## **CHAPTER 8**

# LSD

### KRISTINE PANIK and DAVID E. PRESTI

### Introduction

Lysergic acid diethylamide (LSD) is one famous molecule—in many ways *the* archetypal psychedelic substance. Its fame is underscored by its wide recognition simply as "acid." Its potency, long duration of action, and penetration into society (especially in the United States) during the impassioned 1960s, has created for it an enduring legacy.

Psychedelic medicines are old, very old: peyote spirituality in ancient America, shamanic use of Psilocybe mushrooms, ayahuasca and other medicine plants of Amazonia, iboga in Africa, the mysterious soma of ancient central Asia, and the equally mysterious kykeon of the ancient Greek Eleusinian Mysteries. LSD is new. It has not been found-at least not yet-as a natural product created by plants or fungi, and it was not the first psychedelic chemical to be identified (this being mescaline, many years prior). Its psychoactive properties were discovered in 1943, and it burst onto the cultural scene in the second half of the 20th century via promising clinical investigation and large-scale popular use having far-flung ramifications to philosophical, musical, and artistic expression, and to social activism as well. While legally restricted at the highest level for the past half-century—classified a Schedule I (One) controlled substance in the United States Controlled Substances Act of 1970 and the United Nations Single Convention of 1971—its popularity remains high. Lifetime prevalence of use (2010 survey data) in the United States is estimated to be around 23 million individuals, corresponding to 9% of the population over the age of 12 years (Krebs & Johansen, 2013a).

LSD and other psychedelics may be described as amplifiers or activators of mental processes, leading to heightened awareness of perceptions, thoughts, and feelings, as well as loosening of psychological defenses. This may reveal aspects of mind normally out of awareness and catalyze experiences that are powerfully novel and galvanizing. The complex effects of psychedelics have resulted in a variety of terms applied to describe them: *psychotomimetic* (mimicking the symptoms of psychosis), *hallucinogen* (generating hallucinations), *entheogen* (generating experiences of the divine), and *psychedelic* (mind revealing).

On the one hand, this manifesting or revealing of normally hidden aspects of the psyche may contribute to insight and creativity, catalyze transformative mystical or spiritual experiences, and provide a springboard for psychotherapeutic work. On the other hand, the same amplification of the psyche may contribute to acute anxiety and panic a "bad trip"—and possibly ongoing psychological distress. LSD and other psychedelics, like all drugs, are *pharmakon*—the ancient Greek word from which the English words *pharmaceutical, pharmacy,* and *pharmacology* are derived. *Pharmakon* means "medicine" *and* "poison" at the same time—a profound notion, all too often forgotten.

The acute and long-term effects of LSD and other psychedelics are highly sensitive to *set* and *setting*. *Set* is used to describe what the user brings to the experience: intentions, expectations, prior experience (or the lack thereof), memories, personality, and current state of one's mind and body. *Setting* is the environment in which use takes place: alone, with others, with a therapist or guide, inside in a closed space, outside in a natural setting, and so forth.

The word *psychedelic* was coined in 1956 by psychiatrist Humphry Osmond (1917– 2004). He sought to create a new term that better captured the uniquely powerful qualities of these substances. He shared some of his thoughts on this in correspondence with the author Aldous Huxley (1894–1963; 1977). After considering a number of possibilities, Osmond (1957) settled on *psychedelic* (Greek *psyche* = "soul, mind"; *deloun* = "make visible, reveal") because "it is clear, euphonious, and uncontaminated by other associations."

Osmond formally proposed the name in a paper he delivered at a 1956 meeting at the New York Academy of Sciences on the topic of "psychotomimetic drugs." After listing a small number of substances (including LSD) known at the time to be psychedelic, Osmond (1957, p. 419) remarked,

What an array of substances for daring inquiry! What work for generations to come! . . . We know little enough about the most familiar of these agents, and there are only vague correlations between the physical and mental changes that they cause. Considering their interest in medicine alone, our lack of information is disquieting, but they are of more than medical significance. They reach out to psychology, sociology, philosophy, art, and even to religion. Surely we are woefully ignorant of these agents and this ignorance must be remedied.

#### Chemical and Pharmacological Properties of LSD

LSD is the diethylamide derivative of lysergic acid, the latter being the core structure of the ergot alkaloids, a group of chemicals produced by ergot fungus (Claviceps purpurea). The LSD molecule (see Figure 8.1) possesses two chiral centers at carbons 5 and 8; thus, there are four enantiomeric stereoisomers. Of these, only one—(5R, 8R)-LSD-is known to have significant physiological activity. This isomer is dextrorotatory; thus, the physiologically active isomer is sometimes referred to as (+)-LSD or d-LSD. Hereafter, we will simply designate it as LSD. Inverting (reflecting) the chiral configuration at the 8-position gives (5R, 8S)-diso-LSD. Inverting the configuration at the 5-position gives (5S,8R)-l-iso-LSD. And inverting the chiral configuration at both the 5v-position and the 8-position gives (5S,8S)*l*-LSD (Nichols, 2018a). None of these enantiomers has shown any significant psychoactivity in humans (Shulgin & Shulgin, 1997).

Indeed, most chemical modifications of the LSD molecule result in substantial decreases in potency. A very small number of analogues have been found to have potency comparable to LSD in laboratory animal tests of drug discrimination: the dimethylazetidine derivative of the amide, and the N-6 replacements of methyl with either allyl or ethyl (Hoffman & Nichols, 1985; Nichols, 2018a, 2018b; Nichols, Frescas, Marona-Lewicka, & Kurrasch-Orbaugh, 2002). The N-6 allyl and ethyl analogues



**FIGURE 8.1.** (*5R*,8*R*)-Lysergic acid diethylamide, or *d*-LSD.

have also been described as psychedelically active in humans, with potency comparable to that of LSD (Shulgin & Shulgin, 1997).

LSD is generally referenced as either the free base (molecular weight [MW] = 323.5) or the tartrate salt (MW = 398.5; ratio of two molecules of LSD to one molecule of tartrate). Sometimes in published work it is not stated whether reported quantities refer to the free base or tartrate salt; thus, there may be a degree of uncertainty as to the exact quantity of active drug employed. With respect to stability, renowned chemist Alexander Shulgin (1925-2014) has remarked that "LSD is an unusually fragile molecule, [though] as a salt, in water, cold, and free from air and light exposure, it is stable indefinitely" (Shulgin & Shulgin, 1997, p. 492).

At the time of its discovery, LSD was the most potent psychoactive substance known. Threshold psychoactive dose-the dose below which no alteration of mental state is generally discernable—is around 5-10 ug (0.005-0.01 mg). Fifty to 400 µg is generally considered the typical psychedelic dose range. Although higher doses can and have been administered, there have been no carefully controlled studies of doses outside of this typical range. There are, however, intriguing case reports suggesting that higher doses (e.g., 500-1,500 µg) may confer additional therapeutic benefit for some people (Grof, 1980/2001). An impressive self-report chronicling more than 70 personal LSD sessions using doses of 500-600 µg and conducted on a regular schedule over a period of 20 years described remarkable transpersonal and transcendental experiences of deep and lasting psychological value (Bache, 2019).

Human and rodent studies indicate that tolerance to the behavioral and psychological effects of LSD occurs rapidly, with substantial loss of effect after 2–3 days of repeated use. There is cross-tolerance with other "classical psychedelics"—mescaline and psilocybin. Tolerance also dissipates rapidly, after several days of cessation (Cholden, Kurland, & Savage, 1955; Gresch, Smith, Barrett, & Sanders-Bush, 2005; Hintzen & Passie, 2010; Isbell, Belleville, Fraser, Wikler, & Logan, 1956; Nichols, 2016).

LSD is efficiently absorbed via the oraldigestive route. Time of onset is around 30 minutes, with peak effects generally reached by 2–3 hours. Peak effects may be maintained for another 2–3 hours, and substantial effects may continue for 10–12 hours following administration (Dolder et al., 2017; Hintzen & Passie, 2010).

Following oral-digestive administration of 100 or 200 µg in healthy humans, plasma concentration peaks at approximately 1.3 ng/ml or 3.1 ng/ml, respectively. Peak is reached at about 1.5 hours and exhibits a half-life of 2.6 hours. LSD induces modest increases in blood pressure, with 100-200 µg doses producing peak systolic increases of 15-20 mm Hg and peak diastolic increases of 10 mm Hg. Heart rate increased by 10–15 beats per minute at peak, and body temperature by 0.5 degrees Celsius. Autonomic changes varied in proportion to plasma concentration of LSD (Dolder et al., 2017). The lag between peak plasma concentration and peak subjective effects may be attributable to movement of LSD from the blood circulation to active sites in the brain and/or other mechanisms of delay in cellular-molecular response pathways (Dolder et al., 2017).

Studies in a variety of animals since the 1950s indicate that LSD is metabolized by liver enzymes to structurally related, though physiologically inactive, derivatives (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008). A predominant metabolite is 2-oxo-3-hydroxy-LSD. Very little (~1%) LSD is eliminated in urine as unchanged drug (Dolder et al., 2017).

In the published research studies, LSD has been administered either via capsule by the oral-digestive route, or by intravenous injection. However, illicit LSD used in nonmedical settings is frequently self-administered via the oral-buccal route; that is, small dosage amounts and methods of illicit packaging (e.g., blotter paper, liquid, small tablet) are conducive to simply letting the drug be absorbed in the mouth. Because of hepatic metabolism, one would expect this to have greater bioavailability relative to that of oral-digestive absorption. However, to our knowledge, this comparison has not yet been carefully investigated.

With respect to the comparative effects of LSD administered by intravenous versus oral-digestive routes, it has been noted that an intravenous dose of 75 µg produced similar ratings on an altered state of consciousness assessment scale as an oral dose of 100  $\mu$ g, and lower ratings than an oral dose of 200  $\mu$ g (Liechti, 2017). It has also been noted that the comparative dose effects of LSD administered by intravenous versus oral-digestive routes are far more similar than the comparative dose effects of psilocybin administered by these two routes; psilocybin is approximately 10 times less potent by the oral route compared to the intravenous route (Carhart-Harris et al., 2015).

#### The Discovery of LSD by Albert Hofmann

The story of LSD's discovery as told by Albert Hofmann (1906–2008) is truly one of the great tales in the history of modern science. Hofmann (2013) relates the story eloquently in his autobiographical memoir, *LSD: My Problem Child*.

Following doctoral work at the University of Zurich investigating the chemistry of chitin, the structural material from which invertebrate exoskeleton is composed, Hofmann in 1929 went to work for Sandoz, a pharmaceutical company located in Basel, Switzerland. There he joined a project investigating cardioactive glycosides isolated from squill and foxglove plants. After completing work elucidating the chemical structures of these compounds, he transitioned in 1935 to work on ergot alkaloids.

Ergot (*Claviceps purpurea*) is a fungus that grows on cereal grains and wild grasses, especially rye. Extracts of ergot have been used by midwives for centuries as an aid to childbirth, promoting uterine contractions and facilitating difficult childbirth. Also possessing vasoconstrictive properties, ergot extracts were useful in reducing postpartum bleeding.

Outbreaks of ergot growth on cereal grains appear to have led to mass poisonings of entire villages in Europe during the Middle Ages. Symptoms of ergot toxicity include the central nervous system effects of seizures, mania, and psychosis, as well as painful gangrene resulting from peripheral vasoconstriction. Ergot poisoning was referred to as Saint Anthony's fire, referencing the fiery pain of the condition and the third-century Christian monk Anthony of Egypt (251–356), patron saint in the healing of skin conditions.

