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The Trials of Psychedelic Medicine
LSD Psychotherapy, Clinical Science, and Pharmaceutical Regulation in the United States, 1949-1976

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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2014
Declaration of Originality

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or institute of higher learning.

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Matthew Oram

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Abstract

Over the 1950s lysergic acid diethylamide (LSD) became the subject of widespread psychiatric research in the United States. Early research reported impressive results using the drug as a tool in psychotherapy, in a variety of ways and in a number of conditions. However, over the 1960s LSD psychotherapy research declined, before coming to a complete halt in the 1970s. The demise of LSD psychotherapy has commonly been linked to the growing controversy over the drug’s recreational use in the 1960s. With the drug’s image shifting from medical tool to dangerous public menace, medical opinion turned against it and the US federal government hampered research through strict regulation. This argument, however, often overlooks the broad changes in the regulation of pharmaceutical research and development that occurred during the period, as a result of the Drug Amendments of 1962. This thesis contextualises LSD psychotherapy research within these changes, providing an alternative analysis of its demise. Closely examining the regulation of LSD research through Food and Drug Administration files reveals that, in fact, the government not only did not deliberately hamper research, but also worked to ensure its survival in the mid-1960s. However, the amendments formalized pharmaceutical research and development in a way that frustrated the progress of LSD research. Most significantly, the amendments’ requirement for proof of drug efficacy through controlled clinical trials made mandatory a method of drug evaluation that struggled to accommodate LSD psychotherapy’s complex method of using drug
effects to catalyse a psychological treatment. As explored through researchers’ publications and personal papers, the difficulties in balancing scientific standards in evaluation with the clinical requirements of treatment left them unable to establish a consensus on treatment efficacy. Research subsequently dwindled. In making this argument, this thesis explores how the Drug Amendments of 1962 widened the division between psychiatry’s biological and psychological treatments, and explores the complex interplay between clinical science, regulation, and therapeutics in twentieth century American medicine.
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After relocating from Sydney to Christchurch, in February 2011 a significant earthquake destroyed my office, along with much of my research material. My recovery from this event was significantly helped by the generous provision of a new laptop by the School of Philosophical and Historical Inquiry. For the last two years I have worked from the postgraduate study rooms of the Department of History of the University of Canterbury. Special thanks go to Jane Buckingham for inviting me to engage with the department and offering me access to the workspace. Thanks also to Judy Robertson for facilitating my continued access to a desk, and Peter Field for making me feel welcome. The department was in no way obliged to offer me a place to work. I am enormously grateful for their generous hospitality, and cannot overemphasize the impact it has had on the progress of my work.
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AA</td>
<td>Alcoholics Anonymous</td>
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<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
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<tr>
<td>CIA</td>
<td>Central Intelligence Agency</td>
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<tr>
<td>DPT</td>
<td>Dipropyltryptamine</td>
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<tr>
<td>ECT</td>
<td>Electro-Convulsive Therapy</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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| IND          | Notice of Claimed Investigational Exemption for a New Drug  
(Form FD 1571) |
| LSD          | Lysergic Acid Diethylamide |
| Mcg          | Micrograms |
| Mcg/kg       | Micrograms per kilogram of body weight |
| MDA          | Methyleneoxyamphetamine |
| MMPI         | Minnesota Multiphasic Personality Inventory |
| MPRC         | Maryland Psychiatric Research Center |
| NIMH         | National Institute of Mental Health |
| NDA          | New Drug Application |
| PHS          | Public Health Service |
Introduction

In May 1965, a three-day international conference was held at South Oaks Hospital in Amityville, New York, to discuss clinical research using the hallucinogenic drug Lysergic Acid Diethylamide (LSD) in psychiatric treatment. Entitled “The Use of LSD in Psychotherapy and Alcoholism,” the conference featured thirty-six papers, over half of which were by United States researchers. The presenters almost unanimously reported positively on the safety and effectiveness of the various forms of LSD psychotherapy they employed. Results for “psychedelic” therapy for the treatment of alcoholism were particularly dramatic: Canadian pioneer of the treatment Abram Hoffer pooled the data from eleven North American studies, and found that out of a total of 269 patients, just over 50 percent were “much improved.” Only 30 percent of the patients had not improved to some degree.¹

This conference represented a high point for LSD psychotherapy. LSD had been used in widespread psychiatric research in the US since 1949. Yet despite many positive reports on the drug’s therapeutic usefulness, LSD remained officially an investigational new drug, not approved for sale, or use beyond clinical research. Nevertheless, the conference proceedings demonstrate the sustained enthusiasm for LSD amongst a significant niche group of psychiatric researchers, and the

continual development and refinement of treatment methods over that period. Stretching over seven hundred pages, the volume outlines treatment methods, theoretical rationales, and outcome results for the various forms of LSD psychotherapy, based on the treatment of well over two thousand patients with many thousands of LSD sessions. US LSD researcher and conference participant Betty Eisner has described the proceedings as a “virtual text-book on the use of LSD in psychotherapy.” As the culmination of over fifteen years of research, the apparent consensus over LSD’s safety and usefulness in psychiatry displayed at the conference could have been expected to cement LSD’s place in psychiatry. Instead, LSD psychotherapy research declined over the 1960s, before coming to a complete halt in 1976.

This thesis investigates why more than twenty-five years of LSD psychotherapy research failed to establish LSD as an accepted tool of psychiatry, and why research finally came to a close. I argue that the factors that frustrated research were primarily scientific, resulting from changes in the regulation of pharmaceutical research and development. The initial successes of LSD psychotherapy in the 1950s reflected the loose regulation of pharmaceutical research and development in that decade, which allowed psychiatrists to freely explore methods of treatment that blended biological and psychological techniques. However, the Drug Amendments of 1962 formalized pharmaceutical research and development, and introduced the requirement for proof of drug effectiveness, demonstrated through controlled clinical trials, for a drug to be

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approved for sale by the Food and Drug Administration (FDA). This thesis investigates how this seemingly simple and desirable requirement in practice made mandatory a method of drug research that was poorly suited for evaluating psychological treatments. LSD psychotherapy research dwindled after researchers struggled to demonstrate the efficacy of their treatments through the research methodology. This thesis therefore explores the complex interplay between clinical science, regulation, and therapeutics in mid-twentieth century American medicine, specifically how the 1962 amendments widened the division between psychiatry’s biological and psychological treatment forms.

This analysis challenges the standard narrative of LSD psychotherapy’s demise. Historians and other observers have typically linked the demise of research in the United States to the controversy over the drug’s non-medical use, which increased over the 1960s. The drug first became the topic of a major nationally reported scandal in 1963, as Harvard psychologists Timothy Leary and Richard Alpert were dismissed from their posts at the university following criticism over the conduct of their psychedelic research. The two subsequently became public evangelists for the drug, encouraging young people to use the drug for

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consciousness expansion and to “drop out” of mainstream society. Such non-medical use of LSD increased hand-in-hand with the rise of a youth counterculture movement over the 1960s. For members of that movement LSD had the potential to liberate American society, while mainstream Americans feared the drug could corrupt it. Inflamed by sensationalist media reports, LSD use became a major public and political controversy, and the dominant perception of the drug shifted from an unconventional but promising tool of medicine, to a dangerous drug of abuse. As part of the 1962 amendments, the FDA gained oversight of pre-market clinical drug testing. LSD research almost immediately began to decline. Beginning in 1965, the federal government attempted to curb non-medical use of LSD through increasingly prohibitive legislative measures. By 1970, the drug was prohibited in the same manner as heroin and marijuana. The medical and non-medical histories of the drug have therefore appeared inextricably entwined. In the common analysis, the LSD abuse controversy tarnished the reputation of the drug, discouraging researchers from using it. At the same time, the increasingly tight regulation of LSD inhibited those researchers who did wish to investigate its use, by restricting their access to the drug.

Given that the scale of LSD psychotherapy research began to decline in 1963, at the same time as the drug became the subject of controversy and came under government control, the argument that controversy and legal restrictions caused the demise of LSD psychotherapy appears both obvious and convincing.

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However, this argument struggles to account for several important factors in the history of LSD psychotherapy, as well as the history of drug regulation. Firstly, LSD is far from alone in being a drug with both significant medical and abuse potentials. Many other drugs, such as opiates, amphetamines, and barbiturates, have maintained dual lives as illegal street drugs, and valuable and legitimate tools of medicine. Indeed, running parallel to the LSD controversy was a similar public, medical, and political controversy over the abuse of amphetamines. The first piece of legislation to specifically control LSD—the Drug Abuse Control Amendments of 1965—was in fact primarily aimed at curbing the non-medical use of amphetamines and barbiturates. This and later legislation attempted to limit non-medical drug use through strictly prohibiting activities related to such use, and by closely regulating the legitimate market to prevent both diversion of drugs to the black market, and abuse of the prescription system for the purpose of non-medical drug use. With controversial drugs, increased regulation may have resulted in more limited and cautious medical use, yet the drugs remained available. Drugs such as amphetamine, therefore, were not classified as simply legal or illegal, as either medicines or narcotics. Instead, they were regulated in different ways depending on the context of their use. That non-medical LSD use was the subject of controversy and federal prohibition therefore does not automatically explain why medical use of the drug ended.

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Secondly, although the number of medical researchers using LSD decreased over the 1960s, clinical research did not come to a complete halt until 1976. This was long after both the apex of the controversy over LSD’s non-medical use in the late 1960s, and the passage of laws that put the drug under strict government control. Although 1963 can appear to be the beginning of the end for LSD psychotherapy, that year also saw the commencement of what would become the most extensive and significant clinical LSD research program ever to be conducted in the United States, led by Albert Kurland at Spring Grove State Hospital, Maryland (later moved to the Maryland Psychiatric Research Center).

None of the laws attempting to curb non-medical use of LSD prohibited legitimate research with the drug. Although the laws, and the controversy surrounding LSD, may have tarnished the drug’s reputation in the eyes of many, they did not appear to impede research at Spring Grove. Indeed the psychedelic research program there continuously expanded over the 1960s and early 1970s, growing from a study of the efficacy of psychedelic therapy in the treatment of alcoholism, to encompass numerous clinical trials that explored using LSD and other psychedelic drugs in the treatment of several conditions, with over 750 patients. Kurland was also not alone in continuing research amidst the controversy: between 1967 and 1971 six other research groups published reports on their recent research into the efficacy of LSD therapy for alcoholism. As well as being approved by the FDA, this research was all funded by federal and state government agencies.

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In my analysis, the controversy over non-medical LSD use will play only a very minor role. Closely investigating the regulation of LSD psychotherapy research will reveal that the reduction in LSD research over the 1960s was not a result of deliberate restriction. In fact, the FDA and the National Institute of Mental Health (NIMH) actively supported research over the 1960s, despite displaying some scepticism over its efficacy. This thesis does not deny that controversy tarnished the reputation of LSD, and that some researchers were unable to continue or initiate LSD research under the new regulations of the 1960s. Instead, it will be argued that these developments did not completely kill research, and that the research that remained was the most significant ever conducted. Analysing these later clinical trials will reveal, however, that despite the apparent consensus on the effectiveness of LSD psychotherapy that can be garnered from the proceedings of the 1965 conference, at the time of LSD psychotherapy's demise, efficacy was still the major point of contention between researchers. The central question in the history of LSD psychotherapy research therefore becomes, why, despite more than twenty-five years of research, had a consensus on the efficacy of any form of LSD psychotherapy not been reached?

This question will be addressed by closely analysing the LSD psychotherapy research conducted in the United States between 1949 and 1976, in the context of the changing scientific standards for pharmaceutical research and development. LSD arrived in the United States at a time when drug research was largely unregulated, when safety was the FDA's primary concern when approving drugs for sale, and when the reliability of claims of effectiveness
rested primarily on the experience and integrity of the researchers. LSD research thrived in this context, and the early claims of effectiveness were primarily based on uncontrolled research. Over the 1950s widespread US and international LSD research resulted in the development of two broad forms of LSD psychotherapy. In “psycholytic” therapy, multiple low to medium dose LSD sessions were used to facilitate psychoanalytically orientated psychotherapy. This was the first form of LSD psychotherapy explored in the US. It reflected the prominence of psychoanalysis in post-war American psychiatry, and developed from other forms of drug-assisted psychotherapy. “Psychedelic” therapy, by contrast, typically involved only a single high-dose LSD session, within a framework of brief intensive psychotherapy. The aim was to produce a transcendental or mystical experience that could transform aspects of personality and behaviour in alcoholic patients, leading to sobriety. This treatment method was developed in Canada, however it was well established in the United States by early 1960s. Both treatments reflected the eclectic mix of biological and psychological treatments in post-war American psychiatry.

As a result of the Drug Amendments of 1962 pharmaceutical research and development became a much more formalized and highly regulated process.

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With the new requirement for proof of drug efficacy came an increased focus on the need for rigorous research methods to ensure the accuracy and objectivity of such proof. In practice, the randomized double-blind placebo controlled trial (usually referred to as simply the randomized controlled trial) became the model against which the FDA judged the adequacy of a clinical trial’s design. The methodology had gained favour amongst medical elites over the 1950s as a way of minimizing bias in research. In its purest form, the method involved randomly assigning patients to receive either the experimental treatment or a placebo, with both researchers and patients “blind” to the assignment until after the conclusion of the trial. Researchers placed emphasis on the need for large patient populations and sophisticated statistical analysis to determine the significance of results. This technique theoretically allowed the objective assessment of drugs, as all extrapharmacological factors that could influence the outcome of a treatment—by producing a placebo effect—were equally present in the experimental and control groups. This ensured that any statistically significant difference in the results between the groups could only be due to the drug.

While ideal for evaluating many kinds of drugs, the randomized controlled trial was poorly suited for testing LSD psychotherapies, in both theoretical and practical ways. Analysing this complex incompatibility, and how it impacted

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research and its results, will be a major focus of this thesis. The randomized controlled trial was best suited to evaluate drugs such as antibiotics, which worked through an objective biological process. However, LSD psychotherapists considered LSD to have no inherent beneficial effects. Instead, with the active cooperation of the patient, they used the drug to craft a subjective state of consciousness that could be beneficial as part of a psychotherapeutic process. This made establishing a double-blind with an inert placebo impossible, and complicated the notion of distinguishing between “specific” pharmacological treatment effects, and “nonspecific” extrapharmacological placebo effects.

As researchers attempted to definitively establish the efficacy of LSD therapy in the mid to late 1960s—primarily psychedelic therapy for alcoholism—they faced the difficulties of evaluating LSD psychotherapy through randomized controlled trials. Most of the researchers responded by focusing so heavily on their control designs and statistical evaluations that they ignored the role of treatment technique in influencing outcome. They consequently tested the efficacy of treatment methods that no one had ever claimed were effective. The negative results they found were, however, not challenged by a medical community that also focused on research methodology. Kurland and his colleagues at Spring Grove State Hospital did attempt to balance scientific rigour with the clinical requirements of treatment in several clinical trials. The difficulties involved, however, proved insurmountable: problems emerged in their trial designs that influenced underwhelming or inconclusive results. As these trials all came to an end in the early 1970s, results appeared on the surface to be discouraging at best. Research subsequently dwindled before dying out entirely.
In exploring this narrative and analysis, this thesis will closely follow the career of psychiatrist Charles Savage. While Savage is almost entirely absent from other accounts of the history of LSD, he had the longest and most successful research career with the drug of anyone in the United States. Savage was among the first in the United States to explore the therapeutic potential of LSD, publishing his initial report in 1952, and his use of the drug continued with little interruption until 1973. As a psychoanalyst, he started out using the drug to facilitate conventional therapy. However, from the late 1950s he began exploring psychedelic therapy and was a central figure in the establishment and refinement of that method in the US. In 1965 he joined the then small team at Spring Grove, and helped to expand their studies into the country’s most significant LSD program. Research methodology was a particular focus of Savage’s, and he was the primary designer of the control methods used in the Spring Grove studies, that attempted to balance clinical needs with scientific rigour. Savage was a prominent figure in the research community, well respected by members of the FDA and NIMH, as well as other scientists. He was not, however, a public figure, and his publications and presentations appear to have been solely within the scientific community. This likely explains why his career has not been recognized in previous histories. His career trajectory therefore mirrors the focus of this thesis, as it charts the development of the various forms of LSD psychotherapy, the evolving standards of research, and the frustrations they led to, while engaging little with the public controversy that raged over its non-medical use.
Historiography

LSD research in the United States has been a topic of historical interest for a number of authors since the late 1970s. These authors have included mental health professionals and journalists, as well as historians, and their works have focused on different aspects of LSD’s complex past. Nevertheless, they have all followed essentially the same analytical framework: that the medical and non-medical histories of LSD are inseparable, as non-medical use grew from medical research, and the backlash against non-medical use brought medical research to an end. At least the last part of this argument originates from psychiatrists and psychologists who complained of difficulties in initiating and continuing LSD research in the 1960s. Scientists writing after the close of research then furthered the argument. In their 1979 work *Psychedelic Drugs Reconsidered*, psychiatrists Lester Grinspoon and James B. Bakalar confidently declared that “psychedelic drug therapy did not die a natural death from loss of interest; it was killed by the law.” Consequently, although their work was primarily a review of scientific knowledge and clinical research with psychedelics, written to renew scientific interest in them, the authors dedicated significant attention to the cultural history of the drugs to explain their troubled relationship with western science and the law.

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11 Example of such complaints can be found in, Abramson (ed.), *LSD in Psychotherapy and Alcoholism*, pp. xv-xvi, 3, 253, 328-331, 542.
12 Grinspoon and Bakalar, *Psychedelic Drugs Reconsidered*, p. 233.
Two works written by journalists in the 1980s then expanded on this discussion to present general histories of LSD’s usage in the 1950s and 1960s. Martin A. Lee and Bruce Shlain’s inquiry was sparked by a controversy in the mid-1970s over LSD research conducted by the US Central Intelligence Agency (CIA) and military in the 1950s and 1960s. First exposed by journalist John Marks in 1977, and discussed in his 1979 book *The Search for the Manchurian Candidate: The CIA and Mind Control*, this research explored LSD’s potential as a mind control device, truth serum, and chemical weapon. As well as conducting their own research, the CIA provided funding for outside researchers, both with and without their knowledge. In *Acid Dreams*, Lee and Shlain extended this work by exploring in more depth the connections between the use of LSD by the CIA and military, psychiatrists, intellectuals, and the counterculture. In their argument, CIA funding propelled the psychiatric LSD research of the 1950s, and individuals who took part in such research intentionally or unintentionally sparked the LSD counterculture of the 1960s. In *Storming Heaven*, Jay Stevens traces a similar story, but with less emphasis on the CIA, and a greater focus on the figures at the centre of LSD’s transformation from research drug to cultural phenomenon.

Recent scholarly works have more closely examined psychiatric research with LSD, rather than the drug’s general history, however their overall analyses have not strayed far from the standard narrative framework. Historian Erika Dyck’s significant work *Psychedelic Psychiatry: LSD from Clinic to Campus* has richly fleshed out the story of LSD psychotherapy research in Canada, by closely

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14 Lee and Shlain, *Acid Dreams*.
15 Stevens, *Storming Heaven*. 
following the work of psychedelic therapy pioneers Humphry Osmond and Abram Hoffer. After successes in the 1950s, in the 1960s these researchers and their colleagues struggled to continue their work. As the title of her book suggests, in exploring the demise of LSD psychotherapy Dyck turns to the rise of the counterculture throughout North America, through Timothy Leary and his associates, and the legal backlash to it. The different legal framework in Canada may have more specifically restricted research than in the US, and indeed fewer researchers were active there in the later 1960s. Nevertheless, the mechanisms of this are not clearly outlined, and Dyck’s analysis primarily rests on the transformation of LSD’s image, in the eyes of the public and many medical figures, and the correlation between the end of research in Canada and the passage of punitive laws to curb public use of the drug.16

Other authors that have explored the history of LSD research within the standard narrative include historian Kimberly Hewitt and public policy researcher Rick Doblin. In her PhD thesis “Psychedelics and Psychosis,” Hewitt forcefully claims that the backlash against public LSD use ended US research: she states that “when possession of LSD was criminalized in 1966, all research stopped.”17 Doblin’s PhD thesis, “Regulation of the Medical Use of Psychedelics and Marijuana,” has most thoroughly charted the changing regulation of psychedelic


research in the US in the 1960s. He acknowledges that research continued into the mid-1970s, however he still portrays regulation as the driving force in curtailing research, and government agencies such as the FDA as taking a deliberate part in this.\textsuperscript{18}

Historian Stephen Snelders and psychiatrist Charles Kaplan have investigated the history of LSD psychotherapy in the Netherlands. As in the US, LSD psychotherapy was widely explored there from the 1950s, but suffered a decline from the mid-1960s, at a time when use of the drug by a youth counterculture made LSD a topic of great controversy. Snelders and Kaplan therefore argue that moral panic over LSD’s connection to social upheaval is a more convincing explanation for LSD therapy’s global downfall than any specific local political or legislative factors, as the two phenomena closely coincided in several countries. However, the move towards randomized controlled trials, as the basis of integrity in drug research, was also an international phenomenon. While I will argue that the Drug Amendments of 1962 were crucial in the eventual demise of LSD psychotherapy in the United States, this role was partly symbolic—codifying developing scientific standards rather than outright introducing them. Fierce debates over LSD therapy’s efficacy occurred in Canada, despite the different regulatory system. Snelders and Kaplan dismiss the possibility that the disappearance of LSD psychotherapy was due to a lack of evidence of efficacy, stating that “the lack of results of medical practices has not always led to their abandonment, and we would expect this to continue in the future despite all the current fashionable talk of evidence-based medicine,” and pointing to a lack of

\textsuperscript{18} Doblin, “Regulation of the Medical Use of Psychedelics and Marijuana,” pp. 40-56
clear evidence that efficacy was an issue in the treatment’s demise. This thesis aims to address this lack of evidence.

Historian Steven Novak is the only author to have significantly challenged the standard narrative of LSD psychotherapy’s demise. His challenge, however, has been primarily in regards to timing rather than more fundamentally the role of controversy and prohibitive regulation. In his article “LSD Before Leary,” Novak argues that at the turn of the 1960s, prior to the Harvard scandal and the rise of widespread public LSD use, liberal use of the drug by certain researchers and intellectuals in Southern California had already led to concerns over its safety. This in turn led Sandoz Pharmaceuticals (the manufacturer of LSD) to limit the drug’s availability, and the FDA to “crackdown” on its use once they gained powers to do so under the Drug Amendments of 1962. After the Drug Abuse Control Amendments of 1965 “Congress cut off nearly all LSD research.” This thesis, however, by investigating the implementation of these laws more closely, will show that the reduction in research was not due to any deliberate government effort, and that a significant research continued beyond the mid-1960s.

Why the later history of LSD psychotherapy has been consistently overshadowed by the drug's non-medical history can be partly explained through the actors who have had central roles in most accounts of LSD’s history. These figures

19 Stephen Snelders and Charles Kaplan, "LSD Therapy in Dutch Psychiatry: Changing Socio-Political Settings and Medical Sets," Medical History 46, no. 2 (2002), p. 239.
include psychiatrist Humphry Osmond, author and intellectual Aldous Huxley, psychologist Timothy Leary, and author Ken Kesey. These individuals were indeed the most influential figures in shaping public perceptions of LSD. Through them the narrative of LSD’s history moves through clear links from psychiatric research and experimentation by distinguished intellectuals in the 1950s, to the development of the LSD counterculture from the early 1960s—medical use transforms into non-medical use, leaving medical use behind.21 This narrative accurately portrays the evolving role that LSD played in American society, however it does not tell the full story of its medical use.

Osmond was a pioneer of LSD research in Canada in the 1950s. With his colleagues—particularly Abram Hoffer—he developed both a biochemical theory of the origins of psychosis influenced by his study of mescaline (a hallucinogen produced by certain cacti, most notably the peyote cactus), and psychedelic therapy for the treatment of alcoholism. He also famously coined the word “psychedelic”—meaning “mind-manifesting”—as a term to describe LSD and similar drugs in 1956, in a rhyming couplet sent to Huxley: “To fall in Hell or soar Angelic / You’ll need a pinch of psychedelic.”22 As well as being one of the most significant early LSD researchers, Osmond influenced non-medical interest in psychedelics by administering Huxley his first dose of mescaline in 1953. On the basis of this Huxley wrote The Doors of Perception (1954), and after subsequent experiences with LSD, Heaven and Hell (1956).23 These essays recounted his

21 This narrative, through these four actors, is most clearly and completely laid out in Stevens, Storming Heaven; and Lee and Shlain, Acid Dreams. The following summary of the narrative is based on these works.
22 Dyck, Psychedelic Psychiatry, p. 2.
23 Aldous Huxley, The Doors of Perception and Heaven and Hell (New York: Harper Perennial
experiences and discussed their implications for our understandings of consciousness, visionary experience, and religion. Huxley’s last novel, Island (1962), offered a vision of a utopian society where psychedelics were used for spiritual purposes in rite of passage rituals. Although he did not encourage widespread casual non-medical use of LSD, and this did not occur until over a decade after his first psychedelic writings, Huxley’s works heavily influenced the intellectual direction and cultural vision of the 1960s counterculture movement.

In histories of LSD, Leary, together with his colleague Richard Alpert, have more than any other figures represented the pivotal role in the transformation of the drug’s image in the 1960s. Leary began research with psilocybin (a psychedelic produced by several species of mushroom) at Harvard in 1960. However what started out as sanctioned research into the potential uses and implications of the drug’s effects, quickly devolved into heavy informal use of psilocybin and LSD—under the loosest guise of research—by Leary, his colleagues, students, and associates. This use sparked a scandal at the University, and in 1963 Alpert was fired for supplying psilocybin to an undergraduate student, while Leary was officially dismissed for failing to fulfil his teaching obligations. This was no setback for the pair, who saw the potential of the drugs as much more significant than simply aiding psychological research and therapy. They, particularly Leary, subsequently began to publicly endorse widespread use of psychedelics, and became figureheads for an emerging counterculture. They preached a

Modern Classics, 2009).

25 For more on Huxley’s association with Osmond, and his role in influencing interest in psychedelics outside of strictly clinical applications, see Novak, “LSD Before Leary,” pp. 87-110.
psychedelic philosophy that borrowed heavily from Eastern religions, and in turn religious movements developed that promoted psychedelics as sacraments. Over the decade, Leary’s attempts to lead the youth away from traditional American values and lifestyles—to “tune in, turn on, and drop out”—led to increasing notoriety.26 At one point, President Richard Nixon apparently declared him “the most dangerous man in America.”27

In the case of Kesey it was the research subject, rather than the researcher, who broke LSD out of the confines of the scientific world. Kesey first tried LSD as a volunteer for a study of the effects of various hallucinogenic drugs at the Veterans Administration Hospital in Menlo Park, California, while he was a graduate student in creative writing at Stanford University. He took a strong liking to the drugs, and self-experimented with them while working as an orderly at the hospital. These experiences influenced his writing of the critically acclaimed and highly successful novel One Flew Over the Cuckoo’s Nest (1962).28 As famously recounted in Tom Wolfe’s The Electric Kool-Aid Acid Test (1968), Kesey used his royalties to fund a commune from which a distinct West Coast form of psychedelic culture emerged.29 Compared to the psychological, philosophical, and spiritual focus of Leary’s East Coast movement, Kesey’s group—the Merry Pranksters—adopted a brash chaotic style, characterized by

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26 For more on Leary and Alpert see, Lattin, Harvard Psychedelic Club.
27 This quote is widely reproduced in discussions of Leary, however this author was unable to find its original source or date. See Lattin, Harvard Psychedelic Club, p. 61, 133; Laura Mansnerus, “Timothy Leary, Pied Piper Of Psychedelic 60’s, Dies at 75” New York Times, 1 June 1996 <http://www.nytimes.com/1996/06/01/us/timothy-leary-pied-piper-of-psychedelic-60-s-dies-at-75.html?pagewanted=all&rc=pm> accessed 14 October 2013. Jay Stephens attributes the quote to a federal judge, however again it is unreferenced, see Stephens, Storming Heaven, p. 121. Whether or not the quote is genuine and accurate, it does accurately convey the hysteria surrounding Leary in the late 1960s.
28 Ken Kesey, One Flew over the Cuckoo’s Nest (Camberwell: Penguin Group [Australia], 2008).
bizarre costumes, swirling fluorescent colours, and experimental rock music. The Pranksters confronted mainstream America while travelling the country in an elaborately decorated bus, and hosted large public parties (“Acid tests”) in California, replete with free LSD, experimental light shows, and, often, house band The Grateful Dead.

While previous accounts of LSD’s history all point to controversy and regulation as the ultimate reason that LSD psychotherapy research came to an end, several do also recognize scientific factors that frustrated research. Lee and Shlain comment that the medical establishment’s resistance to LSD therapy was partly because it “could not be evaluated like most other drugs.” They explained that “psychedelics were out of kilter with the basic assumptions of Western medicine,” as they were not specific remedies for specific symptoms. Hewitt more specifically draws attention to the role of the Drug Amendments of 1962, which required “required strict empirical testing for FDA approval [that] LSD could not be acclimated to.” However, as in Lee and Shlain’s work, this discussion remains at the broad theoretical level, concerned with the medical establishment’s inability to comprehend the “psychedelic sensorium,” and how it could benefit patients.

Dyck has more concretely explored the problems researchers faced proving the effectiveness of their treatments. From the early 1960s, researchers who were sceptical of the results of Osmond, Hoffer, and their colleagues, began to criticise

30 Lee and Shlain, Acid Dreams, p. 90.
their work for being poorly controlled. Hoffer and Osmond responded by arguing that the randomized double-blind controlled trial methodology was not suitable for testing LSD therapies, and that traditional research methods based on close observation could be equally reliable. Their refusal to adopt the research methodologies discredited their work in the eyes of many in the research community. Added to this, a separate Canadian group of researchers who conducted a controlled trial of psychedelic therapy found negative results. Hoffer and Osmond argued that this was due to the overly clinical manner in which they administered LSD. In Dyck’s analysis, these methodological conflicts weakened the prospects of LSD psychotherapy finding its place in medicine, however the uproar over non-medical use delivered the “decisive blow.”

By closely exploring the work of US LSD researchers over the 1960s and 1970s, I will argue that, with research continuing despite the controversy and prohibitive legislation, debates over efficacy and research methodology were not just contributing factors in LSD psychotherapy’s demise, but the terminal factors. Exploring this argument not only gives a new perspective on the demise of LSD psychotherapy research, but also has significant implications for the history of psychiatry, as well as pharmaceutical research and regulation.

The decades after the close of the Second World War have been a period of focus for many historians of psychiatry, as it was a time of great transformation for the discipline. At the beginning of this period, hospital psychiatry was

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32 Dyck, *Psychedelic Psychiatry*, pp. 47-51, 73-78, 120.
33 For overviews of the history of psychiatry that dedicate significant attention to this period see Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (New
characterized by overcrowded and poorly resourced asylums, where dramatic and later maligned physical treatments—particularly insulin coma therapy, electro-convulsive therapy, and lobotomy—gave chronic, severely ill patients their only hope of recovery, other than spontaneous remission.\(^{34}\) At the same time, however, psychoanalysis was in its heyday, particularly amongst more elite private practice and academic psychiatrists.\(^{35}\) From the mid-1950s, psychiatry’s treatment landscape was revolutionised, with the development of effective drug treatments for psychosis, depression, anxiety, and mania. These drugs not only gave birth to modern psychopharmacology, but also made the more dangerous physical treatments largely obsolete.\(^{36}\) Hospital populations began to decline, slowly from the mid-1950s, and rapidly after the mid-1960s, due to a variety of complex factors, including an increasing focus on community care, as well as the availability of effective treatments.\(^{37}\) A strong antipsychiatry movement also

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\(^{34}\) For works that focus on hospital psychiatry and somatic treatments prior to the rise of psychopharmacology see Jack D. Pressman, Last Resort: Psychosurgery and the Limits of Medicine (Cambridge: Cambridge University Press, 1998); Edward Shorter and David Healy, Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness (Toronto: University of Toronto Press, 2007); Joel Braslow, Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century (Berkeley and Los Angeles: University of California Press, 1997).


\(^{37}\) See Gerald N. Grob, From Asylum to Community: Mental Health Policy in Modern America.
developed in the 1960s, influenced by intellectuals Michel Foucault, Thomas Szasz, and Ronald Laing, as well as popular authors such as Ken Kesey. The movement featured ex-patients as well as intellectuals and political activists, who challenged the very existence of mental illness, and characterized psychiatry's treatments and institutions as unscientific, and at times barbaric, tools of social control.38

One of the major historiographical discussions running thorough many works covering the history of post-war American psychiatry is the relationship between psychodynamic and biological forms of the discipline. These have often been represented as distinct and competing paradigms: psychodynamic psychiatrists saw mental illness as a product of psychological stresses, often originating from childhood, which could only be resolved through psychotherapy, most notably psychoanalysis. Biological psychiatrists treated mental illness with drugs and somatic therapies, as they believed it to have origins in the brain, as opposed to the mind. Psychodynamic psychiatry was in ascendancy in the years following the war, however biological psychiatry grew to dominate after the breakthroughs in psychopharmacology of the mid-1950s.39 While dogmatic

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adherents of these paradigms certainly existed, and psychiatry’s general focus indeed shifted between these two broad frameworks during the period, recent scholarship has drawn attention to how the practice of psychiatry could be highly eclectic, with psychiatrists often embracing treatments that were seemingly incompatible with their theoretical orientations. Nicolas Rasmussen and Nathan Moon have explored how amphetamines were often used, and marketed as, tools for opening up patients for psychotherapy. Andrea Tone has made the same observation in regards to minor tranquilizers, such as Miltown and Valium; while David Herzberg has further argued that psychoanalysts’ strong focus on anxiety, particularly in relatively functional middle-class outpatients, helped to create the class of patients that these drugs were so successfully marketed for. Jonathan Sadowksi and Mical Raz have even demonstrated that some psychoanalysts not only used electro-convulsive therapy and lobotomy alongside psychotherapy, but also provided psychodynamic explanations for the effectiveness of the procedures. Just as analysts were able to incorporate seemingly biological treatments, Jonathan Metzl has argued that biological psychiatry never fully replaced psychodynamic psychiatry, but instead that psychoanalytic concepts of gender roles have survived in the ways that drugs are used and understood.

