

Abused Substances

The “stepfather of ecstasy,” now 80, believes psychedelics are unfairly anathematized. Tripping, he says, has medical and spiritual uses.

BY ALEXANDER T. SHULGIN

PSYCHOACTIVITY IS A broad term for the action of the many chemicals that affect the function of the brain. There are many classes of these substances, such as stimulants, anesthetics, sedatives, narcotics, depressants, antidepressants—and also psychedelics. The mechanism of action of such drugs always involves psychoneurological systems. Medically valuable psychoactive drugs are most often discovered in animal behavior experiments, and finding out how the drugs work frequently calls upon sophisticated research using appropriately radio-labeled synthetic samples.

But for the past four decades, I have studied psychoactive drugs at the far end of the spectrum: those that affect the *mind*. These substances are usually discovered by people experimenting on humans. Rats have brains, and we can remove them, cut them into slices, and see where experimental drugs have gone—but I am not sure rats have what most people think of as minds.

It should be stated outright that the uses of these drugs are not merely recreational (although of course they are used that way all the time, and for other, more meditative reasons). Recently, several researchers successfully navigated the bureaucratic paperwork necessary to get approval of and permission for clinical studies of psychedelics. A study by Francisco Moreno at the University of Arizona using psilocybin in the treatment of obsessive-compulsive disorder has been completed. And two other studies of psychedelics are under way: one, at the Harbor-UCLA Medical Center, is exploring psilocybin as a treatment for anxiety in patients with advanced-stage cancer; the other, being conducted in South Carolina, studies the treatment of post-traumatic stress disorder patients with MDMA—the drug more commonly known as ecstasy. Additional studies should soon be up and running, including one at Harvard’s McLean Hospital that will investigate the potential value of MDMA in treating cancer patients’ anxieties.

I choose to call these psychoactive compounds psychedelics, but many names have been used for them. Originally they were called psychotomimetics, which meant, literally, drugs that produced a state that imitated psychosis. This was soon superseded by “hallucinogens,” which is a more acceptable term but equally inaccurate. The actions of the psychedelics can involve visual phenomena (color enhancement, shape distortion, unexpected interpretations), but these are recallable from memory—there is none of the amnesia that often accompanies a true hallucination. Other terms have been used, such as entactogens (touching within), empathogens (creating empathy), and entheogens (discovering God within), but I still prefer “psychedelics.” It may be offensive to some people, but at least they know what I am talking about.

The very first psychedelic I experienced (this was 45 years ago) was the peyote-cactus alkaloid, mescaline. It was an awesome experience in several ways. But its most dramatic result was my realization that there was no way the forgotten memories of my childhood that had just resurfaced, and the display of colors of which I had previously been unaware, could be contained in a few hundred milligrams of a white crystalline powder. To me it was inescapable that all the richness of that day had been inside my mind all along, and the drug was just the catalyst that gave me access to it. Since I am a chemist, I can easily synthesize chemicals with subtle structural differences—like a slightly longer carbon chain here or a sulfur in place of an oxygen there—to find the dosages where they become active.

Two or three examples. When I moved one of the methoxy groups of mescaline to an adjacent position, and replaced another one with an ethyl group, I got a beautiful white solid that I named 2C-E. It was fully active in me at 20 milligrams taken orally. The visual activity and color enhancement it effected were very much like those of LSD, but 2C-E had a strange and (for me) novel property. On occasion, during a psychedelic experience, I

would ask myself an important, private question to see what answer might bubble up. If the question turned out to be too complex, or touched on unpleasant subjects, I would drop it and ask another. But 2C-E wouldn’t let me do that. I had to stay with each question until I worked through to an answer.