Ergot contains a diverse array of alkaloids, many of which are derivatives of lysergic acid. Arthur Stoll (1887–1971), Albert Hofmann's supervisor at Sandoz, had spent several years investigating the chemistry of the ergot alkaloids and had isolated and identified ergotamine several years prior to Hofmann's arrival at Sandoz. When Hofmann began work on ergot alkaloids, the intention was to develop chemical derivatives having beneficial medicinal properties, while perhaps also being less toxic. In 1938, Hofmann sought to produce a diethylamide derivative of lysergic acid, drawing inspiration from the commercial pharmaceutical agent Coramine, a respiratory and circulatory stimulant marketed by Ciba, another Basel pharmaceutical company. Coramine is nicotinic acid diethylamide, and Hofmann hoped that lysergic acid diethylamide might be a new and improved respiratory and circulatory stimulant.

Thus, in November 1938, Hofmann synthesized lysergic acid diethylamide (*Lyserg-säure-diethylamid*), labeling it in his notes "LSD-25," because it was the 25th in a series of ergot alkaloid derivatives he had made. Hofmann passed the new chemical along to his colleagues in the pharmacological testing department of Sandoz, where it was found to have unremarkable effects in tests with laboratory animals and deemed not suitable for further exploration. Hofmann moved on to making other derivatives of ergotamine.

The following year, World War II began to consume Europe. Although Switzerland was a neutral country, it nonetheless maintained a small defensive army, and Hofmann spent time engaged in military activities during this period (Hagenbach & Werthmüller, 2011). He also had a growing family, and he and his wife Anita were parents of three young children by 1943. All the while, he continued his work on derivatives of ergot alkaloids. Two of his products of that era later became widely used medications: methylergometrine (Methergine) for stimulation of uterine contractions and reduction of postpartum bleeding, and dihydroergotoxine (Hydergine) to improve cognitive function, especially in elderly persons. And amid all this, Hofmann did not stop thinking about LSD. He had a feeling, an intuition, that this chemical was more interesting than what had been appreciated in the initial investigation of its properties.

And yet I could not forget the relatively "uninteresting" LSD-25. A peculiar presentiment the feeling that this substance might possess properties beyond those established in the first pharmacological studies—induced me, five years after that first synthesis, again to produce LSD-25, so that a sample could be given to the pharmacological department for further tests. This was quite unusual; experimental substances, as a rule, were definitely stricken from the research program when once deemed to be lacking in pharmacological interest. (Hofmann, 2013, p. 18)

Thus, on April 16, 1943, Hofmann resynthesized his creation of 5 years earlier. During the final purification steps, he began to experience unusual sensations. Later, he submitted this description as part of a report to his supervisor:

Last Friday, 16 April 1943, I was forced to interrupt my work in the laboratory in the middle of the afternoon and to go home, being affected by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant, intoxicatedlike condition, characterized by an extremely stimulated imagination. In a dream-like state with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with an intense, kaleidoscopic play of colors. After some two hours this condition faded away. (Hofmann, 2013, p. 18)

Rather than simply dismiss his unusual Friday-afternoon experience, Hofmann surmised that perhaps it resulted from inadvertent absorption of a small amount of the novel chemical he had been synthesizing. He resolved to investigate this possibility the following Monday by intentionally ingesting a small measured amount of LSD. Thus, near the end of his day of work on April 19, 1943, Hofmann measured out a very small quantity of LSD-0.25 mg (250 µg)-an amount chosen to be at the lower limit of any presumed effectiveness of even a very potent ergot alkaloid or other natural product. At 5:00 P.M., 40 minutes after ingesting the LSD, Hofmann recorded in his laboratory notebook:

"beginning dizziness, feeling of anxiety, visual distortions, symptoms of ataxia, desire to laugh." Here the notes in my laboratory journal cease. I was able to write the last words only with great difficulty. By then it was quite clear to me that LSD had been the cause of the remarkable experience of the previous Friday, for the altered perceptions were of the same type as before, only much more intense. I had to struggle to speak intelligently. I asked my laboratory assistant, who had been informed of my self-experiment, to escort me home. We went by bicycle, no automobile being available because of wartime restrictions on their use. On the way home, my condition began to assume threatening forms. Everything in my field of vision wavered and was distorted as if seen in a fun-house mirror. I also had the sensation of being unable to move from the spot. Nonetheless, my assistant later told me that we had bicycled quite rapidly. Finally, we arrived at home. (Hofmann, 2013, p. 19)

My surroundings had now transformed themselves in a most terrifying manner. Everything in the room spun around, and familiar objects and pieces of furniture assumed grotesque, threatening forms... Even worse than these demonic transformations of the outer world were the alterations that I perceived within myself, in my inner being. Every exertion of my will, every attempt to put an end to the disintegration of the outer world and the dissolution of my ego, seemed so much wasted effort. A demon had invaded me, had taken possession of my body, mind, and soul.... My body seemed to be without sensation, lifeless, strange. Was I dying? (Hofmann, 2013, p. 20)

Albert Hofmann was inadvertently experiencing the world's first full-blown acid trip. He was unprepared for the experience, and it was not pleasant. The family physician was summoned, as was Hofmann's wife, Anita. She and their three children had traveled that day to visit her parents in another city. The physician indicated that there were no signs of a threatening illness, extremely dilated pupils being the only abnormal symptom present. After several hours, Hofmann's distress began to abate.

Slowly I returned from a weird, unfamiliar world to my reassuring, everyday reality. The

horror softened and gave way to a feeling of great fortune and immense gratitude; more normal perceptions and thoughts returned, and I became more confident that the danger of insanity was decidedly past. Now, little by little, I could begin to *enjoy* the unprecedented colors and plays of shapes that persisted behind my closed eyes. Kaleidoscopic, fantastic images burst in upon me, alternating, variegated, opening and then closing themselves in circles and spirals, exploding in colored fountains, rearranging and hybridizing themselves in constant flux. It was particularly remarkable how every acoustic perception, such as the sound of a doorknob or of a passing automobile, became transformed into optical perceptions. Every sound generated a vividly changing image, with its own particular form and color. (Hofmann, 2013, p. 21; original emphasis)

Late in the evening Hofmann's wife arrived back home and, exhausted, he was finally able to sleep. Upon awakening the next morning, he was struck by how refreshed he felt.

A sensation of well-being and renewed life suffused me. My breakfast tasted delicious and gave me extraordinary pleasure. When I later walked out into the garden, in which the sun now shown after a springtime rain, everything glistened and sparkled in a fresh light. The world was as if newly created. All my senses vibrated in a state of utmost sensitivity, which lasted for the entire day. (Hofmann, 2013, p. 22)

Hofmann was impressed that his memory of the previous evening's experience of extreme intoxication was clear and vivid, and there were no negative "hangover" effects. He quickly appreciated that he had synthesized a truly amazing chemical—one that generated a novel constellation of powerful psychological effects, having potency unprecedented among known pharmaceuticals, and possibly low physiological toxicity as well. In 1943, there was little appreciation of the brain as a neurochemical system. The only known neurotransmitters at the time were acetylcholine and norepinephrine, and these were known via their actions in the peripheral autonomic and neuromuscular systems, not the brain. Yet here was a chemical-LSD-a very tiny quantity of which had a powerful impact on the psyche,

presumably because of some chemical interaction within the brain. Hofmann and his colleagues proposed that this could be of extraordinary utility as a therapeutic and research tool in psychiatry.

That same year, a report describing LSD's chemical properties was published by Arthur Stoll and Albert Hofmann (1943). In 1947, Werner Stoll, son of Arthur and a physician at the Psychiatric Clinic of the University of Zurich, described the effects of a series of LSD administrations on several dozen healthy individuals, as well as a number of patients suffering from various mental disorders (including schizophrenia). A U.S. patent for LSD as a therapeutic agent was filed in 1948. However, Sandoz believed that more research was needed to explore LSD's potential therapeutic utility. To facilitate this, beginning in the late 1940s (and continuing until 1966), Sandoz produced LSD under the brand name Delysid and made it available to physicians and psychologists for the purpose of conducting clinical and scientific research. The user's manual (package insert) for Delysid indicated the availability of two forms—a sugar-coated tablet (25 µg) and a liquid solution (100 µg)—and provided the following descriptive text (Hofmann, 2013, pp. 40-41):

#### INDICATIONS AND DOSAGE

Analytic psychotherapy, to elicit release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses. The initial dose is 25 mcg. This dose is increased at each treatment by 25 mcg until the optimum dose (usually between 50 and 200 mcg) is found. The individual treatments are best given at intervals of one week.

Experimental studies on the nature of psychoses: By taking Delysid himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease. In normal subjects, doses of 25 to 75 mcg are generally sufficient to produce a hallucinatory psychosis.

Pathological mental conditions may be intensified by Delysid. . . . Delysid should only be administered under strict medical supervision. The supervision should not be discontinued until the effects of the drug have completely worn off.

Hofmann often stated that he did not find LSD, that rather, it found him-that it was a discovery the world needed and he was but the vehicle, a "little Swiss chemist." Hofmann's "scientific discoveries, his philosophical writings, his wisdom and the depth of his humanity, have established his reputation as one of the outstanding personalities of our era" (Feilding, 2008, p. v). LSD has had an enormous and extended impact on the modern world, and Hofmann's scientific work was of the kind deserving a Nobel Prize. However, due to the complex circumstances that followed the emergence of the use of psychedelic chemicals in the wider culture, such honors are not yet within the realm of consideration. Contemporary society is still working to achieve a balanced perspective on LSD.

#### LSD and the Origins of Biological Psychiatry and Neuropsychopharmacology

The early 1950s witnessed the beginnings of conceptualizing connections between brain function and behavior in terms of chemistry. In 1949, the lithium ion's calming effect on mania in psychiatric patients was reported from Australia. In 1952, in Paris, the antihistamine and sedative chlorpromazine was tested on psychiatric patients and found to have dramatic effects in reducing symptoms of mania and psychosis. Not long thereafter, the mood-elevating effects of antituberculosis drugs, later appreciated to be inhibitors of monoamine oxidase, were observed.

Also in 1952, a seminal paper proposing a relationship among brain chemistry, mental illness, and the psychotomimetic effects of mescaline was published by British psychiatrists Humphry Osmond and John Smythies (1922-2019). Another important event in this early trajectory was the 1952 discovery of the chemical serotonin (5-hydroxytryptamine [5-HT]) in the mammalian brain. This substance was known at the time to be present in the gut and in the blood and to affect smooth-muscle contraction and blood-vessel tone (Green, 2008; Twarog, 1988; Whitaker-Azmitia, 1999). The appreciation of serotonin's structural similarity to LSD then led to the proposal that "mental disturbances caused by lysergic acid diethylamide were to be attributed to an interference with the action of serotonin in the brain" (Woolley & Shaw, 1954, p. 229; see also Green, 2008).

In the years that followed, biogenic amine theories of psychosis and depression came to dominate the emerging field of biological psychiatry, and dozens of medications to treat the symptoms associated with psychosis and depression were developed with these hypotheses in mind. This has continued unabated now for more than a half-century. The development of the contemporary disciplines of biological psychiatry, psychopharmacology, and neurochemistry owe a great deal to the discovery of LSD and the connecting of its powerful effects on the psyche to chemical interactions in the brain (Nichols & Nichols, 2008).