41 Tone, Age of Anxiety, pp. 44-45, 74-75.
42 Herzberg, Happy Pills, pp. 30-38.
44 Metzl, Prozac on the Couch.
As a form of drug-assisted psychotherapy, LSD psychotherapy further highlights the complex relationship between psychological and biological concepts and treatments in psychiatry in the post-war period. Psychodynamic psychiatrists developed psycholytic therapy as a way to improve on already established forms of psychotherapy. Biological psychiatrists developed psychedelic therapy in response to observations made while investigating whether the “model psychosis” produced by LSD and similar drugs could help reveal the biological basis of organic psychoses. Both forms of LSD psychotherapy sat awkwardly between being drug treatments and psychotherapies, as it was carefully crafted subjective drug experiences, rather than objective drug effects, that researchers considered therapeutically useful, and even then only as part of a psychotherapeutic program. LSD psychotherapy therefore blurred the boundaries between biological and psychodynamic psychiatry even more than other forms of drug-assisted psychotherapy, as drugs such as amphetamines and minor tranquilizers had more predictable effects, and were most commonly used, and regulated, as more conventional drug treatments.

While LSD psychotherapy demonstrates the lack of a clear division between biological and psychodynamic psychiatry in the 1950s, following psychedelic therapy research after the Drug Amendments of 1962 shows how regulation in fact influenced these two forms of psychiatry to split away from each other. The

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45 When used this way the drugs were referred to as “psychotomimetics,” meaning “madness mimicking” drugs. For discussions of psychotomimetic research, see Healy, *Creation of Psychopharmacology*, pp. 178-206; Hewitt, “Psychedelics and Psychosis,” pp. 182-212. This research will not be discussed in detail in this thesis, as, outside of the genesis of psychedelic therapy, there was little cross-over with LSD psychotherapy research.
amendments required evidence of the efficacy of psychiatry's drug treatments, while leaving psychotherapies unregulated. The randomized controlled trial methodology was developed primarily to distinguish between objective drug effects and placebo effects, and the controlled trials of psychedelic therapy demonstrate how difficult it was to demonstrate the efficacy of a psychological treatment through the methodology. Therefore, by effectively requiring the randomized controlled trial as the method of efficacy evaluation, the regulation cast drug efficacy as an objective biological phenomenon. Subsequently, drug-assisted psychotherapy disappeared from psychiatry's treatment landscape as psychopharmacology became synonymous with biological psychiatry. Where the division between biological and psychodynamic psychiatry had previously existed mainly amongst theorists, the amendments now required treatments to either be purely biological or psychological.

This argument builds on David Healy and Edward Shorter's discussions of the implications of the Drug Amendments of 1962 for psychiatry. In *The Antidepressant Era*, Healy has explored how the amendments supported a medical, or "bacteriological," model of mental illness, as efficacy was regulated in terms of specific treatments for specific diseases. Establishing the efficacy of the recently discovered antidepressant drugs through randomized controlled trials required establishing standardized diagnoses and outcome measures. Therefore, the development of depression as a specific disease concept went hand-in-hand with the evaluation of drugs to treat it.46 Furthermore, Healy has explored

46 Healy, *Antidepressant Era*. Jeremy Greene has made a similar argument for the interaction of drugs and disease concepts outside of psychiatry. He argues that the discovery of safe, effective, and tolerable drugs to treat hypertension, diabetes, and high cholesterol influenced their
debates over the comparative efficacy of psychopharmacology and psychotherapy that heated up from the late 1970s. That the efficacy of drug treatments was supported by a greater amount of data from randomized controlled trials led some influential psychiatrists to argue that prioritizing drug treatments over psychotherapy—particularly psychodynamic forms—was a clinical responsibility for physicians treating depressed patients. Shorter, in *Before Prozac*, has argued that by focusing on the establishment of efficacy through randomized controlled trials that compare the effects of a drug with a placebo, the amendments, through the FDA, have created an industry that favours the newest, rather than the most effective, drugs. This form of clinical research only confirms that a drug’s effects on an illness are not simply due to a placebo effect; it does not establish that the drug is any more effective than other existing treatments. However, pharmaceutical firms more heavily market newer treatments, as their patent protection provides greater profits, therefore less effective new drugs can end up replacing more effective older treatments.47

Outside of psychiatry, the Drug Amendments of 1962 and the rise of the randomized controlled trial have been subjects of enquiry for a number of scholars. Significant works by Peter Temin, Philip J. Hilts, Daniel Carpenter, and Arthur Daemmrich have charted in detail the events and influences behind the evolution of pharmaceutical regulation and the growth in power of the FDA over the twentieth century, with an emphasis on the critical importance of the 1962

\[47\] Shorter, *Before Prozac.*
amendments in shaping the modern American pharmaceutical industry. The amendments famously passed on the back of the thalidomide crisis. A New Drug Application (NDA) for the sedative had been under review with the FDA since 1960, and it would have quickly been approved if not for FDA medical officer Frances Kelsey’s staunch scepticism over its safety data. In 1962 the drug’s teratogenic effects became widely known. Even though the drug had not been approved for sale in the United States, widespread and largely unregulated distribution of the drug under the guise of research had resulted in thousands of patients receiving it. Senator Estes Kefauver had been investigating numerous aspects of the pharmaceutical industry since 1959, and in 1961 had introduced a bill to amend the 1938 Federal Food, Drug, and Cosmetic Act to require—amongst numerous other provisions—that new drugs be proven to be effective as well as safe. The bill had languished due to strong opposition, however in 1962 the renewed public and political concern over drug safety allowed a new version of the to bill pass.


While drug efficacy had always been high drug prices due to industry price fixing. In its final form, however, the bill was re-written to focus on drug safety and effectiveness, and provisions such as patent law reform were left out.
While the amendments formally introduced the requirement of proof of drug effectiveness as part of an NDA, John Swann and Carpenter have argued that efficacy was not a new concern for regulators. While difficult to enforce, earlier laws regulated against fraudulent claims of drug effects, and from 1905 to 1955 the American Medical Association required proof of drug effectiveness before allowing advertising in its publications. Moreover, although proof of efficacy was not required under the 1938 Food, Drug, and Cosmetic Act, FDA officials commonly deemed efficacy as inextricably linked to safety and therefore considered it as part of the safety data required in an NDA. For considerations of efficacy, FDA officials expressed a strong preference for evidence from randomized controlled trials.\(^{51}\)

While the role of the randomized controlled trial in drug development has a close relationship with the regulation of drug efficacy, the methodology was first developed and promoted by scientists. Abraham Lilienfeld, Ted Kaptchuck, Arthur and Elaine Shapiro, and others have traced the various techniques that make up randomized controlled trials back centuries, and charted how they came together in the 1930s and 1940s, through the work of researchers such as Harry Gold and Austin Bradford Hill, to become a formalized methodology.\(^{52}\) Historians Harry Marks and Scott Podolsky have most closely analysed the factors behind the randomized controlled trial’s rise in status to become the pre-

eminent model of drug research in the 1950s. They argue that therapeutic reformers promoted the methodology not simply because it was the most scientifically advanced, but because it provided a basic level of protection against the claims of substandard or dishonest researchers and manufacturers.53

This thesis contributes to this scholarship on American drug research and regulation in the twentieth century by exploring the complex interactions between clinical science, regulation, and therapeutics in the 1950s and 1960s. LSD provides a case study that clearly demonstrates the immediate impact of the Drug Amendments of 1962 on pharmaceutical research and development. While most works have to a greater or lesser extent linked the rise of controlled trials to the efficacy provisions of the amendments, how clearly and strictly the FDA mandated the methodology in the years immediately following 1962, and the effect that this had on researchers, has remained unclear. This reflects the ambiguity of the legislation’s term for the required research standards—"adequate and well-controlled investigations"—and the lack of clear guidelines from the FDA until 1970.54 The case of LSD psychotherapy research, however, shows an immediate and essentially complete uptake of the randomized controlled trial methodology by researchers after 1962, and in the mid-1960s FDA officials made it clear that data from such trials would be necessary to establish the efficacy of any form of LSD psychotherapy.


As a result of the 1962 amendments, the FDA also gained oversight of pre-market clinical drug research, requiring researchers to submit a Notice of Claimed Investigational Exemption for a New Drug (IND) before commencing use of an investigational drug.\textsuperscript{55} The IND provisions of the Drug Amendments of 1962 have received much less attention from historians than the efficacy provisions, however Daniel Carpenter has explored how through the IND regulations the FDA created three “phases” of research, which has significantly shaped the process of drug research and development.\textsuperscript{56} This thesis builds on his claim, by demonstrating other ways in which the IND regulations formalized pharmaceutical research. After the amendments, independent and private-practice researchers, who had previously conducted much research with LSD, struggled to meet the requirements of the IND regulations. The field subsequently transformed into one dominated by large-scale, hospital-based, formal clinical trials.

**Sources and Structure**

This thesis explores the history of LSD psychotherapy research in the United States through a variety of published and archival primary sources. Throughout, my analysis is grounded in the reports that LSD researchers published—in medical journals, monographs, and conference proceedings—from the start of


the 1950s through to the late 1970s. Closely examining the content of these reports reveals not only the development of treatment methods and results attained, but the growing importance of research methods, the difficulties involved in evaluating LSD psychotherapy through randomized controlled trials, and ways in which focusing on treatment technique or research design influenced results. The narrative and analysis developed through these reports is then significantly enriched through the personal papers of LSD researchers, particularly members of the team at Spring Grove State Hospital. Grant proposals, unpublished reports and manuscripts, letters, memoranda and other documents left by Charles Savage help to flesh out the ambitions, successes, difficulties, and frustrations of the researchers there.

The regulation of LSD by the FDA, through the Drug Amendments or 1962 and other legislative and regulatory measures, is explored not only through a close analysis of the legislation, but through FDA files. Documents relating to the assessment of LSD researchers’ INDs reveal that when they were rejected, this was not due to any specific attempt to restrict use of the drug. Furthermore, they reveal that Sandoz Pharmaceuticals, rather than the FDA, was largely responsible for the reduction in the number of researchers using the drug that began in 1963. Meeting minutes also reveal that FDA and NIMH official were much more supportive of LSD research than others have considered them, and that they in fact saved research from coming to a complete close in 1966. Two congressional hearings from 1966 that investigated LSD add further detail as to how the FDA were regulating research, and the reasons behind the drop in scale of research, as well as giving important insights into officials’ attitudes towards this research.
This thesis is structured chronologically. The first chapter establishes the context of psychiatry in the early 1950s from which LSD psychotherapy emerged. The critical aspects of this context are the complex relationship between biological and psychodynamic forms of psychiatry, and the established use of drugs as facilitating agents in psychotherapy. The chapter then follows the introduction of LSD into the United States, and the development of psycholytic and psychedelic therapy over the 1950s, through both international and American research.

Chapter two details the regulation of LSD research by the FDA from 1962 until the end of the 1960s. The focus of the chapter is on the IND provisions of the Drug Amendments of 1962, and how they impacted LSD research. This is explored through examining the INDs of Sandoz Pharmaceuticals, Harold Abramson, and the International Foundation for Advanced Study. Abramson was one of the most prominent psycholytic therapy researchers in the 1950s, while the International Foundation for Advanced Study, founded in 1961, was instrumental in establishing and developing psychedelic therapy research in the US. Both Abramson and the Foundation had their INDs revoked by the FDA and were unable to continue using LSD, however closely examining the FDA determinations in their cases will reveal complex and objective reasons for this.

The Drug Abuse Control Amendments of 1965, and Sandoz’s 1966 withdrawal of its IND, are then discussed, showing that not only did this legislation contain no provisions to restrict legitimate research, but that officials of the FDA and NIMH worked to preserve such research.
Chapter three focuses on the efficacy provisions of the Drug Amendments of 1962, and the potential issues they presented to LSD psychotherapy researchers. In the absence of clear guidelines from the FDA, the chapter attempts to establish the expected standards for research. Comments from FDA officials show a clear preference for randomized controlled trials, while they defer to the opinion of medical experts for an ultimate determination of appropriate methods. The chapter therefore explores the development of the randomized controlled trial methodology, and its status at the time of the amendments’ passage. It shows that by the mid-1950s experts in psychiatry, as well as medicine and pharmacology more broadly, were overwhelmingly convinced that the techniques involved in randomized controlled trials were the best way of insuring accuracy in drug efficacy evaluations. Despite this, the development path of two breakthrough psychiatric drugs in the 1950s demonstrates that prior to the 1962 amendments such research was necessary for neither FDA approval, nor medical acceptance. Having established that the term “adequate and well-controlled investigations” would be interpreted by researchers and regulators alike as referring to randomized controlled trials, the chapter explores how many LSD psychotherapy researchers opposed the methodology, arguing that it was inappropriate for evaluating their unique treatments. Assumptions of biologically based treatment efficacy inherent in controlled trials are discussed, and well as the problematics of the notion of the placebo effect, and how to control for it, in psychotherapy research. Finally, it is shown that although FDA officials had stated that randomized controlled trials need not be utilized in cases where they were inappropriate, they critiqued LSD psychotherapy research on the basis of poor research methodology, and therefore expected it in this case.
The fourth chapter charts the successes of the LSD research program at Spring Grove State Hospital over the 1960s. The program was established to explore the efficacy of psychedelic therapy in the treatment of alcoholism in 1963, the same year that national controversy over the drug erupted, and the FDA gained oversight of research. Nevertheless, over the decade the program continuously expanded, as more experienced and innovative researchers joined the group, and further clinical trials were launched exploring the treatment of neurotic patients, anxiety and depression in terminal cancer patients, and narcotic addiction. Early results were so promising that the researchers began planning for LSD’s eventual use in hospitals across the state. By the end of the decade the program was the largest of its kind in the United States, and had shifted to purpose-built facilities within the new Maryland Psychiatric Research Center. The growth and successes of the Spring Grove research program over the 1960s significantly challenges the standard narrative, which considers LSD research to have died as the public controversy grew over these years.

Chapter five then explores why the Spring Grove research failed to establish the efficacy of psychedelic therapy for any indication. As the Spring Grove researchers’ final results emerged in the early 1970s, internal and external factors undermined the significance of their work. While the researchers put great effort into designing clinical trials that balanced clinical considerations with scientific rigour, problems emerged in their implementation that influenced inconclusive or lacklustre results: specially designed control conditions worked imperfectly, other control conditions could not be implemented as planned, and
randomization failed to evenly distribute important variables amongst treatment groups. External challenges came from the results of six other clinical trials of LSD therapy in the treatment of alcoholism conducted in the years after 1962. These researchers all focused their efforts on implementing rigorous control methods in their trials, however in doing so they ignored the treatment techniques that prior researchers had found successful. To most observers, their negative results established that LSD therapy was ineffective in treating alcoholism.

The final chapter then explores psychedelic research in the 1970s, and why it came to a close in 1976. The Controlled Substances Act of 1970 introduced new registration requirements for LSD researchers. Nevertheless, I argue that the failure of researchers to demonstrate treatment efficacy is a more convincing explanation for the decreasing scale of LSD research. From the early 1970s, the Maryland Psychiatric Research Center was the only site where significant research with psychedelics was continuing. Despite the declining prospects of research, the researchers there continued to progress their work, exploring new treatment techniques, and new psychedelic drugs. They continued to find promising results in pilot studies, but also continued to find implementing controlled trials extremely problematic. As explored through coverage in the *Baltimore Sun*, I show that psychedelic research finally came to a close at the research centre in 1976 due to a management controversy that was essentially unrelated to LSD.
Having established over the thesis the evolution of LSD psychotherapy research from the early 1950s, and the research frustrations that led to its demise in the mid-1970s, I finally discuss further issues that held LSD back from becoming an accepted tool of psychiatry. The case of LSD highlights the distinctions between pharmaceutical research on the one hand and development on the other: while much research was conducted with the drug, it was the subject of little development. After Sandoz withdrew its IND in 1966, researchers were left to develop the drug themselves. Successful development required not only delivering proof of efficacy to the FDA, but defining how efficacy should be conceptualized for the drug, and therefore what kind of proof would be necessary for approval: answering the most medically significant questions was not necessarily required for an NDA. Without the guidance of a developer, researchers worked independently, conducting clinical trials with over-ambitious research questions, and using different treatment and research techniques, making comparing results problematic. The field therefore progressed little. Ultimately, without the backing of a pharmaceutical firm, LSD had little prospect of becoming an accepted tool of medicine.
1. Post War Psychiatry and the Birth of LSD Psychotherapy

LSD arrived in the United States in 1949 and psychiatrists soon began exploring its therapeutic potential. Research in the 1950s reflected the eclectic and innovative context of psychiatry in that decade. Post-war American psychiatry has commonly been represented by historians as divided into two competing and incompatible paradigms of biological and psychodynamic (psychoanalytically orientated) psychiatry, equating to a nature versus nurture debate over the conception of mental illness, and psychological versus somatic and drug treatments.¹ Psychiatrists’ initial reaction to LSD appeared to reflect this, with biologically orientated researchers believing that LSD produced an artificial psychosis, which gave evidence to their theory that mental illness had biological origins. They therefore labelled LSD as a “psychotomimetic” (madness mimicking) drug. Psychodynamic psychiatrists, by contrast, believed that LSD unlocked the unconscious mind, allowing deeper penetration into the psychological roots of their patients’ psychopathologies. Based on this potential they developed psycholytic (mind loosening) therapy. Yet the very fact that psychodynamic psychiatrists eagerly explored using LSD to facilitate

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psychotherapy demonstrates that—as has been explored in recent 
historiography—there was no exclusive divide between psychological and 
biological treatments in psychiatric practice. Furthermore, it was biological 
psychiatrists who developed psychedelic (mind-manifesting) therapy, after they 
found their patients manifesting transcendental, mystical, reactions to the drug, 
rather than psychotic. Psycholytic and psychedelic therapy therefore blurred the 
lines between biological and psychodynamic psychiatry.

As well as reflecting psychiatrists’ professional freedom to explore different 
treatment modes, the successful development of LSD psychotherapies was made 
possible by the loose regulation of drug research and development under the 
1962, researchers had essentially complete autonomy over their work. Research 
could be conducted almost casually, with little planning or funding needed to 
conduct studies with small numbers of patients. This meant that researchers 
could easily explore hunches, suggestions, and unconventional uses for drugs, 
and follow leads when they got unexpected results. With no required 
methodologies for research, psychiatrists could evaluate their treatments as they 
considered appropriate, and leave others to decide for themselves ultimately 
how useful they were. This form of research would have its downsides, as it

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would lead to debates over efficacy and encourage researchers to work independently rather than build on each other's work. However, it also encouraged great exploration and innovation.

**Post-War American Psychiatry**

LSD arrived in the United States to a psychiatric landscape dominated by inpatient treatment in large state hospitals. In the mid-twentieth century, 85 percent of psychiatric beds in the US were in state psychiatric hospitals, which by 1940 held a total population of 480,000. These hospitals were plagued by underfunding, overcrowding, and insufficient staffing, and housed a core population of severely, chronically ill patients. From the mid-1950s, treatment in these institutions would be revolutionized by the discovery of a range of new drugs that appeared to specifically alleviate the symptoms of major mental illness: tranquilizers chlorpromazine and reserpine for psychoses, antidepressants imipramine and iproniazid, and the minor tranquilizer meprobamate for anxiety. Prior to this, effective treatment options were limited and could be dangerous.

Although psychopharmacology is usually portrayed as beginning with the discovery of chlorpromazine in France in 1952, drugs such as sedatives had long

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been used as tools in psychiatry.\textsuperscript{4} These drugs were not used as specific treatments for specific illnesses, but rather to generally increase the comfort and manageability of patients, by calming agitation and inducing sleep. Throughout psychiatry’s history a variety of sedative agents had been utilized, including alcohol, opiates, paraldehyde, and chloral hydrate. Most significant in the mid-twentieth century were the barbiturates, the first of which, barbital (Veronal), was discovered in 1903. In the decades that followed, dozens of new barbiturates were marketed, such as sodium amytal and sodium pentothal. Their use increased exponentially until the start of the 1960s, when the newer drugs took over their market. The drugs were used in outpatient as well as inpatient treatment, particularly in low doses for the treatment of neuroses and depression.\textsuperscript{5} The stimulant amphetamine and its derivatives were also prominent psychopharmaceuticals in the mid-twentieth century. Developed in 1929, amphetamine was marketed as a specific treatment for depression, however its major market was in the treatment of depression’s milder forms outside of the hospital, and it was most commonly prescribed by general practitioners.\textsuperscript{6}

Where drugs could be useful for calming patients and treating mild mental illnesses, for more severely ill hospital patients the more dramatic somatic treatments held out the only hope of cure. Insulin coma therapy, electro-

\textsuperscript{4} For a history of the development of chlorpromazine and the rise of psychopharmacology in the 1950s see, Healy, Creation of Psychopharmacology.


convulsive therapy (ECT), and psychosurgery were all developed in the 1930s in Europe, and were quickly adopted in the US. Insulin coma was predominantly used for schizophrenia, ECT for mood disorders, and psychosurgery for a range of treatment resistant illnesses. In retrospect, these treatments have often been represented as brutal, overused, and unscientific tools of punishment and control, rather than progressive and potentially effective treatments. However, recent historiography has challenged this view, arguing that while such problematic use of the treatments occurred, they were at the same time mainstream, scientifically supported treatments that offered hope to patients who were otherwise unreachable. Whilst putting patients through procedures such as hypoglycemic coma, convulsions, or brain surgery was complicated, psychiatrists faced with great numbers of severely and chronically ill patients considered the potential benefit worth the risk. The efficacy of these treatments remains contested and controversial. Although many psychiatrists then and now argued that insulin coma therapy’s apparent efficacy was due to a placebo effect, one 1957 study found it to be equally effective as chlorpromazine. Furthermore, whilst demonised in the public consciousness, ECT is still in use today and is considered by many psychiatrists to be the most effective treatment for severe

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8 See Pressman, Last Resort; Edward Shorter and David Healy, Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness (Toronto: University of Toronto Press, 2007). Probably the most famous negative depiction of ECT and psychosurgery as brutal, oppressive, and therapeutically useless is Ken Kesey, One Flew over the Cuckoo’s Nest, (Camberwell: Penguin Group [Australia], 2008). Kesey’s novel, originally published in 1962, and the 1975 film adaptation, was highly influential in shaping the public perception of these treatments. For a historical account critical of somatic therapies see Joel Braslow, Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century (Berkeley and Los Angeles: University of California Press, 1997).

depression. Psychosurgery, as historian Jack Pressman expressed, “has become our most visible icon for everything that is dangerous and bad about uncontrolled medical science.” Yet, one review of the treatment in 1943 found that of 618 patients given a lobotomy that year, 408 were improved or recovered, and 251 of those patients had been discharged from hospital and were employed. However Pressman emphasizes that efficacy cannot be easily divorced of its historical context, and therefore these figures cannot be taken at face value: manageability was often considered a marker for improvement, rather than the quality of the internal life of the patient.

While the somatic therapies were the primary means of treating severe mental illness, in the years after the Second World War psychodynamics came to dominate psychiatric theory. Although there were many influential theorists in American psychodynamic psychiatry, undoubtedly chief among them was Sigmund Freud. Over the late nineteenth and early twentieth century Freud developed psychoanalysis as a theory of the nature of the mind, the origins of mental illness (chiefly neuroses), and a psychotherapeutic method for their treatment. By midcentury, psychoanalysis had evolved into a distinct psychiatric

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10 Sadowski, "Beyond the Metaphor of the Pendulum," p. 8
11 Pressman, Last Resort, p. 3, 139.
12 Ibid., pp. 223-225, 433-437.
speciality requiring extensive training through psychoanalytic institutes. Despite being a psychological treatment, training was only open to physicians. As well as attending seminars, candidates were required to undergo a personal training analysis, lasting an average 609 hours over three years, and conduct supervised analyses. Overall, training could take as long as ten years.\(^{14}\) Psychoanalysis would provide the theoretical and treatment framework from which LSD psychotherapy would develop. Over the 1950s and 1960s, new forms of LSD psychotherapy would increasingly deviate from psychoanalysis, however researchers would continue to use analytic terms to describe their treatments. It is therefore significant to briefly explore the theories and techniques of psychoanalysis.

Freud’s theories were particularly complex, focusing on the relationship between the conscious and unconscious mind. Freud argued that thoughts, feelings, experiences, and drives that were offensive to the conscious mind were repressed into the unconscious. They were often of a sexual nature and derived from childhood. Although hidden, the repressions were not harmless, but caused conflict in the psyche, leading to neuroses.\(^{15}\) Freud divided the mind into three components: the “id,” “ego,” and “super-ego.” Dean of the Los Angeles Institute of Psychoanalysis Ralph R. Greenson, elaborated on these components in 1959. The id consisted of instinctual drives and was entirely unconscious. Under the “primary process” the id sought pleasure through the discharge of its drives. The ego was the “control apparatus of the psychic structure...responsible for

perception, thinking, memory, and judgement,” and existed at all levels of consciousness. Compared to the id, the ego was reality orientated, as it considered the consequences of pleasure seeking. The super-ego acted primarily in the unconscious as a conscience “containing the rewarding and punishing qualities and values of the parents.”

Greenson described how conflict between the ego and the id was at the root of neuroses,

The id, completely under the domination of the primary process, is interested only in immediate discharge. The ego, on the other hand, is motivated to avoid unpleasure, that is, to avoid the painful effects of anxiety, guilt, shame, etc...the ego also has at its disposal a variety of methods of defense which it uses in order to accomplish its aim of avoiding pain... Neurotic conflicts occur when the ego turns against demands of the id because the ego perceives the instinctual drives as a danger. The ego defends itself against the id’s incessant demands by instituting defense mechanisms which prevent the discharge of the drives but which consume part of the ego’s energetic reservoir. Intense conflicts and many conflicts eventually deplete the ego’s capacity to ward off the id’s demands, and the eventual result is a neurotic symptom or character deformation.

The super-ego also played a role in the neuroses, as it supplied “inappropriate conscious or unconscious feelings of guilt” over the neurotic conflicts, worsening the condition.

In order to treat neuroses, unconscious conflicts between the id, ego, and super-ego needed to be brought into the conscious where they could be re-evaluated and resolved in a more mature manner. In doing so the ego was strengthened and its relationship to the id, super-ego, and the external world were improved, leaving the patient not only free of their past neuroses, but better equipped to

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17 Ibid., p. 1403.
deal with the stresses and conflicts that could arise in the future.\textsuperscript{18} The analyst gained access to the unconscious primarily through the process of “free association”: patients were encouraged to continuously verbalise anything that came into mind without any form of censorship, while the quiet therapist, seated behind the patient, analysed content and patterns in their thinking to reveal unconscious material. Other methods involved the analysis of patients’ dreams, resistances that blocked free association, and the “transference” phenomenon, where patients unconsciously projected emotions related to someone else in their life onto the analyst.\textsuperscript{19} The classical psychoanalytic method was a gruelling process, with patients ordinarily seeing their analyst five times per week, often for years, and required from the patient high motivation and relatively high mental functionality aside from their neuroses: as Greenson commented, “Actually, one has to be a relatively healthy neurotic in order to be psychoanalysed without modifications and deviations.”\textsuperscript{20}

Two factors are commonly cited as the main influences on the rise of American psychoanalysis following the Second World War. First, an influx of European analysts fleeing Germany and Austria following the rise of the Nazi Party helped to raise the popularity and status of the treatment in the US.\textsuperscript{21} Second, 1,100,000 military personal required psychiatric treatment during the war, despite psychiatrists having rejected 1,875,000 men for duty after pre-screening them

\begin{thebibliography}{9}
\bibitem{18} Ibid., p. 1403.
\bibitem{19} Ibid., pp. 1405-1415; Engel, \textit{American Therapy}, pp. 6-10, 150; Hale Jr., \textit{Psychoanalysis in the United States}, pp. 52-53
\end{thebibliography}
for predisposition for mental illness. This suggested that environmental stress had a greater impact on mental health than biological factors. In addition, military psychiatrists successfully treated soldiers suffering from neurotic conditions through early intervention and non-institutional treatment: instead of being sent to far away hospitals, and separated from peers, the patient progressed through a series of more local treatment stations until they improved, with a focus on rest, psychotherapy, diet, and a chance to normalise. Finally, the war created a greater population of psychiatrists, as demand grew and treatment proved successful. Army medical personnel assigned to psychiatry grew from thirty-five at the time of America’s entry into the war, to 2,400 at its conclusion, a number greater than the 2,295 total members of the American Psychiatric Association (APA) in 1940.

After the war, psychodynamic psychiatry had its greatest influence in psychiatry’s organizations and educational institutions. By 1955, nearly all psychiatric residents were being instructed in psychodynamic principles, and analysts held the top positions in the APA. The first edition of the APA’s nosological text *Diagnostic and Statistical Manual: Mental Disorders* (DSM-I), published in 1952, while not explicitly stating a particular theoretical framework, was couched in dynamic terms. Mental disorders “without clearly defined physical cause or structural change in the brain” (such as those caused by trauma or poison), were defined as “the result of a more general difficulty in

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22 Hale, *Psychoanalysis in the United States*, p. 188
adaption of the individual.”25 The large section on “psychoneurotic disorders” defined the illnesses as broadly arising from individuals’ attempts to handle anxiety that was either conscious, or held in the unconscious by “psychological defense mechanisms,” and which arose from “threats within the personality” such as “supercharged repressed emotions.”26 Instead of psychiatry’s traditional focus on severely ill, usually psychotic, patients, psychodynamic psychiatrists focused their attention on those with neuroses. War experience influenced this shifted focus not only by providing positive treatment experiences, but also by expanding the potential patient population and suggesting a shift in the locale of treatment. With the frequent cases of psychiatric disorders amongst pre-screened military personal, psychiatrists realized that mental illness affected, at least potentially, a far greater population than had previously been thought. These casualties seemingly showed that rather than discrete diseases caused by genetic or biological factors, mental illnesses existed on a spectrum from health to severe illness, that environmental influences could precipitate a shift on this spectrum, and that early intervention could prevent the slide into severe illness, which was much more difficult to treat. This theory led to a push for psychiatrists to find and treat patients in the community, to prevent them from reaching the point where they needed traditional hospital treatment.27

Despite the dominance of psychodynamic theory in midcentury American

psychiatry, psychotherapy was impractical as a primary treatment in hospital psychiatry. Hospital patients were mostly too mentally withdrawn or disorganized to engage in psychotherapy, and where they could, hospitals could simply not accommodate the amount of individual time between psychiatrists and patients that psychotherapy required. Therefore, while somatic and psychodynamic treatments can seem at odds on a theoretical level, for pragmatic reasons psychiatrists often used them alongside each other. Indeed, historian Mical Raz has found that not only was opposition to psychosurgery amongst psychodynamic psychiatrists less common than is often portrayed, but that many saw the treatments as complementary, and patients often received psychotherapy after lobotomy. Furthermore, psychosurgeons and analysts alike frequently explained the efficacy of lobotomy through psychodynamic theory.\(^2\)

Biological and psychodynamic psychiatry also met in the growing field of drug-assisted psychotherapy. Considering the long and difficult process of psychotherapy, many psychodynamic psychiatrists began to look for tools to make it more widely applicable and practical.

Barbiturates were the first drugs to be widely used for facilitating psychotherapy. Psychiatrists used small to moderate doses of the sedatives to create a semi-awake, dreamlike state of “narcosis” in which the patient would often talk more freely than usual, allowing the psychiatrist to obtain information that could be therapeutically relevant. Such use of the drugs was popularized in the post-war period, and it would provide a direct precedent and blueprint for

explorations of LSD’s therapeutic potential. Researchers first published accounts of using barbiturates to elicit information from otherwise unreachable patients at the start of the 1930s. During the Second World War, American military psychiatrists Lieutenant Colonel Roy Grinker and Major John Spiegel then developed a systematic psychotherapeutic treatment utilizing the barbiturate sodium pentothal, which they named “narcosynthesis.” They used this treatment in cases of what they called “war neuroses,” a condition which caused a high proportion of the “living casualties” of the war. Referred to during the First World War as “shell shock” and related to the modern concept of post-traumatic stress disorder, war neuroses were marked by severe anxiety caused by the stresses of war. The condition could lead to a variety of symptoms, including extreme fear, agitation, amnesia, muteness, hysteria, somatic ailments, and near paralysis. As Grinker and Spiegel explained in 1944, narcosynthesis,

causes the patient to re-experience the intense emotions which were originally associated with the actual battle experience and which were perpetuated in various stages of repression up to the moment of treatment. At the same time the action of the drug enables the patient to deal with these revived emotions in an economical and rational manner rather than with catastrophic defensive devices which end in serious neurotic crippling.

The first part of the therapy involved using the barbiturate as an aid to produce a powerful abreaction in the patient—an emotional re-living of past traumatic events. In a private semi-darkened room, the patient was administered the drug

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30 Roy R. Grinker and John P. Spiegel, "Brief Psychotherapy in War Neuroses." *Psychosomatic Medicine* 6, no. 2 (1944), p. 123. Similar techniques were at the same time being developed by the British, especially by psychiatrists W. Sargant and E. Slater, see Leonard Tilkin, "The Present Status of Narcosynthesis Using Sodium Pentothal and Sodium Amytal" *Diseases of the Nervous System* 10, no. 7 (1949), p. 215.
until the desired state of narcosis was reached, and then encouraged to talk 
about their traumatic wartime experiences. In order to facilitate the emotional 
reliving of these events, the therapist evoked battles in which the patient had 
been involved. If resistance was high, or recount difficult, the psychiatrist would 
dramatically play "the role of the fellow soldier, calling out to the patient, in an 
alarmed voice, to duck as the shells come over, or asking him to help with a 
wounded comrade." With persistent use of this technique even complete 
amnesias surrounding a traumatic experience could be reversed. Patients often 
responded by not merely describing a traumatic scene, but by acting it out, 
moving around the room responding to events and communicating with absent 
friends. During this behaviour the psychiatrist continued applying 
encouragement and stimulus to help the patient fully re-live their experiences, 
and provided support and comfort as traumatic scenes unfolded. After the 
abreactive experience had concluded, the second part of the treatment could 
take place. During the abreaction, the traumatic emotions attached to the 
patient’s experiences were detached of their excess anxiety due to the sedative 
qualities of the drug. As a result, after the drug had worn off the memories and 
emotions released could be more easily worked through with the aid of brief 
psychodynamic therapy sessions. The goal of this therapy was “to release 
unconscious psychological tensions, to strengthen the ego forces and decrease 
the severity of the superego’s pressure.” Grinker and Spiegel noted that in 
severe cases it was unlikely that the treatment would allow patients to return to 
combat, and that reclassification for limited duty was often the goal. However,

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33 Ibid., p. 127
34 Ibid., p. 128
they showed great optimism about the efficacy of the treatment, arguing that results could be improved with better resources, and providing case descriptions of many successful treatments.\textsuperscript{35}

After the conclusion of the war, American psychiatrists in hospital and private practice began widely experimenting with narcosynthesis. Many found it to be an aid in establishing dialogue with patients, deepening insight, and quickening the process of psychotherapy. Summarizing the field for prominent journal \textit{Diseases of the Nervous System} in 1949, psychiatrist Leonard Tilkin found that narcosynthesis was “rapidly gaining support as a respected and valuable psychiatric treatment.” Researchers reported greatest success in treating severe anxiety states and hysterical reactions, and also promising results in the treatment of alcoholism. Tilkin expressed great hope and enthusiasm for the treatment, stating, “the future of narcosynthesis is infinite, and the possibilities endless.”\textsuperscript{36} In 1948 the treatment even featured in the influential motion picture \textit{The Snake Pit}. In the film, Virginia Cunningham (Olivia de Havilland), undergoes narcosynthesis during her hospitalized treatment for mental illness. During the treatment she emotionally recounts events in her past, and appears to be re-living them at times. Previously repressed material comes to light, which her psychiatrist sees as significant to the cause of her illness. It is one of a variety of treatments that together eventually lead to her successful recovery.\textsuperscript{37}

\textsuperscript{35} Ibid., p. 128, 131. For positive case studies see Grinker and Spiegel, \textit{Men under Stress}, pp. 396-405

\textsuperscript{36} Tilkin "Present Status of Narcosynthesis," p. 217.

