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A Growing Industry and Menace: Makeshift Laboratory's Designer Drugs

STIMATED TO BE a billion dollar nd growing) industry by the Drug nforcement Administration, so-called esigner drugs represent the flip side specifically engineered legitimate harmaceuticals. They are synthetic emicals designed in makeshift labo-tories to elicit specific responses and ten sold on the street to drug abus-rs.

Another term that some persons ncerned with the problem use for ese drugs is "controlled substances nalogues." Today, these drugs include nalogues of fentanyl; meperidine, par-ularly MPPP (1-methyl-4-phenyl-opionoxypiperidine) and PEPAP (1 -phenylethyl]-4-acetyloxypiperidine); hencyclidine hydrochloride (PCP); the henylisopropylamine methylenedioxy-mphetamine (MDA); and MDA's *N*-ethyl analogue (MDMA).

Designer drugs can be made-to-order substituted without the buyer's nowledge for such drugs as heroin. The term 'designer drugs' was origi-ally coined to mean the manufacture synthetic drugs designed to the onsumer's specifications," Mark W. anford, PhD, clinical director of the athway Society, Inc, in Santa Clara, alif, told a Boston audience at this all's North American Congress of lcohol and Drug Problems. "However, e've now expanded that term to mean nything the kitchen chemist can engi-eer."

Because these synthetic counterparts an be stronger and cheaper than the riginal drug, many investigators be-eve that today's situation represents erely the tip of a much deeper prob-em. Demand for designer drugs soon ay undercut severely that for botani-l narcotics, they suggest.

In fact, J. William Langston, MD, e of the nation's most active spokes-ersons on designer drugs, attributes e recent intensity of interest in esigner drugs to what some observers ggest is national hysteria about drug use: "What we fear is that, with the portation supply [of botanical nar-otics] cut off, someone will resort to ese synthetic drugs—which ultimate-ly could be much more dangerous.

"Of course," he says, "I'm not saying we should stop trying to fight importation and drug abuse. But since every garage is a potential laboratory, I'm afraid we may end up with a worse problem than we have now."

Robert J. Roberton, PhD, former chief of the California Division of Drug Programs, agrees: "In essence, young drug abusers who take these new synthetics are playing a form of Russian roulette. Only it is not lead bullets that they are aiming at their brains, but chemical ones."

When broadly defined, designer drugs are hardly a new phenomenon. According to Roberton, abuse of synthetic drugs has been occurring at least since the 1940s.

By the late 1960s, he says, illicit production, distribution, and use of a number of hallucinogenic amphetamine analogues of mescaline had become a serious national problem. Furthermore, in the 1970s, black market chemists produced chemical variants of methaqualone, PCP, and amphetamines (*J Clin Psychopharmacol* 1985;5:350-352).

A dramatic surge in designer drug use, however, was noticed in the late 1970s when several unexplained deaths occurred in Orange County, California. Superficial evidence in the victims suggested death by narcotic overdose, says Roberton, who is now vice-president and administrator of the American Hospital-Behavioral Health Services, Inc, in Gardena, Calif. Yet, he continues, no evidence of narcotics was found in blood and urine samples.

After several months of investigation, it became clear that these persons had died from α-methyl fentanyl (*J Toxicol Clin Toxicol* 1982;19:1123-1126). This drug is a synthetic analogue of the legitimate drug fentanyl citrate (trade names Sublimaze or Innovar) that was imported into the United States about 15 years ago from Belgium by Janssen Pharmaceutica Inc (which is now a subsidiary of Johnson & Johnson).

Fentanyl itself is a safe, short-acting narcotic analgesic used intravenously in about 70% of all surgical procedures today, says Roberton. Several of its derivatives also have a legitimate use. These include sufentanil (used in cardiac surgery), alfentanil (now undergoing clinical trials for use in dental, minor, and diagnostic surgery), and carfentanil (used in capturing large wild animals).

An investigator who played a leading role in tying the fentanyl analogue to the Orange County deaths was Gary Henderson, PhD, professor of pharmacology at the University of California, Davis, the person often credited with coining the term "designer drugs." Roberton recalls that at the time of the investigation, Henderson predicted that anyone who "wanted to start playing around with" the fentanyl structure would produce a drug that would "do well on the streets."