Compound Interests

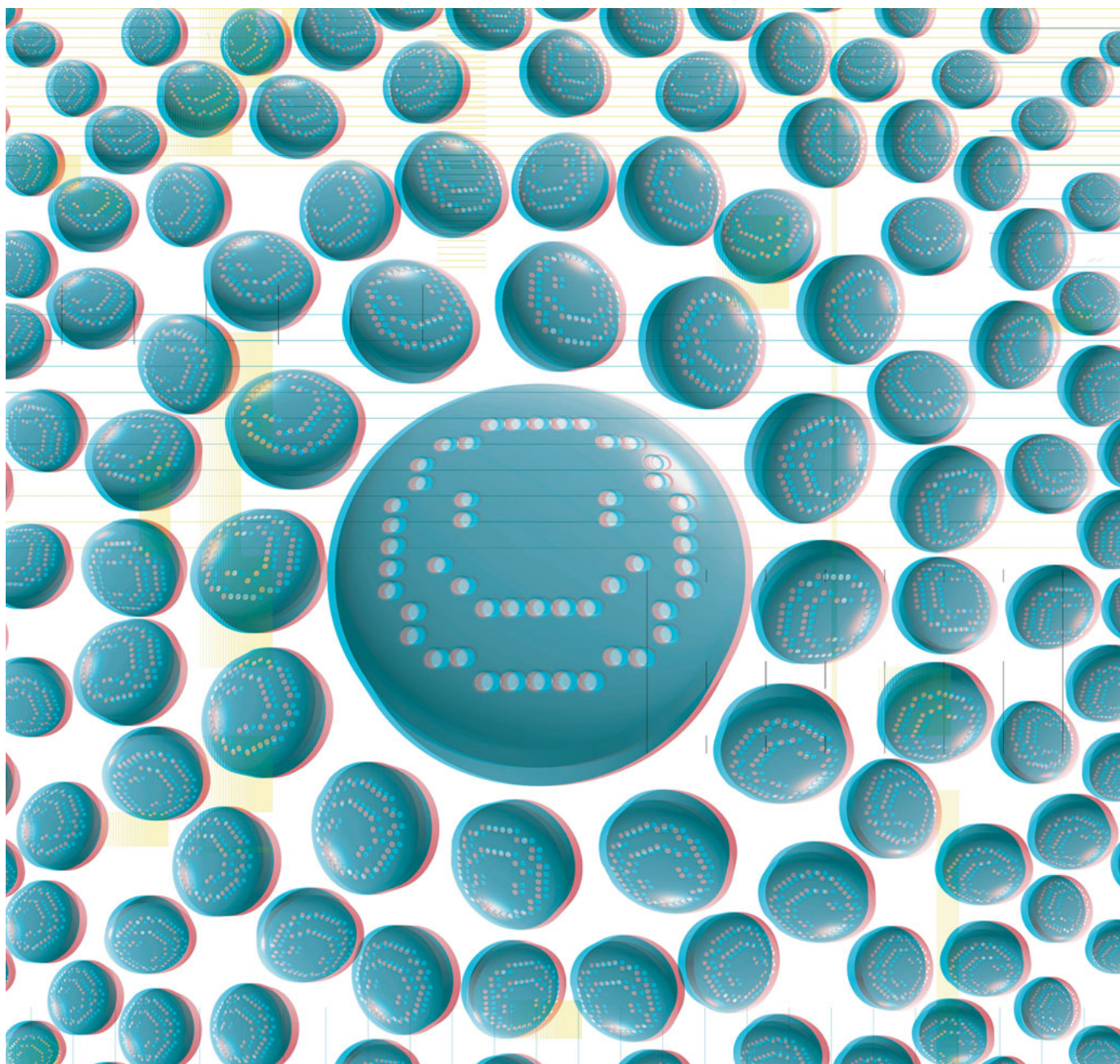
2,5-dimethoxy-4-ethylphenethylamine (2C-E)

N,N-dipropyltryptamine (DPT)

Alpha,O-dimethyl serotonin (O-DMS)

Another example, this one from the other family of psychedelics, the tryptamines. N,N-dipropyltryptamine (DPT) was first synthesized and found to be active in humans by Steven Szara back in 1962. But it exhibits an unusual property if the three-carbon propyl groups are attached to the nitrogen atom by the middle carbon rather than by the end carbon atom. This turns them into isopropyl groups. So I made the compound and called it DIPT. It both lowers and distorts the pitch of sound.

Another example of a subtle modification of a tryptamine molecule involves the well-known neurotransmitter serotonin. Although it plays a major role in enabling neurons to communicate, it cannot enter the brain from the body. There is an effective obstacle called the blood-brain barrier that blocks the passage of most highly polar molecules, although some—certain amino acids and sugars—can get across it because they have specific transport allies. The serotonin-precursor amino acid is one of these exceptions, and once it has gotten into the brain, serotonin can be made from it. Since serotonin is implicated in the effects of most psychedelics, I changed it a little bit. On the right-hand side of the molecule is a primary amino group. Upon the oxidative loss of this amine, the molecule metabolizes rapidly to a carboxylate group, which is very polar. So I added an alpha-methyl group to block that deamination. On the left-hand side of the molecule is a polar phenolic hydroxy group. By converting it to a methyl ether, I neutralized its polarity. I called the compound alpha,O-dimethyl serotonin, or O-DMS (it was also called 5-MeO-AMT for 5-methoxy-alpha-methyltryptamine). Surprise!



It turned out to be orally active in the low-milligram range. In my research group, each person took a sample weighing somewhere between 2.5 and 4.5 milligrams, and all had trips that lasted more than 12 hours. Almost all, once they were finally able to get to sleep, had nightmares.

I have little insight as to how these remarkable compounds do what they do. The human mind is a mysterious and complex thing. There have never been dependable ways to get into it, take it apart, and see how it works. My hope is that psychedelic compounds may be the tools, or may lead to the discovery of tools, that can throw some light on elusive questions about how the mind works. Say a person is called “mentally ill” because he hears God speaking to him. Maybe you can put a positron emitter on a chemical that gives you distortion in sound recognition, inject it into a normal subject who is in a PET scanner, and observe that it goes to a most unusual place in the brain. Maybe

that is where the physician should look for the tumor in the brain of the person who hears from God.

One of the major impediments to the expansion of research in this fascinating area is the war on drugs. The categorization of psychedelics as evil and dangerous keeps them in the Schedule I category, where they are said to have no medical value. Discoveries are not being published, because researchers feel that if new and potentially useful compounds are openly discussed in the medical literature, the U.S. Drug Enforcement Agency will add them to the illegal list. With the series of clinical trials using psychedelics, I hope the wind is shifting. ■

Alexander “Sasha” T. Shulgin is a pharmacologist and biochemist who popularized ecstasy in the 1970s. He was the first to synthesize hundreds of psychedelic compounds, including the 2C family of phenethylamines, most of which have never been made illegal.