\textsuperscript{37} Anatole Litvak (dir.), \textit{The Snake Pit} (Twentieth Century Fox Film Corporation: 1948). The movie was an adaption of Mary Jane Ward’s novel of the same name (1946), however narcosynthesis does not feature in the book, see Mary Jane Ward, \textit{The Snake Pit} (New York: Random House, 1946). The book and film’s depictions of the crowded and often poor conditions
Over the 1950s, other drugs would also become frequently used as facilitators in psychotherapy. Indeed, historian Nicolas Rasmussen has found that in the early 1950s pharmaceutical firm Burroughs Wellcome even advertised its stimulant Methedrine (methamphetamine) for such a use, under the heading “Release the Story for Analysis.” According to the advertisement, intravenous administration of the drug produced from patients a “spontaneous, free flow of speech,” featuring “previously withheld information,” and also facilitated abreaction.38 Similarly, historian Andrea Tone has found that researchers and manufacturers claimed that the early minor tranquilizers mephenesin and meprobamate were useful adjuncts to psychotherapy, however due to their relaxing rather than stimulating properties.39 The psychiatric context in the United States at the start of the 1950s was therefore ideal for the development of LSD psychotherapy. Psychodynamic theory dominated psychiatry, yet psychotherapy’s shortcomings in practice led psychiatrists to explore biological methods of facilitating treatment. Drug-assisted psychotherapy with barbiturates was an established form of treatment, and alongside LSD psychotherapy research amphetamines and minor tranquilizers would increasingly be used to facilitate psychotherapy. At least initially, LSD would be used in the same manner as barbiturates, to break down patients’ defences, reveal repressed memories, and produce powerful abstractions, with dynamic psychotherapy integrating the insights produced.

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39 Tone, Age of Anxiety, pp. 44-45, 74-75.
Over the decade, however, eclectic forms of psychiatric research would lead to more unique uses for the drug.

**LSD Psychotherapy**

The story of LSD's invention has been frequently told, and has reached an almost mythic status.\(^{40}\) The story holds intrigue partly due to its improbability, as the drug's effects were discovered by accident. Partly it is simply the story of a momentous event, the creation of a drug that would fascinate chemists, psychiatrists, intelligence and military agencies, and individuals all over the world. By the end of the 1960s, LSD was simultaneously considered a powerful therapeutic device, the most dangerous drug know to man, and a key symbol of liberation for a mass social movement. The story also appeals due to the personality and achievements of the inventor, Swiss chemist Albert Hofmann. Hofmann not only synthesized the drug and discovered its dramatic effects, but he also immediately recognized the wide range of implications it could have, rather than dismiss it as a toxic substance. He remained a proponent of the potential benefits of psychedelics to individuals and society until his death at the age of 102 in 2008, despite his condemnation of their widespread recreational

Hofmann was a chemist in the pharmaceutical department of Sandoz Ltd. in Basel, Switzerland, where he had been experimenting with alkaloids of ergot, a fungus that grows on rye. Famous for producing mass poisoning throughout European history when baked into bread, ergot had also been used for hundreds of years in obstetrics, to induce contractions and control bleeding after birth. In 1938 Hofmann synthesized d-lysergic acid diethylamide (or LSD-25, so called as it was the twenty-fifth in a series of substances produced) in search of a circulatory and respiratory stimulant. On animal testing, the substance proved of little interest and was abandoned. However in 1943, for reasons he could never explain, Hofmann’s interest returned to LSD. After synthesizing a new batch on 16 April he began to feel odd and returned home, where he “sank into a not unpleasant intoxicated-like condition,” and with eyes closed “perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors.”

He reasoned that the LSD, which he must have somehow accidentally ingested, could be the only explanation for this condition. Hofmann therefore decided to experiment further, and three days later he ingested 250 micrograms (mcg) of LSD, believing this to be the smallest amount that could possibly have an effect. The dose turned out to be in fact very strong, and it overwhelmed him with fear as his surroundings distorted into sinister forms, and all control over his mind was lost. However as the effects diminished, they became pleasant as they had been the first time. Despite the largely terrifying experience, Hofmann concluded that the potency and dramatic effects

\[41\text{ Hofmann, } \textit{LSD}, \text{ p. 47.}\]
of the drug would make it interesting to pharmacologists, psychiatrists, and neurologists.  

Psychiatrist Werner Stoll, the son of Hofmann’s superior Arthur Stoll, performed the first clinical tests with LSD at the University of Zurich. Stoll’s report, published in 1947, discussed the profound mental effects of the drug (as observed in volunteers, patients, and in self-experiments), noting that as well as visual, mood, and cognitive changes, many subjects experienced an upsurge of repressed memories.  

Sandoz soon began distributing the drug free of charge to international researchers, indicated for “Analytical psychotherapy, to elicit release of repressed material and provide mental relaxation, particularly in anxiety and obsessional neuroses” and the “Experimental studies on the nature of psychoses.”  

LSD quickly became the subject of widespread and diverse research in the United States, facilitated by the loose regulation of pharmaceutical research and development under the Federal Food, Drug, and Cosmetic Act of 1938. Under this legislation, for a drug to be marketed in interstate commerce, a sponsor (usually the manufacturer) was required to submit a New Drug Application (NDA) to the FDA. The NDA needed to provide proof of safety for the drug when used as directed. The nature and extent of pre-market clinical research was, however, largely at the discretion of the manufacturer. The manufacturer was free to distribute new drugs to qualified researchers so long as they were labelled for investigational use.

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42 Ibid., pp. 32-52.  
44 Hofmann, LSD, pp. 73, 85.
manufacturer simply had to obtain a written statement from the researcher that they had adequate facilities to perform research with the drug, and that all research would be under their direction.45

Other than providing broad suggestions for use, Sandoz appears to have done little to direct or control research with LSD in the years prior to 1962. While the exact nature of the relationships between Sandoz and researchers are not clear, they appear to have been what Rasmussen has termed “free-lancer” relationships. Rasmussen has delineated three forms of relationship between medical researchers and pharmaceutical companies in interwar America. These ranged from the fully independent and self-motivated free-lancer, to the “efficient,” who conducted trials that were funded, directed, and designed by a pharmaceutical firm, which also oversaw the publication of results. In the free-lancer relationship, pharmaceutical companies provided researchers with drugs upon request, but no funding. While researchers’ requests for drugs were sometimes made in response to offers from firms, the researchers pursued their own interests and were free to publish any findings without censorship. Pharmaceutical firms benefited from this relationship as it allowed a wide variety of research to be undertaken at minimal cost to the company. Such research could potentially find new uses for a drug, help establish its efficacy and safety, or be used as advertising.46 A pharmaceutical company’s role in a clinical

trial, beyond supplying a drug, was not commonly acknowledged in research publications during the period. Therefore, it cannot be definitely established that Sandoz did not supply funding or direction to researchers simply because they did not acknowledge this. Nevertheless, the widespread, disorganised research, that explored many uses for the drug, and that resulted in both positive and negative reports, strongly suggests that it was indeed a free-lancer relationship.

Initial research with LSD in the US followed Sandoz’s recommendations. The drug was first used in 1949 by Max Rinkel at Boston Psychopathic Hospital to produce a model psychosis, to aid in the study of schizophrenia. Soon after, psychodynamically orientated psychiatrists began exploring LSD as a facilitating tool in psychotherapy. They found that the drug could deepen and quicken psychotherapy, through its power to break down patients’ defences, release repressed memories, and deepen psychological insight. Despite the dramatic effects of LSD, psycholytic therapy was not a radical form of treatment. Incorporating LSD into treatment did not present any challenge to the theoretical basis of psychoanalysis, or require any fundamental changes to the therapeutic procedure. It merely provided a tool to aid the process. The treatment also had a precedent in narcosynthesis and other forms of drug-assisted psychotherapy. During the 1950s, psychodynamic therapists in the US and Europe reported great success using LSD with their patients. However, as psycholytic therapy was simply conventional forms of psychotherapy facilitated through LSD, it never

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developed into a truly distinct treatment: particular theories and methods varied between researchers, as they reflected the psychotherapeutic schools to which the researchers ascribed. This would ultimately influence its demise in the 1960s.

In contrast to the straightforward development of psycholytic therapy, psychedelic therapy emerged in a more convoluted manner. Biologically orientated psychiatrists investigating the relationship between LSD's psychotomimetic effects and endogenous psychoses, discovered that at high doses the drug could produce a transcendental, or mystical, reaction. Using this experience to treat alcoholism, the researchers developed psychedelic therapy, which had its own distinct theoretical basis and therapeutic method. This early research was conducted in Canada, however US researchers quickly adopted the treatment. Psychedelic therapy challenged conventional concepts of psychotherapy and pharmacotherapy, yet it reported unbelievably good results and outlasted psycholytic therapy.

While the two treatments differed greatly, they shared some common elements: the therapeutic benefits of LSD did not come from any inherent biochemical effects, but from its subjective effects; the use of the drug was enmeshed in a psychotherapeutic regime; and the mental “set” of the patient, and the setting, were carefully manipulated to achieve the desired drug effect and therapeutic result. Exploring in detail how the treatment techniques developed, and the research methods they used to evaluate their effectiveness, gives critical context to the later downfall of LSD psychotherapy: LSD psychotherapy was a reflection
of the psychiatric and research contexts of the 1950s, and as those contexts changed in the early 1960s, the treatments struggled to survive.

**Psycholytic Therapy**

Psychiatrists Anthony Busch and Warren Johnson published the first report of the use of LSD in a psychotherapeutic context in the United States in 1950. At the St. Louis State Hospital, Missouri, the researchers had been experimenting with ways to open up their chronically psychotic patients to psychotherapy. They had tried forms of narcosynthesis, as well as interviewing patients during insulin coma therapy, or after electroconvulsive therapy. Although helpful, they found these methods had drawbacks: “speech difficulties” under sodium amytal and mental confusion surrounding the somatic treatments. Having noted cases of patients uncovering their internal conflicts while in a state of “toxic delirium,” the researchers took up Sandoz’s suggestion to use LSD to produce this state. For a first trial they chose twenty-one female inpatients, eighteen of whom were diagnosed as schizophrenic, and three as manic. The patients had been hospitalized for varying lengths of time, with dates of admission between 1919 and 1949. They were given small doses of the drug (30-40 mcg), the effects of which were found to last up to eight hours. Busch and Johnson described the mental effects of the drug as,

those of excitation. The patients moved about more, showed greater interest, responded more readily to stimulation, talked more, and exhibited more emotion. With this increase in activity, there was a greater verbal expression of psychopathology. There were occasional short
periods of confusion and disorientation, and occasional transitory visual hallucinations. Most of the patients showed some degree of euphoria.\textsuperscript{48}

The usefulness of the drug reaction varied widely between patients. Some (including all of the manics), became disturbed and needed hydrotherapy to calm their excessive excitation, while others became coherent, expressive, and more focused on their problems. Encouraged by the latter reaction, the researchers decided to try using LSD on eight patients who were already receiving psychotherapy. Four were outpatients, and the group included patients diagnosed with schizophrenia and psychoneurosis. Results for this group were more uniform, and the researchers found the treatment “profoundly influenced the course of their progress.” Two patients improved to the point where treatment was discontinued. In many cases the effect proved more useful than narcosynthesis. Although Busch and Johnson did not give a description of their therapeutic method, or theoretical background, from their description it is clear that they were working within a psychodynamic framework:

\begin{quote}
The effect was in the nature of a transitory toxic state, which disturbed the barrier of repression and permitted a re-examination of significant experiences of the past, which sometimes were relived with frightening realism. With this, some of the patients were then able to re-evaluate the emotional meaning of some of their symptoms, and improved. Most were better able to organize their ideas in relation to real rather than fancied problems and were seen to experience and express relevant emotion.\textsuperscript{49}
\end{quote}

This account closely echoes Grinker and Spiegel’s explanation of the efficacy of narcosynthesis, but the researchers saw LSD as an improvement on that method as it offered more clarity and depth in the emotional recall of past experiences.

\textsuperscript{49} Ibid., p. 243.
Busch and Johnson concluded that LSD “may offer a means for more readily gaining access to the chronically withdrawn patients. It may also serve as a new tool for shortening psychotherapy.” While technique and theory developed over the next decade, this basic theory of efficacy and aim remained the defining feature of psycholytic therapy.

Research lead by psychiatrist Ronald Sandison at Powick Mental Hospital, Worcestershire, England, turned Busch and Johnson’s experimental use of LSD into a fully formed treatment by offering a theoretical rationale, indications for use, and a distinct therapeutic method. Throughout the 1950s and 1960s Sandison was a pioneer and leading figure in psycholytic therapy, a term he coined in 1960. Published in 1954, Sandison’s concept of LSD’s utility was essentially the same as that of Busch and Johnson — opening patients up to psychotherapy, and hastening its progress — but enmeshed in a more particular theoretical framework, and aimed more specifically at treating the psychoneuroses. Beginning from the “generally accepted” theory that psychoneuroses were “the result of a faulty relationship between the conscious and the unconscious,” Sandison utilized LSD to produce an “upsurge of unconscious material into consciousness.” This material was then interpreted through a framework of Jungian analytical psychology, with the aim of “coming to terms with and assimilating the unconscious.” As well as uncovering repressed memories and producing abreaction, Sandison found LSD capable of

\[\text{Footnotes:}\]

\[50\] Ibid., p. 243.


producing vivid experiences of archetypes and archaic images “exactly similar in nature to those experiences of the collective unconscious which patients undergoing deep analysis experience in their dreams, visual impressions and fantasies.” Therefore, Sandison’s treatment departed little from the Jungian framework, but instead facilitated analysis, especially in patients whose “conscious barriers and resistances” made them inaccessible to therapy. Patients considered most appropriate for LSD therapy were psychoneurotics who presented “a more or less complete separation from causative memory and from the inner psyche” and whose primary symptom was “extreme mental tension.”

Sandison and his colleagues used LSD as part of a highly planned treatment regime, placing emphasis on the need for specially trained staff, a controlled environment, and patient preparation. They applied this therapeutic method to both inpatients and outpatients, although outpatients were preferably hospitalized for the first few weeks of therapy. Initial non-drug interviews established the patient’s history and built rapport with the therapist. Following this, sessions with sodium pentothal were used to prepare the patient for drug-assisted therapy. In the first week of LSD treatment, the patient was given the drug several times, in doses increasing from 25 mcg until a sufficient dose was found, after which LSD sessions were conducted on a weekly basis. The duration of treatment depended on the progress of the patient, and in some cases could be as long as twelve months. During the sessions the patient was located in a private room, with constant supervision from a nurse for the purpose of support.

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53 Ibid., p. 508.
The psychiatrist paid periodic visits to the patient throughout the session, usually spending an hour with them at the peak of the drug reaction. Much of the analysis occurred in the days after the LSD session, with the aid of reports that patients wrote of their experiences. Group therapy sessions with LSD patients gave them a chance to share their experiences with each other, and learn more about the treatment.55

Sandison tested this method on thirty-six psychoneurotic patients. The investigation was uncontrolled, but the patients chosen were all either severely ill with a poor prognosis, or were chronically ill and had failed to improve following other treatments. This helped to accurately determine efficacy, as these patients were less likely to spontaneously improve, or manifest a placebo response. Results were reported tentatively, and the researchers pointed out that their study was too small to allow statistical analysis. However, the general impression was positive: of twenty-three patients who had completed treatment at the time of reporting, fourteen were deemed recovered, and only two were not improved. Of twelve still undergoing treatment, eleven were considered improved. The duration of a patient’s illness appeared to have little effect on the outcome of treatment, or the number of session required, which varied from two to fifty-eight. The greatest success rate was with those experiencing obsessional and anxiety states.56

Back in the United States, by the mid-1950s the leading LSD researcher was

55 Ibid., pp. 504-507.
56 Ibid., pp. 501-504.
Harold Abramson of the Biological Laboratory, Cold Spring Harbor, New York. Earlier in his career, Abramson had focused on immunology and physical chemistry, however he had developed an interest in psychiatry and psychotherapy through his private medical practice in the 1930s, and pursued training in the disciplines. Despite his enthusiasm, he found his new field lacking in the laboratory research he was used to. Accordingly, on reading about LSD he became interested in the potential it posed for bringing the laboratory to psychiatry.\textsuperscript{57} Starting in 1951, Abramson and his colleagues conducted a wide variety of research with LSD at the Biological Laboratory. Their work investigated not only LSD's therapeutic potential, but also a range of its physiological and psychological effects, such as its effect on perception, spatial relations, motor performance, recall, attention, concentration, and arithmetic test performance.\textsuperscript{58}

Much of this research was funded by the US Central Intelligence Agency (CIA), as part of its secret MKULTRA program of research into mind control. According to journalist John Marks, Abramson was one of a number of researchers who performed research for the CIA, as well as reporting to the agency the results of


their own work, and other developments within the field.\textsuperscript{59} It is unclear, however, precisely what role the CIA played in shaping Abramson’s research, and their interests most likely lay in the psychological rather than psychotherapeutic aspects of his work. His publications of LSD psychotherapy research emphasize the need to carefully prepare the patient for LSD administration, in order to prevent anxiety reactions, and transcripts from LSD sessions show a caring, intimate, interaction with patients.\textsuperscript{60} This suggests that his psychotherapy research was genuine, rather than a cover for investigating sinister uses for the drug. His high standing in the field of LSD psychotherapy research (he would be a key organizer of two major international conferences on LSD psychotherapy) also strongly suggests that his peers considered his research ethical and valuable.\textsuperscript{61}

Like Sandison, Abramson used low doses of LSD (25-50 mcg) to facilitate psychotherapy. His treatment did have some significant differences to Sandison’s, however these differences reflected the variety of theories and methods of psychotherapy generally, rather than signifying a distinct form of LSD psychotherapy: as LSD was used merely as a tool to aid psychotherapy, the theories and methods behind its use varied with the psychotherapeutic frameworks of individual psychiatrists. Abramson’s emphasis on patient preparation and supervision during the entire period of drug action was similar

\textsuperscript{59} John Marks, \textit{The Search for the "Manchurian Candidate:"
\textsuperscript{61} See Abramson (ed.), \textit{LSD in Psychotherapy}; Abramson (ed.), \textit{Use of LSD in Psychotherapy and Alcoholism}. 
to Sandison’s, but the interaction with the psychiatrist was more intensive—LSD sessions would generally last four hours with the psychiatrist closely directing the experience through an interview style of interaction.\(^62\) His framework was also “quasi-Freudian,” rather than Jungian, therefore Abramson and Sandison’s concepts of how their treatments worked differed.\(^63\) Abramson described the effect of his LSD treatment as “hebesynthesis,” as opposed to a traditional narcosynthesis: “an elated state in which both ego-depression and ego-enhancement may occur simultaneously with the ego-enhancement leading to an increase in the integrative functions of the patient’s ego.”\(^64\) Abramson explained “ego-enhancement” as an improvement in a patient’s ability to identify conflict situations in their lives and reconstruct their adaption to these situations in more suitable ways.\(^65\)

Abramson’s reports do not offer quantitative data on the number of patients treated, their diagnoses, number of sessions given, or results, but instead give detailed accounts of individual patients and how LSD aided their treatment, explored through lengthy transcripts of LSD sessions. These patients were generally neurotic outpatients already undergoing psychoanalysis (often for several hundred hours), who had reached a block or were unable to confront and resolve an important psychological conflict. Results of the LSD sessions were discussed in terms of progress in analytic therapy, such as insights gained and conflicts resolved, rather than more general measures such as “recovered” or “improved.” For example, progress in one patient’s prolonged analysis resumed

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\(^{63}\) Abramson (ed.), \textit{LSD in Psychotherapy}, p. 25.
\(^{65}\) Abramson (ed.), \textit{LSD in Psychotherapy}, p. 34.
following a period of blockage, after feelings of distrust towards Abramson were uncovered during an LSD session and subsequently resolved. Abramson summarized the practical benefits of LSD as an adjunct to psychotherapy as

(a) pharmacologic safety, (b) effectiveness in small doses, (c) conscious cooperation on the part of the patient, (d) elimination of the difficulties of narcosynthesis, (e) feasibility of repeated administration, (f) absence of addiction problems, (g) excellent recall of events and ideas during psychotherapeutic interview.

By 1955 LSD research had become prominent enough to warrant a separate round table discussion at the annual meeting of the American Psychiatric Association. Entitled “Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry,” the session featured papers by eleven LSD and mescaline researchers, which, although often very short, give a good indication of the state of research at that time. Whilst researchers such as Abramson had been exploring LSD’s therapeutic potential, the predominant interpretation of the drug’s effects was still as a psychotomimetic: conference chairman Louis Cholden stated that the purpose of the symposium was “to utilize the tools of lysergic acid diethylamide and mescaline in a multi-faceted assault on the problem of the psychoses...[based on] the conceptual construct that these drugs have a meaningful relationship to the naturally occurring psychotic states.” Much of the meeting was therefore concerned with the method of action of the drugs, their relation to endogenous psychoses, and to other drugs used to treat these illnesses, rather than their therapeutic potential. Nevertheless, several important

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concepts regarding the drugs' therapeutic potential were also explored. Together with Ronald Sandison and Harold Abramson, who summarized their clinical research, Aldous Huxley and Charles Savage moved away from a narrow understanding of LSD and mescaline as psychotomimetics. They argued that the drugs could provoke a great variety of subjective reactions, that a person's reaction largely depended on extrapharmacological factors, and that these reactions could be harnessed for exploring and healing the mind. Huxley's discussion of the similarities between mescaline and visionary experiences is of most relevance to the development of psychedelic therapy, and will be discussed later. Savage, however was working from a roughly psycholytic perspective, and his findings had implications for all LSD psychotherapies. As the annual meeting of the American Psychiatric Association was a large, mainstream and prestigious conference, these presentations were well placed to make an impact on psychiatry.

Savage had been one of the first Americans to use LSD, and his career with the drug would be the longest and most successful of any American researcher, lasting until the early 1970s. Researching at a variety of locations, his use of the drug would evolve through psychotomimetic exploration and psycholytic therapy, to pioneering psychedelic therapy in the US in the late 1950s. Throughout he would remain at the forefront of not only treatment technique, but also research methodology. His attempts to balance these two elements of clinical research will take a central role in this thesis. Born in Berlin, Connecticut, in 1918, Savage studied psychology at Yale University and the University of Chicago, before graduating with his medical degree from the latter in 1945. In
1948 he began training as a psychoanalyst at the Washington-Baltimore Psychoanalytic Institute, from which he would graduate in 1957. He first used mescaline in 1949, while a researcher at the Naval Medical Research Institute in Bethesda, Maryland. There he had been exploring methods of facilitating psychotherapy, and had turned to mescaline after finding barbiturate narcosynthesis disappointing. Finding that the drug produced nausea in patients, he switched to LSD.69

In 1952 Savage published the first report to explore using LSD to treat depression. The precise therapeutic method Savage used in this study is unclear, however it differed significantly from that later described by Sandison and Abramson: rather than only using the drug during psychotherapy sessions, Savage administered low doses to patients daily for one month. This was done to assess whether the euphoria that LSD could produce would be therapeutic, as well as whether it could facilitate psychotherapy. Fifteen inpatients were treated in the study. All had been diagnosed with “depressive reactions,” however most were also diagnosed with schizophrenia, involuntional psychoses, or schizoid personalities. The study was loosely controlled, with the progress of each treated patient over six months compared to that of an untreated patient with a similar diagnosis. This was not only the first use of a control group in LSD research, but it was also a very early example of controlled research in psychiatry. While many

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of the patients improved, the rate of improvement was not different between the treatment and control patients. Despite this disappointing outcome, Savage found that “LSD affords therapeutically valuable insights into unconscious processes by the medium of the hallucinations it produces.” His interest in the drug therefore remained, and in 1955 he published a report describing the LSD “psychosis” through psychoanalytic theory, and exploring its implications for psychoanalytic understandings of endogenous psychoses.

At the American Psychiatric Association round table on LSD, Savage, now researching for the National Institute of Mental Health, presented a paper entitled “The LSD Psychosis as a Transaction Between Psychiatrist and Patient.” In it he explored how extrapharmacological factors could influence the effects of LSD, an understanding critical to the progress of LSD psychotherapy research. While throughout he referred to LSD as producing a psychosis, he described successfully using the drug to unblock a patient undergoing psychoanalysis, which helped progress her treatment. He also recognized that the drug did not always produce a psychosis, and in investigating what determined the patient’s reaction in a given LSD session, he highlighted the importance of many variables—the patient’s physiological state, personality structure, motivation for taking the drug, environmental stresses, and the presence or absence of other persons—which he grouped under the umbrellas of the “mental set of the

individual” and the “experimental setting.” The manipulation of these factors would come to be recognized by psycholytic, and later psychedelic, therapists as the key for producing a therapeutic drug response, and the term “set and setting” would be popularized in the 1960s by Timothy Leary and his cohort. In the mid-1950s, Savage's understanding of LSD’s effects straddled what would come to be called psychotomimetic and psycholytic: LSD as a producer of psychosis, and as a “mind loosening” drug of use to psychoanalysis. As his research progressed, Savage would focus more and more on the variety of effects the drug could produce, and how they could be manipulated and harnessed for therapeutic purposes. This would lead him to begin exploring psychedelic therapy in the late 1950s.

By the end of the 1950s, then, what would come to be called psycholytic therapy was well established both in the United States and internationally. The treatment was defined by the basic method of using small to moderate doses of

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72 Charles Savage, “The LSD Psychosis as Transaction Between the Psychiatrist and Patient,” in Cholden (ed.) Lysergic Acid Diethylamide and Mescaline, p. 41.
74 Savage further discusses his psycholytic use of LSD and mescaline in, Charles Savage, "The Resolution and Subsequent Remobilization of Resistance by LSD in Psychotherapy," Journal of Nervous and Mental Disease 125, no. 3 (1957), pp. 434-437.
LSD (20-200 mcg), in numerous sessions, in order to deepen and quicken the process of psychotherapy, primarily with patients with neurotic illnesses. Despite this framework, psycholytic therapy was never a uniform treatment in terms of theory or method. As LSD was used merely as an adjunct to psychotherapy, more specific theories of efficacy and therapeutic methods varied greatly according to the psychotherapeutic schools under which it was used, and the personal interpretations of individual psychotherapists. The disparity between theories and methods resulted in a field that would struggle to move forward, as researchers worked individually rather than building on each other’s work to spread a testable or easily replicable treatment. This problem was clearly demonstrated at the first major US conference solely concerning LSD’s therapeutic potential, entitled “The Use of LSD in Psychotherapy.” Held in Princeton, New Jersey, in 1959, and sponsored by the Josiah Macy, Jr. Foundation, the conference brought together twenty-six of the leading international LSD researchers to discuss their therapeutic work. The verbatim proceeding of the conference, which was designed as a series of discussions rather than formal presentations, show that while there was little disagreement over LSD having therapeutic benefits, there was little agreement on exactly how to use and interpret the drugs effects: as participant Betty Eisner remembered “there were 26 different ways of looking at psychotherapy as well as LSD: twenty-six different areas of expertise and experience, and 26 opinions on the drug.”76

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From the very beginning of the conference's first discussion, led by Harold Abramson, it was evident that the lack of a common language regarding the specifics of psychotherapy, let alone LSD psychotherapy, was a major difficulty for therapists wanting to pool their experience: just three sentences into Abramson's description of his therapeutic method, the discussion turned to the definition of his framework of "psychoanalytically orientated psychotherapy."\textsuperscript{77}

Despite host Frank Fremont-Smith's initial attempts to steer the discussion away from definitions—as "We certainly won't reach agreement today, tomorrow, or in 20 months on a common definition of any form of psychotherapy with a label attached"—the difficulties of overcoming the participants different theoretical frameworks proved insurmountable: as he later stated "The striking feature of the Conference so far is that we have not communicated. The verbal image that was good for one of us was not good for eight-tenths of the others."\textsuperscript{78}

Terminology used to describe the therapeutic effects of LSD, such as "ego enhancement," "reconstructive therapy," and even "subconscious," had far from universal understandings and often caused confusion amongst the participants.\textsuperscript{79}

Similarly, even the common experiences of patients under LSD were interpreted differently, with the experience of being born, or giving birth, for example, considered a memory by some and a fantasy by others.\textsuperscript{80} Differences in interpretation were not the only difficulties that varying psychotherapeutic orientations caused. Beverly Hills psychiatrist Mortimer Hartman had found in

\textsuperscript{77} Abramson (ed.), \textit{The Use of LSD in Psychotherapy}, pp. 25.
\textsuperscript{78} Ibid., pp. 26, 225-226.
\textsuperscript{79} Ibid., pp. 34-35, 48-49,152-153.
\textsuperscript{80} Ibid., pp. 94-98.
his clinic that the orientation of the therapist fundamentally altered the
experience of the patient and the material they brought forward,

In our group, for instance, which consists of two Freidians and two
Jungians, the latter will get the transcendentental experience in the patient
much faster than the former. The two Freidians, on the other hand, will
evoke the patient’s childhood memories much more quickly than the two
Jungians in the group. These results are due to the different orientations
and different kinds of suggestion on the part of the therapists.\(^81\)

While the theoretical differences between therapists made it difficult to cement a
clearly defined treatment paradigm for LSD as an adjunct to psychotherapy, with
Ronald Sandison concluding that “every physician probably has to administer
LSD in his own way,” the difficulties raised important questions for
psychotherapy research with or without LSD.\(^82\) With reactions under LSD
highlighting the power of the therapist’s conscious or unconscious suggestions,
beliefs, and attitudes in shaping the therapeutic responses of the patient, it
became clear that a greater understanding of the patient-therapist relationship
was needed in order to understand the efficacy of any psychotherapy. The lack of
understanding of LSD psychotherapy’s efficacy was not a failing of the
researchers, but merely reflected the complexity of the task, as Frank Fremont-
Smith expressed in his concluding remarks,

I would like just to touch on the fact that we have been dealing with the
very essence of the nature of therapy of any kind, of the nature of the
psychotherapeutic process, about which we certainly know too little. It
involves the nature of human relationships, because psychotherapy
involves both relationships within the person and between persons…. 
...we should not feel too distressed because we cannot encompass all this;
that would hardly be possible....
Added to these basic problems of human personality and human

\(^{81}\) Ibid., p. 132.
\(^{82}\) Ibid., p. 84
relationships, there is a drug, a pharmaceutical agent, and this both complicates and simplifies the situation. It brings it nearer to science, on the one hand, and throws into bolder relief the very complexity of the problem itself.\textsuperscript{83}

Clearly defining the efficacy of psycholytic therapy would first require defining the efficacy of the forms of psychotherapy that LSD was used to facilitate. In the 1950s, this fact did not pose a threat to LSD psychotherapy’s existence. Even though LSD was still classed as an experimental drug, obtaining supplies from Sandoz was straightforward, and the law did not prevent the clinical use of experimental drugs. Furthermore, psychodynamic therapies held high status in psychiatry and their efficacies were not widely contested. However, Fremont-Smith’s comments foreshadowed the issues that would underlie the downfall of LSD psychotherapy—after the Drug Amendments of 1962 researchers would be required to provide proof of drug efficacy, and thus LSD psychotherapists would be required to provide proof of the efficacy of the psychotherapies that underpinned their treatments. This would ultimately prove an insurmountable challenge.

\textbf{Psychedelic Therapy}

Psychiatrists Humphry Osmond and Abram Hoffer, of the Saskatchewan Mental Hospital in Weyburn, Saskatchewan, Canada, first conceived the idea for using LSD to treat alcoholism in 1953. Over the decade Hoffer and Osmond, with the help of their colleagues, developed the unique therapeutic method of psychedelic

\textsuperscript{83} Ibid., pp. 239-240.
therapy. The therapy’s method focused on manipulating the set and setting of the patient in order to produce the “psychedelic experience,” and the theory behind the treatment combined ideas ranging from the study of mysticism, traditional uses of the mescaline containing peyote cactus amongst Native Americans, and the observation of the circumstances under which chronic alcoholics had spontaneously quit drinking. Psychedelic therapy was a psychological treatment, however, unlike psycholytic therapy, it did not emerge from psychotherapy research, but morphed out of psychotomimetic research. Rather than psychoanalysts, both Osmond and Hoffer were biologically orientated psychiatrists. However, when it became apparent that the drug effects they were observing could have therapeutic potential, they did not turn down the opportunity to explore this. While much of the early research was performed in Canada, the theories and methods of psychedelic therapy quickly crossed the border to the United States, and the treatment was well established there by the start of the 1960s.

Born in England, Osmond began his research career in the years after the Second World War at St George’s Hospital, London, where with colleague John Smythies he began investigating chemically induced hallucinations. Noting the similarities between the effects of mescaline and the symptoms of schizophrenia, and after discovering that mescaline was chemically similar to adrenaline, they put forward an argument that schizophrenia was a biochemically induced illness, the result of a fault in the metabolism of adrenaline, which produced a psychoactive
chemical. In 1951 Osmond moved to Saskatchewan, where he used LSD to continue this line of research with his new colleague Abram Hoffer. Before studying medicine Hoffer had earned a PhD in agriculture, and his interest in biochemistry remained when he later specialized in psychiatry. Together they utilized the psychotomimetic effects of LSD not only to study potential biochemical processes involved in the cause of schizophrenia, but to further their understanding of the nature of the illness by taking the drug themselves. Furthermore, they believed that experiencing the LSD model psychosis had clinical applications, as it increased their understanding and empathy with patients, improving their therapeutic relationship. Their colleague, hospital architect Kiyo Izumi, even used LSD to help design a psychiatric hospital. While performing research for his design of the Yorktown Psychiatric Center, Izumi took LSD in Saskatchewan’s traditional psychiatric hospitals in order to better understand the experiences of patients in these buildings. He found that many elements of their design worsened his feelings of confusion and intimidation. In order to lessen this in his hospital, Izumi’s design emphasized privacy, clear functionality in structural details, spaces that lessened socially intimidating situations—such as being faced by a crowd when entering a room—and the avoidance of jarring changes in the look, feel, and acoustics of different spaces.