LSD has high affinity for many neurotransmitter receptors in the brain and body, in particular receptors for serotonin and dopamine (Nichols, 2016; Nichols et al., 2002). The major psychedelic effects of LSD, as well as other classical psychedelics (psilocybin, mescaline, DMT), have been largely associated with agonist actions at the serotonin type-2A  $(5-HT_{2A})$  receptor (Nichols, 2016). Elegant studies have revealed elements of the complex molecular orchestrations activated by the binding of LSD (as well as other ligands-neurotransmitters and drugs both psychedelic and nonpsychedelic) to serotonin receptors (Kim et al., 2020; Wacker et al., 2013, 2017).

Additional support for the interaction between LSD and monoamine neurotransmitter systems comes from interview data assessing the impact of chronic use of several psychiatric medications on the magnitude of LSD's psychedelic effects. Use of tricyclic antidepressants or lithium was found to be associated with subjective increases in hallucinatory and psychological responses to LSD, while use of selective serotonin reuptake inhibitor or monoamine oxidase inhibitor antidepressants was found to decrease or even eliminate the subjective response to LSD (Bonson, Buckholtz, & Murphy, 1996; Bonson & Murphy, 1996).

Serotonin and multiple types of serotonin receptors are located throughout the body and brain, and serotonin is known to be involved in the regulation of numerous processes, including modulatory effects on mood, anxiety, arousal, sleep, sexual activity, appetite, memory, perception, and emotion (Nichols & Nichols, 2008).

While LSD's effects at 5-HT<sub>2A</sub> and other serotonin receptors is a key aspect of its interaction with human physiology, it is good to keep in mind our inclination to oversimplify the complexity of living organisms. We often seek straightforward explanatory pictures revolving around single identified neurotransmitters and receptors, and simplistic ways of thinking about brain circuits. However, the functioning of even a single living cell is well beyond our capacity to explain in detail, and certainly there are many pieces of the cellular and molecular story linking LSD and its psychedelic effects yet to be discovered.

#### The First Phase of Clinical Research: 1950s and 1960s

Throughout the 1950s and 1960s, there were numerous clinical studies of the therapeutic utility of LSD in diverse circumstances. Among these were facilitation of psychological exploration in analytic psychotherapy; production of "model psychoses" in order to investigate and appreciate experiences of psychotic patients (e.g., psychiatrists, other clinicians, and researchers working with psychoses could ingest the drug to induce a personal experience of the symptoms); treatment of anxiety and depression associated with terminal illness; treatment of alcoholism and other addictions; and treatment of chronic depression, manic-depression, and psychosis (schizophrenia).

Many of these studies were conducted rather informally in the clinics and offices of psychotherapists. And even when investigations were conducted in research institutions associated with medical centers and universities, they were conducted at a time that lacked today's standards of institutional oversight and scientific meticulousness. An excellent review of this era indicates that "the standards for scientific reporting on clinical studies were often much less rigorous than they are today and relied heavily on the judgment of clinical investigators (rather than on validated outcome measures). . . . Thus, the early studies with LSD are best understood as providing valuable pilot data on safety and efficacy, as well as testable hypotheses for future studies" (Bonson, 2018, pp. 592, 598).

The first human clinical study with LSD published in English appeared in 1950 and described the administration of LSD to 29 psychiatric patients, most of whom were diagnosed with schizophrenia and other severe conditions (Busch & Johnson, 1950). The study was intended to facilitate the expression of material that might be of use in analytic psychotherapy. While other clinical investigations of this era also administered LSD to patients having psychosis, it is often concluded that there is little evidence that it produced beneficial results in such cases (Bonson, 2018). Nonetheless, pioneer LSD clinical researcher and psychotherapist Stansilav Grof (born in 1931) describes examples of successful treatment of select psychotic individuals in highly structured, intensive inpatient settings (Grof, 1975, 1980/2001).

As a component of the psychotherapeutic treatment of anxiety and mood disorders, LSD was primarily explored in two different ways (Pahnke, Kurland, Unger, Savage, & Grof, 1970). So-called psycholytic therapy involved using smaller doses of LSD (e.g., 25-150 µg) on a periodic basis as a component of ongoing psychoanalytic therapy, to loosen psychological defenses and facilitate exploration and processing of emotionally charged material. Psychedelic therapy used larger doses (>200 µg) with the intention of producing ego dissolution and perhaps a full mystical experience. In this circumstance, LSD's transformative power is proposed to derive from some sort of dramatic reconfiguration of neural and psychological dynamics.

Another area of significant clinical research during the 1950s and 1960s was the treatment of alcohol addiction (Dyck, 2006, 2008; Grinspoon & Bakalar, 1979/1997; Liester, 2014; Mangini, 1998). While many of these projects claimed to be effective in reducing alcohol abuse, they suffer, like other investigations of that era, from lack of clear standards of outcome and well-designed controls (Bonson, 2018). Nonetheless, a meta-analysis of six published studies from the 1960s—all of which were conducted using randomized controls-showed efficacy of LSD in decreasing drinking behavior from a single high dose (210-800 µg) administered in the context of a therapeutic treatment program (Krebs & Johansen, 2012).

The initial investigation of alcoholism treatment in the early 1950s (Humphry Osmond and collaborators) operated from a hypothesis that a psychedelic-induced state of somatic and cognitive chaos might have similarities to the life-threatening delirium tremens (DTs) of alcohol withdrawal, and foster such a psychic shaking-up that sobriety would be a result. Later the hypothesis shifted away from any specific association with DTs and more toward the evocation of a transformative mystical experience, wherein the subject would experience illuminative insights that resulted in lasting changes of reduced self-destructive behavior (e.g., addictive use of alcohol).

These studies drew the attention of Bill Wilson (1895–1971), a recovering alcoholic who in the 1930s cofounded the very successful self-help network of Alcoholics Anonymous (AA). Wilson's own recovery from alcoholism had been catalyzed by a spiritual (mystical) experience he had while in treatment in 1934 (Alcoholics Anonymous, 1984). By the late 1950s, Wilson had been abstinent from alcohol for more than 20 years, but he was nonetheless interested in seeing what the LSD experience was about, and whether it would be something that AA ought to recommend to those who were still struggling with breaking free from the grip of alcohol dependence.

Between 1956 and 1958, Wilson traveled to California and engaged in several LSD psychotherapy sessions at the UCLA/ LA Veterans Administration Medical Center with Drs. Sidney Cohen (1910-1987) and Betty Eisner (1915–2004). He found these experiences to be similar to the experience that propelled him into recovery years before and was thus optimistic that LSD might be of help to other alcoholics. However, the AA directorship was not supportive of the idea of recommending a psychoactive drug to individuals suffering from a drug (i.e., alcohol) addiction; thus the use of LSD as a therapeutic tool was not further discussed within the AA organization (Alcoholics Anonymous, 1984; Walsh & Grob, 2005).

Reviews of clinical work with LSD in those early decades, covering tens of thousands of drug administrations in controlled settings, describe wide-ranging results while speaking to valuable therapeutic potential and very low rates of adverse reactions (Cohen, 1960; Malleson, 1971; Pahnke et al., 1970). The early era of clinical research was ripe with promise and set the stage for further and more careful exploration of the complex effects of LSD on the psyche.

### The Cultural Context of the 1960s

In parallel with the academic and clinical investigation of LSD in the 1950s, the U.S. government (the Central Intelligence Agency [CIA] and various components of the Department of Defense) sponsored secret programs of investigation that explored the use of LSD as a chemical weapon, one that could mentally incapacitate an enemy without killing them. Also of interest was the possibility that LSD might aid interrogation, placing individuals in a vulnerable state of mind more conducive to disclosing information. While some of the academic and clinical investigations taking place at legitimate research institutions received funding through these government programs, other programs were more covert and blatantly unethical, such as those that administered LSD and other intoxicating drugs to individuals without their knowledge or consent, in order to observe the effects. Although many of the records of these projects appear to have been destroyed or redacted, enough remains for journalists, using the U.S. Freedom of Information Act, to have produced several comprehensive exposés of the era (Kinzer, 2019; Lee & Shlain, 1985; Marks, 1991; Stevens, 1987). And at least one of the researchers has recalled and recorded events of that era as well (Ketchum, 2006).

Concern developed at the time regarding dependence on a foreign company (Sandoz in Switzerland) to supply LSD, prompting the CIA to ask an American pharmaceutical company to develop a means of syntheses that could be independently patented. Thus, a total synthesis of lysergic acid—one not requiring ergot fungus as the starting material—was published in 1956, and a patent was filed the same year (Kornfeld et al., 1956). Eventually the U.S. government abandoned these programs exploring the weaponization of LSD (Lee & Shlain, 1985).

By the end of the 1950s, information about psychedelic substances was penetrating popular American culture. The influential author Aldous Huxley (1954) had written *The Doors of Perception*, detailing his experience with mescaline, and R. Gordon Wasson (1898–1986) had authored an article in 1957 in the popular weekly magazine *Life* describing his experience with shamanic ceremonial use of hallucinogenic mushrooms in Mexico. Poet Allen Ginsberg (1926–1997) wrote in 1959 a 154-line poem on "Lysergic Acid" and another on "Mescaline" (Ginsberg, 1961), and the popular philosopher of Asian spiritual traditions Alan Watts (1915–1973) wrote glowingly of the psychological power and potential of LSD in 1960 and 1962.

For several years beginning in 1958, Ken Kesey (1935-2001) was affiliated with a postgraduate writing program at Stanford University in California. Nearby, at the Menlo Park Veterans Administration Hospital, government-funded research projects were taking place, administering LSD and other powerful psychoactive substances to volunteer subjects and recording their effects. Kesey, who previously had no appreciation of such substances, volunteered to ingest LSD and answer questions put to him about his experience. Around the same time, he also worked as a clinical aid in the psychiatric treatment unit at the same hospital. All this contributed to the creation of his highly acclaimed novel One Flew Over the Cuckoo's Nest (1962).

Kesey went on to become a public advocate of LSD, traveling far and wide in a wildly painted bus named *Further*—including a trip across the breadth of the United States in 1964. He and a group of friends, the "Merry Pranksters," orchestrated a series of West Coast LSD parties called "Acid Tests," with music provided by a new band, The Grateful Dead. At one point, the author Tom Wolfe (1930–2018) tagged along with the Pranksters for several weeks and subsequently birthed a widely read and highly acclaimed book describing the philosophy and adventures of Kesey and the Pranksters: *The Electric Kool-Aid Acid Test* (1968).

Meanwhile, on the East Coast at Harvard University, Timothy Leary (1920–1996) and Richard Alpert (1931–2019) began their Psilocybin Research Project in 1961. In 1963 they were dismissed from Harvard as a result of the psychic turmoil that can ensue with use of psychedelics (Dass, Metzner, & Bravo, 2010; Lattin, 2010). Immediately after this, their focus of exploration shifted to LSD. They produced a classic guidebook of sorts—*The Psychedelic Experience: A Manual Based on the Tibetan Book of the Dead* (Leary, Metzner, & Alpert, 1964) appreciated for its recommendations in use of the psychedelic experience as an opportunity for psychological and spiritual learning and growth.

Unfettered by the etiquette of the academy, Leary attracted a great deal of media attention with his flamboyant and provocative style. He gave numerous public lectures promoting personal experimentation with LSD and other psychedelics (Leary, 1983). Alpert journeyed to India in 1967 and came back as Ram Dass (Dass, 1971; Walsh & Grob, 2005). His writings and public lectures over the decades have contributed to the introduction of Asian spiritual philosophies into American culture. Ralph Metzner (1936-2019), a graduate student who worked with Leary and Alpert at Harvard, went on to become a pioneering scholar of consciousness and its transformations, academic educator, renowned shamanic teacher, and psychotherapist (Metzner, 1968, 2017).