Time proved him right. An estimated 20% of California's 200 000 heroin addicts are now using unapproved fentanyl analogues, which include α-methyl fentanyl and para-fluoro fentanyl (which the Drug Enforcement Administration has classified as Schedule I drugs, meaning no approved medical use and addiction potential); α-methyl acetylfentanyl; benzyl fentanyl (non-narcotic); and, the latest and most potent derivative, which is 3-methyl fentanyl.

Fentanyl is 100 times as strong as morphine and 20 to 40 times as strong as heroin; sufentanil and lofentanil are, respectively, 2000 and 6000 times as strong as morphine. Furthermore, fentanyl's onset of action is extremely rapid and its effects last about 30 to 60 minutes. Some anesthesiologists say users can become addicted after one injection.

The designer derivatives have comparable or even greater potency. In fact, the lastest derivative introduced onto the streets, 3-methyl fentanyl, is 2000 times as potent as morphine. Therefore, minuscule amounts of very potent drugs can have serious consequences.

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As Roberton explains: "If you took a handful of flour or sugar—that's 200 grams—it would be [the same amount as] 200 doses of 3-methyl fentanyl. . . . There must be a state-of-the-art chemist making it and cutting it in order not to kill every addict in California. . . .

"One chemist working eight hours a day for a week can make enough to supply the whole United States for six months—and put it in three shoeboxes," Roberton says. "There are 2 micrograms in each dose, and you can put enough 3-methyl fentanyl on the head of a pin to kill 50 people."

High potency also complicates control measures, because the fentanyl analogues pose toxic risks for narcotics agents. "If you accidentally sniff too much 3-methyl fentanyl, you could die," says Roberton.

Already, 12 deaths in the San Francisco Bay area have been attributed to 3-methyl fentanyl. In fact, to date the fentanyls have been blamed for more than 100 deaths, nearly all in California (although designer drugs now plague both coasts and the state of Texas), says Roberton. All cases involved known heroin users, mostly male but from diverse geographic areas and varied social, economic, and ethnic groups.

An unexpected (and, according to Roberton, growing) group of addicts comprises some anesthesiologists who use fentanyl in their operating rooms. At the Boston meeting, Roberton showed a film, *Death by Design*, that depicted a young anesthesiologist hooked on fentanyl. The physician told how she couldn't believe a person like herself—a person "who could always control everything"—ended up passed out on the floor with broken ampules all around her.

"But I kept on using it," she recalls. "It was insane."

Going through medical school, the anesthesiologist continued, she never learned to deal with normal life crises. Thus, when faced with the tension, overwork, hunger, and fatigue of her new profession, she found that the first thing she turned to was this readily accessible chemical.

The film's young physician is hardly unique. In fact, in a 1983 study of 289 anesthesiology training programs, 74% of the 247 responding schools reported some addiction among faculty and residents in the previous decade. Meperidine and fentanyl were the drugs most frequently mentioned, and the authors observed that use of the latter has become widespread in the past decade because of its "rapid onset, preservation of cardiovascular stability, and short duration of action" (*JAMA* 1983; 250:922-925; *Millit Med* 1984;149:227-228).

Sometimes the dangers of designer drugs result from sloppy manufacture rather than high potency. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) provides the classic example.

In 1976, a drug addict trying to synthesize a personal supply of a meperidine analogue, MPPP, used an unproven shortcut, the steps of which still are not entirely clear. After only three days of self-administration, he developed a severe syndrome reminiscent of classic Parkinson's disease.

It turned out that this flawed MPPP was a substance now known as MPTP. This drug is a neurotoxin that lodges in the zona compacta of the substantia nigra and, apparently, destroys the same cells that seem to malfunction in Parkinson's disease (*Ration Drug Ther* 1985;19:5-7).