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The idea of using LSD to treat alcoholics came to Hoffer and Osmond in the early hours of one morning in 1953, after the two had had been unable to sleep while travelling on business. Discussing problems facing psychiatry, their minds turned from schizophrenia to the large population of alcoholics in their hospital, for whom there was no effective treatment. They considered that in Alcoholics Anonymous (AA), “hitting bottom” was often regarded as a crucial prerequisite for recovery. While what constituted “bottom” was subjective to the individual, commonly it was experiencing delirium tremens. Caused by withdrawal from alcohol after long bouts of heavy drinking, the condition was characterized by tremors, hallucinations, and agitation, and was fatal in approximately 10 percent of sufferers. Therefore, while it may have been an effective turning point for chronic alcoholics, it was a dangerous and unpredictable event to wait for. However, Hoffer and Osmond postulated that LSD’s psychotomimetic effects could be used to mimic delirium tremens, causing patients to artificially hit bottom. Not only would this be safer, but it could also be performed earlier, and in a controlled supportive environment where the experience’s potential for positive impact could be enhanced.

On their return, Hoffer and Osmond immediately tested the hypothesis, giving LSD to two alcoholic patients at the Saskatchewan Hospital, with success for one. On the basis of this, their colleague Colin Smith undertook a larger study

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89 Hoffer, "Treatment of Alcoholism," p. 344.
with twenty-four alcoholics, and published results in 1958. In order to establish efficacy, patients were chosen for the severity of their problems and poor prognosis: most had failed AA and had further psychiatric complications. The study was uncontrolled and patients were given a strong dose of LSD (200-400 mcg) or mescaline after two to four weeks of psychotherapy. The patients were accompanied throughout the session, which included a long interview focusing on their problems in which they were given strong suggestions to stop drinking. The session was discussed with the therapist over the next few days, before they were discharged and encouraged to join AA. Follow-up, through AA, ranged from two months to three years, and found half of the patients either improved or much improved after the treatment. Smith considered as critical to the success of the treatment both an intense drug reaction and the psychotherapeutic regimen it was enmeshed in. While the theory was to help patients hit bottom there was no effort to scare the patient into the psychotomimetic reaction. Instead the therapist used a “technique of exhortation, persuasion and suggestion” in order to help the patient to increase their self-understanding, gain a new perspective on their drinking habits, and develop the motivation to quit drinking.\textsuperscript{90} This effect was displayed on one patient who, under 300 mcg of LSD, commented,

\begin{quote}
This treatment has brought back many thoughts. When I think of it, what a fool I made of myself these last 22 to 23 years...I wanted to stop drinking for a long time, but it's lack of will-power. I started drinking at 18. My stepfather was a heavy drinker. I drank to get even for I felt the more we had the less he had...This is an experience worth going through. I feel I can stay away from alcohol now.\textsuperscript{91}
\end{quote}


\textsuperscript{91} Ibid., p. 414.
Early on the Saskatchewan researchers realized that although the treatment was working, great numbers of the patients were not experiencing the model delirium tremens they set out to create. Instead patients were having experiences that were “exciting and pleasant, and yielded insight into their drinking problems,” with some even “escaping into a spiritual or religious type of experience.”

They soon learnt that this kind of treatment had a precedent, as members of the Native American Church of North America used peyote to commune with God and combat drinking. The researchers would also point to renowned psychologist William James’s observation that powerful transcendental or religious experiences could cure alcoholics, as discussed in his 1902 work *The Varieties of Religious Experience*. Such an experience had also famously led Bill W. to quite drinking and develop AA in the 1930s.

Osmond took a particular interest in the transcendental effects that LSD and mescaline could produce. As well as harnessing them clinically, he began exploring their non-medical significance with prominent British author Aldous Huxley. Now residing in Los Angeles, Huxley had a keen interest in mysticism and he contacted Osmond in 1953 after reading reports of his early research.

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Osmond subsequently visited Huxley and administered him mescaline. The next year Huxley published *The Doors of Perception*, an account of this experience that would influence not only LSD researchers, but also the psychedelic counterculture of the 1960s.95

At the 1955 American Psychiatric Association round table on LSD and mescaline, Huxley presented his interpretation of his mescaline experience to the psychiatric community. Whilst his paper concerned the interpretation and significance of mescaline’s effects on healthy individuals, utilizing the type of experience he described would come to be the basis of psychedelic therapy as it further developed. Huxley described the similarities between the “classic mescaline experience” (as described by himself and notable nineteenth century peyote experimenters neurologist Silas Weir Mitchell and physician and sexologist Havelock Ellis) and the spontaneous experiences of history’s visionaries, such as William Blake. To Huxley, mescaline seemed to open usually inaccessible parts of the mind:

Let us use a geographical metaphor and liken the personal life of the ego to the Old World. We leave the Old World, cross a dividing ocean, and find ourselves in the world of the personal subconscious, with its flora and fauna of repressions, conflicts, traumatic memories and the like. Travelling further, we reach a kind of Far West, inhabited by Jungian archetypes and the raw materials of human mythology. Beyond this region lies a broad Pacific. Wafted across it on the wings of mescaline or lysergic acid diethylamide, we reach what might be called the Antipodes of the mind. In this psychological equivalent of Australia we discover the equivalents of kangaroos, wallabies, and duck-billed platypuses—a whole host of extremely improbable animals, which nevertheless exist and can be

From these kind of visionary experiences, Huxley suggested, came the descriptions of the “other world” found in various religions and folklore—the worlds of gods, often described as “of surpassing beauty, glowing with color, bathed in intense light,” featuring “buildings of indescribable magnificence” and “fabulous creatures...superhuman angels and spirits, who never do anything, but merely enjoy the beatific vision.”97 Audience member Roland Fisher dismissed Huxley’s experience as “99 per cent Aldous Huxley and only one half gram mescaline...some of us are visionaries and others just dry scientists.” In an indirect response, Huxley criticised the use of the term “hallucinogen” to describe LSD and mescaline, due to its “pejorative overtone”: “To call an experience a hallucination is, implicitly, to condemn it as unreal and in some way discreditable.” Instead, he argued, the notion of what was “real” needed to be more critically examined: rather than impose visual distortions, the drugs could unleash latent potential in the mind, allowing the user to see the world as it was, “fresh, living, blazing with color and charged with infinite significance.”98

Osmond presented his new multifaceted understanding of the effects of LSD and mescaline to the scientific community in 1957, at a meeting of the New York Academy of Sciences. He connected the Saskatchewan research to cultural and intellectual traditions varying from the relatively recent work of figures such as William James and psychiatrist Carl Jung, to the ritualistic and religious use of

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97 Ibid., p. 49
98 Cholden (ed.) Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry, pp. 67, 77-78
drugs by cultures throughout time: “We are the latest of generations of experimenters who, from before the dawn of history, in every part of the world, have sought for means by which man could alter, explore, and control the workings of his own mind, thus enlarging his experience of the universe.”

Osmond believed the drugs had uses in studying psychotic illnesses, psychotherapy, training mental health workers, and “exploring the normal mind under unusual circumstances.” Their mystical effects also had social, philosophical, and religious implications, as they could “help us to explore and fathom our own nature,” through their ability to strip the user of their acquired beliefs and “see the universe again with an innocent eye.”

In light of their variety of effects and uses, Osmond felt that “psychotomimetic” was too narrow a term for the LSD-like category of drugs, and instead proposed the term “psychelic.” Meaning “mind-manifesting,” the name was designed to “include the concepts of enriching the mind and enlarging the vision” and to escape the negative connotations of terms such as “psychotomimetic” and “hallucinogen.”

Whilst the term was designed to encompass all the possible effects of the drugs, it soon came to represent their transcendent or mystical qualities.

Hoffer, Osmond, and colleagues were not the only researchers to be exploring the psychedelic effects and uses of LSD. In British Colombia, American Alfred M. Hubbard had been simultaneously developing a treatment for alcoholism that similarly focused on the patient attaining a psychedelic reaction, but with more

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100 Ibid., p. 420, 429, 430.
101 Ibid., p. 429.
advanced techniques of ensuring this happened. Contact between Hubbard and the Saskatchewan researchers led to a refining of their therapeutic method. Hubbard, a lay therapist working under the medical guidance of J. Ross MacLean at Hollywood Hospital in Vancouver, was a mysterious character who had been a United States Office of Strategic Services operative during the Second World War before becoming one of LSD’s greatest advocates during the 1950s. While he had no background in medicine or psychology, he made up for this in the mid-1950s by obtaining a PhD in Bio-Psycho-Dynamic Sciences, although this was most likely purchased. Despite his suspect credentials Hubbard was skilled in the use and manipulation of LSD’s effects. In 1957 he visited the Saskatchewan researchers to demonstrate his therapeutic method. His innovation was to manipulate the set and setting of the patient, through the use of a specially designed treatment room and visual and auditory stimuli, to help the patient relax and to foster the psychedelic experience. The room was not a clinical environment, but instead used furnishings such as drapes, sofas, and rugs to create a comfortable, tranquil atmosphere. Music, photographs, artworks, flowers, and other stimuli were used during the sessions to help patients relax, to direct their emotions, to help them explore their enhanced perception, and to focus them towards a spiritual experience.

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103 Oliver Field to Lynn Gunn, September 10, 1959, folder 9, box 482, collection 471, Historical Health Fraud and Alternative Medicine Collection, American Medical Association, Chicago, Illinois.
Adopting these changes, Nick Chwelos led a new study at the Saskatchewan Hospital with sixteen alcoholics. Results, published in 1959, found that after an average follow-up period of six months, all but one patient was improved and ten were much improved. As well as the addition of visual and auditory stimuli, the new method involved a greater emphasis on the nature of the therapist’s attitude and interaction with the patient: emphasis was placed on an accepting attitude, encouraging patients towards self-acceptance while stressing that they had the power and responsibility to change the pathological attitudes that became apparent. The researchers also placed emphasis on the need for the therapist to have experienced LSD in order to be able to understand the patient’s experience and effectively use it. The exact nature of the psychedelic experience, due to its individual, subjective, and otherworldly nature was difficult for patients or researchers to easily describe. Similarly the mechanism by which the experience could help the alcoholic was highly complex, but can be seen as involving a change in their perspective of themselves, their drinking, and their relationship to others. The researchers explored how some of the common experiences, such as “being able to see oneself objectively,” “feeling of being at one with the universe,” and a “change in the usual concept of self,” had a therapeutic effect,

Because the drug makes him feel he is infinite in essence it is much easier for him to accept himself completely and it readily becomes evident that he can only accept the outside world to the exact degree that he accepts himself. ...This equalizing effect tends to remove any form of pride, prejudice, guilt or anxiety. The person then sees that faith which is the acceptance of himself as infinite and love which is the acceptance that everything around him is equal to him in substance is the clue to a smooth, pleasant, useful LSD experience, and he generalizes this to everyday experience. The patient then ceases the tragedy of desiring to be other than

he is in essence and realizes that he can only be other than he is in terms of his acts. The energy diverted from attempts to alter his basic nature can now be used to alter his feelings and acts in a way which makes his life more peaceful and satisfying and his outlook more compassionate.  

With Chwelos’s study, the psychedelic therapy paradigm had fully developed: a single, high-dose LSD treatment, embedded in ongoing psychotherapy, utilizing visual and auditory stimuli, with a therapist acting as supportive and encouraging guide, rather than analytic interviewer, in order to produce a psychedelic experience that could fundamentally change an alcoholic’s attitudes, perspective, and behaviour, leading to sobriety.

In the United States, interest in the psychedelic effects of LSD began to grow near the end of the 1950s, primarily in California. Rather than a simple replication of the Canadian psychedelic therapy, much of the psychedelic research was explorative in nature, approaching the effects of LSD from philosophical and religious, as well as psychiatric, perspectives. Philosophical and religious perspectives were most notably explored by Aldous Huxley and philosophers Gerald Heard and Alan Watts, who shared Huxley’s interest in the relationship between psychedelic and religious experiences, across cultures and throughout history.  

This intellectual interest was not divorced from clinical research, as Huxley and Heard, as well as Los Angeles psychiatric researcher Sidney Cohen, were members of the Commission for the Study of Creative Imagination, a collective formed to share and support psychedelic research, which also included Hubbard, Hoffer, Osmond, and other researchers from Canada, the US, England,

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106 Chwelos et. al., "Use of d-Lysergic Acid Diethylamide," pp. 584, 588.
and Mexico. Therefore through the collaboration of intellectuals and clinical researchers, the psychedelic theory and method soon radiated out of Canada.

Cohen and his research partner, psychologist Betty Eisner, were early adopters of some of the Canadian researchers’ techniques, at the Los Angeles Veterans Administration’s Neuropsychiatric Hospital. Their use of LSD was theoretically and methodologically between psycholytic and psychedelic therapy. Patients with a wide variety of diagnoses were treated, in multiple sessions, with doses building up to 125 mcg, and the goal was more effective psychotherapy through conventional channels such as abreaction, and enhanced insight and recall. However elements of psychedelic therapy were also present—music, mirrors, and photographs were used to aid relaxation, direct emotions and promote insight, and a therapist who was personally experienced with the drug was present for the length of the drug reaction. The researchers also noted that the drug could produce “an experience of integration for the patient wherein he was able to see himself in proper perspective and in relation to his environment,” which was a key factor in the therapeutic potential of the psychedelic experience. Eisner and Cohen’s personal experiences with the drug had also been in the psychedelic realm: both first tried the drug in 1955, with Eisner reporting “being drawn into a mystical experience—the sense of unity with all things in the universe” and Cohen, who expected to be catatonic, writing “I seemed to have finally arrived at the contemplation of the eternal truth...At one moment I was a timeless spirit.” The pair were also notable for

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108 Dyck, *Psychedelic Psychiatry*, pp. 9, 6-98.
110 Eisner, *Remembrances of LSD Therapy Past*, p. 5; Sidney Cohen, *The Beyond Within: The LSD
administering LSD to AA founder Bill W., who likened his experience to the
religious revelation that had led to his sobriety.111

In 1960 an LSD symposium was held at the Napa State Hospital in California,
where three researchers from the Palo Alto Medical Research Foundation's
Mental Research Institute—James Terrill, Donald Jackson, and Charles Savage—
discussed the psychedelic effects and implications of the drug. Terrill had
administered LSD to both volunteers and psychiatric patients in an atmosphere
and physical environment similar to that of the Canadian researchers. He found
that patients had a wide variety of reactions, including the transcendental, that
were the result of a “complex interaction of the drug, the psychological and
physical environment, the personality structure of the subject and therapist, and
the set or expectancy as to what the drug would do.”112 In therapeutic sessions,
beneficial results came from changes to patients’ value systems, rather than
through the traditional channels of psychotherapy, and were “in the direction of
a higher valuation of esthetic, creative, philosophic and perhaps even religious
interests.”113 Jackson echoed Terrill’s emphasis on the importance of set and
setting in determining a patient’s reaction to LSD, and discussed how the
transcendental reaction could

lead to a lessening of alienation, to a rediscovery of the self, to a new set of
values, to the finding of new potential for growth and development and to

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113 Ibid., p.428.
a new beginning. This many be followed by a change in behavioural patterns, as in the cessation of drinking.114

Savage drew on his experience with twenty alcoholic patients to explore how LSD could promote sobriety. The patients had been treated with 150 to 500 mcg of LSD in a psychedelic therapy setting, and 50 percent had stopped drinking.115 Like Hoffer and Osmond, Savage discussed psychedelic therapy’s precedent in the Native Americans’ use of peyote to cure or prevent alcoholism, which, he argued, worked by not only giving a renewed connection with religion, but an increased faith in and identification with their culture in the face of European domination. He also similarly explored the theories of William James as an explanation for both the causes of alcoholism and how LSD could be of use in treating it. He argued that for some patients, LSD treatment closely mirrored the sobriety inducing conversion experiences mentioned by James, which had prompted James to remark, “The cure for dipsomania is religiomania.”116 The religious experience that LSD could produce, seemed to Savage to produce a powerful feeling of forgiveness that could break the cycle of “drink to still guilt, and drink giving rise to guilt.”117 However religiosity was not the only way LSD could bring about the cure of alcoholism. James had postulated that alcohol’s allure came from its “power to stimulate the mystical faculties of human nature.”118 It did this, however, only in a fleeting manner, leading the seeker of these experiences to destructive overindulgence. Drawing on the theories of

116 Ibid., p. 430. The original quote from James was “The only radical remedy I know for dipsomania is religiomania” and was credited to “some medical man.” James, *The Varieties of Religious Experience*, p. 263 n. 1.
118 James, quoted in Ibid., p. 432.
psychoanalyst Erich Fromm, Savage argued that the need for mystical experience was based in feelings of alienation, and therefore the more powerful mystical experience that LSD could produce could give a more lasting resolution of these feelings, relieving the patient’s desire to drink:

Many drinkers drink because their lives have lost purpose and meaning. The old drunk might drown his sorrows; the modern drunk fills the emptiness of his existence. The alcoholic attempts to find himself, to fulfil himself with drink; but the attempt fails and now the guilt over drink and the wasted opportunity has him trapped. How then may LSD help with this situation? It may provide a genuine transcendental or mystic experience instead of the spurious one “bit of mystic consciousness” which the alcoholic has been seeking. The artificial distinction between subject and object, self and world, conscious and unconscious, ego, id and superego are all abolished. The person is at one with the universe. In his mystic selflessness he awakens with a feeling of rebirth, often physically felt, and he is provided with a new beginning, a new sense of values. He becomes aware of the richness of the unconscious at his disposal; the energies bound up in and by repression become available to him.\textsuperscript{119}

In the years after this conference, psychedelic therapy became the dominant form of LSD psychotherapy being researched in the United States, and in fact, the US overtook Canada as leading country for psychedelic therapy research.

\textbf{Conclusion}

Over the 1950s, LSD psychotherapy developed out of the eclectic and innovative context of psychiatry in the United States and internationally, and was facilitated by the loose regulation of pharmaceutical research. Whilst psycholytic and psychedelic therapy were very different, both involved using a drug to facilitate a psychotherapeutic process. They both, therefore, bridged any theoretical divide.

\textsuperscript{119} Ibid., pp. 432-433.
between biological and psychodynamic psychiatry. The effectiveness of both
treatments seemed evident to essentially all who had explored them. Ultimately
the efficacy of psycholytic therapy was tied to the effectiveness of the
psychodynamic forms of psychotherapy LSD was used to facilitate. Therefore,
with psychodynamic theory dominant in 1950s psychiatry, the efficacy of
psycholytic therapy was not under particular scrutiny. Results reported for
psychedelic therapy in the treatment of alcoholism were particularly dramatic.
While the treatment was unconventional, and the research was uncontrolled, its
success with otherwise refractory patients left researchers convinced of its
effectiveness. The treatment had the potential to make a significant impact on
the well-being of alcoholics, as psychiatrists had previously had little success
with these patients. At the turn of the 1960s, therefore, LSD psychotherapy was
an established field of research, which promised to eventually result in LSD
finding an accepted place in psychiatry. This promise, however, was never
realised.
2. Regulating Research: Access to LSD After 1962

Over the 1950s and early 1960s, the 1938 Food, Drug, and Cosmetic Act had afforded LSD researchers great freedom in the initiation and conduct of their clinical research. Under these conditions, LSD psychotherapy research had flourished. With the passage of the Drug Amendments of 1962, however, the field of pharmaceutical research and development changed significantly. The two major changes introduced by the act were FDA oversight of pre-market clinical research, and the requirement for proof of effectiveness, as well as safety, in a New Drug Application (NDA). This first provision had an immediate impact on LSD research. Research sponsors were required to submit to the FDA a Notice of Claimed Investigational Exemption for a New Drug (IND) before commencing pre-market clinical research. The IND outlined the proposed research, the qualifications of the researchers, and data on the investigational drug that justified its clinical use. If the FDA were not satisfied with the contents of an IND, it would be terminated, and the sponsor would no longer be permitted to conduct clinical research with the drug. As Sandoz Pharmaceuticals had not submitted an NDA for LSD, clinical research with the drug could now only be performed under the approval of the FDA.

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Whilst LSD psychotherapy research continued under the IND regulations, the scale of research decreased in the years after 1962. This coincided with an increase in the drug’s non-medical use, and the public and political controversy accompanying it. As a result of the controversy, LSD was listed among the drugs controlled by the Drug Abuse Control Amendments of 1965. This legislation aimed to curtail the abuse of certain non-narcotic drugs through the prohibition of their manufacture, distribution, sale, and possession outside of legitimate, registered, channels. The FDA was charged with enforcing the new law. Whilst this legislation did not directly concern LSD researchers, it cemented LSD’s status as a dangerous drug of abuse. Shortly after the Drug Abuse Control Amendments, the scale of LSD research in the United States decreased further.

Histories of LSD research have generally argued or implied a causal link between the LSD controversy, increasing regulation, and the demise of LSD psychotherapy: when the FDA gained oversight of LSD research they began restricting it, and as the controversy increased, and regulation expanded, the FDA’s stranglehold on research tightened. Historian Steven Novak has clearly argued that the government deliberately shut down LSD research. He states that following the passage of the Drug Amendments of 1962, Congress began

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“progressively tightening regulation of investigational drugs until research on LSD virtually ground to a halt,” and in 1966 “Congress cut off nearly all LSD research.” LSD researchers who had their INDs terminated in the mid-1960s have supported this perspective. Myron Stolaroff recollected that in 1965, the new FDA commissioner James Goddard “brought a halt to all LSD research in the nation.” Harold Abramson described in 1967 that LSD research was being “seriously hampered in the U.S. by the curtailment of Government approval.” Private practice physicians were especially being prevented from conducting research, due to the government’s inability to “distinguish between the medical use of LSD and the sociological problems engendered by all drugs that influence the mind.”

That the government deliberately restricted LSD research appears almost self-evident given how closely the decline in research followed the drug’s growing abuse and regulation. However, closely analyzing the provisions of the new regulations, and their implementation, will reveal a far more impartial role for the FDA. Whilst many researchers found themselves unable to continue their research under the new regulations, this was not due to any specific attempt to restrict LSD research on the part of the FDA. Instead, the reduction in research was due to two factors: Sandoz’s own initiative to restrict LSD to hospital based government funded studies, and the difficulty of fulfilling the new IND

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requirements as an independent researcher. These factors reflected a formalization of pharmaceutical research in the United States engendered by the Drug Amendments of 1962. Where LSD psychotherapy research had progressed in a disorderly fashion, with a large and diverse population of researchers all conducting their own small and varied studies, the field was reorganized into a smaller number of formal clinical trials. Those who continued research were approved on their scientific plan, qualifications, and their institutional setting.

This chapter will closely examine the relationship between the FDA and LSD researchers through following the INDs submitted by Sandoz, Abramson, and Stolaroff’s research foundation, the International Foundation for Advanced Study. FDA files, as well as testimony from congressional hearings, reveal that although the formalization of research left experienced and significant researchers, such as Abramson and Stolaroff, unable to conduct clinical LSD research, there were objective reasons for this. Rather than thwarting LSD research, the FDA merely evaluated applications to conduct research according to objective criteria. Where the LSD controversy had its major impact was in influencing Sandoz to withdraw its sponsorship of LSD research in 1966. This made LSD’s development into a marketable pharmaceutical much less likely, as researchers were not normally responsible for pushing drugs through the NDA process without the support of a pharmaceutical company. However, the controversy did not result in the government shutting down LSD research. In fact, in 1966, after LSD had been criminalized and Sandoz had withdrawn its IND, the FDA, together with the National Institute of Mental Health (NIMH), voluntarily worked to ensure its survival.
The IND Regulations and Sandoz Pharmaceuticals

The IND regulations of the Drug Amendments of 1962 emerged as a result of FDA concerns that drug manufacturers were using the premarket phase of a drug's development for more than just research. From the mid-1950s, FDA officers had been aware of their inability to prevent widespread distribution of investigational drugs to physicians for the ulterior purpose of establishing their place in the market prior to official release. The danger of this practice became evident in the case of thalidomide, the teratogenic sedative that could cause phocomelia—characterized by a shortening of the limbs so that hands and feet appeared to join straight to the body—when ingested during pregnancy.

Although FDA medical officer Frances Kelsey had withheld approval of William S. Merrell Company’s NDA for thalidomide in 1960, the firm had distributed the drug widely to physicians recommending its routine usage. As a result, an estimated 16,000 patients received thalidomide. It was mostly luck that only seventeen confirmed cases of phocomelia were found in the United States: most of the patients who were pregnant did not receive the drug in their first trimester, when damage to the fetus occurs. Therefore, as was also the case for the Drug Amendments of 1962 in general, the thalidomide tragedy pushed through investigational drug reforms that had long been promoted by the FDA,

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but which had previously languished due to public disinterest, and political and industry opposition.⁹

In order to safeguard against dangerous and non-research investigational drug use, the Drug Amendments of 1962 granted the FDA oversight of drug research and development. The legislation provided that a drug manufacturer, or other investigative sponsor, would be granted an exception allowing them to use a drug without an accepted New Drug Application after providing the FDA with details of preclinical research which justified its use in humans. Assurance also needed to be given that patients would be under the personal supervision of the investigators, that the experimental drug would not be supplied to anyone outside of the investigation, and that data resulting from research would be recorded so that it could be reported to the FDA in order to determine the safety and effectiveness of the drug.¹⁰

In order to enact these provisions of the Drug Amendments of 1962, the FDA drew up new investigational drug regulations, which became effective on 7 February 1963. Earl Meyers, chief of the controls evaluation branch of the FDA’s Division of New Drugs, described the intent of the regulations as ensuring that adequate preclinical research had been performed to justify clinical testing, that

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investigators were qualified to perform clinical research with the drug, and that a scientifically sound program of research would be followed.\textsuperscript{11} The regulations centred on the creation of the IND form, officially entitled “Form FD 1571” or “Notice of Claimed Investigational Exemption for a New Drug.” Before commencing clinical research with an investigational drug, the potential sponsor needed to submit this form to the FDA. Approval of the IND was not required; research could start immediately on submission. However, if the FDA was not satisfied with the contents of an IND, the sponsor’s exemption could be terminated.\textsuperscript{12}

Following the intentions of the regulations, the information required by the IND form focused on drug data, the investigators, and the plan of research. Drug data required included its chemical structure, the composition of the preparation, manufacturing and quality control standards, and details on preclinical investigations, including animal studies, which suggested reasonable safety for use in clinical studies. Details regarding the investigators included their names, qualifications, and experience, as well as a statement of the qualifications and experience considered appropriate for the study. Investigators were also required to submit a separate, more detailed, individual statement of their qualifications, facilities, plans, and responsibilities. The plan of investigation required designating the “phase” of the research: phase one consisted of basic clinical pharmacology, testing issues such as toxicity, metabolism, absorption, and elimination. Phase two tested the drug in an initial small series of patients,

\textsuperscript{11} Meyers, “Investigational Drugs,” p. 3.  
\textsuperscript{12} Bureau of Enforcement to Directors of Bureaus and Divisions, and Directors of Districts, 7 May 1963, folder 505.51 April—May, box 3572, RG 88.
whilst phase three established the drug’s safety and effectiveness in a large number of patients with a reasonably standardized protocol. Further details included the number of subjects involved, their selection criteria, the clinical trial design, testing methods, and the duration of treatment.\textsuperscript{13}

For drugs that were already involved in human research, a deadline for the submission of IND forms was set for 7 June 1963.\textsuperscript{14} Shortly before the deadline, Sandoz Pharmaceuticals submitted INDs for the clinical investigation of LSD and psilocybin. Sandoz had isolated psilocybin from hallucinogenic mushrooms in the late 1950s, and had subsequently synthesized it and distributed it in a similar manner to LSD.\textsuperscript{15} The INDs were very broad in their scope and light on details. They proposed phase three clinical trials, which were already under way, as phase one and two studies had been completed. The drugs were being investigated in the “treatment of varied psychotic and psychoneurotic disorders”—including chronic alcoholism and autism in children—as a facilitator of, and adjunct to, psychotherapy, and as an analgesic for intractable pain. A proposed adult dose range for LSD was given, ranging from 1 microgram per kilogram of body weight (mcg/kg) once to twice a week, to the unprecedentedly massive 200-300 mcg/kg in two doses over five weeks. A minute dose of 1 to 5 mcg per day, over an indefinite period, was indicated for children. The application emphasized that the determination of dosage and the duration of


\textsuperscript{14}Meyers, "Investigational Drugs."

treatment would ultimately lie with the individual investigator. The INDs were more specific on who would be able to research the drugs under their sponsorship: access was restricted to those working under grants from, or the authority of, the National Institute of Mental Health (NIMH), state agencies, or the Veterans Administration, with all research to be conducted in a hospital setting.\(^{16}\) The reason for this restriction is unclear, however it may have been in reaction to the growing controversy surrounding the use of psychedelics by Harvard psychologists Timothy Leary and Richard Alpert. The pair had been initially been involved in sanctioned research with psilocybin, however their increasingly widespread use of psychedelics outside of formal research had led to their dismissal from the university earlier that year.\(^{17}\)

The FDA’s pharmacology department made their initial review of the Sandoz LSD and psilocybin INDs in August and September 1963. They found the INDs lacking in toxicity data. While the results of some animal research were submitted, these were “related more to autonomic and central effect rather than to acute, subacute or chronic systemic toxicity studies.” These missing data were considered important as the IND suggested long term usage for both of the drugs. Studies of the effects of the drugs on reproduction were also deemed

\(^{16}\) J. F. Reilly to Kelsey re. IND #311—Psilocybin Tablets, 15 August 1963, folder 505.51 August, box 3570, RG 88; William D’Aguanno to Kelsey re IND #305—LSD-25 Substance, 19 September 1963, folder 505.51 Sept., box 3570, RG 88. The LSD dose of 200-300 mcg/kg is so huge as to suggest an error—by 1967, 1500 mcg was the largest single dose that had been reported, and 200-300 mcg was a standard single high dose. Similarly, the dose of 1 to 5 mcg seems infinitesimal even for children—25 mcg was considered the threshold dose for adults, and standard doses were frequently given to children. Therefore 1-5 mcg/kg may have been the correct dose range. However these doses are listed in several versions of the FDA report, and could merely represent the dose range considered nontoxic. For dose ranges see A. Hoffer and H. Osmond, with a contribution by T. Weckowicz, *The Hallucinogens* (New York: Academic Press, 1967), pp. 103-104, 178.

\(^{17}\) For an account of the exploits of Leary and his colleagues see Stevens, *Storming Heaven*. 
necessary if they were to be given to women of childbearing age. In light of this, the reviewers concluded, “As no toxicity data are available to assess the safety of this compound we recommend that consideration be given to the termination of the clinical investigations.” However, the FDA’s Bureau of Medicine considered the fact that the LSD IND was supported by a bibliography of over one thousand scientific papers that detailed a wide variety of research, conducted over more than twenty years, which had resulted in no deaths or serious side effects. As there was no “serious doubt as to toxicity” and the literature attested to promising effectiveness, the Bureau of Medicine decided that clinical investigation could be continued, with a request for further data. Further review of the research confirmed that there existed sufficient data to allow research under the Sandoz IND.

Initially Sandoz sponsored seventeen LSD investigators. These researchers investigated LSD’s effects and applications in a wide variety of ways. Keith Ditman at the University of California, Los Angeles, had compared the effects of LSD to delirium tremens, and reported on the positive benefits experienced by subjects given LSD in an experimental, rather than therapeutic, setting. Dietrich Heyder, of the Norfolk Mental Health Center, Virginia, had found success using

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18 Reilly to Kelsey re. IND #311, 15 August 1963; D’Aguanno to Kelsey re IND #305, 19 September 1963.
19 Drug Safety (Part 5, Appendices, and Index), Hearings before a Subcommittee on Government Operations, House of Representatives, 89th Congress, 2nd Session, March 9, 10; May 25, 26; June 7, 8, and 9, 1966 (Washington: U.S. Government Printing Office, 1966), pp. 2134-2135. The psilocybin IND was also approved, presumably after similar deliberation.
20 The investigators are listed in George P. Larrick to L. R. Fountain, 17 September 1963, box 3587, RG 88.
LSD with an otherwise treatment resistant psychotherapy patient.\textsuperscript{22} Eric Kast, of Chicago Medical School, studied LSD's analgesic effects, and Lauretta Bender of Creedmoor State Hospital, California, treated autistic schizophrenic children with the drug.\textsuperscript{23} Albert Kurland, of Spring Grove State Hospital, Maryland, and Harry Hook, of Mendocino State Hospital, California, would go on to publish studies of psychedelic therapy in the treatment of alcoholism.\textsuperscript{24} Additional investigators were added to the IND over the next three years, reaching approximately seventy by 1966. The criteria for eligibility were also expanded to include grantees of “approved national agencies” such as the National Science Foundation.\textsuperscript{25}

With Sandoz’s decision to restrict their sponsorship of research to those working under certain federal and state organizations, privately funded researchers who had been using LSD found themselves cut off. However, nowhere in the new regulations did it say that only a drug’s manufacturer could act as a sponsor, so independent researchers were free to submit their own IND forms for human research with LSD. Two independent INDs were in fact submitted, however they were both terminated once thoroughly reviewed by the FDA. Closely analyzing these failed applications will reveal that the struggle to gain access to LSD in the years immediately following the Drug Amendments of 1962 was not due to any

\begin{itemize}
\item \textsuperscript{22} Dietrich W. Heyder, "LSD-25 in Conversion Reaction," \textit{The American Journal of Psychiatry} 120, no. 4 (1963), pp. 396-397.
\item \textsuperscript{25} Organization and Coordination of Federal Drug Research and Regulatory Programs: LSD, Hearings before the Subcommittee on Executive Reorganization of the Committee on Government Operations, United States Senate, 89\textsuperscript{th} Congress, 2\textsuperscript{nd} Session, May 24, 25, 26, 1966 (Washington: U.S. Government Printing Office, 1966), p. 62.
\end{itemize}
specific restrictions from the government, but instead the result of Sandoz's own efforts to limit research, and the general difficulty in meeting the IND requirements as an independent researcher. The IND rules supported a move away from a landscape of drug research characterized by numerous small independent research groups, each working in their own direction, towards a more formalized, larger scale, manufacturer directed and institutionally based research landscape.