There were multiple other foci of experimentation with LSD during the 1960s. A legendary and enigmatic character of the era, Al Hubbard (1901–1982), sometimes called the "Johnny Appleseed of LSD," introduced key individuals far and wide to its powerful experiential effects (Lee & Shlain, 1985; Fahey, 1991). And in the San Francisco region later known as Silicon Valley, a group of engineers and psychologists investigated LSD's potential to aid creative problem solving (Fadiman, 2011; Walsh & Grob, 2005).

As millions of doses of LSD were being ingested in a vast array of uncontrolled settings, adverse reactions to its powerful psychological effects may have been anticipated. The impressive safety record and positive outcomes of LSD used in controlled therapeutic and research settings did not necessarily extend to situations of uncontrolled and ill-prepared use, and the adverse events that did occur were often exaggerated by the media (Siff, 2015). By 1966 there were widely read magazine stories with headlines such as "LSD: The exploding threat of the mind drug that got out of control. Turmoil in a capsule: One dose of LSD is enough to set off a riot of vivid colors and insights—or of terror and convulsions" (*Life* magazine cover of March 25, 1966).

Research concluding that LSD produced chromosome damage and birth defects appeared in prominent scientific and medical journals and was repeated often in the popular press. While these findings were soon discredited, the additional negative contribution to LSD's reputation had been accomplished and there was no going back (Dishotsky, Loughman, Mogar, & Lipscomb, 1971; Presti & Beck, 2001).

Genetic damage was only one of many 1960s-era myths that sprang up around this powerful substance. Others were that users frequently "went crazy" and remained crazy: "Use LSD seven times and you are legally insane," went one such myth. Staring at the sun and going blind, thinking one can fly and jumping from a high place, and ingesting LSD often contaminated with additives such as strychnine and amphetamine were among other pervasive myths (Presti & Beck, 2001). The social discourse related to LSD very likely had substantial impact on how users interpreted their experiences: Was one dealing with the complexities of the psyche and the state of the world, or was one going permanently insane? The development of informed-user subcultures in the 1960speer groups that could educate and counsel one another—likely helped to modulate and reduce potential adverse reactions (Becker, 1967).

In 1966, Sandoz withdrew Delysid from the market. But it was clear already that Delysid (diverted from clinical and research projects) alone could not provide for the demand engendered by the growing popularity of LSD. Other sources were necessary; thus, there emerged a number of underground chemists who operated with an intention to synthesize LSD and make it widely available. This began in the United States and Europe in the early 1960s. Among these chemists who became publicly well known were Augustus Owsley Stanley (1935–2011), known as Owsley, who produced LSD between 1965 and 1967; Tim Scully (born in 1944), who produced LSD from 1966 to 1969; and Nicholas Sand (1941-2017), who produced LSD on and off between 1966 and 1996. All were arrested at various times, and all spent periods in prison for manufacturing LSD. Tens of millions of doses were synthesized and distributed. And to this day, LSD continues to be available in the illicit market.

For at least some of these underground chemists, their mission was self-described as alchemical—a bow to the ancient discipline that preceded modern chemistry. Alchemy was concerned both with transformations of matter (here, the synthesis of LSD) and with transformations of the psyche (here, the belief held by the chemists that their work would shift and transform the collective human mindset) (for a beautiful exposition on alchemy and LSD, see Metzner, 2017). Quoting Nicholas Sand (2001, p. 39; Grimes, 2017): "This planet must be lovingly cared for or we are all doomed. We are the guardians of life and planetary harmony. This is where we are going. That is what I have seen in my visions, and that is what I have been working for all of my life. That is what I will continue to do until my last breath."

The high potency of LSD requires that small quantities be accurately partitioned into individual dosage units. Sandoz's Delysid came packaged as a tablet or liquid solution of precise concentration. The LSD produced by chemists such as Owsley and his contemporaries was primarily distributed in tablet or capsule form. Another method of dose packaging was called "windowpane"-LSD-impregnated gelatin. In the 1960s, the dosage unit of illicitly synthesized and distributed LSD was typically in the 200- to 333-µg range—a strong psychedelic dose. Sometime in the 1970s, "blotter" LSD began to appear, a mode of distribution that has remained a dominant form of illicit LSD for nearly five decades. Here, absorbent paper is saturated with LSD in solution, calibrated so that the quantity of LSD absorbed into a small measured area (onefourth inch square) contains a one-unit dose of drug. The blotter paper is perforated, so that the dosage units can be easily divided and a sheet of blotter paper typically has 30  $\times$  30 = 900 dosage units. In addition, over the decades, LSD blotter paper has been imprinted with an astounding panoply of colorful art. Beginning in the early 1970s, illicit LSD began to appear in reduced dosage: Rather than 200+ µg per dosage unit, a unit dose was found to often be in the 60 to 100  $\mu$ g range (based on estimates determined from blotter acid confiscated by law enforcement).

Perhaps the single most important factor in bringing about the severe legal restrictions on LSD was its association with the 1960s counterculture, driven in large part by opposition to the war in Southeast Asia, but also very much opposing the growing military-corporate control of society in general. The impact of this association is difficult to overestimate in its import to the demonization of LSD and subsequent draconian legal control (also applied to other psychedelics, and to cannabis as well) (Lee & Shlain, 1985; Stevens, 1987).

The first laws against LSD were instituted in 1966, including U.S. federal prohibition of manufacture and sale (although not yet possession). An increasing set of legal restrictions at state and federal levels developed over the following years. In 1968, LSD possession was outlawed federally, and when the comprehensive Federal Controlled Substances Act was implemented in 1970, LSD (as well as other known psychedelic chemicals) were deemed Schedule I controlled substances-drugs lacking approved medical use and considered highly dangerous and prone to abuse as well. The following year, the United Nations Convention on Psychotropic Substances pronounced LSD to be Schedule I internationally. Once widely accepted for its therapeutic and research potential, LSD was now illegal at the highest level, worldwide.

While it has sometimes been convenient to place blame for this severe regulation as a response largely catalyzed by the activities of a few specific individuals—with the most frequently scapegoated individual by far being Timothy Leary—it seems highly likely the complex course of events of the 1950s and 1960s would have resulted in a similar outcome no matter what individuals with their unique personalities had been involved. LSD and other psychedelics are incredibly powerful, and contemporary Western society lacked the shamanic and spiritual infrastructure to guide and contain that power. It is important to remember this as we move forward with the benefits—such as they may be-of hindsight.

#### Adverse Effects and Toxicity

For LSD (and other psychedelic substances) the most significant adverse effects are acute anxiety and panic-the so-called "bad trip." Such adverse effects can be minimized or contained with appropriate attention to set and setting. Actually, in the context of a therapeutic process, such firsthand contact with difficult psychological material can be the springboard for significant positive shifts-a transformational antecedent rather than an adverse effect. This may be supported by a skilled therapist or guide, and also may happen within the course of one's own internal process. Any single experience with LSD may contain both positive and negative mood states. The longer-term takeaway from an experience depends altogether on how one relates to psychological material that emerges and, very importantly, how one then integrates the experience into one's life.

There are reports of individuals suffering long-term anxiety, depression, and psychosis in association with LSD use. Even so, reviews of clinical administrations of LSD during the 1950s and 1960s have documented very low rates of adverse effects (Cohen, 1960; Malleson, 1971). Moreover, the published literature from this era suggests that chronic adverse effects, when they do occur, are most often associated with psychological instability prior to exposure to LSD (Grinspoon & Bakalar, 1979/1997; Strassman, 1984). For example, persons with certain personality disorders, active bipolar or psychotic conditions, or latent mental disorders (e.g., a positive family history for schizophrenia, suggesting a possible genetic risk for developing psychosis) may have symptoms triggered from LSD use and suffer chronic problems thereafter. Such individuals would also be at risk from exposure to a variety of other environmental stressors.

More recently, assessments of LSD and other psychedelic use in uncontrolled nonmedical settings have been conducted by analyzing comprehensive survey data compiled annually in the United States via the National Survey of Drug Use and Health (NSDUH). Analyses of NSDUH data between 2001 and 2004 (Krebs & Johansen, 2013b) and between 2008 and 2012 (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015; Johansen & Krebs, 2015) found no relationship between lifetime use of psychedelics (LSD, psilocybin-containing mushrooms, mescaline, peyote cactus) and any negative mental health outcomes-including symptoms characteristic of a variety of mood, anxiety, and psychotic disorders, other serious psychological distress, and engagement with mental-health treatment (inpatient, outpatient, psychiatric medication). One of these studies found an association between lifetime psychedelic use and reduced likelihood of psychological distress, suicidal ideation, and suicidal behavior (Hendricks et al., 2015). By way of contrast, lifetime prevalence of use of other illicit drugs (cocaine, stimulants, sedatives, opioids, cannabis) was associated with increased psychological distress and suicidal ideation, as well as suicide planning and attempts (Hendricks et al., 2015).

It is now generally agreed that LSD is physiologically safe, especially when moderate doses are used. Cardiovascular and other autonomic effects are modest. There has never been a documented death due to LSD use at typical recreational doses (Erowid, 2018a; Nichols & Grob, 2018). Moreover, there have been cases of individuals consuming massive doses and surviving without any reported residual effects. For example, eight individuals insufflated a very high dose of LSD, believing it to be cocaine (Klock, Boerner, & Becker, 1974; Nichols & Grob, 2018). They received emergency medical treatment 15 minutes after insufflating the drug, at which point five were comatose. Three required assisted ventilation. Tachycardia was also present, as well as hyperthermia and generalized bleeding in some of the patients. Blood analyses measured up to 26 ng/ml, and gastric analyses up to 7 mg/100 ml. There were no seizures reported, and none of the eight patients required supportive treatment extending past 12 hours. "Most did not remember being brought to the hospital; otherwise no apparent psychologic or physical ill effects were noted in a year of follow-up examinations of five patients" (Klock et al., 1974).

While there have been fatalities associated with engaging in dangerous behavior while intoxicated, there appear to be only a very small number of such reports involving LSD—impressively low when contrasted with the tens of millions of doses of LSD consumed over more than 50 years of widespread popular use. Other deaths initially associated with LSD were later ruled to be due to excessive restraint by police or to ingestion of drugs other than LSD (Nichols & Grob, 2018).

The advent of synthetic drugs unrelated to LSD but possessing substantial physiological activity at submilligram doses has given rise to a situation wherein blotter sold at festivals, concerts, and other venues and portrayed as "blotter acid" containing LSD actually may contain no LSD and rather, on a number of occasions, has been found to instead contain potent synthetic intoxicants that carry dangers not associated with LSD. One such substance, 25I-NBOMe (4-iodo-2,5-dimethoxy-N-[2-methoxybenzyl]phenethylamine), is powerfully active at submilligram doses. Unlike LSD, the NBOMe substances can produce potentially lethal effects such as hyperthermia, hypertension, tachycardia, agitated delirium, seizure, and rhabdomyolysis (Erowid, 2018b; Gee, Schep, Jensen, Moore, & Barrington, 2016; Nichols, 2016; Nichols & Grob, 2018; Walterscheid et al., 2014).

