

Future Drugs: the Next 10 Years

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Twenty years ago, I received a contract from the National Commission on Marihuana and Drug Abuse to write a report speculating what new drugs the next two decades might bring. Some of these speculations proved to be accurate and some fell quite wide of the mark. All of them called upon the existence of a large body of published literature that had been ignored or not recognized by policy makers.

The accurate predictions succeeded either because of economic factors or because certain types of drugs attracted a great deal of attention from the government and the press while others did not. The less accurate guesses were wrong not because of faulty pharmacology, but because the majority of non-medical drug users did not choose to explore those directions.

One way to imagine the creation of new drugs is to visualize a series of open doors, each new and undiscovered door being somewhere beyond the earlier known one. If an explorer who is searching for some personal grail goes through one door, he knows that there is another up ahead. The discovery of a new compound, be it a stimulant, a sedative, a

narcotic or a psychedelic, is a passage through a door. Even if it is subsequently closed by law enforcement, there is no way of hiding the next discovery. These doors of perception are not closed by legal proscription; they are discovered because of it. They would not be sought were the prohibitions not in effect.

Making predictions about a controversial topic is always uncomfortable. Unlocking future possibilities might be seen as providing guidelines for the actions of others. People will blame the messenger for the message. However, I am presenting these ideas simply as possibilities based upon existing scien-

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tific fact and logical scientific extrapolation.

General predictions: more potency and more variety

The emphasis of the illicit chemist will be placed on ever increasing potency, even though this might require a correspondingly increased difficulty in synthesis. The reason is simple; high potency translates to small bulk. As an active dosage becomes smaller, the scale of synthesis becomes smaller. The procurement of raw materials, the concealment of the laboratory, and the ultimate distribution of product all be-

come easier. Furthermore, a smaller dosage will make any detection of the drug in urine more difficult. In general, increased potency is a natural by-product of illegality.

The new drugs will be modifications of known drugs, rather than discoveries that are new and unpredictable. The illicit chemist does not have the capacity for creating, screening and developing new chemical systems. The modification of known compounds is historically the most common process of drug development. Even in industrial pharmaceutical research, most new materials are simply older, known drugs that have undergone some minor structural modifications. Because of economics, companies produce patentable competitors to prototype drugs, which already have patents and which enjoy medical popularity and large sales. A structural modification of a commercially successful drug may allow circumvention of an existing patent, while still maintaining the desired effect. In a completely analogous manner, a structural modification of an illegal drug may allow circumvention of an existing scheduled status, while still maintaining the desired effect.

New drugs will appear in five areas. One of these, the anabolic steroids, will not be discussed here as it lies completely outside of my own experience. The enhancement of the psychotropic aspects that can accompany steroid use is not the primary goal of the user. The other four areas are: sedatives (including narcotics and depressants), stimulants (including antidepressants and energizers), dissociative anesthetics, and the psychedelics. Each has its own prognosis.

Depressants: heroin and heroin substitutes

There will certainly continue to be a significant supply of heroin. The opium crops in Southeast Asia and other places are larger than ever before. Some of the native alkaloids of opium can be converted to variations of the so-called Bentley compounds, which are of exceptional potency and could prove difficult to detect. But the continual, inexpensive availability of heroin will mini-

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mize the need for the introduction of synthetic substitutes that call upon opium components such as morphine, oripavine or thebaine.

New drugs that act like heroin, but which can be made without plants, will surely include structural variations of the dramatically potent narcotic, fentanyl. The total active dose of these drugs for one individual is less than a microgram (one millionth of a gram). A tablespoonful will be able to keep a large city supplied for a year.

Modifications of the structure of meperidine (Demerol) and of the closely related narcotic MPPP have led to drugs with a thousandfold increase of potency. Many of these have been in the literature for years, and they can be synthesized without the use of sophisticated equipment. Structural modifications of these high-potency substitutes would be a relatively uncomplicated task.