Harold Abramson

Harold Abramson had been conducting research with LSD since 1951, and had been a leading developer of psycholytic therapy in the United States. By 1963, he was the director of research at the South Oaks Research Foundation, a division of the South Oaks Psychiatric Hospital, Amityville, New York. Founded in 1882, the private hospital averaged a population of two hundred patients, and treated all psychiatric disorders. Sandoz had initially listed Abramson as an LSD investigator in its IND, however he was quickly removed once the company decided to restrict its sponsorship to those working under the NIMH, state agencies, and the Veterans Administration. Abramson first contacted the FDA in May 1963, under the impression that he had been deemed unqualified to perform research under the new drug rules. Having used LSD for over ten years, he wished to clarify his qualifications “in order to eliminate what at present is

26 Abramson (ed.), The Use of LSD in Psychotherapy and Alcoholism, p. xiii.
27 Craig Burrell to Frances Kelsey, 5 March 1964, folder 521.6-525.091, box 3758, RG 88.
damaging to my position professionally.” The FDA advised him to take up the issue with Sandoz, as it was a drug’s sponsor, not the FDA, who initially determined the adequacy of researchers’ qualifications. Subsequently, Abramson decided to become a sponsor for LSD research himself, and the FDA instructed him to submit an IND form.

In November 1963, Abramson met with Frances Kelsey and Merle Gibson of the FDA’s Investigational Drug Branch to discuss submitting an IND for LSD research. The FDA officers again emphasized that Sandoz’s criteria for researching LSD under its IND had nothing to do with the new drug regulations. The decision was voluntary, and had come out of discussion between Sandoz and the NIMH. Clearly taking Sandoz’s criteria personally, Abramson suggested that they might have denied him access to LSD because of his criticism of Sansert—another Sandoz drug that he had experimented with. He had argued that Sansert could produce similar effects to LSD, but with greater potential danger.

Abramson also stated that he had been turned down for a NIMH grant due to the agency’s disbelief of his work with Fighting Siamese Swordtails. In 1954, Abramson had published research reporting that the fish uncharacteristically swam nose up, tail down, when exposed to LSD. This behaviour increased with the concentration of LSD in their water. He had suggested that by exposing the fish to human urine, this phenomenon could be observed as a bioassay for the presence of LSD. Considering LSD to produce a model psychosis, he had also

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28 Harold A. Abramson to FDA, 9 May 1963, box 3750, RG 88.
29 C. E. Beisel to Harold A. Abramson, 13 June 1963, box 3750, RG 88; C. E. Beisel to Harold A. Abramson, 22 August 1963, box 3750, RG 88.
30 Memorandum of Interview between Harold A. Abramson, Merle L. Gibson and Francis O. Kelsey, 8 November, 1963, folder 521.6-525.091, box 3758, RG 88.
suggested that exposing the fish to schizophrenics’ urine might help uncover a naturally occurring substance causing the illness.\textsuperscript{31}

Further defending his position to the FDA officials, Abramson attested to his extensive experience with LSD, through the military’s Chemical Warfare Division, which had included self-experimentation and administration to subjects for long periods. He had found that LSD was a very safe drug that was not addictive. He still had stock of LSD that had previously been supplied by Sandoz. His wished to use this in research treating mental illness, particularly schizophrenia. Abramson also believed that LSD psychotherapy was valuable in the treatment of alcoholism, although he did not believe Humphry Osmond’s results of a 50 percent cure rate. Presenting a drafted IND form, Abramson was told that it was lacking in chemical control data, and that he should request this from Sandoz.\textsuperscript{32}

Three days after the meeting, Abramson wrote to the US headquarters of Sandoz in New Jersey. He stated that he wished to become his own sponsor for LSD research, which he was able to do “provided that Sandoz Pharmaceuticals will supply me with data covering items 1 to 6” of the IND form. These sections covered preclinical data such as the drug’s chemical structure, composition and manufacturing controls, as well as details of animal and other research that indicated that it was reasonably safe to conduct human research. Only a drug’s manufacturer could produce much of the chemical and manufacturing data, whilst the rest could theoretically be produced by anyone with supplies of the


\textsuperscript{32} Interview between Abramson, Gibson and Kelsey, 8 November 1963.
drug, but only at great expense and difficulty. Abramson appealed to Sandoz to “be kind enough to give me the required information since this can be obtained from no other source.” Sandoz’s Leonard Achor replied coolly, reiterating the company’s criteria for LSD investigators, and stating,

For the record, it is necessary to advise that Sandoz Pharmaceuticals will remain the sole sponsor of LSD-25 in the United States as per Company policy. Accordingly, it will not be possible to supply you with the information contained in items one through six in the form #1571.

Frustrated by this response, Abramson replied that Sandoz’s statement directly contradicted advice he had received from the FDA’s Bureau of Enforcement, that “Anyone may become a sponsor for an investigational drug.” If “for reasons which are obscure to me” Sandoz was unwilling to supply the data he requested, Abramson inquired whether the information was already filed with the FDA, and whether it was in the public domain. If this was the case he could use it to become his own sponsor, thus “relieving Sandoz of any responsibility.” He also drew attention to the implications of his situation for drug research more generally: “in this period of transformation” brought about by the new regulations, it was important to make sure that “unnecessary obstacles” did not hamper “freedom of medical investigation.” In response, Achor again emphasized that Sandoz would remain the sole sponsor for LSD. He stated that

33 Harold A. Abramson to Rudolph Bircher, 11 November 1963, folder 521.6-525.091, box 3758, RG 88. Emphasis original. For parts 1 to 6 of the IND form see Larrick, “Regulations; Investigational Use,” p. 179.
34 Leonard B. Achor to Harold A. Abramson, 18 November 1963, folder 521.6-525.091, box 3758, RG 88.
35 Harold A. Abramson to Leonard B. Achor, 21 November 1963, folder 521.6-525.091, box 3758, RG 88.
the necessary data had been supplied to the FDA, however it was given in confidence and was “not, I repeat not, in the public domain.”

Reaching a dead-end with Sandoz, Abramson forwarded his correspondence with the company to Kelsey at the FDA. He complained that “Sandoz refused to acknowledge the right to self-sponsorship” which the FDA had made clear to him. Unable to complete an IND, he asked how he could proceed. He pointed out that as he already had stocks of LSD, he did not need the company's cooperation to perform his proposed research.

However instead of the sympathetic support that Abramson was hoping to receive, the FDA began to view him with suspicion. Kelsey had heard that Abramson was “rather an LSD enthusiast,” and Sandoz had confirmed that he was no longer listed as one of their investigators. She therefore became concerned that Abramson was using the drug on humans without filing an IND, and decided to investigate. Sandoz had also informed Kelsey that the LSD supplied to Abramson prior to 1963 had been for animal use. This was significant. If Abramson had obtained LSD for human use prior to the Drug Amendments of 1962, then the new regulations would not apply to that stock, and he would be free continue human research with it. However as the LSD was for animal use only, human research with that batch had not been covered by the

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36 Leonard B. Achor to Harold A. Abramson, 12 December 1963, folder 521.6-525.091, box 3758, RG 88.
37 Harold A. Abramson to Frances O. Kelsey, 2 January 1964, folder 521.6-525.091, box 3758, RG 88.
38 Frances O. Kelsey to C. J. Karadimos, 23 March 1964, folder 521.6-525.091, box 3758, RG 88; Craig D. Burrell to Frances O. Kelsey, 5 March 1964, folder 521.6-525.091, box 3758, RG 88.
previous legislation. Therefore he needed to submit an IND for the new use.\textsuperscript{39} Kelsey and Charles Karadimos, of the FDA’s Bureau of Field Administration, decided to send an FDA inspector to visit Abramson. The inspector was to examine his stock of LSD in order to ascertain its quantity, manufacturer, and labeling, as well as to investigate whether or not he was currently using the drug in human research. If there was any evidence of this, a sample of the drug was to be taken, on which seizure could be based.\textsuperscript{40}

On 22 May 1964, New York FDA Inspector Irwin Schorr telephoned Abramson to arrange an inspection of his LSD stocks. Obviously taken by surprise, Abramson took great offence at the request, and refused to comply without an official written request, that would be assessed by his lawyer, or a court order. Abramson questioned Schorr’s qualifications and jurisdiction, referencing higher FDA officials he had consulted with, such as Kelsey. He objected to being treated like a “criminal” and raved about his work for the Department of Defense and his publications. He argued that he was “not just an ‘ordinary practicing doctor’ but an expert on LSD,” and that Schorr should have looked him up in a “Who’s Who.” Schorr tried to emphasize that he was not wishing to interrogate Abramson, but simply inspect his stock of LSD. However this did not calm him. Abramson instead threatened to take the matter to his senator, and told Schorr that if his IND was not approved he would “take the matter to court.”\textsuperscript{41}

\textsuperscript{39} Frances O. Kelsey to Charles J. Karadimos, 24 January 1964, box 3750, RG 88; Kelsey to Karadimos, 23 March 1964.
\textsuperscript{40} C. J. Karadimos to Director, New York District Division of Field Operations, 15 April 1964, folder 521.6-525.091, box 3758, RG 88.
\textsuperscript{41} Irwin Schorr to Director, New York District, 29 June 1964, folder 521.6-525.091, box 3758, RG 88.
Three weeks later, Schorr and a partner visited Abramson at the South Oaks Research Foundation and issued him with a Notice of Inspection. Having been advised to cooperate by a senior FDA official, Abramson was now “extremely cordial.” He described having received a “huge quantity” of LSD from Sandoz over the past thirteen years, though exactly how much he did not know. When his current stock was gathered together for inspection a week later, he was found to have 604.1 milligrams of LSD, which Schorr described as enough for over 20,000 doses. Abramson stated that he had not used the drug on humans since the new drug regulations. However this was not because the FDA prohibited it, but due to his fear of malpractice suits, as his LSD was labeled for investigational use only. In fact, he felt that the government had no jurisdiction over his right, as a doctor, to “administer any drug to his patients in the course of treatment.” Instead of human research, Abramson was presently using LSD with fish. Particularly, he described how his observation of the effects of LSD on fish had led New York State to experiment with using the drug to rid its streams of the “trash fish” carp. This use was not widely practiced, however, as apparently there was “much public objection to putting LSD into streams which run into the reservoirs of New York City.”

Regarding his IND application, Abramson complained about the need to supply preclinical data that Sandoz had already filed with the FDA. Since he was using Sandoz LSD, he logically argued that requiring him to provide the data himself was unnecessary. However he was told that he needed Sandoz’s written consent to refer to their data. Abramson again claimed that Sandoz’s refusal to permit

42 Ibid.
him to use the data was due to his assertion that Sansert produced similar effects to LSD. He also re-emphasized his qualifications and experience in the use of LSD, and similar drugs, even offering to act as a consultant to the FDA on them. Schorr was sympathetic, stressing to Abramson that there were no doubts as to his qualifications, and nothing personal in the delayed decision over his IND—“it was just a matter of law.”43

Following the visit, Schorr reported to his superiors that he was satisfied that Abramson was not using his supplies of LSD on humans whilst his IND was under review. No sample for seizure was therefore taken. He wrote that Abramson was “extremely anxious” to have his IND approved and resume clinical research with the drug, and that he might test the law in court if the IND was terminated. However, in the interim, he felt it “doubtful that he would do anything to jeopardize his position as a prospective investigator/ sponsor or doctor.”44

On 11 May 1965 FDA commissioner George Larrick sent Abramson the results of his IND review. The review concluded that Abramson’s IND “fails to contain sufficient data to support a conclusion that it is reasonably safe to initiate the intended clinical investigations with the drug.” This determination was based on the application’s lack of information on both preclinical investigations and the “methods, facilities, and controls used for manufacturing, processing and packing the investigational drug.” The letter acknowledged that Abramson had

43 Ibid.
44 Ibid.
referenced Sandoz’s data in regards to these sections of the IND, however it stated that the FDA could not refer to data already on file “without written authorization” from the original submitter. Abramson was given ten days to remedy the situation, otherwise his IND would be terminated.\(^{45}\) No additional data was submitted. On 23 July Larrick sent notice to Abramson that his IND for LSD was terminated.\(^{46}\)

In August 1965, Abramson was visited by an FDA Inspector in order to confirm that he was complying with his IND termination, and to again inspect his supplies of LSD. With his lawyer present, Abramson expressed the great offence and humiliation he experienced as a result of the FDA denying him approval to conduct clinical LSD research. He found the process a “personal affront to his professional integrity.” Abramson and his lawyer argued that the FDA had overstepped its jurisdiction by interfering with a physician’s right to administer a drug that had been safely used for many years, and that it was unreasonable to require him to provide manufacturing data that the Administration already had on file. They again threatened to take the issue to court, and to lay a complaint with their local member of Congress. Abramson emphasized his embarrassment at meeting younger and less experienced physicians and psychologists who could use LSD simply because they worked in a state institution. He had also encountered embarrassing situations where patients had offered him black market supplies of the drug after he had been forced to deny their requests for LSD therapy. The inspector found that Abramson was complying with the law by

\(^{45}\) Geo. P. Larrick to Harold A. Abramson, 11 May 1965, Box 3750, RG 88.
\(^{46}\) Geo. P. Larrick to Harold A. Abramson, 23 July 1965, Box 3750, RG 88.
only using his LSD in animal research, and that his stock was largely unchanged since the previous inspection. As his stock had been obtained prior to the Drug Amendments of 1962, and was not being used in human research, it could not be seized. Therefore the matter was laid to rest. Abramson continued his animal research with LSD, however he never resumed his clinical research with the drug.

The correspondence between Abramson, Sandoz, and the FDA reveals three distinct attitudes regarding who was entitled to perform research with investigational new drugs. Sandoz felt that it had the right, as the drug’s manufacturer, to control access to the drug. Abramson, by contrast, felt that his rights as a physician came first: as a qualified, experienced, physician, he was entitled to use drugs in treatment and research as he saw fit. The FDA’s position was theoretically neutral—anybody could sponsor clinical research with a drug as long as they could complete the necessary paperwork showing that it was reasonably safe to do so. However this seemingly simple, impartial, requirement in fact put much control in the hands of the manufacturer, as they were the only party practically able to produce much of the necessary data. The manner in which the FDA handled submitted data protected the manufacturer’s control over research sponsorship. With IND data held in confidence, the FDA did not officially compile knowledge on a drug, or specific preparation thereof. Such a practice would result in subsequent sponsors only needing to prove the adequacy of their qualifications, research plan, and facilities to use a drug of

47 Robert T. Dee to Director, New York District, 10 August 1965, folder 521.6-525.091, box 3758, RG 88; A. Harris Kenyon to A. E. Rayfield, 10 September 1965, folder 521.6-525.091, box 3758, RG 88.
48 Merle L. Gibson to Harold A. Abramson, 18 June 1969, folder 505.51 June, box 4247, RG 88.
established safety. Instead the FDA read each IND with official ignorance, unable to accept the safety of a preparation unless the data was in front of them, even though it had already been approved. The Drug Amendments of 1962 therefore undermined the rights that Abramson believed the physician had, as research could only be conducted with an investigational new drug with the permission of both the FDA and the manufacturer.

Abramson's struggle, and ultimate failure, to gain approval to conduct clinical research with LSD under the Drug Amendments of 1962, was therefore not due to any effort to restrict LSD research on the part of the FDA. Instead it was the result of a law that effectively empowered a drug's manufacturer to regulate research. A manufacturer could not itself sponsor research without the FDA’s approval, however it could prevent others from using stocks of their preparations for research that the FDA would otherwise approve. Sandoz used this power to limit LSD research to government sponsored, hospital based, projects under its IND, while deliberately maintaining a monopoly over LSD sponsorship. Despite Abramson's claim that Sandoz’s rejection of his requests was personal, there is little evidence to support this—Sandoz set up clear company policy for how it wished LSD research to proceed, and Abramson did not meet the criteria.

The FDA made no negative judgments on the validity of Abramson’s qualifications, experience, plan of research, or facilities, they simply could not accept his application without the required preclinical data, regardless of the fact that this data was already on file. When questioned at a congressional hearing in
1966 as to why Sandoz’s IND had been approved with incomplete preclinical data, but Abramson’s had not, FDA commissioner James Goddard replied that it was because his stock was labeled for animal use.\textsuperscript{49} The FDA therefore may have been more flexible with Sandoz than Abramson, but they still did not proactively cut off his access to the drug. Instead they objectively judged his application according to the law.

\textbf{The International Foundation for Advanced Study}

The International Foundation for Advanced Study, of Menlo Park, California, also submitted an independent IND to the FDA for human research with LSD in 1963. The IND also included psilocybin. It was eventually terminated in February 1965.\textsuperscript{50} Like Abramson, the researchers struggled to provide the preclinical data required by the IND form without the cooperation of Sandoz. Although this problem alone could have resulted in their IND’s termination, the FDA review also cited another issue—the qualifications of the investigators. A non-profit organization founded to explore the potential of LSD, the Foundation was at the forefront of establishing the Canadian psychedelic method of LSD administration in the United States. Reflecting the unconventional nature of this form of drug research, the members of the Foundation came from a variety of backgrounds: experience was a more relevant qualification than medical credentials. Prior to 1962, this situation had not proved problematic. However after the IND rules of

\textsuperscript{49} Drug Safety, pp. 2205-2206
\textsuperscript{50} Ibid., p. 2202.
the Drug Amendments of 1962 formalized access to investigational drugs, the Foundation's position became untenable.

The International Foundation for Advanced Study was founded by Myron J. Stolaroff in 1961. Stolaroff had found success as an engineer in the 1950s at the Ampex Corporation—a pioneering firm for magnetic recording—where he had risen to the position of assistant to the president for long range planning. Outside of work, he was involved with the Sequoia Seminar, a spiritual group led by Stanford professor of business law Harry Rathbun. Through the group, Stolaroff came to know Gerald Heard, the Los Angeles based, British intellectual and author. An expert on mysticism and Eastern religions, Heard introduced him to the idea that LSD could be a profound spiritual tool, and encouraged him to contact Alfred Hubbard in Canada, one of the pioneers of psychedelic therapy. Hubbard and Stolaroff first met in February 1956, and connected immediately. In April that year, Stolaroff travelled to Hubbard’s home in Vancouver, where he was administered LSD for the first time. The 66 microgram dose, while relatively low, produced a profound experience and convinced him that LSD was “the most important discovery man has ever made,” and that he should devote himself to studying the drug.\footnote{Stolaroff, \textit{Thanatos to Eros}, pp. 18-24.}

Stolaroff took LSD back to the Sequoia Seminar, out of which he formed a research group. Members took turns taking the drug, with the others present for support, and the experiences were discussed at later meetings. However, some of the members found Hubbard’s larger than life personality disagreeable, and
subsequently moved away from his guidance, much to Stolaroff’s disapproval.
Stolaroff also took LSD to Ampex, where he suggested that the drug effects could be used to enhance problem solving, by creating a state of mind where “Fresh ideas and perspectives flow unhindered.” His idea, however, met with strong resistance.

In 1959, Stolaroff took a stronger than usual 150 microgram dose of LSD, which resulted in a powerful mystical experience. This convinced him to dedicate himself full time to the study of LSD. Subsequently, Stolaroff left his job at Ampex and his disappointing research group, and self-funded the non-profit International Foundation for Advanced Study, which he established with Hubbard. Together they collected a number of researchers who came from a variety of backgrounds, but had a common interest in psychedelic drugs, and set up specially furnished offices above a beauty parlor in downtown Menlo Park. The researchers included psychiatrist Charles Savage, Stanford University professor of engineering Willis Harman, Stanford graduate student in psychology James Fadiman, and San Francisco State College associate professor of psychology Robert Mogar. Savage, who was hired as medical director, was the most qualified, experienced, and esteemed member of the Foundation. As well as his previously discussed research at the Naval Medical Research Institute, the NIMH, and the Palo Alto Medical Research Foundation, Savage had also conducted LSD research in

52 Ibid., p. 25.
California at the Center for Advanced Studies in Behavioral Sciences, the Napa State Hospital, and the Palo Alto Veterans Administration Hospital. As psychologists, Mogar and Fadiman were also qualified to perform LSD psychotherapy research, at least under medical supervision. Mogar brought to the group significant experience in evaluating therapeutic outcome with objective rating instruments. He was therefore useful in raising the scientific standards of the Foundation’s research. However, Hubbard, Stolaroff, and Harman were objectively laymen. The Foundation justified the use of lay researchers on the grounds that there were simply not enough therapists who had both training in psychiatry, or clinical psychology, and experience with psychedelics. They considered psychedelic therapy “an art which can be adequately learned only by personal participation in the therapeutic process,” and that “orthodox training may actually prove to operate as a handicap to learning.” Savage indeed found value in Harman’s background, even though it was not in psychiatry: he described that “Harman brings to the project a background in scientific method, research design, communication and statistical theory, as well as an interest in the scientific basis of values and beliefs.”

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54 Drug Safety, p. 2212.
56 Hubbard claimed to have a PhD from the Taylor University of Bio-Psycho-Dynamic Sciences, however the American Medical Association recognized this institution as a diploma mill. Oliver Field to Lynn Gunn, 10 September 1959, folder 9, box 482, collection 471, Historical Health Fraud and Alternative Medicine Collection, American Medical Association, Chicago, Illinois.  
trained in psychedelic therapy would come from formal mental health backgrounds.\(^{59}\)

By the time of the enactment of the Drug Amendments of 1962, research at the Foundation was well established. The research program was broad, encompassing the study of many aspects and implications of the psychedelic experience in a variety of populations. The program was conceived as a direct continuation of the work of Hubbard, Humphry Osmond, and Abram Hoffer, the Canadian developers of psychedelic therapy. The Foundation researchers’ basic concept of the value of the psychedelic experience was that “just as a single traumatic incident can have lasting untoward effects, so can a single propitious experience, if sufficiently profound, have lasting beneficial effects.”\(^{60}\) The transcendental psychedelic experience could allow the patient to see themselves, and the world around them, from an entirely new perspective, resulting in lasting changes in their values and beliefs. These changes were usually “in the direction of aesthetic, creative, philosophic and religious interests; deeper realization of the vastness of the self; and increased feeling of oneness with other persons and with the universe in general.”\(^{61}\) These changes in the patient’s "value-belief system" could in turn influence their behavior and personality. Changes in behaviour and personality were typically, in the direction of increased self acceptance, reduced anxiety and guilt, reduction in feelings of inadequacy accompanying the increased self esteem, greater freedom to develop and use potential abilities, and

\(^{59}\) "Research Program of the International Foundation for Advanced Study," p. 3.
\(^{60}\) Ibid., p. 5.
\(^{61}\) Savage and Harman “LSD-25,” p. 11.
increased ability to form satisfying relationships with and communicate with others.\textsuperscript{62}

Having observed this process, the Foundation’s research was directed at furthering their understanding of how positive changes in values, beliefs, personality, and behaviour came about and interplayed, and how to maximize the likelihood of a given patient experiencing such changes.

The first publication to emerge from their work appeared in the \textit{Journal of Neuropsychiatry} in 1962. Entitled “The Psychedelic Experience—A New Concept in Psychotherapy,” the paper outlined the theory and method of their treatment, and results attained with twenty-five treated outpatients. The male and female patients had come to the Foundation’s clinic requesting treatment for a variety of problems, categorized as: marital problems, alcoholism, ineffectual personality, neuroses, and one described as “near homicidal.”\textsuperscript{63} Preparation for the drug session lasted a minimum of two weeks, during which the patient was instructed to surrender totally to the experience, be receptive to insights that challenged their normal beliefs, and trust their unconscious and those around them. To aid in developing these states of “willingness and trust,” the patient was administered inhalations of 30 percent carbon dioxide, 70 percent oxygen, which produced brief alterations in consciousness.\textsuperscript{64} These experiences helped the patient to practice letting go, and helped the therapist to determine whether they were ready for their psychedelic session. The treatment session then lasted eight and a half hours, and took place in a room that was comfortably furnished and

\textsuperscript{62} “Research Program of the International Foundation for Advanced Study,” p. 4.
\textsuperscript{64} Ibid., p. 72
featured a record player and art. The patient was administered 100-200 mcg of LSD, as well as 200-400mg of mescaline. Ten milligrams of methamphetamine was given later in the day to intensify the session and improve their ability to integrate their experiences. Of the twenty-five patients treated, the researchers classed twelve (48%) as “much improved,” nine (36%) as “improved,” and four (16%) were not improved.65

Also in 1962, the International Foundation for Advanced Study drew up proposals to expand their clinical research of the psychedelic experience. The intended studies were significantly more advanced than any that had previously been conducted. They proposed to study both the process and outcome of psychedelic therapy in a diverse population, and to more specifically test its efficacy in treating alcoholism. Importantly, the studies were to be at least partially controlled, with significant numbers of subjects, objective and extensive outcome assessment procedures, and substantial follow-up periods. The complexity of psychedelic therapy’s procedure, and the dramatic effects of LSD, had resulted in few prior researchers attempting controlled studies, however the Foundation researchers devised creative ways to provide reasonable control without undermining their therapeutic method. The studies would provide a greater depth of understanding on the process and outcome of psychedelic therapy, in a variety of subjects, and would carry a scientific weight that could potentially convince skeptics of the validity of results.

65 Ibid., p. 74.
In July 1962, the Foundation submitted a research grant application to the Department of Health, Education, and Welfare (the parent organization of the NIMH and the FDA), for a study entitled “LSD-25: Value Changes in the Psychedelic Experience.” Savage was listed as principal investigator. The study aimed to demonstrate two hypotheses: firstly that “following the psychedelic experience there is a change in the person’s value-belief system, and that this change is followed by a change in behavior,” and secondly that “the shift in behavior will be in the direction described by Maslow for the “self-actualizing’ person.” Savage explained prominent US psychologist Abraham Maslow’s concept of the self-actualizing person,

The term self-actualizing is used to denote the characteristic of being “growth motivated” rather than “deficiency motivated.” The former connotes previous gratification of the basic emotional needs for safety, belongingness, love, respect, self-esteem, and of the cognitive needs for knowledge and for understanding. Thus it implies that the person is in the process of developing to the full stature of which he is capable, with full use of talents, capacities, and potentialities, motivated not to satisfy some need, real or imagined, but activated by the sheer joy of growing and becoming.

The study was to be partially controlled, with one hundred and twenty subjects studied, only half of whom would receive LSD. These two groups were to be further divided: thirty of the LSD subjects would be psychiatric patients referred to the clinic, with only “pre-psychotics” excluded, and thirty would be “normal” volunteers. These volunteers were professionals interested in the potential of the experience to enhance self-understanding, awareness and creativity. Thirty of the non-LSD controls would be undergraduate psychology students, expected to change little over the time period. The other thirty would be graduate

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66 Ibid., p. 6.
students taking a Stanford seminar entitled “The Human Potentiality.” These students would control for the influence of exposure to new concepts for self-understanding, and new values, without the psychedelic experience. Results would be determined thorough administering a battery of psychometric tests—both purpose-made questionnaires and rating scales, and conventional instruments such as the Minnesota Multiphasic Personality Inventory—before treatment and at various stages the over six months afterwards.68

Savage recognized that this design did not control for whether or not the subjects’ value changes arose from their experience, or were impressed on them by the enthusiastic therapist while they were under a state of increased suggestibility. However he argued that experience had shown that value changes were often not in the direction of the therapists’ own values, indicating it was not simply suggestion, and that it was hard to control this aspect “since a cold impersonal scientific attitude inhibits the psychedelic experience.”69 The design also did not control for the possibility that subjects who volunteered themselves for LSD therapy were already disposed towards value changes in the direction hypothesized. If the hypotheses were proven correct in this study, Savage suggested that these two issues could be satisfied with a further study that used an active placebo, such as scopolamine, in a double-blind design, and that randomly assigned patients between the treatment and control groups.70

68 Ibid., pp. 7-8.
69 Ibid., p. 9.
70 Ibid., p. 9.
In the same year, Savage drafted another application for a research grant from the Department of Health, Education, and Welfare on behalf of the Foundation. The study proposed to test the efficacy of their psychedelic therapy procedure in alcoholic patients. The ambitious proposal was controlled, with two hundred patients divided into four groups: no treatment, treatment with only 30 percent carbon dioxide, 70 percent oxygen inhalations, psychedelic therapy with a low dose of psilocybin, and psychedelic therapy with a high dose of LSD. The low dose of psilocybin was intended to work as an active placebo, as it would produce a “pleasant aesthetic experience” but not a psychedelic reaction.

Assignment to each of the four groups would be random, and in the case of the two psychedelic therapy groups, double-blind.71 Another proposal expanded this design into a multi-hospital study. Each of an undetermined number of hospitals would study two hundred of their alcoholic patients, divided into the same four groups as above. The researchers anticipated that the hospital staff would be junior and inexperienced with LSD, and they planned to train them simply by providing basic instructions, and having them undergo a psychedelic experience at the Foundation. Therefore to control for therapist skill, a further control group was added—fifty patients who would undergo the high-dose LSD treatment at the Foundation with highly experienced therapists.72

Exactly what came of these applications is unclear. In 1966, Savage and Foundation researchers published a report of a study that closely resembled the

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first proposed study of value, belief, personality, and behavioural changes following psychedelic therapy, but with a more limited protocol: seventy-seven persons (one third patients, two thirds “normals” dissatisfied with life), who received LSD therapy between July 1962 and April 1963, were evaluated over six months. The researchers reported that most patients significantly benefited from the treatment. The report lists partial funding from both the private Ittleson Family Foundation, and a Public Health Service Fellowship, so the application may have been at least partially successful. The proposed alcoholism studies appear not to have come to fruition.

While the researchers received some funding from the government, the Foundation certainly was turned down for grants from the Department of Health, Education, and Welfare. This was attested to at 1966 congressional hearings that investigated the FDA’s implementation of the Drug Amendments of 1962 and the Drug Abuse Control Amendments of 1965, held by the Intergovernmental Relations Subcommittee of the House Committee on Government Operations. Entitled “Drug Safety,” the hearings featured extended discussion with FDA officials on the regulation of LSD research. The subcommittee questioned Frances Kelsey as to why the International Foundation for Advanced Study was turned down for a grant, and if it was because the research was not “bona fide,” or because some of the investigators were unqualified. She replied that the

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National Institutes of Health, which administered the grants, “think very highly and thought very highly of Dr. Savage.” She could not remember if she had been told a specific reason why the grant had been turned down, but opined that “There are usually a great deal more applications than there are funds for.” Subcommittee senior investigator W. Donald Gray added that the National Institutes of Health had informed him that the rejection “wasn’t necessarily on the basis of the proposed research, but largely the fact that there was some question about the reliability of some of the people there.” The grant proposals listed Harman as co-principal investigator, and knowledge that laymen Stolaroff and Hubbard directed the Foundation could have influenced suspicion of the personnel other than Savage. Savage, commenting in 1965 on a rejected grant proposal of Harman’s, after he himself had left the Foundation, echoed Kelsey’s assumption: “I don’t know what the basis of the rejection was, but I have a hunch that the project was too costly.” Therefore, although the precise reasons that the Foundation was denied major federal funding remains unclear, it appears that it was not due to any objection to funding LSD research in general, or to the Foundation’s specific form of research.

Despite receiving some funds from the Public Health Service, the International Foundation for Advanced Study evidently did not fit Sandoz’s sponsorship criteria, perhaps due to the outpatient clinic setting, and was excluded from its IND. Subsequently, the Foundation submitted its own IND for LSD and psilocybin.

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74 Drug Safety, p. 2206.
75 Charles Savage to Willis Harmen [sic], 7 December 1965, folder “Correspondence June-Dec. 1965,” box Addition 1, Savage Papers. The two year general process and outcome study was estimated to cost $74,400.40, Savage and Harman, “LSD-25,” p. 3. The three year single site alcoholism study was costed at $214,158, Savage and Harman, “LSD-25 and Alcoholism,” p. 3.
on 5 June 1963. Soon afterwards, the FDA’s Division of Pharmacology recommended its termination. On 7 October 1963, FDA Division of Pharmacology reviewer William D’Aguanno wrote to Kelsey, concluding, “the animal data [supplied] are insufficient to support clinical studies.” The IND had referred to Sandoz’s IND for animal data, however, like Abramson, they had not provided authorization from Sandoz to use this confidentially filed data. D’Aguanno also recognized that insufficient pharmacological data was a problem with all current IND submissions for these drugs.\(^{76}\)

Despite this immediate recommendation, the Foundation’s IND was not terminated until February 1965. At the 1966 “Drug Safety” congressional hearings, Chairman Lawrence Fountain questioned the FDA as to the reasons for this delay. He drew attention to numerous recommendations for termination from several different FDA officers, due primarily to the lack of preclinical and manufacturing control data, which had been given between the initial October 1963 review and final termination. Kelsey explained that they respected Savage as a “distinguished scientist” with great experience with LSD, and had wished to avoid unnecessarily terminating potentially useful research. They therefore gave the Foundation a chance to provide the necessary data, particularly on the nature of their stocks of LSD. The Foundation claimed to have received their LSD from Sandoz, however the labels were missing. Therefore the FDA was concerned as to its exact composition and condition. The researchers promised

\(^{76}\) William D’Aguanno to Kelsey, re. IND #486—d-lysergic acid diethylamide, psilocybin, 7 October 1963, folder 505.51 October, box 3570, RG 88.
to collect all the necessary data, and offered to suspend their clinical work while their IND was under review. However they were unable to obtain the data.\footnote{Drug Safety, pp. 2202-2203.}

Ultimately, the final nail in the coffin of the Foundation’s IND came with Savage’s departure: by September 1964, Savage had accepted a new job at Spring Grove State Hospital, Maryland, where he would continue his psychedelic research from February 1965.\footnote{Albert A. Kurland to Charles Savage, 28 September 1964, folder “Clippings, Correspondence, Reprints, Manuscripts,” box Addition 1, Savage Papers. The exact date Savage stopped working with the Foundation is not clear.} For Kelsey, with the requested data not supplied, Savage’s departure was the deciding factor in termination.\footnote{Drug Safety, 2203.} Additionally, by 1964 the FDA was growing suspicious that the Foundation was using LSD outside of legitimate research. In November an undercover agent was sent to the Foundation to try and obtain LSD treatment. He was unable to even attain a promise of treatment, however “the inference seemed to be that possibly it could be arranged.” The FDA were also increasingly suspicious of the Foundation’s stocks of LSD, with Commissioner Goddard suggesting that they had LSD “in a fruit jar buried in the ground.”\footnote{Ibid., p. 2204.} At the December meeting of the FDA’s Advisory Committee on Investigational Drugs, Kelsey gave a scathing report of the Foundation’s IND, criticising Hubbard’s qualifications, the lack of a “reasonable investigation plan,” and the absence of controls. In response, committee member Sidney Merlis stated, “the sponsor should not be dignified by a site visit—it should be terminated.”\footnote{Food and Drug Administration, Summary of Proceedings, Thirteenth Meeting, Advisory Committee on Investigational Drugs, 3 December 1964, Washington, DC, folder 1, box 13, Frances Oldham Kelsey Papers, Manuscript Division, Library of Congress, Washington, DC (hereafter Kelsey Papers), p. 5.} The Foundation researchers had attempted to bring
credibility back to their application by hiring a new psychiatrist as medical
director, however his location in New Jersey suggested his token position.\(^82\)

Finally, on 6 January 1965 the FDA sent the International Foundation for
Advanced Study a notice of the deficiencies in its IND application. If corrections
were not provided within ten days, the IND would be terminated. The notice
listed deficiencies in the preclinical and manufacturing data needed to confirm
the drugs were reasonably safe for clinical use, just as Abramson’s notice had.
However it also judged the investigators and their plans to be inadequate:

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\text{In our opinion, the proposed co-investigators, Willis W. Harman, Alfred M.}
\text{Hubbard and Myron J. Stolaroff, do not possess the necessary}
\text{qualifications for undertaking the proposed clinical investigations; in}
\text{addition, the data submitted do not support the use of psychotomimetic}
\text{compounds in such syndromes or diseases such as asthma, colitis,}
\text{psoriasis, etc. Furthermore, the supervision of the project in California by}
\text{the principal investigator in New Jersey, is unsatisfactory.}\(^83\)
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The inclusion of asthma and other physical ailments in the Foundation’s
investigative plans suggests that the researchers had proposed branching into
psycholytic therapy: whilst not a common indication of psychedelic therapy,
many psychoanalysts researched and treated asthma, believing it to be
psychosomatic. Evidently, sufficient emendations were not made to the IND, and
on 2 February it was terminated.\(^84\)

\(^{82}\) *Drug Safety*, p. 2137.
\(^{83}\) John L. Harvey to Myron J. Stolaroff, 6 January 1965, box 3750, RG 88.
\(^{84}\) *Drug Safety*, p. 2202. For a discussion of psychoanalytic asthma research see Nathan G. Hale Jr.,
From its inception in 1961, the International Foundation for Advanced Study had led the field of psychedelic therapy research in the United States. Not only had the researchers been among the first to adopt the Canadian method, but they had attempted to advance the field by improving the rigour of clinical trial designs. Whilst some of their plans were not realized, they accrued great experience with psychedelics, administering them to approximately 350 subjects, and published their findings in mainstream journals such as the *International Journal of Neuropsychiatry*. Whilst several of the core researchers of the Foundation had no formal training in medicine or psychology, they were not merely making excuses when emphasizing the importance of experience over medical credentials. LSD administration was known to cause few medical complications; its effects, contraindications, and dangers were all related to psychological factors. Additionally, medical training did not prepare a therapist for handling the powerful and variable effects of the drug, as carefully manipulating set and setting were not normal aspects of medical drug administration. Indeed the experience and innovation of Hubbard was highly regarded by many psychiatrists researching LSD with whom he had collaborated, such as Ross MacLean, Humphry Osmond, and Abram Hoffer in Canada.