Another possible adverse effect that is often associated with LSD, especially in popular discussion, is the notion of a *flashback*. This word was introduced in early 20thcentury English to describe insertion into the temporal sequence of a narrative or film of events taking place at an earlier time. By 1970, it had appeared in the popular media in association with LSD (Linkletter & Bell, 1970) and soon thereafter was used in the clinical literature (Shick & Smith, 1970). Years later Timothy Leary (1983) would poetically use the word as the title for his autobiographic memoir. (The word has also been applied as a descriptor of dissociative reaction in the diagnostic criteria for posttraumatic stress disorder [PTSD], for example, in the Diagnostic and Statistical Manual of Mental Disorders [DSM]).

In their excellent discussion of the flashback notion applied to LSD and other psychedelics, Grinspoon and Bakalar (1979/1997, p. 159) have this to say:

Studies of flashbacks are hard to evaluate because the term has been used so loosely and variably. On the broadest definition, it means the transitory recurrence of emotions and perceptions originally experienced while under the influence of the drug. It can last seconds or hours; it can mimic any of the myriad aspects of a trip; and it can be blissful, interesting, annoying, or frightening. Most flashbacks are episodes of visual distortion, time distortion, physical symptoms, loss of ego boundaries, or relived intense emotion lasting a few seconds to a few minutes. Ordinarily they are only slightly disturbing, especially since the drug user usually recognizes them for what they are; they may even be regarded lightheartedly as "free trips." Occasionally they last longer,

One way of conceptualizing flashbacks is that memories may be recorded more robustly in the psychedelic state and may subsequently be more prone to reactivation and recall. Another related conceptualization of flashbacks is psychodynamic, a reemergence of conflictual material encountered during the time of the drug action and not yet fully processed: "Sessions in which the drug activates areas of difficult emotional material and the individual tries to avoid facing them can lead to prolonged reactions, unsatisfactory integration, subsequent residual emotional or psychosomatic problems, or a precarious mental balance that becomes the basis for later 'flashbacks'" (Grof, 1980/2001, p. 134).

and in a small minority of cases they turn into

frightening images or thoughts.

In the 1980s a small number of case reports detailing hallucinatory visual sensations persisting beyond the phase of acute intoxication with psychedelics led to the introduction of a new diagnostic category in DSM-III-R (American Psychiatric Association, 1987): posthallucinogen perception disorder. The diagnostic criteria were slightly modified in DSM-IV (American Psychiatric Association, 1994) and the diagnosis given a new name: hallucinogen persisting perception disorder (flashbacks). This condition is abbreviated as HPPD and has continued as a diagnosis (without the inclusion of the word flashbacks) in DSM-5 (American Psychiatric Association, 2013). There are claims that HPPD is more commonly associated with LSD than with other psychedelics.

Note that the early reviews of adverse effects associated with tens of thousands of

administrations of LSD in clinical settings did not report any occurrence of persisting sensory disturbances or other flashback-type symptoms (Cohen, 1960; Malleson, 1971). Nor did the more recent analysis of NSDUH data reveal anything that looked like symptoms of HPPD or flashbacks (Krebs & Johansen, 2013b). Attempts to study the validity and prevalence of HPPD have concluded that while it may be a genuine, although uncommon, condition, and that symptoms may indeed develop in association with psychedelic use, it is perhaps more related to exacerbation of preexisting psychological and neurological conditions of anxiety and/or disturbances of visual processing (Baggott, Coyle, Erowid, Erowid, & Robertson, 2011; Halpern, Lerner, & Passie, 2018; Halpern & Pope, 2003).

Because of its legal classification as a Schedule I controlled substance, which, by definition, possesses a "high potential for abuse," LSD is often assumed to be addictive. However, LSD, like other classical psychedelics, has negligible addictive potential, and very low potential for people to use repeatedly and suffer adverse consequences as a result (Nichols, 2016).

#### The Renewal of Human Research with LSD

The legal restrictions imposed on LSD beginning in the late 1960s resulted in virtually no formal human investigation for nearly 40 years. The emergence of the current phase of sanctioned clinical and scientific investigation with LSD began after human studies using other Schedule I psychedelic substances (DMT, 3,4-methylenedioxymethamphetamine [MDMA], and psilocybin) had paved the way.

Beginning in the first decade of the 21st century, survey research (> 500 persons) indicated that individuals suffering from painful cluster headaches reported shortening of headache duration and extended periods of remission from oral doses of self-administered LSD (or psilocybin, in the form of mushrooms), sometimes with doses that were infrequent and subpsychedelic (Schindler et al., 2015; Sewell, Halpern, & Pope, 2006). The therapeutic efficacy of LSD and psiloLSD

cybin mushrooms in this regard was seen as comparable to or better than the best of the conventional available medical treatments. There has also been one small study (five patients) demonstrating therapeutic efficacy in cluster headache of the nonpsychoactive LSD analogue 2-bromo-LSD, a derivative originally synthesized by Hofmann and colleagues at Sandoz in the 1950s (Karst, Halpern, Bernateck, & Passie, 2010; Troxler & Hofmann, 1957).

One of the therapeutic indications for ergot-based pharmaceuticals produced by Sandoz since the early days has been treatment of migraines and cluster headaches. Ergotamine tartrate, sometimes used in conjunction with caffeine (Sandoz: Cafergot) has long been available. Another lysergic acid derivative is methysergide (1-methyl-Dlysergic acid butanolamide; Sandoz: Deseril and Sansert). The use of these ergot-derived pharmaceuticals has been largely eclipsed by the introduction of triptan medications, beginning with sumatriptan in the early 1990s. There has yet to be a controlled clinical study of LSD for the treatment of headaches.

The first controlled (randomized, doubleblind, placebo-controlled) clinical study of LSD since circa 1970 was conducted in Switzerland and initial findings published by Gasser and colleagues (2014). Twelve patients with anxiety associated with lifethreatening illness were treated with LSDassisted psychotherapy using a moderate dose (200 µg) or an active placebo (20 µg). The participants who received the psychotherapy with the active dose showed a significant reduction in state, or short-term, anxiety at 2-month follow-up. A 12-month follow-up study reported sustained reductions in both short-term and long-term, or trait, anxiety and increases in quality of life, with no reported adverse effects (Gasser, Kirchner, & Passie, 2015).

A major aspect of the current human studies with psychedelics (LSD and, even more extensively, psilocybin) has been to revisit some of the themes that emerged from the first phase of human research (e.g., treatment of anxiety and depression associated with life-threatening illness, treatment of addiction, and capacity to occasion spiritual experience) now applying modern standards of rigorous controls and validated assessment instruments. Another major aspect is to bring to bear the technologies of functional brain imaging (functional magnetic resonance imaging [fMRI], electroencephalography [EEG], magnetoencephalography [MEG], etc.) and cellular and molecular biology to further elucidate physiological mechanisms associated with the actions of LSD and other psychedelics on the human

brain and body. Studies (double-blind, placebo-controlled) with healthy human subjects in Switzerland have resulted in a number of published reports commenting on phenomenology, physiology, and psychological effects, as well as data on neural correlates of LSD-induced states of mind (summarized in Liechti, 2017). These studies used either 100 or 200 µg of LSD orally. Various physiological and psychological changes are described, including increased happiness, closeness to others, openness, trust and empathy, and impaired recognition of fearful faces (Dolder, Schmid, Müller, Borgwardt, & Liechti, 2016; Schmid et al., 2015).

Several reports describe neural correlates related to perceptual, cognitive, and emotional experiences, and hypothesize relationships between regional brain activity and emotional processing, as well as neural network connectivity and subjective experiences (Mueller et al., 2017; Müller et al., 2017, 2018; Schmidt et al., 2018). Another study out of Switzerland linked LSD-induced effects, including induction of a dream-like state of consciousness and attributions of personal meaningfulness, to 5-HT<sub>2A</sub> receptor agonism and also to activity in particular brain regions (Kraehenmann et al., 2017; Preller et al., 2017).

Studies in London (using intravenous doses of 40–80 µg LSD, found to be approximately equivalent to 100 µg by oral administration) looked at a number of psychological outcome measures, as well as measures of brain activity using fMRI and MEG. Researchers commented on imagination, mental imagery, synesthesia, psychosis-like symptoms, emotional response to music, heighted mood, and increases in optimism and trait openness (Carhart-Harris et al., 2015; Carhart-Harris, Kaelen, et al., 2016; Kaelen et al., 2015; Terhune et al., 2016). Also described were increases in cortical and thalamic functional connectivity and its relationship with subjective reports of *ego dissolution* (defined as a lessening of a sense of a "self" or "ego" distinct from others and separate from the environment) (Carhart-Harris, Muthukumaraswamy, et al., 2016; Tagliazucchi et al., 2016).

The capacity of LSD-catalyzed experiences to have long-term (perhaps lifelong) impact on behavior suggests that LSD may have profound impact on neuronal connectivity and memory formation. At cellular and molecular levels, LSD and other psychedelics have been found (both in vivo and in cell culture) to enhance processes associated with synaptic plasticity, such as growth of dendritic spines and other neuronal processes (Ly et al., 2018). LSD has also been found to influence the expression of genes associated with transcription factors and other mediators of synaptic plasticity (Martin & Nichols, 2018; Nichols & Sanders-Bush, 2002).

#### Microdosing of LSD

Microdosing is a term used in pharmacology to describe administration of miniscule doses of a drug, well below the threshold for therapeutic activity (Passie, 2019). Lately it has been applied in reference to ingesting a small, subperceptual amount of a psychedelic substance-usually about one-tenth of a moderate dose generally used for a full psychedelic trip—and has reportedly grown in popularity over the past several years (Anderson et al., 2019; Passie, 2019). A commonly used microdose of LSD is in the range of 5-10 µg. However, it is important to bear in mind that contemporary information about microdosing of LSD comes primarily from users in informal settings who often do not know precisely what dose they are taking.

A study of the impact of small doses of LSD (4–20  $\mu$ g) on 14 individuals was conducted in the 1950s (Greiner, Burch, & Edelberg, 1958). And the effects of subpsychedelic doses (e.g., 20–50  $\mu$ g), although not generally subperceptual doses, were often researched in the early days of LSD clinical investigation (Passie, 2019). In addition, some of the pioneer investigators occasionally ref-

erenced the potential psychological value of lower (subpsychedelic) dosages. Albert Hofmann speculated in a 1970s interview that perhaps doses of circa 25  $\mu$ g might be useful to investigate for potential antidepressant effects (Hofmann & Horowitz, 1976).

Contemporary interest in microdosing has been in part catalyzed by James Fadiman (born in 1939), a psychologist whose involvement in LSD research dates to the early 1960s (Walsh & Grob, 2005). Fadiman (2011) has offered a protocol to personally assess the effects of microdosing by taking the subperceptual dose on the morning of every fourth day for a period of perhaps 1 month, tracking and recording any perceived differences between these different days, all the while engaging in one's regular daily activities. This protocol avoids the buildup of tolerance, as well as provides opportunities to contrast one's experience of "on" versus "off" days. Accounts of individuals using this protocol describe things such as improvement in focus of attention and productivity, and sometimes improvement in mood. Reports were summed up as indicating that many respondents related "positive and valuable" experiences. A common denominator of several stories was offered-that these individuals reported functioning "a little better than normal" (Fadiman, 2011; Fadiman & Korb, 2019).

Currently, the number of published studies on the microdosing of LSD or other psychedelics is very small and largely uncontrolled. Internet-based surveys have addressed selfreported effects of respondents to microdosing of a variety of psychedelics (Johnstad, 2018) and personality differences between individuals who microdose versus nonmicrodosing controls (Anderson et al., 2019). An unblinded study in the Netherlands using microdoses of psilocybin-containing mushrooms found increases on several measures of creative thinking (Prochazkova et al., 2018). The first randomized, double-blind, placebo-controlled study of LSD microdosing (5, 10, and 20 µg), conducted in the United Kingdom, reported the only significant effect of small doses of LSD was overestimation of intervals of elapsed time by the participants (Yanakieva et al., 2019).