Subsequently, designer drug authority Langston (who is chief of neurology at the Santa Clara Valley Medical Center) and his associates discovered a small group of young addicts in northern California who had recently developed signs and symptoms of severe and irreversible parkinsonism. The physicians attribute this development to use of a new "synthetic heroin" that contains high concentrations of MPTP.

Langston, who also is a neurologist at San Jose's Institute for Medical Research, says that positron emission tomography scanners—which are not widely available—may provide a way to predict future victims by identifying striatal dopamine deficiency before symptoms develop. In the next year, he adds cautiously, there may be a magnetic resonance imaging technique available, but this method remains experimental.

In January 1985, the Centers for Disease Control, Atlanta, and the National Institute on Drug Abuse, Rockville, Md, began to track persons possibly exposed to MPPP and MPTP since 1982. They found approximately 50 cases in which the use of MPPP and/or MPTP has produced symptoms similar to those found in parkinsonism victims.

In fact, more than 400 persons may have been exposed to MPTP in California (*J Clin Psychopharmacol* 1985; 5:350-352). Langston is convinced that many remain unidentified.

Because MPTP is used by chemical companies in manufacturing other chemicals, it remains a legal substance. Therefore, bona fide chemists exposed to MPTP in laboratories unprotected by fume exhaust hoods also may risk chronic parkinsonism (*Ration Drug Ther* 1985;19:5-7).

MPTP's effects also have lent credence to the theory that there may be an environmental source involved in other forms of parkinsonism (*Br Med J* 1984;289:1401-1402). New evidence suggests certain distinctions between the two forms of parkinsonism, however. A recent study (*N Engl J Med* 1985; 312:1418-1421) comparing six patients with MPTP-induced parkinsonism to eight patients with Parkinson's disease showed that, in both conditions, the cerebrospinal fluid levels of dopamine's major metabolite, homovanillic acid, were reduced.

However, the cerebrospinal fluid levels of norepinephrine's major brain metabolite, 3-methoxy-4-hydrophenylethylene glycol (MPHG), after adjustment for plasma MPHG, were elevated (>6.0 ng/mg) in MPTP-induced parkinsonism, but reduced (<6.0 ng/mg) in Parkinson's disease. The authors conclude that these patterns of change are consistent with selective destruction of dopaminergic neurons by MPTP with a sparing of noradrenergic neurons.

As the MPTP story shows, drug abusers do not always know what they're getting when they use designer drugs. This is true for the fentanyl analogues as well.

Before the fentanyls are sold on the street, says Roberton, they are cut with large amounts of lactose or sucrose. This process leaves less than 1% active drug, too small an amount to contribute to the color, odor, or taste of the sample, which can be any color desired.

In fact, according to Langston, "dealers can easily change the appearance of any of these substances so that you cannot tell whether a drug is synthetic or real by the way it looks." (He adds, however, that California drug users can send samples of drugs of the amphetamine, fentanyl, or meperidine families in to the Santa Clara Health

Department and receive free and totally confidential analyses—both quantitative and qualitative—of their drugs in about seven days. If federal funding is approved, this will become a nationwide service.)

Despite the toxicity and unpredictability of designer drugs, most investigators in the field believe that illegal synthetics will pervade society and that they are part and parcel of the technological revolution. Roberton regards the future as "bleak." He explains: "I think we're going to see more neurodegenerative disease and we're going to have more catastrophes like we've had in California with MPTP."

Given the large demand, minimal initial cost output, and nonexistent quality control during manufacture, concocting these drugs means high markups and tremendous profits for people Roberton calls "entrepreneurial chemists." According to the Pathway Society's Stanford, for example, there is a great monetary incentive to mix up a batch of PCP for an initial cash output of $500 and a markup of 600%. (See also *Bull Narc* 1985;37:7-17 and *J Clin Psychopharmacol* 1985;5:350-352.)

Nor do these chemists need much training. Langston recalls one San Diego chemist who was tracked down and arrested in a Los Angeles motel. "In his briefcase was a Xeroxed paper on how to make MPPP," says Langston. "People were making money just by selling these instructions. And, to make matters worse, the sheet had an asterisked footnote that said, 'Caution: if made improperly may cause Parkinson's [*sic*] in your clients'—and they cited my paper!"