Stimulants: cocaine and methamphetamine will remain dominant

The development of new and highly potent stimulants is not anticipated, as there seems to be a completely satisfied cocaine and methamphetamine market. A new route of administration (smoking) has been promoted, but the chemical identities are unchanged. If, due to some change in production or marketing, cocaine were to become less available, I believe that domestically synthesized methamphetamine and acceptable substitutes would become increasingly popular. If more law enforcement were to be directed to the currently popular precursors and "essential" reagent chemicals, then changes would certainly be seen in the manufacturing process. There would be a renewed search for methods and precursors that attract less official attention.

Ephedrine, phenylpropanolamine, and phenylacetic acid (or some precursor to it) will remain plentiful, easily obtainable and will have industrial uses outside of the illicit stimulant trade. Scientific literature already offers many new ways of employing these raw materials. Phenylpropanolamine (norephedrine) can be condensed with simple ketones such as acetone, to provide oxazolidines that are known to be effective stimulants. Easily made oxazolines can be modeled after methylaminorex, U-4-E-uh, which

comes directly from ephedrine and cyanogen bromide. Both of these heterocyclic systems are amenable to imaginative variation. The simple oxidation of ephedrine with either potassium permanganate or dichromate, produces the stimulant ephedrone, which has been available in the street trade in the Soviet Union but is still relatively unknown elsewhere.

Dissociative anesthetics: a steady market for escape from pain

The availability of, and demand for, PCP and ketamine are well established. As a result, there is little reason to expect much change in drug use patterns in this area. If the raw materials needed to make PCP were not available, similar known drugs could be brought into the traffic picture. Some have already appeared and have been criminalized. A commercially available drug with a similar action profile, tiletamine had been considered for criminalizing by the U.S. Drug Enforcement Administration. Remarkably, the DEA has ignored it. There have been many research studies made on dizocilpine (MK-801) and related benzylamines, which are being cautiously introduced into clinical practice and share some properties with the PCP family.

Simple piperazines, such as N-(m-trifluoromethylphenyl)piperazine and N-benzylpiperazine have had some popularity in Europe. The first is reported to be a hallucinogen reminiscent of PCP, and the second is more stimulant-like in nature. Both are extremely simple molecules to synthesize, both are readily modifiable structurally, and either they or simple relatives might appear if there is a need to explore some PCP substitute.

The principal use for drugs in the dissociative anesthetic area is in affording some escape from pain, either physical or emotional. If this need cannot be met with drugs in this particular pharmacological category, it will be met with substitutes from the narcotic world, which would serve this purpose equally well.

Psychedelics: an active process of change and development

Only this group of pharmacological agents appears to be actively changing and developing. Whereas new develop-

DEA Power to Prohibit Drugs to be Reviewed by U.S. Supreme Court

Does the U.S. Drug Enforcement Administration, a law enforcement agency, have the unlimited power to decide which drugs are legal, regardless of medical evidence?

The Supreme Court is considering this question now in a criminal case (*Touby v. United States*, No. 90-6282) involving 4-methylaminorex, a stimulant known as U-4-E-uh (pronounced "euphoria"). The DEA has illegalized U-4-E-uh by placing it under Schedule 1 of the Controlled Substances Act of 1970. Schedule 1 drugs cannot be sold over the counter or prescribed by a doctor. In 1984, Congress gave the DEA, through the Attorney General, emergency scheduling authority. The DEA may now temporarily schedule a drug without holding any hearings and without receiving health and medical findings from any other agency. The decision of the DEA also cannot be reviewed by a court. In essence, Congress gave the DEA the authority to overrule the Food and Drug Administration, the National Institute on Drug Abuse, the Department of Health and Human Services and even, some think, the courts and Congress.