The question of therapeutic benefits aside, one may wonder whether the regular and frequent use—even if not daily use—of small doses of LSD or other psychedelic substances might result in subtle, or not-so-subtle, withdrawal symptoms when regular dosing is curtailed, as has been found to occur with antidepressant medications—so-called "antidepressant discontinuation syndrome" (Horowitz & Taylor, 2019). Given the role that serotonergic mechanisms likely have in withdrawal effects that occur after stopping daily antidepressant medications, one may surmise that analogous mechanisms could be operative with regular microdosing of LSD.

As other facets of human LSD research have been initiated or renewed within the last decade, we can expect more well-controlled and published investigations of microdosing in the near future. Such investigation should be able to establish more definitively the effects on human cognition and emotion of ingesting tiny doses of LSD. Until this is accomplished, it is impossible to say which and how much of the reported effects of subperceptual doses are due to specific pharmacological interaction of LSD with brain physiology, and how much may be attributed solely to belief and expectation-so-called "placebo effects." Such expectation effects might even be enhanced as a result of LSD's complex and colorful history; that is, how could something not be expected from such a remarkable substance? Placebo effects in pharmacology can be and often are substantial, and this alone is a profound statement about the power of the mind-body connection.

#### Coda: Shamans, Medicines, and the Nature of Mind

The most salient aspect of LSD and other classical psychedelics is the effect they can have on the psyche—shaking it up, opening it to new information and insight, even transforming one's worldview. Somehow this is related to interactions with brain physiology, although the details are likely to be more subtle and complex than what are presently envisioned. This metamorphic potential of LSD, used under suitable conditions, could transform the landscape of treatment for conditions of mental distress, such as depression and anxiety.

The discovery of LSD set Albert Hofmann

on a lifelong path investigating the chemistry of plants and fungi used by indigenous cultures around the world in spiritual and healing ceremonies. All the while, he continued his work at Sandoz in pharmaceutical chemistry, going on to become the director of the department of natural products (Hagenbach & Werthmüller, 2011). Hofmann collaborated with mycologist-botanist Roger Heim (1900–1979) and ethnomycologist R. Gordon Wasson to investigate *Psilo*cybe mushrooms used by Mazatec shamans of southern Mexico. Conducting extractions and separations, with subsequent testing on himself for psychoactive effects, Hofmann identified the molecules psilocybin and psilocin from Psilocybe mushrooms and established their psychedelic activity (Hofmann, 2013; Hofmann, Heim, Brack, & Kobel, 1958).

His work with Psilocybe mushrooms led Hofmann to investigate the chemical constituents of another shamanic substance from southern Mexico known as ololiuhqui in the ancient language of the region, the seeds of flowering morning glory plants: Turbina (Rivea) corymbosa and Ipomoea *violacea*. Here, he identified the surprising presence of lysergic acid amide and other related alkaloids similar to what had been previously identified in ergot. He furthermore concluded the psychoactive potency of lysergic acid amide to be at least 10 times less than that of LSD and far less interesting in its effects (Hofmann, 2013; Hofmann & Tscherter, 1960).

In 1962, Hofmann accompanied Wasson to Mexico to collect samples of a novel plant used in Mazatec healing ceremonies. Ritual use was documented, and plant samples were obtained and brought back for botanical and chemical investigation. Botanical identification established the plant as one not previously described, and it was given the name Salvia divinorum. Hofmann's attempt to identify the psychoactive chemical component was not successful, in that the material he carried back with him to Switzerland no longer retained psychoactivity. Twenty years later, the primary psychoactive chemical component was isolated and identified by Mexican scientists and named salvinorin A (Hofmann, 2013).

Hofmann collaborated with renowned ethnobotanist Richard Evans Schultes (1915–2001) to write two books on psychoactive plants and fungi used by indigenous cultures for healing and shamanic rituals: The Botany and Chemistry of Hallucinogens (Schultes & Hofmann, 1980) and Plants of the Gods: Origins of Hallucinogenic Use (Schultes & Hofmann, 1979; later expanded in Schultes, Hofmann, & Rätsch, 2001). And he collaborated again with Wasson and with scholar of classics Carl Ruck (born in 1935) to propose that the kykeon beverage consumed by the participants in the sacred ritual of the Eleusinian Mysteries of ancient Greece may have contained hallucinogenic ergot alkaloids (Wasson, Hofmann, & Ruck, 1998).

Ancient and contemporary spiritual and shamanic traditions may hold wisdom about the nature of mind and world that modern biophysical science-and psychology, psychiatry, and medicine-is perhaps poised to receive and integrate into our evolving understanding of who we are as conscious beings and how we relate to the physical world. As Grof (1980/2001, p. 12) wrote in the reissue of his classic 1980 book LSD Psychotherapy, "It does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation."

LSD and other psychedelics expand our capacity to probe mental states directly and open the psyche to far-reaching new kinds of experience. Let us be propelled by the inspiring winds of this venture, deepening our understanding of mind and allowing us to more clearly chart a course toward personal and societal healing and transformation.

#### References

- Alcoholics Anonymous. (1984). "Pass it on": The story of Bill Wilson and how the A.A. message reached the world. New York: Alcoholic Anonymous World Services.
- American Psychiatric Association. (1987). Diagnostic and statistical manual of mental disorders (3rd ed., rev.). Washington, DC: Author.
- American Psychiatric Association. (1994). Diag-

nostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author.

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.
- Anderson, T., Petranker, R., Rosenbaum, D., Weisman, C. R., Dinh-Williams, L. A., Hui, K., et al. (2019). Microdosing psychedelics: Personality, mental health, and creativity differences in microdosers. *Psychopharmacol*ogy, 236, 731–740.
- Bache, C. M. (2019). LSD and the mind of the universe: Diamonds from heaven. Rochester, VT: Park Street Press.
- Baggott, M. J., Coyle, J. R., Erowid, E., Erowid, F., & Robertson L. C. (2011). Abnormal visual experiences in individuals with histories of hallucinogen use: A web-based questionnaire. *Drug and Alcohol Dependence*, 114, 61–67.
- Becker, H. S. (1967). History, culture and subjective experience: An exploration of the social bases of drug-induced experiences. *Journal of Health and Social Behavior*, 8, 163–176.
- Bonson, K. R. (2018). Regulation of human research with LSD in the United States (1949– 1987). Psychopharmacology, 235, 591–604.
- Bonson, K. R., Buckholtz, J. W., & Murphy, D. L. (1996). Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. *Neuropsychopharmacology*, 14, 425–436.
- Bonson, K. R., & Murphy, D. L. (1996). Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium. *Behavioural Brain Research*, 73, 229–233.
- Busch, A. K., & Johnson, W. C. (1950). L.S.D. 25 as an aid to psychotherapy: Preliminary report of a new drug. *Diseases of the Nervous System*, 11(8), 241–243.
- Carhart-Harris, R. L., Kaelen, M., Bolstridge, M., Williams, T. M., Williams, L. T., Underwood, R., et al. (2016). The paradoxical psychological effects of lysergic acid diethylamide (LSD). *Psychological Medicine*, 46, 1379–1390.
- Carhart-Harris, R. L., Kaelen, M., Whalley, M. G., Bolstridge, M., Feilding, A., & Nutt, D. J. (2015). LSD enhances suggestibility in healthy volunteers. *Psychopharmacology*, 232, 785–794.
- Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., et al. (2016). Neural correlates of the LSD experience revealed by multi-modal neuroimaging. *Proceedings of the National Academy of Sciences of the USA*, 113, 4853–4858.
- Cholden, L. S., Kurland, A., & Savage, C. (1955). Clinical reactions and tolerance to LSD in

chronic schizophrenia. Journal of Nervous and Mental Disease, 122, 211–221.

- Cohen, S. (1960). Lysergic acid diethylamide: Side effects and complications. Journal of Nervous and Mental Disease, 130, 30-40.
- Dass, R. (1971). *Be here now*. San Cristobal, NM: Lama Foundation.
- Dass, R., Metzner, R., & Bravo, G. (2010). Birth of a psychedelic culture: Conversations about Leary, the Harvard experiments, Millbrook, and the Sixties. Santa Fe, NM: Synergetic Press.
- Dishotsky, N. I., Loughman, W. D., Mogar, R. E., & Lipscomb, W. R. (1971). LSD and genetic damage. *Science*, 172, 431–440.
- Dolder, P. C., Schmid, Y., Müller, F., Borgwardt, S., & Liechti, M. E. (2016). LSD acutely impairs fear recognition and enhances emotional empathy and sociality. *Neuropsychopharma*cology, 41, 2638–2646.
- Dolder, P. C., Schmid, Y., Steuer, A. E., Kraemer, T., Rentsch, K. M., Hammann, F., et al. (2017). Pharmacokinetics and pharmacodynamics of lysergic acid diethylamide in healthy subjects. *Clinical Pharmacokinetics*, 56, 1219–1230.
- Dyck, E. (2006). "Hitting highs at rock bottom": LSD treatment for alcoholism, 1950–1970. Social History of Medicine, 19, 313–329.
- Dyck, E. (2008). *Psychedelic psychiatry: LSD from clinic to campus.* Baltimore: Johns Hopkins University Press.
- Erowid. (2018a). The vaults of Erowid: LSD (acid) fatalities/deaths. Retrieved April 19, 2019, from *erowid.org/chemicals/lsd/lsd\_death.shtml*.
- Erowid. (2018b). The vaults of Erowid: 25I-NBOMe. Retrieved April 19, 2019, from erowid.org/chemicals/2ci\_nbome.
- Fadiman, J. (2011). The psychedelic explorer's guide: Safe, therapeutic, and sacred journeys. Rochester, VT: Park Street Press.
- Fadiman, J., & Korb, S. (2019). Might microdosing psychedelics be safe and beneficial?: An initial exploration. *Journal of Psychoactive Drugs*, *51*, 118–122.
- Fahey, T. B. (1991, November). The original Captain Trips. *High Times Magazine*, pp. 18–23.
- Feilding, A. (Ed.). (2008). Hofmann's elixir: LSD and the new Eleusis. Oxford, UK: Beckley Foundation.
- Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., et al. (2014). Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *Journal of Nervous and Mental Disease*, 202, 513–520.
- Gasser, P., Kirchner, K., & Passie, T. (2015). LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective

effects. Journal of Psychopharmacology, 29, 57-68.