This was not a view, however, that the FDA could support. Charles Savage, who was clearly qualified through both medical training and experience, was well respected at the NIMH. Therefore, whilst Savage was the principle investigator,

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85 Stolaroff, *Thanatos to Eros*, p. 26; Savage et al., "Effects of Psychedelic (LSD) Therapy."
the FDA had delayed terminating the Foundation’s IND in order to give them a chance to collate the necessary preclinical and manufacturing data. However once he left, and it became clear that the objectively unqualified Stolaroff, Hubbard, and Harman were the primary investigators, the IND was terminated. With Savage’s departure, the planned scope of investigations may have also widened, with the loss of some of its credibility. The Foundation’s struggle to continue research after the Drug Amendments of 1962 therefore had nothing to do with the fact that they were researching psychedelics. Instead it was the result of the formalization of drug research that the amendments ushered in.

The Drug Abuse Control Amendments of 1965, the Sandoz IND Withdrawal, and the FDA

In July 1965, the first legislation to specifically control LSD was signed into law. The Drug Abuse Control Amendments of 1965 amended the Federal Food, Drug and Cosmetic Act to specifically prohibit the manufacture, sale, distribution and possession (except for personal use) of depressant, stimulant, and hallucinogenic drugs outside of legitimate channels of commerce and research. Increased registration and record keeping requirements were placed on those involved in the legitimate manufacture and distribution of the drugs. For enforcement, the Bureau of Drug Abuse Control was established within the FDA. The Bureau staffed offices nationwide with agents authorized to make arrests, carry firearms, serve warrants, and make seizures.

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87 Drug Abuse Control Amendments of 1965, Sec. 3.
Whilst the increased control over hallucinogens reflected growing public and political concern over their non-medical use, the legislation was primarily intended to target the abuse of amphetamines and barbiturates. Congressman Oren Harris, chairman of the House Committee on Interstate and Foreign Commerce, which held hearings on the amendment’s bill, estimated that over nine billion amphetamine and barbiturate tablets were produced annually in the US, and that half of these found their way onto the black market.89 The hearings, as well as the House and Senate reports on the bill, were almost exclusively concerned with the dangers of depressant and stimulant drug abuse, how these drugs entered the black market, and how best to prevent this.90 However, the Amendment’s definition of a “depressant or stimulant drug,” as well as specifying barbituric acid, amphetamine, and their chemical derivatives and relatives, included

any drug which contains any quantity of a substance which the Secretary, after investigation, has found to have, and by regulation designates as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect.91

Justification for including hallucinogenic drugs was only given in passing. FDA commissioner George Larrick referred to the abuse of hallucinogens “around

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91 Drug Abuse Control Amendments of 1965, Sec. 3, (a).
some of our larger educational and research institutions” which had resulted in “rather extensive publicity a few years ago.” He was most likely referring to the controversy around the use of the drugs by Harvard psychologists Timothy Leary and Richard Alpert. Larrick described LSD as “capable of inducing lasting changes in the mental and emotional stability of some users.” This had led some college students to become “disturbed to the point that they had to leave college or even enter mental institutions.” He also stated that the drug could produce “strong suicidal tendencies.” The FDA had successfully prosecuted two men under the existing provisions of the Food, Drug and Cosmetic Act, for attempting to sell a large quantity of LSD to an undercover FDA agent in April 1963. The judge in the case had recommended legislation to specifically control drugs such as LSD. ⁹²

The Drug Abuse Control Amendments of 1965 had no provisions that would directly impact LSD researchers working under an IND. However, in April 1966, Sandoz would withdraw its IND for LSD research. As Sandoz had maintained itself as the drug’s sole sponsor, this would mean that all research was in jeopardy. The scale of LSD research in the United States would indeed drop significantly as a result. However, a joint initiative of the FDA and the NIMH would prevent research from ending entirely.

By late 1965, the FDA and NIMH were aware that Sandoz was planning to withdraw its sponsorship of LSD, as its patent for the drug had expired. At that time, the NIMH was supplying grants to approximately twenty investigations

using LSD. Therefore Jonathan Cole, chief of the NIMH’s Psychopharmacology Service Center, called a conference between representatives of Sandoz, the NIMH and FDA, to discuss the future of LSD research. The conference was held on 7 December 1965. Cole considered that there was “some evidence of benefit” with LSD therapy in the treatment of alcoholism, treatment resistant neuroses, and “hardcore sociopathic personalities.” He therefore wished to ensure that Sandoz’s withdrawal would not prevent NIMH grantees, and other legitimate investigators, from having access to the drug.93

The Sandoz representatives suggested that they could hand over their remaining supplies of LSD to the NIMH, which could act as the sponsor itself. The NIMH was, however, unable to take on this role. Three other prospects were discussed. Firstly, the NIMH could find a new source for LSD, and supply investigators who individually submitted their own INDs. Secondly, the FDA could give LSD an effective New Drug Application “under very restrictive labeling.” Seeming to support this possibility, Kelsey pointed out that research “could not go on indefinitely without some attempt at obtaining an approved NDA.” Indeed, the IND regulations stipulated that the “sponsor shall not unduly prolong distribution of the drug for investigational use but shall submit an application for the drug...with reasonable promptness after finding that the results of such

93 Memorandum of conference between representatives of Sandoz Pharmaceuticals, NIMH, and FDA, 7 December 1965, folder 521.6-525.091, box 3758, RG 88. A 23 August 1965 letter from Sandoz halting the production and distribution of LSD is reproduced in Albert Hofmann, LSD: My Problem Child. Reflections of Sacred Drugs, Mysticism and Science, trans. Jonathan Ott, (Santa Cruz: The Multidisciplinary Association for Psychedelic Studies, 2009), pp. 85-87. The letter cites their withdrawal as due to the drug’s growing abuse, resulting from growing publicity, inadequate legal control, and increased availability after the expiration of their patents in 1963. It is unclear, however, who this letter was sent to, and what impact it had, as Sandoz did not withdraw its sponsorship of LSD in the US at this time.
investigation appear to establish the safety and effectiveness of the drug.”

However Sandoz, although open to being a bulk supplier of LSD, was “not considering submitting an NDA.” Cole suggested the final prospect: if some individual or organization, possibly Sandoz, would take on sponsorship, the NIMH could cover all costs involved. The conference ended with all parties agreeing that this last scenario was a possibility.

Three months later, on 8 April 1966, Sandoz contacted the FDA to inform them that it intended to withdraw its sponsorship of LSD and psilocybin without delay. Sandoz had not planned to take any measures to ensure continued legitimate research with the drugs. The company’s American medical director, Craig Burrell, explained that the withdrawal was a result of the increased misuse of the drugs outside of medicine. Although Burrell was convinced that “no Sandoz produced LSD and Psilocybin reached black market channels,” the increased publicity around the drugs, and increasing black market production, created a situation where “we can no longer bear the responsibility for the allocation and distribution of these substances.” Sandoz’s cessation of LSD and psilocybin distribution was worldwide. The earlier plan of sharing the burdens of sponsorship between Sandoz and the NIMH was now off the table. Concerned by this prospect, officials from the FDA, the NIMH, and the Veterans Administration discussed the matter with Sandoz. Together they decided that while most of the approximately seventy investigators would have their stocks of LSD recalled, twelve would be allowed to continue using the drug while they wrote up and

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95 Conference between Sandoz, NIMH and FDA, 7 December 1965.
96 Organization and Coordination: LSD, pp. 80-81.
submitted their own INDs. On 11 April, Sandoz sent official notices to all LSD researchers, except the twelve, informing them of the cancellation of their sponsorship, and recalling any stocks of the drug. Sandoz then topped up the twelve remaining investigators’ supplies of LSD and delivered the rest of their stock, approximately twenty grams, to the NIMH, who would now take over the role of distributor.97

The decline in LSD research following Sandoz’s IND withdrawal was a topic of much discussion at May 1966 congressional hearings entitled “Organization and Coordination of Federal Drug Research and Regulatory Programs: LSD,” held by the Senate Committee on Government Operation’s Subcommittee on Executive Organization. Senator from New York Robert Kennedy had called the hearings to investigate “whether the Government has fulfilled its responsibilities in connection with research on LSD and regulation of its use,” in response to the growing controversy over its illegitimate use.98 Although the growing abuse of LSD was of great concern to the subcommittee, Kennedy stressed that the government’s reaction should not thwart legitimate research. Concerned that Sandoz’s withdrawal had resulted in the number of LSD research projects dropping from seventy down to nine (with twelve investigators), Kennedy repeatedly questioned FDA officials as to why they had allowed this to happen. Kennedy argued that the reduction in research indicated that either not all of the seventy projects had been worthwhile, or that valuable research had been terminated. Either interpretation was damning for the FDA—the FDA had either

97 Drug Safety, pp. 2135-2136.
been too permissive, or was now too restrictive, in approving research. FDA commissioner Goddard confirmed that all of the seventy investigations had been worthwhile. Kennedy therefore argued that the FDA should have done more to ensure their continuation: "if they were worth while I would think you would let them continue...It was helpful [research] 6 months ago, why is it not helpful now?"

Goddard, however, with NIMH director Stanley Yolles, argued that the situation was much more complicated. The regulation required that all investigators worked under an IND. Therefore, with Sandoz's withdrawal, investigators had to submit individual INDs if they wished to continue using LSD. The reason for some projects not being cut off was that they used the drug on a daily basis; the disruption caused by the approval process would have had a major detrimental effect on their research. They still had to submit INDs, but were allowed to continue using LSD in the interim. The reduction was also partly because some of the research projects had been concluding at the time. Those investigators that did not require constant access to LSD were invited to submit INDs if they wished to continue using the drug. Ultimately, it was not the FDA's responsibility to stimulate research, but simply to assess the adequacy of research proposals: as Goddard stated “We certainly do not want to be in the position of thwarting research that is needed...However, the responsibility for initiation does lie with the individual scientist.” Yolles stressed that the NIMH had accepted Sandoz's supplies of LSD precisely to ensure that valuable research continued. The NIMH

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99 Ibid., p. 59.
100 Ibid., p. 57.
had been under no obligation to become LSD’s distributor, and could have easily had the stocks destroyed. Yolles also confirmed that if they found research that needed to be performed, but had not attracted scientists, the NIMH was willing to stimulate the research and carry it out.\(^{101}\)

On 14 July 1966, the FDA published new regulations for the investigational use of hallucinogenic drugs. The regulations required an IND to be approved, rather than simply submitted, before drugs such as LSD could be sold or delivered to a researcher for clinical testing. FDA approval was also now required for researchers to receive the drugs for laboratory or animal research.\(^{102}\) These regulations prevented dishonest persons, or inadequate researchers, from gaining access to legal supplies of hallucinogenic drugs by either abusing the loose regulation of drug access for preclinical research, or the period between IND submission and termination. For bona fide researchers, these regulations could potentially delay the commencement date of new clinical research. However it is unlikely that these regulations would have had any real impact on such research. The NIMH was by this time the sole legal distributor of LSD, and it is unlikely that it would have distributed the drug to anyone before being thoroughly satisfied of their credentials and having consulted with the FDA. Indeed, the same expert committee advised the FDA on the adequacy of IND applications for research with psychedelics, and the NIMH on requests for access to its stocks of the drugs. Therefore, IND and drug request applications were likely assessed simultaneously. The FDA had established this committee in 1964

\(^{101}\) Ibid., pp. 55-57, 73, 77.

on an ad hoc basis, and in 1967 it became an official joint FDA and NIMH public advisory committee, the FDA-PHS Psychotomimetics Advisory Committee.103 It was one of twenty-six FDA public advisory committees, each of which advised on issues related to a different medical field, such as dentistry, oncology, and obstetrics.104 The psychotomimetics committee was composed of twelve distinguished scientists, however none of its members had recent or extensive experience with the therapeutic use of psychedelic drugs.105 In the first eighteen months after Sandoz’s withdrawal, the NIMH received 114 requests for supplies of psychedelics. After review from the committee, all but six requests were approved. According to the committee’s executive secretary, John Scigliano, those declined had proposed to use the drug in therapy rather than research.106

103 Records of the establishment and activity of this committee are scarce. For an overview of its role, written by its executive-secretary, see John A. Scigliano, "Psychotomimetic Agents," Journal of the American Pharmaceutical Association, n.s., 8, no. 1 (1968), pp. 28-29. Planning for the committee began in the FDA in May 1964, though it is not clear when it began operating. See Food and Drug Administration, summary of proceedings, tenth meeting of the Advisory Committee on Investigational Drugs, Washington, DC, 28 May 1964, folder 1, box 13, Kelsey Papers.

104 For a list of the FDA’s public advisory committees in 1967 see, Carpenter, Reputation and Power, p. 314.

105 An initial list of suggested committee members included several prominent LSD psychotherapy researchers, including Humphry Osmond and Albert Kurland, (Kurland’s research will be discussed in chapters four and five), however for unknown reasons their names had subsequently been crossed out, see Joseph F. Sadusk to Clem O. Miller, 27 July 1964, folder 4, box 13, Kelsey Papers. A 1969 list of committee members included only one member who had published a report on therapeutic research with psychedelics. That researcher, Sidney Merlis, appears to have only done limited psycholytic therapy research in the 1950s. For the list of members see, Members FDA-PHS Psychotomimetic Agents Advisory Committee, 21 January 1969, folder "F.D.A.-PHS Psychotomimetic Advisory Committee, box 1, Savage Papers. For Merlis’s research see, Herman C. B. Denber and Sidney Merlis, "A Note on Some Therapeutic Implications of the Mescaline-Induced State," Psychiatric Quarterly 28, no. 1 (1954), pp. 635-640. Other members, such as Daniel X. Freedman, Joel Elkes, and Carl Pfeiffer, had used LSD in biological and other nonclinical research, see Daniel X. Freedman, "Psychotomimetic Drugs and Brain Biogenic Amines," American Journal of Psychiatry 119 (March 1963), pp. 843-850; P. B. Bradley and J. Elkes, "The Effect of Amphetamine and D-Lysergic Acid Diethylamide (LSD 25) on the Electrical Activity of the Brain of the Conscious," The Journal of Physiology 120, supplement (1953), pp. 13P-14P; Carl C. Pfeiffer et al., "Time-Series, Frequency Analysis, and Electrogenesis of the EEGs of Normals and Psychotics before and after Drugs," The American Journal of Psychiatry 121, no. 12 (1965), pp. 1147-1155.

Conclusion

Had the FDA wished to curtail LSD research, in 1966 it had had the perfect opportunity. Rather than have to deny approval to researchers, or cancel already approved projects, the FDA simply had to do nothing but let it die. With Sandoz’s withdrawal, the only legal supply of LSD in the United States had disappeared, and every clinical research project had had its authority to conduct research automatically revoked. Had the FDA not acted, LSD research would have come to a complete halt. However, together with the NIMH and the Veterans Administration, the FDA acted voluntarily to ensure continued supplies of LSD were available to researchers. They even bent their own rules to allow certain clinical researchers to temporarily continue their use of the drug without an IND, in order not to disrupt their research. Ultimately, the decline in LSD psychotherapy research in the 1960s was the result of the actions of Sandoz Pharmaceuticals rather than the government.

The LSD researchers that had their INDs terminated by the FDA had not been denied approval because of government opposition to the drug. Instead, the formalization of pharmaceutical research, brought about by the Drug Amendments of 1962, was characterized by a system of research approval that focused on procedural correctness rather than subjective evaluation. This resulted in the termination of Abramson’s IND due to his inability to reproduce data that the FDA already had on file. Although this was not particularly fair, it was the result of an objectively enforced policy. The Savage led Foundation
struggled with the same requirement, however once Savage left, its IND was terminated on the grounds of the researchers’ qualifications, as well as the missing data. Despite their experience, Stolaroff, Harman, and Hubbard were objectively not qualified to perform drug research. This determination would have been made no matter what drug they were researching.

Although the scale of LSD research declined after the Drug Amendments of 1962, and even more dramatically after Sandoz withdrew its IND, the research that continued was significant. Rather than uncontrolled research projects that had existed prior to 1962, the clinical trials that progressed over the later 1960s were methodologically sophisticated. This reflected both the growing concern for objectivity in research that had been developing over the previous decades, and the second major requirement of the Drug Amendments of 1962: proof of drug effectiveness through “adequate and well-controlled trials.”107 Satisfying this requirement, however, would prove more difficult than gaining approval to conduct the research.

107 Drug Amendments of 1962, Title 1, Part A, Sec. 102, (c)

The Drug Amendments of 1962’s requirement that researchers submit a Notice of Claimed Investigational Exemption for a New Drug (IND) before initiating clinical research with an investigational new drug had an immediate and relatively clear impact on LSD psychotherapy research. The impact of the amendment’s requirement for proof of drug efficacy through controlled clinical trials, however, was far more complex and indirect. Yet it was this second requirement that would ultimately have the most profound impact. LSD research survived the formalization of drug research and development brought about by the IND regulations, and Sandoz’s reaction to them, and even survived the withdrawal of Sandoz’s sponsorship. Although at a diminished scale, and with less likelihood of resulting in a New Drug Application (NDA), LSD research would continue alongside the intense controversies over the drug’s recreational use in the 1960s, not coming to a close until the mid-1970s. Yet by that time there would still be no clear consensus on the efficacy of any of the form of LSD psychotherapy. This would lead research to peter out. A critical question in the history of LSD therefore becomes, why could researchers not clearly establish the efficacy of LSD psychotherapy?

Although proof of drug effectiveness was a seemingly simple and common sense requirement, it raised the thorny issues of what was efficacy, and how could it be
Where the IND rules established clear gatekeeping authority for the FDA, the efficacy provisions were written in broad subjective terms. Medical experts as well as the FDA had the responsibility of interpreting these terms. In the years immediately following the legislation’s passage they would provide nebulous understandings of research standards rather than clear guidelines. The value of clinical trials increasingly became determined by the scientific rigour of their design, and the randomized double-blind placebo controlled trial (usually referred to simply as the randomized controlled trial), which had been heavily promoted by research experts in the previous decade, rose in status to become the gold standard of research methodology. Although the methodology was not strictly mandated, anything less would provoke intense scrutiny.

Whilst the FDA and researchers alike advocated the randomized controlled trial as simply the most accurate and scientifically advanced research methodology, its focus on isolating drug effects from psychological influences reflected a “magic bullet” concept of drug efficacy. This hidden assumption clashed, on both practical and theoretical grounds, with LSD psychotherapy’s unique method of using a drug to catalyse a psychological treatment. This would frustrate the progress of research. As well as providing a deepened insight into the downfall of LSD psychotherapy, examining LSD research in the context of the amendment’s efficacy provisions, and the rise of the randomized controlled trial, also reveals the broader implications that the legislation had for psychiatry. Where psychiatry’s treatment landscape had encompassed a complex mix of psychological, physical, and pharmaceutical methods, drug treatments were now singled out for strict efficacy testing. The controlled trial’s assumption that drug
therapies worked through a direct biological action would widen the gulf between psychiatry's pharmaceutical and psychological treatments: drugs were treated as acting objectively on the brain, psychotherapy as acting subjectively on the mind.

This chapter will first scrutinize how both the FDA and medical experts interpreted the efficacy provisions of the amendments, in order to establish the standards of research to which LSD psychotherapists would be expected to conform. How LSD psychotherapy clashed with the randomized controlled trial will then be analysed, before exploring how the amendments related to psychiatry more broadly.

**Mandating Efficacy**

The need to scrutinize how the efficacy requirements of the Drug Amendments of 1962 were interpreted arises from the broad and subjective nature of the provisions in the legislation. An NDA was required to provide “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.” “Substantial evidence” was defined as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to
have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.¹

This definition did not provide great clarity as to the requirements, as “adequate and well-controlled investigations” was an equally subjective term as “substantial evidence.” The FDA did not provide an official elaboration of the requirements until 1970.² Between 1962 and 1970, drug researchers therefore had to provide proof of drug efficacy in an NDA without official guidelines as to what form of proof would be considered “adequate and well-controlled.”

The evolution of drug research methodology, the FDA and experts’ increasing concern for drug efficacy, and the passage of the efficacy provisions of the Drug Amendments of 1962, have all been topics of interest for a number of historians. However, they have largely treated these issues separately, with little analysis of their interplay and impact on drug research in the years immediately following the legislation. For example, Harry Marks’ authoritative work on the history of US drug research in the twentieth century, The Progress of Experiment, focuses on the role of “therapeutic reformers” in bringing about changes in research methodology. He skips over the 1962 amendments, instead pointing to the FDA’s official elaboration of the efficacy requirements in 1970 as the moment when high standards of research became mandated.³ Daniel Carpenter has published the most thorough study of the 1962 amendments, and most closely analysed the

¹ Drug Amendments of 1962, 87 P.L. 781; 76 Stat. 780, October 10, 1962, Title 1, Part A, Sec. 102, (c).
FDA’s stance on drug efficacy. He draws attention to the FDA’s concern for efficacy and preference for controlled trials prior to 1962, and the conceptual as well as gatekeeping powers that the FDA gained as a result of the amendments, which influenced many aspects of drug research. But just what research standards became in practice, and how researchers were impacted, remains unexplored.\(^4\) Arthur Daemmrich has come somewhat closer to addressing these questions, revealing the FDA’s careful scrutiny of clinical trial designs in the decade after the amendments: the Administration delayed the approval of the beta-blocker propanolol’s NDA in the late 1960s and early 1970s due to concerns over the level of control in clinical trials, even though the sponsor had utilized double-blinding.\(^5\)

Instead of examining the impact of the efficacy provisions on new research, much of the discussion over implementation has focused instead on the FDA’s analysis of the efficacy of drugs already on the market, known as the Drug Efficacy Study. Commenced in 1966, this study was initiated to evaluate the efficacy of the thousands of drugs that had received NDA’s between 1938 and 1962, without supplying proof of efficacy. It was contracted out to the National Academy of Sciences’ National Research Council. The study resulted in hundreds of drugs being removed from the market. Legal challenges from the manufacturers of those drugs pushed the FDA to produce its 1970 elaboration of what constituted “adequate and well-controlled investigations.”\(^6\) Faced with the impractical

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\(^6\) See Carpenter, *Reputation and Power*, pp. 345-357; Philip J. Hilts, *Protecting America’s Health:*
prospect of requiring new clinical trials for all of the drugs under review in order to provide adequate proof of efficacy, the Drug Efficacy Study panels opted to assess all available evidence, consider expert opinion, and designate drugs “probably” and “possibly” effective when evidence was not of a high calibre. The final determination on the appropriate action to take then fell to the FDA. Although the study is of great significance in the history of drug efficacy regulation, its format of evaluation meant that it did not necessarily reflect the standards to which developers of new drugs in the same period would have had to conform.

In the absence of official guidelines, what was considered “adequate and well-controlled investigations” can be deduced from two sources: comments on standards by FDA officials, and the opinions of medical experts. In the years immediately following the passage of the Drug Amendments of 1962, FDA officials addressed the drug research and development community on the changes brought about by the legislation. These discussions conveyed the FDA’s general stance on appropriate research methods, yet stopped far short of providing clear standards for researchers. In these statements, the agency showed a strong preference for double-blind placebo controlled trials, while appreciating that these were not always possible.

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In February 1963, the FDA held a conference in Washington, DC, to outline its planned implementation of the Drug Amendments of 1962. All interested parties were invited to the conference to hear papers from FDA officials detailing the new requirements of the legislation, and generally how they would be applied. Attendees were invited to participate in an extended question and answer session, where specific questions as to the FDA’s interpretation of terms and requirements in the legislation were first voiced. Despite direct questions as to the standard of evidence required for proof of effectiveness, the answers of FDA officials remained vague. One audience member queried, “What standard will be used in determining effectiveness of a drug? What are the accepted characteristics of a controlled trial?” to which the acting director of the FDA’s Division of New Drugs, Arthur Ruskin, replied simply, “We’ll have to go to scientific authorities in the matter…. But I think all of us know, in general, what a controlled study is, and where double blind studies can be used.” When further questioned “what will constitute adequate study, and subsequently adequate proof of efficacy?” in relation to tranquilizers, Ruskin elaborated somewhat: “It would include some sort of control investigation, with the use of a placebo and perhaps other tranquilizers that have known effectiveness, and possibly double blind studies.” He did concede that, “Perhaps the most difficult area to have double blind studies is in the area of psychopharmacology.”

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Over the next few years, FDA officials travelled the country giving talks to groups involved in pharmaceutical research and development, explaining the new requirements of the law. Regarding efficacy, FDA medical director Joseph Sadusk delivered the most notable of these addresses in 1964, before the American College of Physicians. As far as establishing standards of research methodology, the talk moved little past the view expressed by Ruskin. However, as Carpenter has argued, the speech powerfully asserted the FDA’s new authority in this scientific matter precisely through its ambiguity.10 Entitled “The Definition of the Efficacy of a Drug Under the Law,” the paper again set out the double-bind placebo controlled trial as the ideal method of research,

Obviously, many experimental factors must be controlled and, in general, the effect on the disease process in patients receiving the drug needs to be compared with patients with similar disease conditions who do not receive the drug. This is preferably done by placebo comparisons in well-designed double-blind clinical studies.11

However, Sadusk emphasized that “this is not the only type of study that can be called well-controlled,” and cautioned that the method could not always be utilized due to ethical or practical concerns. In such cases he did not suggest a clear alternative method, but instead stated that the FDA would weigh the

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adequacy of a trial on factors such as its design, the expertise of the investigator, the methods used to record and assess results, and the nature of, and status of knowledge on, the disease being treated.

Ultimately, as Carpenter has argued, the term “adequate and well-controlled” became a descriptor given to a trial based on a subjective evaluation by the FDA, rather than a standard defined by protocols that a researcher could check off when designing a trial. As Sadusk stated,

> What we want, and what the law requires, is data that would enable the appropriately qualified experts to say responsibly whether or not the drug may be expected to perform as it is represented. This kind of evidence is not hard for the qualified person to recognize when he sees it.¹²

Researchers would not determine a drug’s efficacy, with the FDA checking that they used appropriate methods; the FDA would determine efficacy based on experimental data furnished by the researcher. The double-blind placebo controlled trial was the surest way of satisfying the FDA’s standards, however every trial would be judged on a case by case basis, in the light of expert opinion on the adequacy of the research methods for the drug and disease in question. More thoroughly determining what could be considered an “adequate and well-controlled” trial therefore requires examining expert opinion on research methods. What did experts argue were the factors that could complicate the determination of a drug’s efficacy? What were the best methods for overcoming those obstacles? Ultimately, expert opinion was much more insistent on the randomized double-blind placebo controlled trial methodology.

¹² Sadusk, “Efficacy of a Drug.”
Determining Efficacy- Medical Experts and the Evolution of Drug Research

Over the decades prior to the Drug Amendments of 1962, drug evaluation had become a topic of increasing interest for medical scientists. The field had evolved from entrusting the determination of efficacy to the opinion of experts, to focusing on attaining objectivity through removing the biasing influences of the human participants in research. As the field of pharmacology expanded rapidly in the twentieth century, the need to quickly and accurately determine drugs’ effectiveness became imperative to ensure increased drug production resulted in improved therapeutics. As researchers came to recognize how factors such as methods of patient selection, researcher or patient enthusiasm for a treatment, the placebo effect, variety in the natural course of disease, and methods of evaluating data could skew the results of research, techniques were developed to eliminate their influence. Randomization, blinding, standardized rating scales, and statistical analysis became tools to control clinical trials in order to determine if a drug was responsible for therapeutic effects. These elements were all combined to create the ideal objective drug assessment, the randomized double-blind placebo controlled trial, which was well established, at least in theory, by the time of the Drug Amendments of 1962.

The randomized controlled trial was not an isolated invention of the mid-twentieth century, but a coming together of various experimental techniques in
order to address an increasing recognition of the factors that could compromise therapeutic evaluation. The historiography of the randomized controlled trial has therefore often focused on tracing the development of the theory and methods of these techniques through historical antecedents, which become increasingly frequent and sophisticated before eventually crystallizing into an ideal model for research. Perhaps the simplest and earliest of these antecedents was recognition that the results of a treatment cannot be evaluated in isolation. Rather, a comparison is needed to argue that results improve on either the natural course of an illness, or another treatment. Abraham Lilienfeld has found evidence of the use of comparative controls as far back as the Old Testament, and highlights Scottish naval surgeon James Lind’s 1747 comparative study of six different scurvy treatments as a significant early example the technique. In the nineteenth century interest in the comparative analysis of drug treatments, and other medical interventions, became more common, especially in Europe. Researchers emphasized not only the need for patient samples to be as identical as possible, to ensure fair comparison, but also as large as possible, showing an understanding of the need for statistical significance in results: as the natural course of illness was often unpredictable, spontaneous remission could easily skew results when comparing small numbers of patients. Utilizing historical controls, where the results of a treatment were compared to existing data on prognosis, was one method of generating adequate control data.\textsuperscript{13}

Early cases of blinding have been described by Ted Kaptchuk in eighteenth century France. Here blinding was used by sceptics to examine the practice of mesmerism. Scientists conducted a series of trials where they examined the influence that the patient’s knowledge of the mesmerist’s activity had on their experience of that procedure: in one example a patient reported feeling the effects of mesmerism when falsely told that it was being projected on her from an adjoining room, yet felt nothing when left ignorant of it actually being practiced. With the goal of “excluding from these [mesmeric] effects all the illusions which might mix with them,” the researchers showed an appreciation of the placebo effect— that belief in the effectiveness of an inert procedure could cause it to have effect.\textsuperscript{14} Kaptchuk traces the use of an inert placebo to 1830s France, where Armand Trousseau evaluated the efficacy of homeopathy by examining the effects an inert substance produced when administered enthusiastically as an effective homeopathic remedy. Blind assessments became not uncommon in the nineteenth century, particularly in Europe, although often to interrogate controversial procedures such as these, rather than for establishing the efficacy of mainstream treatments.\textsuperscript{15}

Starting in the 1930s, several drug trials were conducted which advanced the theory and methods of controlled clinical trials significantly, and which historians have pointed to as the chief influences on the growing formalization of the controlled trial methodology. Cornell University pharmacologist Harry Gold pioneered the use of placebo controls and double-blinding in his trials of

\textsuperscript{15} Ibid., pp. 400-414.
xanthines for the treatment of pain caused by angina pectoris. Suspicious of the effectiveness of the drugs, Gold and his colleagues began comparing their use with a placebo in one hundred patients in 1932. Rather than a distinct control group, each patient was switched between periods of xanthine and placebo treatment. The trial was initially single blind—only the patients were ignorant of the use of a placebo—but the researchers became aware that the administering physicians were influencing patients’ reports of the treatments’ effects. As a result, they too were blinded so that all patients would be evaluated alike. The study revealed xanthine treatment to be ineffective. Arthur Shapiro has argued that this trial was significant not simply for its growth into a double-blind placebo controlled methodology, but for more fundamentally influencing the field’s attitude towards placebos. Rather than a useful research tool, most physicians had understood “placebo” as describing inert drugs used by dishonest physicians to deceive patients. Following his experience, Gold became a firm believer in, and promoter of, the double-blind method.16

The final major element of the controlled trial, randomization, was introduced by way of agricultural research. In the 1920s, British geneticist Ronald Fisher devised a way of comparing the yields of two grains. Rather than grow them separately in two fields, where environmental variations could affect results, Fisher divided two fields into narrow strips and randomly allocated the strips to the two grains. The random allocation not only removed the influence of

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environment, but also allowed a more sophisticated statistical analysis of results. British statistician and epidemiologist Austin Bradford Hill first utilized randomization in medical research. In a trial commenced in 1946 of streptomycin in the treatment of tuberculosis, Hill randomly assigned 107 patients between treatment and control groups, with results then blindly assessed. The trial did not use a placebo in the control group, due to practical considerations rather than ignorance or contempt for the practice: enduring up to four daily injections of placebo for six months, in order to mirror the administration of streptomycin, was considered more than a patient could fairly be subjected to for research. Hill argued that randomized allocation removed the conscious or subconscious bias that could undermine researchers’ efforts to match experimental and control groups, which was never accurately possible given the multitude of possibly important variables. Historians have considered Hill’s trial as the pivotal study in the history of the randomized controlled trial in Britain and the United States, as he combined the techniques of comparative control, randomization, and blinding.