The issue in the *Touby* case is whether the authority of the DEA is an unconstitutional delegation of legislative authority to the executive branch. The District Court upheld the DEA's emergency scheduling authority, and the Third Circuit Court of Appeals agreed in a 2-1 decision. *Touby v. United States*, 909 F.2d 759 (3rd Cir. 1990). However, the Third Circuit decision is inconsistent with a unanimous 10th Circuit decision concluding that the authority was unconstitutional. *United States v. Widdowson*, 916 F.2d 587 (10th Cir. 1990). The Supreme Court is reviewing the case to deal with the split among circuit courts.

ments of narcotics and stimulants produce changes largely limited to potency and to legal risk, slight changes in molecular structure of psychedelics can effect dramatic changes in the quality of the psychological action.

I do not anticipate any variation of marijuana in the foreseeable future. It is a plant, and not even the principal active component (tetrahydrocannabinol, which could only be modified with great effort) is a satisfactory substitute for it. The only changes that will occur in the near future will concern techniques of plant genetics and methods of indoor cultivation.

There will be a search for alternatives to MDMA, largely to separate from it the animal neurotoxicity that casts a shadow on its acceptability for medical use. So far, there are few hints of anything promising.

Within the area of overtly psychedelic drugs, many developments can be anticipated. Structural variations of LSD have been published (N-alkyl-nor-LSD homologues) that are of equal or greater potency but cannot presently be identified in urine analyses.

Psychedelic mushrooms are ever increasing, and they have now been either discovered or translocated throughout the world. Mushrooms are essentially without legal control. There are many score analogues of DOM and 2C-B in the scientific literature, with both preparative details and pharmacological profiles. A wealth of tryptamines and carboline derivatives of synthetic and natural origins are known and can quite easily be prepared from innocent commercial starting materials. And, of course, there are always the unexpected discoveries from nature, such as the smoking of toad venom, that found by the perennial ethnopharmacologists. Few of these have yet been introduced into any broad social context, but if the availability of the currently used materials were to drop off, they could very well fill the demand.

If we want to create a healthier society in the next decade, our drug policy emphasis should be reversed and be focused on the legal drugs rather than the illegal ones. It should be focused on prevention through education, rather than prohibition through law enforcement.

Drug policy should focus on legal drugs, not illegal ones

What can one expect the drug problem to be 10 years from now? To a large measure, barring some unexpected interruption of current supplies to the present demand, there is no reason to expect dramatic change. The drugs of demand are available, and there is no reason to introduce new drugs into a satisfied market.

The primary force for change in the illicit drug trade will continue to be its own illegality. The criminalizing of drugs encourages chemists to produce drugs that are not yet illegal. The enforcement of drug laws encourages the production of increasingly potent drugs and novel distribution techniques. The next decade will see an advancement in these areas, in reaction to the drug laws. This evolution will be quickened if law enforcement efforts escalate. Thus, an unintended consequence of "successful" law enforcement will be the creation of new and more potent drugs of abuse.

Over the coming 10 years, the major drug problems in the United States will remain unchanged. Tobacco and alcohol will remain the greatest threats to public health and together will account for an annual death inventory of over half a million citizens. It

is here that the drug prevention efforts of the future must be directed. All of the illegal drugs mentioned here will contribute to perhaps 5,000 deaths a year, a trivial fraction in comparison. The death rate associated with the psychedelics (including MDMA, marijuana, mushrooms and LSD) may be, annually, a thousandth of this, perhaps five or 10 each year. This low public health risk is due primarily to the pharmacology of the drugs rather than to any government policy or to any limited drug availability.

Spending resources on drug prevention and education for the legal drugs — tobacco and alcohol — would be of greatest value. The cost of drug prevention and education for the illicit drugs should be small by comparison. If we want to create a healthier society in the next decade, our drug policy emphasis should be reversed and be focused on the legal drugs rather than the illegal ones. It should be focused on prevention through education, rather than prohibition through law enforcement.

International Conference on Drug Policy Reform

November 13-16, 1991

The Hyatt Regency Washington on Capitol Hill
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