- Gee, P., Schep, L. J., Jensen, B. P., Moore, G., & Barrington, S. (2016). Case series: Toxicity from 25B-NBOMe—a cluster of N-bomb cases. *Clinical Toxicology*, 54, 141–146.
- Ginsberg, A. (1961). *Kaddish and other poems:* 1958–1960. San Francisco: City Light Books.
- Green, A. R. (2008). Gaddum and LSD: The birth and growth of experimental and clinical neuropharmacology research on 5-HT in the UK. British Journal of Pharmacology, 154, 1583–1599.
- Greiner, T., Burch, N. R., & Edelberg, R. (1958). Psychopathology and psychophysiology of minimal LSD-25 dosage: A preliminary dosage-response spectrum. AMA Archives of Neurology and Psychiatry, 79, 208–210.
- Gresch, P. J., Smith, R. L., Barrett, R. J., & Sanders-Bush, E. (2005). Behavioral tolerance to lysergic acid diethylamide is associated with reduced serotonin-2A receptor signaling in rat cortex. *Neuropsychopharmacology*, 30, 1693–1702.
- Grimes, W. (2017, May 12). Nicholas Sand, chemist who sought to bring LSD to the world, dies at 75. *New York Times*, p. A24.
- Grinspoon, L., & Bakalar, J. B. (1997). Psychedelic drugs reconsidered. New York: Lindesmith Center. (Original work published 1979)
- Grof, S. (1975). Realms of the human unconscious: Observations from LSD research. New York: Viking Press.
- Grof, S. (2001). *LSD psychotherapy* (3rd ed.). Sarasota FL: Multidisciplinary Association for Psychedelic Studies. (Original work published 1980)
- Hagenbach, D., & Werthmüller, L. (2011). Mystic chemist: The life of Albert Hofmann and his discovery of LSD. Santa Fe, NM: Synergetic Press.
- Halpern, J. H., Lerner, A. G., & Passie, T. (2018). A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. Current Topics in Behavioral Neuroscience, 36, 333–360.
- Halpern, J. H., & Pope, H. G., Jr. (2003). Hallucinogen persisting perception disorder: What do we know after 50 years? *Drug and Alcohol Dependence*, 69, 109–119.
- Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., & Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology*, 29, 280–288.
- Hintzen, A., & Passie, T. (2010). The pharmacology of LSD: A critical review. Oxford, UK: Oxford University Press.

- Hofmann, A. (2013). LSD: My problem child (J. Ott, Trans.). Oxford, UK: Oxford University Press. (Original German publication, LSD: Mein Sorgenkind, 1979; original English translation, 1980; new English translation, 2013)
- Hofmann, A., Heim, R., Brack, A., & Kobel, H. (1958). Psilocybin, ein psychotroper Wirkstoff aus dem mexikanischen Rauschpilz *Psilocybe mexicana* Heim. *Experientia*, 14, 107–109.
- Hofmann, A., & Horowitz, M. (1976, July). Interview with Albert Hofmann. *High Times Magazine*, 11.
- Hoffman, A. J., & Nichols, D. E. (1985). Synthesis and LSD-like discriminative stimulus properties in a series of N(6)-alkyl norlysergic acid N,N-diethylamide derivatives. Journal of Medicinal Chemistry, 28, 1252–1255.
- Hofmann, A., & Tscherter, H. (1960). Isolierung von Lysergsäure-Alkaloiden aus der mexikanischen Zauberdroge Ololiuqui (*Rivea corymbosa* (L.) Hall. f.). *Experientia*, 16, 414.
- Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry*, 6(7), 561–562.
- Huxley, A. (1954). *The doors of perception*. New York: Harper & Brothers.
- Huxley, A. (1977). Moksha: Writings on psychedelics and the visionary experience (1931– 1963) (M. Horowitz & C. Palmer, Eds.). New York: Stonehill.
- Isbell, H., Belleville, R. E., Fraser, H. F., Wikler, A., & Logan, C. R. (1956). Studies on lysergic acid diethylamide (LSD-25): I. Effects in former morphine addicts and development of tolerance during chronic intoxication. AMA Archives of Neurology and Psychiatry, 76, 468–478.
- Johansen, P. Ø., & Krebs, T. S. (2015). Psychedelics not linked to mental health problems or suicidal behavior: A population study. *Journal* of Psychopharmacology, 29, 270–279.
- Johnstad, P. G. (2018). Powerful substances in tiny amounts: An interview study of psychedelic microdosing. Nordic Studies on Alcohol and Drugs, 35, 39-51.
- Kaelen, M., Barrett, F. S., Roseman, L., Lorenz, R., Family, N. Bolstridge, M., et al. (2015). LSD enhances the emotional response to music. *Psychopharmacology*, 232, 3607– 3614.
- Karst, M., Halpern, J. H., Bernateck, M., & Passie, T. (2010). The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: An open, non-randomized case series. *Cephalalgia*, 30, 1140–1144.
- Kesey, K. (1962). One flew over the cuckoo's nest. New York: Viking Press.
- Ketchum, J. S. (2006). Chemical warfare: Secrets

almost forgotten. Santa Rosa, CA: Chem-Books.

- Kim, K., Che, T., Panova, O., DiBerto, J. F., Lyu, J., Krumm, B. E., et al. (2020). Structure of a hallucinogen-activated Gq-coupled 5-HT<sub>2A</sub> serotonin receptor. *Cell*, 182, 1574–1588.
- Kinzer, S. (2019). Poisoner in chief: Sidney Gottlieb and the CIA search for mind control. New York: Henry Holt.
- Klock, J. C., Boerner, U., & Becker, C. E. (1974). Coma, hyperthermia, and bleeding associated with massive LSD overdose: A report of 8 cases. *Western Journal of Medicine*, 120, 183–188.
- Kornfeld, E. C., Fornefeld, E. J., Kline, G. B., Mann, M. J., Morrison, D. E., Jones, R. G., et al. (1956). The total synthesis of lysergic acid. *Journal of the American Chemical Society*, 78, 3087–3114.
- Kraehenmann, R., Pokorny, D., Vollenweider, L., Preller, K. H., Pokorny, T., Seifritz, E., et al. (2017). Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. *Psychopharmacology*, 234, 2031–2046.
- Krebs, T. S., & Johansen, P. Ø. (2012). Lysergic acid diethylamide (LSD) for alcoholism: Metaanalysis of randomized controlled trials. *Journal of Psychopharmacology*, 26, 994–1002.
- Krebs, T. S., & Johansen, P. Ø. (2013a). Over 30 million psychedelic users in the United States. F1000 Research, 2, 98.
- Krebs, T. S., & Johansen, P. Ø. (2013b). Psychedelics and mental health: A population study. *PLOS ONE*, 8(8), e63972.
- Latin, D. (2010). The Harvard Psychedelic Club: How Timothy Leary, Ram Dass, Huston Smith, and Andrew Weil killed the fifties and ushered in a new age for America. New York: HarperCollins.
- Leary, T. (1983). *Flashbacks: An autobiography*. Los Angeles: Tarcher.
- Leary, T., Metzner, R., & Alpert, R. (1964). The psychedelic experience: A manual based on the Tibetan Book of the Dead. New Hyde Park, NY: University Books.
- Lee, M. A., & Shlain, B. (1985). *Acid dreams: The CIA, LSD, and the sixties rebellion.* New York: Grove Press.
- Liechti, M. E. (2017). Modern clinical research on LSD. *Neuropsychopharmacology*, 42, 2114–2127.
- Liester, M. B. (2014). A review of lysergic acid diethylamide (LSD) in the treatment of addictions: Historical perspectives and future prospects. *Current Drug Abuse Reviews*, 7, 146–156.
- Linkletter, A., & Bell, J. N. (1970). We must declare war on drugs. *Good Housekeeping*, 170(4), 94–95, 158, 160–162.

LSD: The exploding threat of the mind drug. (1966, March 25). Retrieved from *www.psy-chedelic-library.org/magazines/lifelsd.htm*.

LSD

- Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., et al. (2018). Psychedelics promote structural and functional neural plasticity. *Cell Reports*, 23, 3170–3182.
- Malleson, N. (1971). Acute adverse reactions to LSD in clinical and experimental use in the United Kingdom. *British Journal of Psychiatry*, 118, 229–230.
- Mangini, M. (1998). Treatment of alcoholism using psychedelic drugs: A review of the program of research. *Journal of Psychoactive Drugs*, 30, 381–418.
- Marks, J. (1991). The search for the "Manchurian candidate": The CIA and mind control: The secret history of the behavioral sciences (rev. ed.). New York: Norton. (Original work published 1979)
- Martin, D. A., & Nichols, C. D. (2018). The effects of hallucinogens on gene expression. *Current Topics in Behavioral Neuroscience*, 36, 137–158.
- Metzner, R. (1968). *The ecstatic adventure*. New York: Macmillan.
- Metzner, R. (2017). Ecology of consciousness: The alchemy of personal, collective, and planetary transformation. Oakland, CA: New Harbinger.
- Mueller, F., Lenz, C., Dolder, P. C., Harder, S., Schmid, Y., Lang, U. E., et al. (2017). Acute effects of LSD on amygdala activity during processing of fearful stimuli in healthy subjects. *Translational Psychiatry*, 7(4), e1084.
- Müller, F., Dolder, P. C., Schmidt, A., Liechti, M. E., & Borgwardt, S. (2018). Altered network hub connectivity after acute LSD administration. *NeuroImage: Clinical*, 18, 694–701.
- Müller, F., Lenz, C., Dolder, P., Lang, U., Schmidt, A., Liechti, M., et al. (2017). Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations. *Acta Psychiatrica Scandinavica*, 136, 648– 657.
- Nichols, C. D., & Sanders-Bush, E. (2002). A single dose of lysergic acid diethylamide influences gene expression patterns within the mammalian brain. *Neuropsychopharmacol*ogy, 26, 634–642.
- Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews*, 68, 264–355.
- Nichols, D. E. (2018a). Chemistry and structureactivity relationships of psychedelics. Current Topics in Behavioral Neuroscience, 36, 1–43.
- Nichols, D. E. (2018b). Dark classics in chemical neuroscience: Lysergic acid diethylamide (LSD). ACS Chemical Neuroscience, 9, 2331– 2343.

- Nichols, D. E., Frescas, S., Marona-Lewicka, D., & Kurrasch-Orbaugh, D. M. (2002). Lysergamides of isomeric 2,4-dimethylazetidines map the binding orientation of the diethylamide moiety in the potent hallucinogenic agent N,N-diethyllysergamide (LSD). Journal of Medicinal Chemistry, 45, 4344–4349.
- Nichols, D. E., & Grob, C. S. (2018). Is LSD toxic? Forensic Science International, 284, 141–145.
- Nichols, D. E., & Nichols, C. D. (2008). Serotonin receptors. *Chemical Reviews*, 108, 1614–1641.
- Osmond, H. (1957). A review of the clinical effects of psychotomimetic agents. Annals of the New York Academy of Science, 66, 418–434.
- Osmond, H., & Smythies, J. (1952). Schizophrenia: A new approach. *Journal of Mental Science (British Journal of Psychiatry)*, 98, 309–315.
- Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., & Grof, S. (1970). The experimental use of psychedelic (LSD) psychotherapy. *Journal of the American Medical Association*, 212, 1856–1863.
- Passie, T. (2019). *The science of microdosing psychedelics*. London: Psychedelic Press.
- Passie, T., Halpern, J. H., Stichtenoth, D. O., Emrich, H. M., & Hintzen, A. (2008). The pharmacology of lysergic acid diethylamide: A review. CNS Neuroscience and Therapeutics, 14, 295–314.
- Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Philipp, S., et al. (2017). The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. *Current Biology*, 27, 451–457.
- Presti, D. E., & Beck, J. E. (2001). Strychnine and other enduring myths: Expert and user folklore surrounding LSD. In T. B. Roberts (Ed.), *Psychoactive sacramentals: Essays on entheogens and religion* (pp. 125–137). San Francisco: Council on Spiritual Practices.
- Prochazkova, L., Lippelt, D. P., Colzato, L. S., Kuchar, M., Sjoerd, Z., & Homme, B. (2018). Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting. *Psychopharmacology*, 235, 3401–3413.
- Sand, N. (2001). Moving into the sacred world of DMT (Published under the pseudonym:  $\infty$  Ayes). *Entheogen Review*, 10(1), 32–39.
- Schindler, E. A. D., Gottschalk, C. H., Weil, M. J., Shapiro, R. E., Wright, D. A., & Sewell, R. A. (2015). Indoleamine hallucinogens in cluster headache: Results of the Clusterbusters medication use survey. *Journal of Psychoactive Drugs*, 47, 372–381.
- Schmid, Y., Enzler, F., Gasser, P., Grouzmann, E., Preller, K. H., Vollenweider, F. X., et al.