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19 Shapiro and Shapiro, Powerful Placebo, p. 146. For more on Hill’s clinical trials and their place in the development of the randomized controlled trial see Peter Armitage, "Bradford Hill and the Randomized Controlled Trial," Pharmaceutical Medicine 6 (1992), pp. 23-37; Matthews, Quantification, pp. 127-140.
20 Marks, Progress of Experiment, pp. 145-146.
Like Gold, Hill became a leading figure in the promotion of the randomized controlled trial’s theory and methods. In 1951, he published a detailed discussion of clinical trial methodology that included all of the major techniques for the randomized double-blind controlled trial and their justifications. The following year he spread his theories to the United States via a similar article published in *The New England Journal of Medicine*, originally a presentation delivered at Harvard Medical School. Hill argued that controlled clinical trials were needed due to the rise in the number of drugs being developed with similar effects. Where penicillin’s efficacy had been unquestionable given its dramatic and unparalleled effects, determining the comparative efficacy of the various antibiotics developed subsequently was much more complicated. The most common complaint against randomized controlled trials was that it was unethical to withhold a treatment believed to be effective in the name of research. Given this, Hill emphasized the need to start controlled trials with a drug immediately on discovery, before unsubstantiated claims of efficacy could be promoted, and countered that it was unethical to widely use a drug of unconfirmed efficacy.

Hill argued that in order to accurately evaluate drugs, clinical trials required patient samples of a size relative to the variability of the disease in question: where outcome was predictable, such as in leukaemia, small samples could suffice, however where the natural course of the disease was unpredictable, a large sample was needed in order to distinguish the results of the treatment from chance. Patients then needed to be divided into treatment and control groups on a random basis in order to avoid an intentional or unintentional bias,
such as patients who could be expected to favourably respond to treatment being mainly allocated to the experimental group. If significant variables that could be expected to impact results (such as patient age) were present in the patient sample, then a method for insuring an equal distribution from randomization was needed. Blinding both the patients and the researchers as to whether the patient was in the experimental or control group was then necessary in order to equalize the influence of their enthusiasm or scepticism over the treatment, and avoid a skewed analysis of results. Establishing this blind was best achieved through the use of an inert placebo in the control group, however practical issues or ethical concerns could require another technique to be devised. Determining a clear treatment regime and objective measures for results prior to the trial’s commencement further ensured the elimination of bias.

At the start of the 1950s the theory and method of the randomized double-blind controlled trial was fully established and had been promoted in the United States. This, however, did not guarantee widespread support for the method amongst experts. Indeed Harry Marks and Scott Podolsky have argued that the increasing promotion of the randomized controlled trial in the mid-twentieth century cannot be explained simply through epistemological developments—researchers by and large were not motivated to change their methods purely for the sake of scientific ideals. Indeed, prior to the 1950s, many researchers rejected the control techniques. They argued that while ideal in theory, true

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control was never possible; therefore faith in control methods could give false authority to the results of a trial. They also argued that laboratory and well-conducted uncontrolled clinical research was sufficient.\footnote{Scott H. Podolsky, \textit{Pneumonia before Antibiotics: Therapeutic Evolution and Evaluation in Twentieth-Century America} (Baltimore: The Johns Hopkins University Press, 2006), pp. 37-42; Scott H. Podolsky, "Antibiotics and the Social History of the Controlled Clinical Trial, 1950-1970," \textit{Journal of the History of Medicine and Allied Sciences} 65, no. 3 (2010), pp. 354-360.}

Such resistance to control methods was overcome primarily as a result of reformers, largely academic researchers, promoting the controlled trial as a defence against therapeutic claims for drugs that ranged from inaccurate to fraudulent. With the massive growth in the development of new drugs in the mid-twentieth century, the need for accurate methods of separating the wheat from the chaff gained a new imperative, especially in the face of intense marketing from pharmaceutical companies: successful promotion of ineffective, or less effective, new drugs threatened to undermine the achievements of medical science. This fear was based in a growing mistrust in the ability any of the human participants in research to guard against the intentional or unintentional corruption of objectivity, which could creep in at any level. Marks found reformers commonly warned against

> the gullible physician; the researcher misled by the hope (or the glories) of easing suffering; the nurse whose natural sympathies make her an unreliable research instrument; above all, the manufacturer who exploited gullibility, ambition and even compassion.\footnote{Harry M. Marks, "Trust and Mistrust in the Marketplace: Statistics and Clinical Research, 1945-1960," \textit{History of Science} 38, no. 3 (2000), p. 349.}

Reformers therefore promoted controlled trial methodology as not only a way of increasing the accuracy of research, but for providing an easy way for physicians...
to be able to judge the impartiality and reliability of the claims of manufacturers. As Marks argues, the evolution of clinical trial methodology was propelled less by the triumph of scientific theory, than by “mistrust” in the industry to discern and promote the best medicines.  

The Randomized Controlled Trial in Psychiatry

If this was the case for medicine in general, what was the standard of research in psychiatry? In the 1950s psychiatry was revolutionized by a wave of new drugs, beginning with the discovery of the first tranquilizer, chlorpromazine, in France in 1950. Over the decade, the discovery of the minor tranquilizer meprobamate and the antidepressants imipramine and iproniazid, firmly established the field of psychopharmacology as a chief concern of psychiatry. The dramatic discovery of new drugs to treat previously chronic intractable mental illnesses in many ways paralleled the pharmacological revolution for infectious disease that had occurred over the past twenty years with the discovery of antibiotics. However there were some stark differences between the fields. Where the etiology of infectious disease and the therapeutic action of antibiotics was understood, the origins of mental illness and the mechanisms of action for the new drugs were largely mysterious. Indeed the new drugs ran counter to the predominant etiological theory in the United States, that mental illness was a result of psychological rather than biological factors. This made accurate clinical trials

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both more vital and more difficult. Without a firm understanding of the biological basis of mental illness and the mechanisms of action for the drugs, and the inability to test them in vitro, the clinical trial was the only method for determining efficacy. With mental illness being highly placebo responsive, and both illness and treatment involving so many potentially significant, though little understood variables, clinical trials that would maximize objectivity and neutralize the impact of non-pharmacologic factors were needed in order for efficacy to be established to a reliable level. However, controlling the myriad variables in psychiatry was very difficult, and the fact that all diagnoses and determinations of results were based on the interpretation of symptoms and their variation made establishing objectivity and standardized methods for evaluating research very difficult.

In 1956 a major conference was held in Washington, DC, to discuss the evaluation of the new psychoactive drugs. Sponsored by the National Institute of Mental Health, the National Academy of Sciences—National Research Council, and the American Psychiatric Association, the conference gathered together the nation’s leading authorities on pharmacology and psychopharmacology, attracting a crowd of nearly 1000. The conference proceedings offer a unique window into expert opinion on drug research methodology at the mid-1950s, displaying the level of consensus on appropriate methods, difficulties in their application, and the level and nature of dissent.

Provoked by the inconsistent and largely inadequate quality of the reports on the efficacy of the tranquilizers chlorpromazine and reserpine, the conference was
intended to examine the efficacy of these drugs through interrogating the
problems involved in research, in order to guide future studies.\textsuperscript{26} For most of the
participants, the basic elements of the randomized controlled trial —
comparative controls, randomization, placebos, double-blinds, and statistical
analysis—were well understood and accepted as ideals in clinical research. As
Johns Hopkins pharmacologists Louis Lasagna and Victor Laties commented,
“Placebo and double-blind controls are of proven value in experimental work,
and the reasons for their use should not need to be discussed at length in the
year 1956.”\textsuperscript{27} Therefore instead of explaining and justifying the need for these
basic elements in research, the conference was concerned with a more detailed
analysis of the problems involved in trying to put the ideals into practice.

Performing valuable and accurate research required balancing the need for high
levels of standardization and control, with the practical realities of treatment. A
precise research question needed to be established, and complex theoretical
questions needed to be addressed: What level of difference between the results
of the experimental treatment and control would be considered significant?
What was an acceptable risk versus benefit ratio for the illness being tested?
What constituted “improvement” in the illness? This last question was
particularly pertinent for research in psychiatry, as results could not be easily
determined through the biological analysis of the presence of disease. Was a
patient improved if they were simply quieter or more manageable, or did there
need to be a significant reduction in symptomatology? The answer would depend

\textsuperscript{26} Jonathan O. Cole and Ralph W. Gerard (eds.), \textit{Psychopharmacology: Problems in Evaluation}
\textsuperscript{27} Louis Lasagna and Victor G. Laties, “Problems Involved in the Study of Drug-Modified Behavior
upon the research question of the trial. If symptom reduction was the goal, which symptoms should be the focus, what constituted “significant” reduction, and how could this be reliably and objectively measured? The preferred method for evaluating results was with a clinical rating scale: a standardized test that usually consisted of interview questions, with a choice of predetermined answers that allowed scoring and quantification. However, the conference participants found that the available rating scales provided as many questions as answers, as their reliability, objectivity, accuracy, and comprehensiveness were poorly understood.\textsuperscript{28}

Even seemingly simple practical issues in trial planning, such as what dosage of a drug to use, could on close analysis become very complicated. Using a fixed dose was the simplest way of establishing a standardized and objectively delivered treatment that allowed easy quantification and comparison. However the dosage might be too low or high, not frequent enough or too frequent, thus obscuring the drug’s efficacy. Allowing flexible doses would better ensure the drug’s potential was picked up, but as this relied on the skill of administering physicians to find the optimum dose for individual patients, an important variable was added to the trial which needed to be accounted for in its design.\textsuperscript{29} Deciding on the duration of the experiment and the route of drug administration required considering and balancing similar factors.

The issue of control was of primary concern at the conference. The participants

\textsuperscript{29} Cole and Gerard (eds.), Psychopharmacology, pp. 605-606.
found a wide range of variables that needed to be controlled in addition to the natural course of illness and the placebo effect. These included changes in the patients’ environment, routine, activities, and staff. Historical controls were considered unsatisfactory, given the inability to control many variables, while using the patient as their own control—switching them between a placebo and the experimental treatment—was only appropriate with certain conditions and drugs, where response to treatment could be expected to reliably “turn off and on like water from a tap.”

Several participants highlighted the difficulty of establishing a secure double-blind with an inert placebo if the experimental treatment had conspicuous side effects. They therefore suggested that an “active placebo” could be used: a drug that produced similar side effects to the experimental drug, but did not interfere with the illness being treated. However this could cause complications, as it would be hard to guarantee that the drug would have no effect on the illness. Indeed the drug could have a psychologically negative effect on treatment due to its unpleasant effects, even if it had no biological effect on the illness.

Given the complexities of designing clinical trials that put the ideals of the randomized double-blind controlled trial into practice, one of the major recommendations to come out of the conference was precise reporting of trial design in research publications. Reports should include all available data on patient selection, controls, variables considered, treatment schedules, statistical analysis, methods of evaluation, and any other aspects of research considered.

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30 Ibid., p. 607.
significant. Although designing a perfect trial was impossible, openly reporting these factors would allow the reader to make an informed assessment of the weight of the results, and accurately compare them to other research.\textsuperscript{32}

Whilst the majority of the conference participants accepted the ideals of the randomized controlled trial, a significant minority of participants voiced concerns over the limitations of statistically driven research methods. As well as the practical difficulties of implementing the randomized controlled trial model, these physicians argued that drug treatment was not a purely objective process, but involved the “art of medicine.” Consequently, they argued that the standardizing focus of the methodology was not well suited to appreciate the diversity of factors that contributed to a treatment’s efficacy. These concerns foreshadow those that LSD psychotherapy researchers would voice in the 1960s, as they faced pressure to incorporate controlled trial methods into their research.

Psychiatrist Lincoln Clark, of the Salt Lake City Veterans Administration Hospital, Utah, was particularly critical of the degradation of respect for clinical observation that accompanied efforts to increase objectivity in research. He argued that, “while we like to think of ourselves as scientists and understandably feel more secure with reliable methods, we have to admit that most of the clinically useful information we now have about the psychological effects of drugs was acquired by clinical observation.” Indeed, he felt that “the premature use of particular rating scales, standard methods of interviewing, content

analysis, etc., because of anxiety about reliability, can be very inefficient if not misleading.”\(^\text{33}\) This was because a drug might have effects or uses that a rating scale could not discern, as the questions it contained were based on a different concept of treatment efficacy. He therefore argued that it was particularly critical that early stages of drug research were based on clinical observation. Audience member Dr Kalinowsky also attacked the declining reputation of clinical observation, by further highlighting the great achievements of uncontrolled research in psychiatry:

I would like to remind you of the fact that all of the treatments in psychiatry, drugs as well as the previous treatments, were all introduced through studies which were not well planned, which were not planned at all, but they were introduced on the bases of the observations of some clinicians in relatively small hospitals...I might add that the large statistical studies which were done later added very little to the indications suggested by those small original studies.\(^\text{34}\)

Clark extended his critique of the randomized controlled trial by challenging the validity of its ideal of isolating a “pure” drug effect from other influencing variables, which he argued could only produce a shallow understanding of a drug’s efficacy. Indeed learning how to manipulate these variables to draw the greatest efficacy from a treatment was a goal of research that was lost in the controlled trials.

Psychopharmacological agents do not produce a constant effect under all circumstances but a variety of responses which depend upon non-drug factors...In the artificial situation of an experiment these factors would be regarded as intervening variables which the investigator would seek to control in order to isolate the drug effect, but it is important to remember that such variables will not be controlled in the eventual clinical use of the drugs...What we gain in reliability and validity by using, for example,

\(^{33}\) Ibid., p. 327.
\(^{34}\) Ibid., p. 624.
formal, double-blind studies of groups of subjects under standard conditions, reliable rating scales, or other quantifiable methods, we lose in knowledge of the richness and depth of the psychological processes occurring in the drug response of the individual case. Yet such information may be the key to an effective use of the drug in the individual patient or lead to an understanding of why a drug benefits some cases in an experimental population and fails in others.\textsuperscript{35}

Audience member Dr Gardner further argued that extrapharmacological variables were not complicating factors to be neutralized, but vital components of treatment. In his experience the new drugs were not very effective when used “by themselves in a mechanical way.” Instead their usefulness was as a “psychiatric catalyst between the patient and those trying to communicate with him and help him.” By opening up communication with patients, the drugs made them amenable to psychological and environmental treatments, which would combine with the drug’s effects to have an impact on the patient greater than the drug or other treatments alone. Studying the drug treatment in a “vacuum,” Gardner argued, was akin to asking “how strong must a hearing aid be for a person to be interested in what is being said”—it was based on the incorrect assumption that the drug’s biological action was the only relevant aspect of treatment.\textsuperscript{36}

In response to these arguments, conference participants supporting the randomized controlled trial ideal asserted that there was nothing special about psychiatry that precluded the use of methodology, and that if there were non-drug variables deemed an important component of treatment, they could be incorporated into a trial’s design. Lasagna, who perhaps significantly was not a

\textsuperscript{35} Ibid., pp. 327-328.
\textsuperscript{36} Ibid., p. 626.
psychiatrist, was particularly dismissive of claims that psychiatry provided insurmountably unique challenges to the researcher, and that the art of medicine was lost in clinical trials. He argued that, “Any field which is in a disordered state prefers to believe that the reason for intellectual chaos is the overwhelmingly difficult problems confronting it,” and commented, “I, myself, would prefer to see a little more science and a little less art in this field.”

Jonathan Cole, one of the conference’s primary organizers, and chief of the new Psychopharmacology Service Center in the National Institute of Mental Health, was also a strong supported of the randomized controlled trial, having studied under pioneer Harry Gold during medical school in the mid-1940s. He argued that extrapharmacological elements in a treatment need not be eliminated from research, but instead their influence in the treatment also needed objective evaluation before being worked into an overall efficacy trial design. That a drug was a catalyst for wider treatment was not a militating factor for a controlled trial, but an additional hypothesis that also needed exploring—everything was “open to scientific test.”

Conference chairman Ralph Gerard, professor of neurophysiology at the University of Michigan, echoed this opinion, stating, “Obviously, if one feels that the effect of the drugs is primarily to make the patient accessible to other kinds of therapy, then the experiment must be designed to include that variable, which is perfectly possible.”

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37 Ibid., p. 605, 615.
39 Cole and Gerard (eds.), Psychopharmacology, p. 626.
40 Ibid., p. 627.
The conference proceedings therefore suggest that in the mid-1950s psychopharmacology was at the cutting edge of clinical trial methodology. The majority of the participants supported the need for objective, standardized, and statistics driven clinical trials to determine the efficacy of drugs, and saw the methods of the randomized double-blind controlled trial as the best way of doing so. Those who expressed doubts regarding the superiority of randomized controlled trials were at least familiar with their theory and methods, and were more concerned that other forms of research retain respect in light of situations where the methodology might not be ideal, rather than objecting to its use outright. Given the organizing bodies of the conference, and the fact that the participants were considered to be the leaders in their fields, the conference's proceedings can be seen as representative of expert opinion, and would have carried prestige and influence.

**Standard of Practice**

Assessing the impact that the efficacy provisions of the 1962 amendments had on drug research and development depends on whether they introduced new research standards, or merely reflected changing practices in the discipline. Historians have tended to emphasize the latter, charting research experts' increasing concern for drug efficacy, and the attendant rise in stature of the randomized controlled trial, in the decades before the amendments. Furthermore, John Swann and Daniel Carpenter have argued that both government and private organizations had attempted to regulate drug efficacy
long before it was specifically legislated. For example, from 1905 until 1955 the American Medical Association had used its influential position to promote efficacious drugs. The organization required proof of a drug’s quality and effectiveness before allowing its promotion in their publications. Since the Pure Food and Drug Act of 1906, the FDA had had the power to prosecute the manufacturers of drugs labelled with a “curative or therapeutic effect…which is false and fraudulent.”  

41 However, this power was rendered ineffective and unenforceable by the requirement for proof of deliberate fraud, and the restriction of jurisdiction to only the drug’s labelling. Most significantly, after the Federal Food, Drug, and Cosmetic Act of 1938, the FDA considered efficacy when evaluating the proof of drug safety that was required in an NDA, as they considered the issues inextricably linked. This was especially important for drugs designed to treat life-threatening conditions, where risk had to be weighed against potential benefit, and the danger of wasting time with ineffective drugs had to be taken into account. For the evaluation of efficacy, FDA officials had expressed a preference for double-blind trials.  

42 Taken together, arguments for the strong concern over drug efficacy and preference for controlled trials among both medical experts and the FDA prior to 1962, could suggest that the amendments’ efficacy provisions merely formalized existing standards. However evidence strongly suggests otherwise: that despite efforts to promote sophisticated efficacy testing, adopting the complex and expensive techniques of the randomized controlled trial remained ultimately

voluntary. As Earl Meyers, chief of the Controls Evaluation Branch of the FDA’s Division of New Drugs, described in 1963, the FDA’s powers to regulate efficacy were limited: although after 1938 they

invariably considered efficacy in connection with safety in clearing new drugs when they were for a progressive or life-threatening condition or when they had a significant toxic potential...the new drug provisions did not authorize us to control exaggerated claims or to exclude from the market worthless but essentially innocuous products.43

University of Utah pharmacologist Louis Goodman further described the reality of drug development at the 1956 psychopharmacology conference. Drugs came to market on the back of “poor clinical publications...Really good, definitive, critical, convincing, and properly controlled clinical studies are published only years after the drug has made the grade or has begun its well-deserved disappearance from the therapeutic scene.”44 In order to evaluate the effect that the 1962 amendment’s efficacy provisions had, it is therefore necessary to examine the standard practice of drug research and development in the years before its passage.

Just as Goodman noted, the breakthrough psychiatric drugs of the 1950s passed to market on the back of very limited and poorly controlled clinical studies, with methodologically sophisticated trials being reported only after the drugs were already in widespread use. Indeed in the case of the tranquilizer chlorpromazine, commonly considered the greatest therapeutic breakthrough in psychiatry, most

44 Cole and Gerard (eds.), Psychopharmacology, p. 589.
of the pre-market clinical testing did not even concern its psychiatric potential.\textsuperscript{45}

In 1952, chlorpromazine's French developer Rhône-Poulenc approached US pharmaceutical companies to license the drug, eventually signing an agreement with Smith, Kline, and French Laboratories. Fearing that there was not a market for a drug to treat psychosis, as this was such an unprecedented concept, Smith, Kline, and French believed that the quickest path for development, and the largest market, would be found through one of the drug's more conventional physiological effects: countering nausea and vomiting. The firm received approval from the FDA to market chlorpromazine in 1954 for nausea, vomiting, and in neuropsychiatry. Although its psychiatric use was approved in the NDA, and was considered throughout the development phase, the vast majority of effort in research and development was centered on the drug's antiemetic properties. Research submitted to the FDA included over 1000 patients treated for nausea and vomiting, compared to just 104 psychiatric patients. The research performed with psychiatric patients was also relatively conventional, testing its use as a sedative rather than its unique antipsychotic properties, although its unique non-hypnotic effects were noted.\textsuperscript{46}

In 1954, reports of the first independent psychiatric clinical trials of chlorpromazine in North America began to be published. They consisted of impressions of efficacy garnered through researchers' clinical observation of treated hospital patients with a variety of diagnoses. The reports focused on closely monitoring the effects of the drug on patients' symptoms, and their

\textsuperscript{45} For chlorpromazine's status in the history of psychiatry and psychopharmacology see David Healy, \textit{The Creation of Psychopharmacology} (Cambridge: Harvard University Press, 2002).
psychological effects. There were no indications of controls being used, and results were crudely tabulated with little information as to how they were evaluated. The trials all found chlorpromazine to be highly effective.47

Over the next two years a number of researchers published results from controlled trials of chlorpromazine. Although these trials all attempted a double-blind comparison with an inert placebo, and in some cases other sedatives, their designs varied significantly and contained several flaws: patients were not randomized into treatment and control groups, blinks were often imperfect, and, although psychotic illnesses were the primary indication for research, patients with various diagnoses, or from various psychotic subgroups, were frequently included. Results reported varied from strong to insignificant evidence of efficacy.48 Interestingly, the most methodologically sophisticated clinical trial of chlorpromazine in the mid-1950s reported negative results. In 1955, Robert Hall and Dorothy Dunlap reported the results of a trial at the Agnews State Hospital, California, that randomly allocated 175 “semi-disturbed chronic schizophrenic” patients between chlorpromazine and inert placebo in a double-blind fashion, and used rating scales to evaluate results. The blind was partially broken due to


revealing side effects and a flawed drug coding system. Results found that although patients significantly improved during the trial, there was no significant difference in improvement between the experimental and placebo groups. The researchers concluded that chlorpromazine “has an action that is principally sedative, and...has little value for non-tense schizophrenics except possibly those with the paranoid subtype.”

In 1960, the results of the first large scale, multi-hospital study of the efficacy of chlorpromazine in the treatment of schizophrenia were published. The trial included 692 patients with “schizophrenic reactions,” treated in thirty-seven Veterans Administration hospitals. Researchers divided the patients into four diagnostic subgroups, from which they were randomly allocated to receive chlorpromazine, promazine, phenobarbital, or an inert placebo. The trial was double-blind, with standardized doses and conditions of treatment, three rating scales used to evaluate results, and a detailed statistical analysis of the data. The results clearly demonstrated the superior efficacy of chlorpromazine compared to the other treatments. However, by this time chlorpromazine was already well established as a treatment for psychosis. Within eight months of being marketed as Thorazine in 1954 it had been given to two million patients, and had increased the firm’s sales by one third within a year. Therefore, although clinical trial designs were improving in the decade before the Drug Amendments

of 1962, their results seem to have had little influence on the popularity of chlorpromazine. Controlled trials were not required for the drug to enter the market, and negative reports of efficacy from the most sophisticated trial of the mid-1950s appear to have had little impact on its uptake. By the time chlorpromazine’s efficacy was conclusively established, clinical experience had already long cemented its place in psychiatry. Controlled clinical trials appear to have been purely academic, performed for the scientific interest of researchers.

The development path of iproniazid, the first monoamine oxidase inhibitor (MAOI) antidepressant, even more dramatically shows how unimportant clinical trial methodology was in determining a new drug’s uptake in psychiatry prior to the Drug Amendments of 1962. Like chlorpromazine, iproniazid was approved for sale on the basis of a physiological effect. Therefore, when its unique psychoactive effects were discovered, the fact that it was already on the market helped to ease its uptake in psychiatry. Iproniazid, a derivative of the German V2 rocket fuel hydrazine, was synthesized in 1951 and found to be useful in the treatment of tuberculosis. It quickly passed to market, and soon side effects of mild euphoria and stimulation were noted, with a now famous newspaper report of tuberculosis patients at Sea View Hospital, Staten Island, dancing in the halls.52 Several researchers began experimenting using the drug with psychiatric patients, however they struggled to clearly identify its usefulness.53

52 Shorter, Before Prozac, p. 52.
Psychiatric research with iproniazid began in earnest in 1956 at Rockland State Hospital, New York, prompted by the search for a “psychic energizer” that could relieve depression. Prominent psychiatrist and psychopharmacologist Nathan Kline, whose earlier research with reserpine would earn him the prestigious Lasker Award in 1957, led this research. Together with colleagues John Saunders and Harry Loomer, Kline began clinically investigating iproniazid with depressed outpatients, and seventeen chronic hospital patients who they described as “withdrawn, regressed, deteriorated, colorless and of flattened affect,” and who had failed to respond to other treatments. Results, published in 1957, found that after five weeks 47 percent of the hospital patients improved, which climbed to 70 percent after five months. These results were supported by case studies of individual patients who represented the various responses to treatment, such as a positive responder who went from being “mute and withdrawn” to “talkative and, at times, even a bit noisy,” especially significant considering the patient had been hospitalized for twenty years. The trial was uncontrolled and the results were based on clinical impressions. However, the researchers justified the absence of controls not only on the basis that it was a pilot study, but that the failure of the patients to respond to any other treatment made them their own controls. A placebo effect caused by enthusiasm for a new treatment could not explain efficacy, as such enthusiasm would have been equally present in previous attempts to use new treatments. Furthermore, the

55 Healy, Antidepressant Era, p. 64.
57 Ibid., p. 136.
chronic unresponsive nature of their illnesses argued against spontaneous remission or general fluctuations in the severity of their pathology. Significantly, this trial was methodologically almost identical to the first psychedelic therapy trial reported by Canadian Colin Smith in 1958, which tested twenty four alcoholic patients, similarly chosen for the severity of their condition, included case studies to demonstrate the treatment’s effect, and found half of the patients improved or much improved after an average follow-up period of one year.\footnote{Colin M. Smith, "A New Adjunct to the Treatment of Alcoholism: The Hallucinogenic Drugs," \textit{Quarterly Journal of Studies on Alcohol} 19 (1958), pp. 406-417. For another close comparison see J. Ross MacLean et al., "The Use of LSD-25 in the Treatment of Alcoholism and Other Psychiatric Problems," \textit{Quarterly Journal of Studies on Alcohol} 22 (1961), pp. 34-45.}

Given that Loomer, Saunders, and Kline’s trial of iproniazid was designed as a pilot study, it is not surprising that it was uncontrolled. The researchers were looking to explore the drug’s therapeutic potential rather than provide definitive proof of efficacy of a well-defined treatment. More significant is that this level of research is what propelled iproniazid into widespread use. Between the first presentation of their research at an American Psychiatric Association conference in April 1957, and February 1958, approximately 380,000 patients received the drug.\footnote{Nathan S. Kline, "Monoamine Oxidase Inhibitors: An Unfinished Picaresque Tale," in Frank J. Ayd and Barry Blackwell (eds.), \textit{Discoveries in Biological Psychiatry} (Philadelphia: J. B. Lippincott Company, 1970), pp. 200-202; Nathan S. Kline, "Antidepressant Drugs and Liver Damage," \textit{British Medical Journal} 1, no. 5384 (1964), p. 694.} This ease and speed of uptake was possible as iproniazid was already available to physicians, who after hearing of its psychiatric use could immediately try it themselves. Physicians did not have such access to LSD, therefore similar research led only to further studies. The only difficulty that had arisen in the development of iproniazid as an antidepressant was convincing the drug’s manufacturer, Hoffmann-LaRoche, to support its development due to side
effects that had accompanied its high-dose use with tuberculosis. However Kline’s insistence convinced them, and his personal promotion of the drug in newspaper interviews and even before Congress did much to popularize the drug.\textsuperscript{60} In 1964, Kline was awarded a second Lasker Award for discovering the antidepressant effects of iproniazid.\textsuperscript{61}

\textbf{“Adequate and Well-Controlled Investigations”}

Prior to the Drug Amendments of 1962 there was, therefore, a great division between the theoretical state of the art and the common practice of clinical drug research, particularly in psychiatry. The ideals of the randomized double-blind controlled trial were well established and actively promoted by elite researchers. Yet the methods were not common in the practice of drug development, as drugs could be approved by the FDA on the back of limited clinical trials, and then find their place in medicine through widespread clinical use. What then could be considered an “adequate and well-controlled” trial? This would obviously depend who was being asked—an industry representative, a psychiatrist wishing to determine whether a drug was useful or not, or a scientist specifically interested in the issues of drug efficacy and research techniques. However it is evident that by the end of the 1950s, randomized controlled trials were not only firmly entrenched in the theory of experts, but were increasingly common in


\textsuperscript{61} Debate subsequently ensued over whether the credit for the discovery should have gone to Kline, Saunders, or Loomer. After several court cases, one-third of Kline’s award was given to Saunders. See Healy, \textit{Antidepressant Era}, pp. 68-69.
practice, even if only for academic purposes. They were also widely understood as a high standard of research amongst those who did not use them—although the iproniazid researchers did not employ the methods in their study, they did feel the need to justify that decision. It is also perhaps unsurprising that many researchers and pharmaceutical companies would not perform complex randomized controlled trials if not required to. Therefore although uncontrolled research was common, this does not equate to it being widely considered adequate. The proceedings of the 1956 conference on psychopharmacology, published in 1959, although representing the ideals of the elite rather than reality, could be read as a textbook due to the authority of its sponsors and authors, as well as its comprehensiveness.

Therefore, although regulators may not have been able to fairly expect the randomized double-blind controlled trial to be fully realized in all clinical research by 1962, it was nonetheless the pre-eminent model on which to evaluate the quality of research. On this basis, it can reasonably be concluded that an “adequate and well-controlled” trial could be considered one that made a deliberate attempt to address issues such as bias, the placebo effect, influencing variables, chance, and natural variation in disease, through techniques such as comparative control, blinding, placebo comparison, randomization, standardized treatments, environments and measures, and statistical analysis. This interpretation is consistent with the FDA’s publicly expressed preference for double-blind placebo controlled trials where possible, with a weighing of various research factors when not. It is also consistent with the FDA’s 1970 official description of the research requirements for efficacy testing, that similarly set
out the components of randomized controlled trials as the necessary building blocks of a trial’s design.\textsuperscript{62}

As historians have argued, the Drug Amendments of 1962 did not introduce the issue of drug efficacy, or the methodology of the controlled trial, to either drug researchers or the FDA. However the amendments were significant in establishing a new regime for drug development that made those two previously subsidiary matters central requirements for research. The FDA and research experts, charged with interpreting and enforcing the requirement for “substantial evidence” of drug efficacy through “adequate and well controlled investigations,” were strongly convinced of the randomized controlled trial’s supremacy. Therefore, deviating from the methodology would now invite intense scrutiny and suspicion.

\textbf{LSD and the Randomized Controlled Trial}

The cementing of the randomized double-blind controlled trial as the model for pharmaceutical research posed a significant challenge to LSD psychotherapists.

\textsuperscript{62} The FDA laid out requirements such as assignment of subjects to treatment groups “in such a way as to minimize bias,” comparative controls that permit “quantitative evaluation,” documentation of the level and methods of “blinding” utilized, and the “appropriate statistical methods” used. The FDA stipulated that as well as placebo or active treatment control groups, patients left untreated or even historical data on the natural progression of an illness could form an adequate control group. However no-treatment controls were only applicable in certain cases where “objective measurements of effectiveness are available and placebo effect is negligible,” and historical controls only where the course of the disease was highly predictable, such as in diseases with high mortality rates. Like in the earlier statements of FDA officials, in special cases where required research techniques were not appropriate, the FDA could make a special case. However, as will be discussed below, it appears that FDA officials would not have considered LSD psychotherapy such a special case. Edwards, “Adequate and Well-Controlled Clinical Investigations,” pp. 7252-7252.
The lack of “adequate” controls in the large body of research amassed over the previous decade rendered the results insufficient to establish efficacy, despite their consistently impressive nature. New trials that would satisfy both the scientific community and the FDA were therefore needed if any consensus on the efficacy of any form of LSD psychotherapy were to be reached, let alone an NDA submitted and approved. However, performing controlled trials with LSD would not be a straightforward task, as the dramatic effects of the drug, and LSD psychotherapy’s complex therapeutic processes, clashed with the randomized controlled trial methodology in both practical and conceptual ways.

Many researchers adamantly opposed the requirement for controlled trials, arguing that the prescribed research methodologies were neither appropriate nor possible. At the May 1965 “Second International Conference on The Use of LSD in Psychotherapy and Alcoholism,” held in Amityville, New York, the issue of controlled trials arose frequently as a topic of debate. Conference organizer Harold Abramson was particularly opposed to double-blind statistical methods of research. After pointing out that a double-blind was impossible to establish when administering LSD or an inert placebo due to the drug’s dramatic psychoactive effects, Abramson argued that statistical methods were fundamentally inappropriate for the study of psychotherapy: “whenever the psyche is involved...It is difficult to understand how the result of extensive study, based on patient group averages rather than on individuals, can have direct implications with respect to improvement in the psychotherapy of patients.”

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He also argued that the number of potentially important variables in a patient population rendered the prospect of true control unfeasible. Dutch psychiatrist Cornelius Van Rhijn agreed that controlled trial methods were inappropriate for psychotherapy research, as psychiatry lacked objective measures needed to allow fair comparison of cases:

In psychotherapy...there is no general agreement upon diagnosis, favorable or unfavorable cases, or the outcome of any form of treatment. So I think you are wasting your time and money on controlled experiments and double-blind studies on subjects, patients or cases, which cannot be divided into fixed classes with a fixed diagnosis of a fixed disease with a fixed or sure outcome with some sort of therapy. The only thing I can believe in is carefully controlled studies in which certain patients can act as their own controls.

