately protects the interests of pharmaceutical companies. A spokesman for Squibb says that closing the designer drug loophole is necessary but that the company hopes the language of the legislation is made more precise so as not to interfere with legitimate research.

The Justice Department obviously believes that the proposed law can withstand challenges. Some lawyers are not so sure. A San Francisco lawyer who has defended a number of clients on drug distribution charges says that the law may well be "unconstitutionally vague because it defines a designer drug as a substance substantially similar to another substance. It is not clear what substantially similar in structure or effect means," he says.

That definition bothers a number of scientists. Says one: "What does 'substantially similar' mean? To me, that is almost a meaningless phrase." Another scientist points to MDMA as an example of the difficulty. MDMA is the *N*-methyl analog of 3,4-methylenedioxyphenylisopropylamine (MDA), a hallucinogen; the 3,4-methylenedioxy analog of amphetamine, a stimulant; and the α -methyl analog of 3,4-methylenedioxyphenethylamine, an antitussive. Pharmacologically, however, it resembles none of those drugs.

Henderson points out that two chemical structures that appear similar to one person, particularly a nonscientist on a jury, may well appear dissimilar to another person. "I think it will produce a field day for the lawyers," he says.

The scope of the designer drug problem is a matter of some debate. The problem so far has remained confined to California. DEA's Sapienza points out. "I personally don't think that many people are involved right now," he says. "I think that if we use our enforcement arm to prosecute those individuals, we will do a lot to wipe it out. I do not see it as a nationwide problem." Although there have been claims of over-

dose deaths due to fentanyl analogs in Florida and Baltimore, he says that those remain unsubstantiated.

Although agreeing that designer drugs are primarily a California problem, other observers believe that the fentanyl and meperidine analogs will start appearing elsewhere and that the underground chemists will discover other parent compounds to work their tricks on. Robertson points to PCP to make his point. When PCP, which can cause hallucinations and extremely violent behavior, first started being used in areas of Los Angeles in the mid-1960s, it was considered a bizarre California phenomenon. Its use has now spread across the country and is epidemic in some cities, Robertson says.

Based on his analysis of specimens from drug treatment centers, Henderson believes that the problem of fentanyl analogs already is widespread in California. He speculates that up to 20% of the heroin being sold in the state is, in fact, 3-methyl fentanyl, and that in some counties the figure could reach 90%. The lure of the potential profits that can be made will prove irresistible to other underground chemists, Henderson believes.

"It is hard to believe that this is not going to catch on," Langston says. "Obviously, it already has in California. These illicit chemists can make huge amounts of money, they have no problems with importation, and they cannot be prosecuted."

Langston says that a raid on a clandestine laboratory in southern California turned up a photocopied set of very simple instructions for making MPPP. "The story we got was that it had been purchased," Langston says. "I think some people have turned to selling the formulas rather than trying to make the drug themselves. That's scary because it is so easy to produce the toxin. Even a good chemist might produce some MPTP."

One aspect of those instructions provides a clue to the brutal callousness of the manufacturers of designer drugs. At the bottom of the page, Langston says, was a warning that read: "Caution. If made improperly, this may damage your clients. See attached reprint." Attached was a copy of an article on MPTP and Parkinson's disease.

Beyond new legislation, controlling designer drugs presents the same dilemmas that have confronted efforts to control other types of drugs. Robertson has been involved in prevention and drug treatment for more than 30 years, and he remains an optimist. His department, he says, has stepped up its education and prevention efforts. "If we can get to the moms and dads of this world, and the kids at an early age, then we stand a better chance."

Henderson is not so optimistic. "This is part of the evolution of drugs of abuse," he says. "It has gone from natural products to semisynthetic derivatives of natural products to stolen pharmaceuticals. Now pharmaceuticals are so tightly restricted, people are simply making their own. In 10 or 20 years, people will be using drugs that are far different from the ones available today. However, they will still be abusing drugs." □