(2015). Acute effects of lysergic acid diethylamide in healthy subjects. *Biological Psychiatry*, 78, 544–553.

- Schmidt, A., Müller, F., Lenz, C., Dolder, P. C., Schmid, Y., Zanchi, D., et al. (2018). Acute LSD effects on response inhibition neuronal networks. *Psychological Medicine*, 48, 1464– 1473.
- Schultes, R. E., & Hofmann, A. (1979). Plants of the gods: Origins of hallucinogenic use. New York: McGraw-Hill.
- Schultes, R. E., & Hofmann, A. (1980). The botany and chemistry of the hallucinogens (2nd ed.). Springfield IL: Charles C Thomas.
- Schultes, R. E., Hofmann, A., & Rätsch, C. (2001). *Plants of the gods: Their sacred, healing, and hallucinogenic powers* (rev. & expanded ed.). Rochester, VT: Healing Arts Press.
- Sewell, R. A., Halpern, J. H., & Pope, H. G., Jr. (2006). Response of cluster headache to psilocybin and LSD. *Neurology*, 66, 1920–1922.
- Shick, J. F. E., & Smith, D. E. (1970). Analysis of the LSD flashback. *Journal of Psychedelic Drugs*, 3(1), 13–19.
- Shulgin, A., & Shulgin, A. (1997). TiHKAL: The continuation. Berkeley, CA: Transform Press.
- Siff, S. (2015). Acid hype: American news media and the psychedelic experience. Champaign: University of Illinois Press.
- Stevens, J. (1987). Storming heaven: LSD and the American dream. New York: Grove Atlantic.
- Stoll, A., & Hofmann, A. (1943). Partialsynthese von Alkaloiden von Typus des Ergobasins. *Helvetica Chimica Acta*, 26, 944–965.
- Stoll, W. A. (1947). Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe. Schweizer Archiv für Neurologie und Psychiatrie, 60, 279–323.
- Strassman, R. J. (1984). Adverse reactions to psychedelic drugs: A review of the literature. *Journal of Nervous and Mental Disease*, 172, 577–595.
- Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S., Murphy, K., et al. (2016). Increased global functional connectivity correlates with LSD-induced ego dissolution. *Current Biology*, 26, 1043–1050.
- Terhune, D. B., Luke, D. P., Kaelen, M., Bolstridge, M., Feilding, A., Nutt, D., et al. (2016). A placebo-controlled investigation of synaesthesia-like experiences under LSD. *Neuropsychologia*, 88, 28–34.

Troxler, F., & Hofmann, A. (1957). Substitu-

tionen am Ringsystem der Lysergsäure: III. Halogenierung. 45. Mitteilung über Mutterkornalkaloide. *Helvetica Chimica Acta*, 57, 2160–2170.

- Twarog, B. M. (1988). Serotonin: History of a discovery. Comparative Biochemistry and Physiology, 91C, 21–24.
- Wacker, D., Wang, C., Katritch, V., Han, G. W., Huang, X. P., Vardy, E., et al. (2013). Structural features for functional selectivity at serotonin receptors. *Science*, 340, 615–619.
- Wacker, D., Wang, S., McCorvy, J. D., Betz, R. M., Venkatakrishnan, A. J., Levit, A., et al. (2017). Crystal structure of an LSD-bound human serotonin receptor. *Cell*, 168, 377–389.
- Walsh, R., & Grob, C. S. (Eds.). (2005). Higher wisdom: Eminent elders explore the continuing impact of psychedelics. Albany: State University of New York Press.
- Walterscheid, J. P., Phillips, G. T., Lopez, A. E., Gonsoulin, M. L., Chen, H. H., & Sanchez, L. A. (2014). Pathological findings in 2 cases of fatal 25I-NBOMe toxicity. American Journal of Forensic Medicine and Pathology, 35, 20-25.
- Wasson, R. G. (1957). Seeking the magic mushroom. *Life*, 42(19), 100–120.
- Wasson, R. G., Hofmann, A., & Ruck, C. A. P. (1998). The road to Eleusis: Unveiling the secret of the Mysteries. Los Angeles: William Dailey Rare Books. (20th anniversary edition, original work published 1978)
- Watts, A. W. (1960). *This is IT: And other essays* on Zen and spiritual experience. New York: Pantheon/Random House.
- Watts, A. W. (1962). The joyous cosmology: Adventures in the chemistry of consciousness. New York: Pantheon/Random House.
- Whitaker-Azmitia, P. M. (1999). The discovery of serotonin and its role in neuroscience. *Neuropsychopharmacology*, 21(Suppl. 2), 2S–8S.
- Wolfe, T. (1968). *The electric kool-aid acid test*. New York: Farrar, Straus & Giroux.
- Woolley, D. W., & Shaw, E. (1954). A biochemical and pharmacological suggestion about certain mental disorders. *Proceedings of the National Academy of Sciences of the USA*, 40, 228–231.
- Yanakieva, S., Polychroni, N., Family, N., Williams, L. T., Luke, D. P., & Terhune, D. B. (2019). The effects of microdose LSD on time perception: A randomized, double-blind, placebo-controlled trial. *Psychopharmacology*, 236, 1159–1170.

## Handbook of **MEDICAL** HALLUCINOGENS

#### edited by

**Charles S. Grob Jim Grigsby** 

Sp THE GUILFORD PRESS New York London

Contents

#### PART I. Overview of Hallucinogens CHAPTER 1. The Pharmacology of Psychedelics 3 DAVID E. NICHOLS and CHARLES D. NICHOLS CHAPTER 2. Plants for the People: The Future of Psychedelic Therapies 29 in the Age of Biomedicine DENNIS J. McKENNA CHAPTER 3. Anthropology, Shamanism, and Hallucinogens 46 MICHAEL J. WINKELMAN CHAPTER 4. A Short, Strange Trip: LSD Politics, Publicity, and Mythology-68 from Discovery to Criminalization MARIA MANGINI CHAPTER 5. History of the Use of Hallucinogens in Psychiatric Treatment 95 TORSTEN PASSIE PART II. Neuroscience of Hallucinogens CHAPTER 6. Human Neuroimaging Studies of Serotonergic Psychedelics 121

ENZO TAGLIAZUCCHI

# Handbook of **MEDICAL** HALLUCINOGENS

edited by **Charles S. Grob Jim Grigsby** 

Copyright © 2021 The Guilford Press A Division of Guilford Publications, Inc. 370 Seventh Avenue, Suite 1200, New York, NY 10001 www.guilford.com

All rights reserved

No part of this book may be reproduced, translated, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise, without written permis from the publisher. ssior

Printed in the United States of America

This book is printed on acid-free paper.

Last digit is print number: 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data Names Grob, Charles S., 1950 – editor. I Grigoby, Jim, editor. Title: Handbook of medical hallucinogens / edited by Charles S. Grob, Jim Grigsby. Description: New York, NY : The Guilford Press, [2021] | Includes

Description: New York, NY: 1: In Cultitori rress, [2024] rransmass bibliographical references and index. Identifiers: LCCN 2020028890 11589 9781462345445 (cloth; alk. paper) Subjects: LCSH: Hallucinogenic drugs—Therapeutic use. Psychotherapy. Classification: LCC RM324,8 H355 2021 11DDC 615.7/883—dc23 LC record available at https://lccn.loc.gov/2020028890

xvi		Contents
CHAPTER 7.	Memory Reconsolidation in Psycholytic Psychotherapy JIM GRIGSBY	134
PART III.	Individual Hallucinogens	
CHAPTER 8.	LSD KRISTINE PANIK and DAVID E. PRESTI	159
CHAPTER 9.	Psilocybin STEPHEN ROSS, SILVIA FRANCO, COLLIN REIFF, and GABRIELLE AGIN-LIEBES	181
CHAPTER 10	Therapeutic Potential of Fast-Acting Synthetic Tryptamines RAFAEL LANCELOTTA and ALAN K. DAVIS	215
CHAPTER 11.	Mescaline WILL VAN DERVEER	227
CHAPTER 12	MDMA MICHAEL MITHOEFER and ANNIE MITHOEFER	233
CHAPTER 13	Therapeutic and Social Uses of MDMA SCOTT SHANNON, ROB COLBERT, and SHANNON HUGHES	264
CHAPTER 14	Biological and Psychological Mechanisms Underlying the Therapeutic Use of Ayahuasca DRÁULIO BARROS DE ARAÚJO, LUÍS FERNANDO TÓFOLI, STEVENS REHEN, and SIDARTA RIBEIRO	277
CHAPTER 15.	The Ibogaine Project: Urban Ethnomedicine for Opioid Use Disorder KENNETH ALPER	294
CHAPTER 16	Salvia divinorum ANA ELDA MAQUEDA	313
CHAPTER 17.	Ketamine GARY BRAVO, ROBERT GRANT, and RAQUEL BENNETT	327

Contents		xvii
PART IV.	Therapeutic Considerations	
CHAPTER 18	. Set, Setting, and Dose J. C. CALLAWAY	347
CHAPTER 19	The Use of Music in Psychedelic Therapy MENDEL KAELEN	363
CHAPTER 20	The Role of the Guide in Psychedelic-Assisted Treatment MARY COSIMANO	377
CHAPTER 21	Comparative Phenomenology and Neurobiology of Meditative and Psychedelic States of Consciousness: Implications for Psychedelic-Assisted Therapy MILAN SCHEIDEGGER	395
CHAPTER 22	Adverse Effects KELAN THOMAS and BENJAMIN MALCOLM	414
PART V.	Indications and Purpose	
CHAPTER 23	Utility of Psychedelics in the Treatment of Psychospiritual and Existential Distress in Palliative Care: A Promising Therapeutic Paradigm ANTHONY P. BOSSIS	441
CHAPTER 24	Classic Psychedelics for Treatment of Alcohol Use Disorder MICHAEL P. BOGENSCHUTZ and SARAH E. MENNENGA	474
CHAPTER 25	Psychedelics in the Treatment of Addiction MATTHEW W. JOHNSON	493
CHAPTER 26	The Treatment of Depressive Disorders with Psychedelics DAVE KING and JONNY MARTELL	501
CHAPTER 27	Hallucinogens in Headache EMMANUELLE A. D. SCHINDLER	515

xviii		Contents
PART VI.	Mystical/Religious Experiences and Philosophical Considerations	
CHAPTER 28.	Mystical/Religious Experiences with Psychedelics WILLIAM A. RICHARDS	529
CHAPTER 29.	Philosophical Considerations Concerning the Use of Hallucinogens in Psychiatric Treatment CANDICE L. SHELBY	536
	Author Index	547
	Subject Index	565



#### LSD: Lysergic Acid Diethylamide

Kristine Panik<sup>1</sup> and David E.  $\mathrm{Presti}^2$ 

<sup>1</sup> Counseling and Psychological Services, University Health Services, University of California, Berkeley <kpanik@berkeley.edu>

<sup>2</sup> Division of Neurobiology, Department of Molecular and Cell Biology, University of California, Berkeley cpresti@berkeley.edu>

Chapter 8 (pp. 159-180) in Handbook of Medical Hallucinogens.

Edited by Charles Grob (UCLA Medical School) and Jim Grigsby (University of Colorado Medical School, Health Psychology). New York, NY: Guilford Publications (2021).