Furthermore, the entrepreneurial chemists can avoid the legal hassles of importation and, at least for a while, the legal sanctions against older drugs. Currently, the Drug Enforcement Administration is empowered by the 1970 Controlled Substances Act to categorize drugs based on their medical value and abuse potential.

Schedule I drugs, such as LSD and phencyclidine (PCP), have no medical use but have a very strong abuse potential. Schedule II drugs, such as meperidine and morphine, have a medical use but also are addictive with a strong abuse potential.

But new designer drugs escape classification because they are not structurally identical to their parent compounds. The problem is inherent in the synthetic nature of these drugs: if one analogue is added to the restricted list, an enterprising chemist can just change a molecule here or there and create another perfectly legal drug with similar pharmacologic properties.

In 1984, Congress empowered the Drug Enforcement Administration to place a drug on the Controlled Substances Act schedule on an emergency basis for up to one year if such scheduling was thought necessary to preclude an imminent public safety hazard. Since the enactment of this provision, several of the most dangerous and/or frequently abused designer drugs have been placed on Schedule I. Even so, the potentially infinite variety of designer drugs makes this provision inadequate.

Therefore, Congress and some state legislatures now are trying to come up with broader laws. One of the most promising is the Analogue Enforcement Act, which has passed the Senate and is now before the House. This act would restrict the use of any compound that resembles in structure or effect an already proscribed designer drug.

While sympathetic to the intent of this legislation, many investigators and drug enforcement officials think it is too broad. Some suggest alternative control measures, such as compassionate intervention programs in schools and workplaces and intense public education about drug abuse and addiction.

But even these are seen as only stopgap measures because designer drugs are inherently almost impossible to control. Langston, for one, notes: "To make a designer drug, you need to know very little chemistry. Anybody can do it, and even with that new law (which may be unconstitutional because it's so broad), the profit incentives are so unbelievable that I don't think we can stop it [the manufacture of designer drugs]."

Another major challenge to control is the difficulty of detection. In particular, says Roberton, the extremely high potency of drugs like the fentanyls means that standard indicators fail to identify any of the fentanyl analogues by normal methods. Only a very few laboratories in this country are equipped with the radioimmunoassay tests necessary to detect parts per billion of a given drug in body fluids.

More sophisticated laboratories (see accompanying article) would help, as would physicians prepared to recognize patients who may be using designer drugs. Because the new drugs often produce unfamiliar signs and symptoms, physicians and clinic staff may inappropriately release or misdiagnose patients.

Roberton says that, several years ago, "coroner's offices in California were burying people without detecting these analogues because we had only one lab in California [Henderson's laboratory at the University of California, Davis] that was equipped to test for these." (See *Proc West Pharmacol Soc* 1976;19:237-238.)

Langston, who believes that right now the general public probably knows more about designer drugs and their effects than some physicians do, fears "that in five or ten years, young people will start staggering into their doctor's office with symptoms of Parkinson's disease, and the doctors won't have any idea at all about these drugs."

To avoid these situations, Stanford stresses the importance of physicians and treatment centers constantly being alert to new signs and symptoms, as well as networking with colleagues. "We can't simply sit back and wait for the media, the feds, or the state to tell us about a new compound," he says. "Nor can we ignore the situation and hope that an analogue neurotoxin does not come to our clinic's area."

Already it is clear that physicians should suspect fentanyl use in patients if they see all the signs and symptoms of narcotic addiction but find no evidence of drugs in the blood or urine, says Roberton. "You may not even see tracks," he adds, "since these substances may be snorted."

He also suggests suspecting MPTP use in any patients—especially younger patients—with choreiform movements. These patients should be referred to neurologists, he says.

But, again, such steps do not get to the heart of the designer drug problem: prevention. And as far as that is concerned, the best physicians can do right now is to caution potential victims.

"Drug users are guinea pigs," Roberton says he tells addicts. "There is simply no way to know [the effects of a designer drug] until after you've taken it. . . . Remember: there are no quality controls in this business. They don't care if they cut your dope with battery acid."—by Terra Ziporyn, PhD

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