Canadian psychedelic therapy pioneer Abram Hoffer also featured among the staunch opponents of double-blind placebo controlled methodology. He argued that not only was the use of an inert placebo impractical, but the logical alternative of an active placebo was conceptually problematic. In order to sustain a double-blind, an active placebo would have to mimic the symptoms of LSD intoxication, whilst lacking its therapeutic qualities. However, it was these subjective effects—the psychedelic experience—that were considered the therapeutic component in treatment, therefore “Any drug which produces a psychedelic experience should...be as effective as LSD.” The use of an active placebo capable of adequately mimicking a psychedelic reaction would therefore result in a trial where “One merely would have a comparison between two sets of psychedelic experiences,” essentially an uncontrolled test of psychedelic

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64 Ibid., p. 233.
65 Ibid., p. 221.
The results of such a trial would misleadingly show a lack of efficacy for psychedelic therapy, as there would not be a significant difference between the results of the control and LSD groups. Hoffer also more generally attacked the double-blind method by turning around the call for proof of efficacy from treatments to the method itself:

I would like to state categorically that the double-blind is not scientific, has never been validated, and has been repudiated by mathematicians. It is a theoretical procedure which has never been proven, as far as I can tell, and I have challenged many people to give me evidence that the double-blind does what it is supposed to do.67

Delving deeper into the conceptual incompatibility of LSD psychotherapy and the randomized controlled trial reveals assumptions inherent in the methodology that conflicted with the therapy's theory and method. The randomized controlled trial rose in status in the post-war period on the grounds of its objectivity—its ability to neutralize the impact of influencing variables and thereby isolate a drug's true effects. Hidden in this notion of objectivity in drug study was a "magic bullet" concept of drug efficacy, whereby a treatment should work unconsciously, independent of potential non-drug influences, through a biological interaction between drug and disease or affliction. German medical scientist Paul Ehrlich had first used the term "magic bullet" in the early twentieth century to describe the effect of antibodies in serum therapy: they selectively bound to, and killed, intruding disease cells, while leaving healthy tissues

untouched. He hypothesized that drugs could work in the same way, a form of treatment he called "chemotherapy." Both a growing understanding of bacteriology in the period, and his research into the mechanism by which dyes could selectively stain certain tissues, had influenced Ehrlich’s concept of potential drug actions.\textsuperscript{68} The magic bullet concept was seemingly realized with the development of the antibacterial sulfonamides in the 1930s, and penicillin in the 1940s. These drugs revolutionized medicine, providing miraculous cures for infectious diseases that were leading causes of disability and mortality.\textsuperscript{69}

Randomized controlled trials were ideal for testing magic bullet type drugs, where treatment involved simply administering a medication. This form of treatment allowed the easy use of placebos, double-blinds, and standardized procedures, environments, and measures, as with the biological activity of the drug considered the only relevant factor in treatment efficacy, ignorance regarding the administration of an experimental or placebo treatment could not only be achieved, but also posed no threat to the treatment’s potential effect. The magic bullet antibiotics were not just ideal candidates for randomized controlled trial testing, but also influenced the uptake of the methodology: the two rose in prominence together over the 1940s and 1950s through the pioneering research of Austin Bradford Hill, and the need to accurately evaluate and differentiate the influx of new antibiotic drugs. Antibiotics were the most successful drugs ever

\textsuperscript{69} For the history of sulfonamides see Lesch, \textit{First Miracle Drugs}. For penicillin see Robert Bud, \textit{Penicillin: Triumph and Tragedy} (Oxford: Oxford University Press, 2007).
developed, and the most advanced drug efficacy testing methods were best suited to test drugs such as antibiotics that worked through an objective biological action. Therefore, the magic bullet concept became not just an ideal form of drug efficacy, but the dominant model. A drug's pharmacological activity increasingly came to be considered the only "specific" aspect of treatment, with all other "nonspecific" non-pharmacological influences merely clouding the accurate judgment of a treatment's efficacy. The breakthrough psychiatric drugs of the 1950s largely conformed to this magic bullet theory of drug efficacy—whilst their method of action was unknown, the new antipsychotics, antidepressants, and anxiolytics seemed to work regardless of the treatment environment or the interpersonal skill of the physician. Pharmacotherapy became simply fitting a diagnosis to a medication.

LSD psychotherapy was completely at odds with the magic bullet theory of drug efficacy. Rather than a specific biological treatment, LSD was merely a tool in a psychotherapeutic process—a catalyst for attaining states of consciousness or experiences that could be used by a skilled therapist to therapeutic ends. The drug had no inherent beneficial effects. Instead, its efficacy lay in the psychological impact of the subjective drug experience, which was crafted through a unique relationship between the patient, therapist, and drug. The controlled trial's alliance with the magic bullet form of drug efficacy would therefore make providing proof of LSD psychotherapy's efficacy through the methodology very difficult. The conceptual incompatibility of LSD psychotherapy

\[70\] For the history of the concepts of specificity and nonspecificity in medicine see Michael Shepherd, "The Placebo: From Specificity to the Non-Specific and Back," Psychological Medicine 23, no. 3 (1993), pp. 569-578.
and the standard randomized controlled trial was explored by psychologist Robert Mogar at the American Psychological Association’s third “Research in Psychotherapy” conference, held in 1966. Mogar, who had conducted LSD research with the International Foundation for Advanced Study, argued that efforts to perform controlled research with LSD were flawed due to a fundamental misconception: “The major conceptual fallacy, usually implicit, is the assumption that only drug specific effects are real, valid, and lawful. Nonspecific variables that are difficult to define and measure rigorously are random, insignificant, and sources of error.”

Considered “extraneous,” non-drug variables produced placebo effects, which, although often powerful, due to their nonspecific nature were judged to confound an accurate evaluation of the specific treatment. However, Mogar argued that if any form of psychotherapy was to be accepted as a legitimate form of treatment, attitudes towards the placebo effect needed re-evaluating. Drawing attention to the “nonspecific-extraneous-placebo fallacy,” he quoted psychiatrist Arthur Shapiro’s statement that, “The placebo is defined as the psychological elements in treatment; psychological elements constitute psychotherapy; therefore, psychotherapy is a placebo.” Research had shown that LSD produced no invariant effects aside from an “increased sensitivity to both internal and external stimuli…a markedly lowered threshold for arousal.” Therefore, he argued, the notion of “drug specific effects” needed adjusting in the case of LSD,

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72 Ibid., p. 505.
73 Ibid., p. 508.
where non-drug variables powerfully shaped the patient’s reaction to the drug. These variables could be categorized as those relating to the patient, therapist, therapist-patient interaction, and situation (set and setting). Before a valid assessment of the efficacy of a form of LSD psychotherapy could be performed, the precise role of these non-drug factors in creating a desired reaction needed to be better understood. Mogar suggested that research on this topic could involve inverting the standard form of controlled trial—where drug administration is the tested variable—by keeping drug administration as a constant, while varying the nature of non-drug factors. Once a specific LSD reaction was well defined and could be reliably produced, a study of treatment efficacy would need to be designed which would provide a comparative control for the treatment as a whole, rather than just one influencing variable. 74

The common element underpinning these arguments was that LSD psychotherapy was not a drug treatment, but a psychotherapy. However, because LSD psychotherapy utilized a drug, it came under the regulation of the FDA, and thus proof of its efficacy needed to be established in the same manner as required for a drug treatment. The randomized controlled trial was not designed to test the efficacy of psychotherapies, which was a much more complicated task than testing drug efficacy. While testers of psychopharmaceuticals had to face the difficulties of establishing standardized diagnoses and outcome measures, and faced many potentially impacting nonspecific variables, the specific element of their treatment—drug administration—was clearly defined and could easily be manipulated for the

74 Ibid., pp. 507-509.
purpose of experiment. In contrast, there was little agreement amongst the numerous schools of psychotherapy—such as Freudian, Jungian, interpersonal, or humanistic—on any aspect of psychiatric illness or its treatment.

Psychotherapeutic schools offered different theories of the nature of the mind, the origins of mental illness, and the methods for treating it. Even within a school, the notion of specificity was complicated, as many conditions could be treated through the same methods. The goals of treatment also ranged from the reduction of specific symptoms to more difficult to define goals such as increased self-understanding and adjustment to life. Even if a form of psychotherapy was standardized for a particular patient population, and for a specific goal, the fact that the treatment relied on active cooperation between two individuals meant that significant variables existed outside of the treatment framework.

Summarizing the American Psychological Association’s 1961 “Research in Psychotherapy” conference, proceedings editors Lester Lubrosky and Hans Strupp found that discussed variables fell into four major categories: the techniques of therapy, the therapist, the patient, and the match between therapist and patient. Due to the critical nature of these personal and interpersonal variables, many psychiatrists regarded psychotherapy as an art as well as a treatment based in science. Randomized controlled trials required the manipulation of a hypothesized specific therapeutic element in treatment while all nonspecific variables remained constant. However with such a blurred boundary between the specific and nonspecific elements in psychotherapy,

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devising a method of evaluating any form of psychotherapy presented formidable challenges. As prominent psychotherapy researcher Jerome Frank commented, the complexity of psychotherapy had resulted in researchers either attempting to encompass all aspects of psychotherapy at the expense of accuracy, or focusing on a manageably small element of treatment and “achieving rigor at the expense of significance.”

A major methodological issue in psychotherapy research was finding a control condition that would allow comparison between the outcome of psychotherapy and the natural course of illness. The need for this was particularly significant for psychotherapies that were conducted over long periods of time, where not only significant natural fluctuations in pathology could be expected, but major changes in the patient’s circumstances as well. Controlled trials accomplished this through the use of the double-blind placebo comparison, however this was not possible with psychotherapy: too little was known about the process of psychotherapy for a therapist to deliver a convincing but ineffective form of treatment to the patient. Even if this were possible it would only be single-blind, as the therapist could not be made ignorant of the fact they were delivering a sham treatment. In lieu of an adequate placebo treatment, researchers could compare treated patients with similar patients who were left untreated. A common method of attaining such a group was to enrol patients for treatment, but then assign them to a long waiting list. Their changing pathology over time could then be compared with that of similar patients who entered treatment.

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immediately. However experience proved the no-treatment waiting list problematic and hard to maintain: only patients with non-urgent problems could ethically be held back from treatment, refusal of immediate treatment could psychologically affect patients, and patients would inevitably drop off the list or find another form of formal or informal psychotherapy while they were waiting. An alternative method was to compare two or more different forms of psychotherapy in the treatment of similar patients. This method had the benefit of theoretically equalizing nonspecific variables between treatments, as all patients would be receiving therapy from trained and committed practitioners. However such studies would struggle to find differential efficacy between treatments. This suggested that the nonspecific common elements of all psychotherapies were more significant than their specific theories and methods.

As well as these difficulties in designing controlled trials for psychotherapy, research lagged behind drug research due to the resistance of researchers to attempt outcome studies at all. In summarizing the American Psychological Association’s first “Research in Psychotherapy” conference, held in 1958, Morris Parloff and Eli Rubinstein found that researchers avoided outcome studies partly due to the stigma that it was “applied” research, rather than more prestigious “basic” research, such as studying the process of psychotherapy to extend theory.


78 Lester Luborsky, Barton Singer, and Lise Luborsky, "Comparative Studies of Psychotherapies: Is It True That ‘Everyone Has Won and All Must Have Prizes?’" Archives of General Psychiatry 32, no. 8 (1975), pp. 995-1008.
The history of poor research methodology in outcome research exacerbated this stigma. Researchers also feared confirming that nonspecific factors were responsible for psychotherapy’s effectiveness, as this could undermine their careers as trained and committed specialists. Additionally, as Mogar had argued, the placebo concept was a much more complex concept for psychotherapy than psychopharmacology, as the need to control psychological influences appeared to many psychiatrists and psychologists irrelevant in the context of a psychological treatment. The placebo effect, itself a form of psychological treatment, was a component of psychotherapy rather than a phenomenon that masked its true efficacy. Ultimately, the reality was that all research was purely academic, as psychotherapies did not need to be of proven efficacy in order to be practiced: “talk therapies” did not involve any physically invasive procedures, making them of little interest to federal regulators and outside the jurisdiction of the FDA.

Like other psychotherapies, LSD psychotherapy was therefore a poor fit for the randomized controlled trial on both conceptual and practical grounds. Due to the treatment’s lack of a clear division between specific and nonspecific impacting variables, the concept of a placebo effect was complicated and an adequate control treatment was difficult to design. Due to the drug’s obvious effects, and the required active participation of both therapist and patient in treatment, blinding was practically problematic. These problems were significant for both

the psycholytic and psychedelic forms of LSD psychotherapy, however certain factors would make controlled research with psycholytic therapy even more difficult. Psycholytic therapy was simply the use of LSD to facilitate various forms of psychodynamic psychotherapy, therefore the treatment had no standardized theory, method, goals, treatment course, or outcome measures. Proving the efficacy of psycholytic therapy would therefore require first standardizing such aspects of treatment. Psychedelic therapy at least had a standard method and goal in treating alcoholism, a short course of treatment, and a standard, objective outcome measure in drinking behaviour. Psycholytic therapy research would fade in the US more quickly than psychedelic therapy. As well as the research difficulties, several factors likely influenced this: Sandoz’s restriction of its IND sponsorship to hospital based researchers, as psychodynamic psychiatrists were often in private practice or small clinics; the difficulties of submitting an independent IND, as we have seen earlier in the case of psycholytic research Harold Abramson; and the fact that most psycholytic therapists were not committed drug researchers, but psychotherapists who would return to practising the drug-free form of their treatment when faced with the challenges of continuing LSD research. Psychedelic therapy was better suited to large-scale, hospital based clinical trials, and in many ways had a greater medical significance. Nevertheless, as the rest of this thesis will explore, despite the advantages that psychedelic therapy had over psycholytic for performing controlled research, the difficulties involved would still prove insurmountable.

The incompatibility between LSD psychotherapy and the randomized controlled trial highlights how the different regulation of psychopharmacology and
psychotherapy would widen the divide between psychiatry’s biological and psychological treatments. Psychopharmacology would become increasingly wedded to the magic bullet construct of drug efficacy, as drugs were required to prove their efficacy through a testing methodology that presumed a direct biological action. For psychiatrists interested in drug research and treatment, only a drug’s long-term objective effects on restoring normal psychological functioning fit the biological concept of treatment. These would therefore become the only desirable drug effects. Immediate subjective psychological drug effects would increasingly be considered merely side effects due to their nonspecific nature. By treating mental illness in this fashion, the psychiatrists’ role would increasingly mirror that of the physician treating infectious disease.

The efficacy requirements of the Drug Amendments of 1962 would therefore unintentionally help to turn psychopharmacology into a purely biological form of treatment. Whilst a theoretical divide had long existed between biological and psychodynamic psychiatrists, the former had not had a monopoly on drugs, as psychodynamic psychiatrists explored how their subjective effects could be used to explore and manipulate psychology. This, however, would no longer be practically possible, as proving the efficacy of such a use through controlled trials would present formidable challenges. Psychodynamic psychiatrists would therefore retreat from psychopharmacology to their mainstay of psychotherapy, which had a much greater tolerance for subjective and nonspecific influences in treatment. Each now having a monopoly on distinct forms of treatment, biological and psychodynamic psychiatry would become distinct specialities to a much greater extent than before the 1962 amendments.
As I have established, the FDA and researchers would generally interpret the amendment’s term “adequate and well-controlled investigations” as referring to the randomized controlled trial, and LSD psychotherapy was incompatible with that form of efficacy testing. However, the FDA’s Joseph Sadusk had acknowledged that controlled trial methods were not always possible, and stated that in such cases other forms of research could be judged adequate by the FDA. Therefore it could be expected that the FDA would not have required LSD psychotherapists to utilize the randomized controlled trials. However, statements from FDA commissioner James Goddard suggest that the FDA would accept nothing less than evidence from sophisticated controlled trials to support LSD’s efficacy. In 1966 Goddard appeared before three congressional hearings investigating aspects of LSD’s regulation. Although the hearings focused on LSD’s growing recreational use, medical research was also discussed and was treated as an entirely separate issue. In all three hearings Goddard criticised LSD psychotherapy research on the grounds of poor methodology, concluding that there was no proof of efficacy. Indeed he even claimed that “there is as yet no substantial evidence based on adequate and well controlled investigations to support the use of [LSD] for any medical purpose”—terms lifted directly from the Drug Amendments of 1962.81 Furthermore, he described the available data on LSD as “very crude” and, when asked why there was no consensus on the drug’s efficacy after ten years of research, replied that difficulty in finding an active placebo that would allow double-blind testing was a “problem that has

confounded much of the research up to now.”82 Stanley Yolles, director of the National Institute of Mental Health, stated that LSD use needed to be strictly restricted to “carefully controlled experiments until incontrovertible data are available documenting LSD’s efficacy and safety.”83 That LSD psychotherapy researchers began attempting to employ controlled trials shortly after the passage of the Drug Amendments of 1962 also strongly suggests that the need to use the methodology had been made clear to them.

Conclusion

With the passage of the Drug Amendments of 1962, LSD psychotherapy researchers were placed in a unique and difficult position. They were the first researchers required to provide proof of efficacy for a form of psychotherapy, and at a time when there was no consensus on an accurate method for doing so. With LSD psychotherapy officially recognized as a drug therapy, researchers were required to adopt the techniques of the pre-eminent model of pharmaceutical research, the double-blind randomized controlled trial. This methodology, however, carried with it the assumption that a drug’s efficacy was based on a direct biological action. LSD psychotherapy was the antithesis of this

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83 Organization and Coordination: LSD, p. 33. Emphasis mine. The quote was originally from the New York County Medical Society; Yolles reproduced it as a representation of the NIMH's view.
magic bullet form of treatment, as it utilized the drug’s psychological, rather than biological, effects. The beneficial psychological effects were not even specific to the drug, but emerged out of the interplay between the drug, the mind-set of the patient, and the setting it was taken in. This situation would frustrate the progress of LSD psychotherapy research, as psychiatrists struggled to design a clinical trial that would balance the need for scientific standards with the treatment’s unique therapeutic pathway. For many LSD researchers, the desire to conform to the new standards of efficacy evaluation would lead them to ignore the therapeutic methods that had been central to the original claims of efficacy, leaving them with negative results. Researchers who put more emphasis on therapeutic method would have the scientific rigour of their trials questioned, and their more positive results dismissed. Through this pattern, research would move sideways instead of forwards, with more clinical trials resulting in more confusion, rather than a clearer picture of LSD psychotherapy’s efficacy.
4. Research Amidst the Controversy: The Spring Grove Experiment

In 1963 a study of the efficacy of psychedelic therapy was initiated at Spring Grove State Hospital, Maryland. In many ways the timing of its inception was unfavourable. In that year the first major national LSD scandal erupted, as psychologists Timothy Leary and Richard Alpert were dismissed from Harvard University over the conduct of their psychedelic research there. Rather than an isolated incident, this event would come to represent a watershed moment in the creation of the LSD infused counterculture that would cause increasing social and political upheaval over the rest of the decade. It was, at least symbolically, the beginning of the transformation of LSD’s reputation from a tool of medical research to a dangerous drug of abuse. The same year also saw the Drug Amendments of 1962 come into effect. While this legislation contained no provisions specific to LSD, the formalization of pharmaceutical research that ensued, and Sandoz’s conservative sponsorship of LSD research, saw an immediate reduction in the scale of LSD research being conducted. Yet, despite these discouraging developments, the LSD research program at Spring Grove would grow to become the longest, largest, most sophisticated, and most successful program ever undertaken in the United States.

The Spring Grove study was designed to evaluate the efficacy of the psychedelic therapy in the treatment of alcoholism. Initiated by psychiatrist Albert Kurland
and psychologist Sanford Unger, the study replicated and developed the therapeutic method of the Canadian pioneers of psychedelic therapy, Humphry Osmond, Abram Hoffer, Alfred Hubbard, and Ross MacLean. Like those researchers, they used a single high dose of LSD to produce a psychedelic experience, which they believed had the potential to bring about profound personality and behavioural change in their patients. To foster the psychedelic reaction, the LSD session was enmeshed in a framework of intensive psychotherapy, and a therapist utilizing visual and auditory stimuli carefully guided the session. In testing this treatment, however, the Spring Grove researchers attempted to raise the scientific rigour of previous research by using the randomized double-blind controlled trial methodology. Doing so brought their research into line with the prevailing scientific standards of the day, and the FDA’s expectations for efficacy evaluation under the Drug Amendments of 1962. The Spring Grove research therefore promised to provide convincing evidence for or against psychedelic therapy’s efficacy in the treatment of alcoholism.

Rather than a fringe operation, the Spring Grove LSD research program represented the cutting-edge of experimental psychopharmacology. While their treatments may have been unorthodox, the researchers themselves were highly orthodox, and their work was fully supported by the National Institute of Mental Health (NIMH). Kurland was the director of research for the Maryland State Department of Mental Hygiene, and since the early 1950s he had established an impressive track record in psychiatric and psychopharmacological research. Unger had first started investigating psychedelics while employed by the NIMH.
Colleagues there had supported this work, and they subsequently put him in touch with Kurland in order to help progress it. The LSD program at Spring Grove would be fully government funded, and the researchers would continue to collaborate with NIMH officials to design their trials.

However, as the 1960s progressed, the context for LSD research worsened. Increasing public and political concern over the non-medical use of LSD led to the criminalization of its illegitimate manufacture, sale, distribution, and possession (except for personal use) under the Drug Abuse Control Amendments of 1965.\(^1\) This, however, did little to deter its non-medical use, and the next year the controversy increased dramatically: historian Erika Dyck found that reports on LSD in the *New York Times* jump from five in 1965 to over five hundred in 1966.\(^2\) Typical stories from the period contained sensationalized accounts of prolonged psychotic breakdowns and violent behaviour, often leading to death, following LSD ingestion. A 1966 survey of LSD researchers found many experiencing difficulties as a result of the controversy, including increased patient fear, trouble recruiting appropriate patients, and decreasing institutional support for their work.\(^3\)

In April that year, adverse publicity led to Sandoz’s withdrawal of LSD research sponsorship. This significantly endangered the future of LSD research and made its development into an approved medicine much less likely. By May a subcommittee of the Senate Committee on the

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Judiciary was already holding hearings considering whether further federal control of the drug was necessary. The increased control came in 1968, when personal possession of LSD became criminalized, and the penalties for other LSD related offences were increased. While the legislation did not directly concern legitimate research, the dominant public perception of LSD was now firmly that it was a dangerous drug of abuse.

Yet at Spring Grove, LSD research continued to flourish. Over the decade the number of clinical trials grew from one to four, as new indications for psychedelic therapy were investigated: firstly neuroses, then anxiety and depression associated with terminal cancer, and finally narcotic addiction. Additional staff also joined, leading to Spring Grove becoming a world centre of expertise in psychedelic drugs. Significant members included the highly experienced Charles Savage, who brought with him innovative ideas for designing control treatments for the double-blind trials. Walter Pahnke joined on the back of his groundbreaking research into the relationship between psychedelic experiences and mystical states of consciousness. Stanislav Grof, from Czechoslovakia, was one of Europe's most prominent and experienced LSD researchers. He had begun research with the drug in 1956, and by 1968 he had been present at 1,100 LSD and psilocybin sessions. Together the researchers would not only improve the scientific standards of clinical trials for LSD

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psychotherapy, but they would also focus their attention on refining the therapeutic method of psychedelic therapy. As a result they developed a more sophisticated understanding of the psychedelic experience, as well as improving techniques for ensuring patients achieved this reaction. By the end of the 1960s, highly encouraging preliminary results began emerging from Spring Grove. All signs suggested that in time the clinical trials would confirm the efficacy of psychedelic therapy for a variety of indications.

Despite the scale, sophistication, and early successes of the Spring Grove LSD program, its place in the history of LSD psychotherapy has been largely forgotten. Most histories of LSD have concluded their discussions of legitimate research in the mid-1960s, when the dangers of its abuse became the dominant focus of media, medical, and political attention. However, psychedelic research at Spring Grove would not come to a close until 1976, well after the peak of the public controversy. Over the 1970s, the Spring Grove program would operate at a diminishing scale, and problems would emerge in the designs of the clinical trials, influencing somewhat lacklustre final results. However, before analysing the demise of the Spring Grove LSD program, it is significant to follow its rise during the 1960s. Doing so demonstrates not only that LSD psychotherapy was

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8 Yensen and Dryer, "Thirty Years of Psychedelic Research," p. 90.
not thwarted by the increasing regulation of that decade, nor completely extinguished by the stigma of controversy, but also demonstrates how research changed under the formalized model of pharmaceutical research ushered in by the Drug Amendments of 1962. While the era of small-scale, independent LSD research had come to a close, government funded, institutionally based research was still possible. With this setting came the resources—patients, staff, facilities, and funding—that were necessary for the kind of large-scale, carefully controlled, and statistically driven clinical trials needed to provide convincing proof of LSD psychotherapy’s efficacy. The great challenge now was designing trials that balanced the need for scientific rigour with the complex nature of LSD psychotherapy’s clinical procedure.

**Inception and Expansion**

Albert Kurland, born in Wilkes-Barre, Pennsylvania, in 1914, entered psychiatry following his experiences as a battalion surgeon during the Second World War. During his overseas rotation Kurland had witnessed the effects of extreme stress on troops, which had led to death by friendly fire and suicide. This influenced him to seek training in psychiatry on his return to the US, including some training in psychoanalysis. In 1949, Kurland joined the staff at Spring Grove State Hospital on the outskirts of Baltimore in order to complete his certification in psychiatry. At the time, Spring Grove catered to a patient population of over 2,700 with just twenty-three psychiatrists. Kurland was assigned to manage a sixty-five bed unit for the criminally insane. Considering the hospital’s extremely
low staff to patient ratio, Kurland concluded that he would receive little supervision or training. He therefore decided to further his education through research, despite having to conduct it in his own time with no hospital funding. 9 His early publications included reports of an evaluation of drama therapy, and a study of “wife murderers.” 10 In recognition of his work, Kurland was appointed as the hospital’s director of research in 1953, although initially his only staff was a secretary. The following year Kurland entered the field of psychopharmacology, investigating the emerging reports of the tranquilizing effects of chlorpromazine. He conducted an uncontrolled clinical trial with the drug, and published positive results in 1955. 11

Kurland’s first contact with LSD came through the NIMH. In the mid-1950s Charles Savage and Louis Cholden of the NIMH contacted Spring Grove seeking a place to conduct LSD research. As the director of research, Kurland collaborated on their work. In light of the prevailing opinion that LSD induced a psychotic state similar to those that occurred in illnesses such as schizophrenia, the researchers attempted to assess the effects of the drug on chronic schizophrenic patients. Cholden, Kurland, and Savage’s research, published in 1955, resulted in several significant findings. Firstly, they discovered that the double-blind

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placebo controlled experimental design was not useful with LSD: with an initial four patients who had been administered LSD or placebo in such a fashion, it was obvious who had received LSD. Secondly, patients developed a rapid tolerance to the drug. On the second consecutive day of LSD administration the effects of the drug were diminished, and on the third day the drug appeared to produce no effect. It then took four to six days for this tolerance to completely disappear. Lastly, they found that the clinical effects of LSD in chronic schizophrenic patients varied widely: some patients showed only minimal behavioural changes, others had their normal symptoms intensify, and some dramatically improved. However any positive reactions could not be maintained due to the rapid onset of tolerance. LSD was therefore of little use as a chemotherapeutic treatment for schizophrenia. With these findings, Cholden and Savage left Spring Grove and Kurland continued to pursue other research interests.\textsuperscript{12}

It was not until 1963 that LSD would be brought back to Spring Grove. The impetus for research would again come from the NIMH, however this time from a young psychologist named Sanford Unger. Born in New York City in 1931, Unger had been awarded a PhD in human development from Cornell University in 1959, and joined the NIMH’s Laboratory of Psychology as a research psychologist in 1960.\textsuperscript{13} In 1962, reports making widely divergent claims for LSD’s effects caught the interest of Unger’s department. Taking a particular interest in the drug’s potential applications in creativity research, Unger volunteered to conduct

\textsuperscript{12} Louis S. Cholden, Albert Kurland, and Charles Savage, "Clinical Reactions and Tolerance to LSD in Chronic Schizophrenia," \textit{The Journal of Nervous and Mental Disease} 122, no. 3 (1955), pp. 211-221.

an extensive review of the literature on the drug, in order to try and bring some clarity to confusion over its effects.  

Unger's report, published in *Psychiatry* in 1963, considered how the variety of effects claimed for LSD, mescaline, and psilocybin related to extra-drug variables, and how personality change associated with the drugs related to specific types of experiences. Unger found that through the reports of the drugs' variable effects, a few consistent effects could be ascertained: an “‘orgy’ of vision” characterized by the experience of intense images, colour, and light; a profound distortion in the subject's sense of self, a form of depersonalization or dissociation; the ability to clearly observe and report mental changes, a clarity of consciousness clearly distinguishing the drug state from delirium; and, finally, that the experience was looked back on as one of awesome power and significance, no matter whether it was experienced positively or negatively. The variable effects of the drugs were then largely dependent on the attitudes of those administering them, with experimenters expecting anxiety finding it, and those administering the drug in psychotherapy finding experiences relevant to their theoretical framework. Unger therefore concluded that by deliberately manipulating the expectations and attitudes of a patient, their reaction to LSD type drugs could be “systematically directed.” Studying the increasingly frequent reports of rapid personality change following LSD, particularly leading to sobriety in alcoholics, Unger found that such change was invariably associated with a transcendental, or mystical, drug reaction. Given the dramatic nature of these reports, and the

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considerable public health implications if they were accurate, Unger concluded that this use of the drugs deserved “intensive investigation.”

Having discovered all he could from the literature on LSD, Unger’s next step was to try the drug. He therefore had a colleague administer him with 200 micrograms (mcg) of LSD. The colleague had had some clinical experience with the drug and held a psychedelic view of its effects. Unger’s experience was profoundly psychedelic: he found his “awareness to be literally constituted by, or suffused with...bliss, awe, harmony.” His section chief and the director of clinical investigations at the NIMH also tried the drug, and they supported Unger’s desire to further investigate its therapeutic potential. Subsequently, Unger travelled the country visiting LSD researchers to further explore the research that was already underway. Jonathan Cole, of the NIMH’s Psychopharmacology Service Center, put Unger in touch with Kurland at Spring Grove.

By 1963, Kurland had built up considerable experience in the therapeutic evaluation of psychotropic agents. He had continued researching the efficacy of tranquilizers, progressing from uncontrolled studies to sophisticated randomized double-blind placebo controlled trials. As well as being director of research at Spring Grove, in 1960 Kurland had been appointed director of

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16 Ibid., p. 118, 125.
research for the Maryland State Department of Mental Hygiene. In this role he had been under increasing pressure from the state commissioner of mental hygiene to find more effective methods for treating alcoholism, due to the growing population of alcoholics in the state’s psychiatric hospitals. In response, Kurland had overseen research at Spring Grove testing the efficacy of the new monoamine oxidase inhibitor antidepressant nialamide, and the minor tranquilizer chlordiazepoxide, in the treatment of the addiction. Both trials had returned largely negative results. Kurland had therefore been reading the emerging reports of the successful treatment of alcoholics with LSD with great interest. He noted, however, that controlled studies were needed to confirm the efficacy of the treatment.

Kurland and Unger therefore decided to collaborate on controlled research of LSD in the treatment of alcoholism and, with the support of Cole, they applied to the NIMH for funding. Cole was sceptical of the uncontrolled research that had led to claims of LSD’s therapeutic effectiveness, and the unconventional mystical descriptions of the therapeutic process. He was even sceptical of the value of the kinds of personality changes associated with the drug, commenting that “If a person becomes more relaxed and happy-go-lucky, more sensitive to poetry or music, but less concerned with success or competition, is this good?”

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19 Kurland, “Curriculum Vitae.”
Nevertheless, he was concerned about the problem that alcoholism posed to the public health system; therefore he was not ready to disregard a treatment that could be useful. Cole also held Kurland's previous psychopharmacology research in high regard. The proposed research therefore promised to bring better scientific standards to the unconventional field. Kurland and Unger's application was approved and funding for the study began in 1964. Unger left the NIMH to work on the research full-time at Spring Grove.  

LSD psychotherapy research at Spring Grove began with a pilot study of sixty-nine male inpatients of the hospital's Alcoholic Rehabilitation Unit. The pilot phase was intended to build experience with the psychedelic procedure, establish its safety and explore its therapeutic potential. From the start, the researchers' intention was to directly replicate the therapeutic method of the Canadian pioneers of psychedelic therapy. Like those researchers, Kurland and Unger therefore focused on carefully manipulating the mind-set of the patient, and the setting LSD was administered in, in order to produce the psychedelic experience that they considered therapeutically useful to the alcoholic. The researchers believed that the life of the alcoholic was one of severe alienation. The psychedelic experience could alleviate this situation by helping the patient to “foster the growth of new contact with himself and life,” leading to “a major reorientation in the alcoholic patient’s view of his own worth and his

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prospects.” Prior to the administration of LSD, the patient spent an average of twelve to fifteen hours with their therapist, over two weeks, preparing for the experience. This intensive preparation included both psychotherapy—to bring the patient to a level of psychological readiness for change, and to build a strong rapport between the therapist and patient—and specific preparation for the LSD experience. Throughout the ten to twelve hour 450 mcg LSD session, the patient was accompanied by their therapist and a nurse. Rather than giving formal psychotherapy, their role during the session was,

    guiding, shaping, and programming the course of the session, remaining flexibly attuned to the patient’s progress, giving reassurance, aborting anxiety or other turbulent or disruptive episodes, and mobilizing and integrating affective responses and dynamic material as the patient’s experiences unfold.

Music, eyeshades, and other items such as photographs and mirrors were used throughout the session to help the therapist guide the patient’s experience. Further psychotherapy in the days following the LSD session was used to work through any unresolved conflicts that had emerged in the session, and to cement positive insights and experiences into the patient’s personality to help ensure they led to positive change.

The effect of this treatment program was assessed through the Minnesota Multiphasic Personality Inventory (MMPI), which was administered prior to treatment, and shortly afterwards. The results, averaged from the data for all the

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25 Ibid., p. 1206.
patients, showed statistically significant improvements in all measures of psychopathology except hypomania. Particular improvements were found in ratings of depression and psychasthenia, a condition the researchers described as characterized by "rumination and preoccupation with negative, distraught though content."27 On a smaller series of patients, the researchers also administered the MMPI on the day before LSD administration, in order to judge whether the effects of the treatment were due primarily to the preparatory psychotherapy. Results suggested that this was not the case. A follow-up conducted six months after treatment found that one third of the patients had remained abstinent. The experience with these sixty-nine patients also demonstrated that the psychedelic procedure of treatment was safe: both MMPI data and clinical evaluations confirmed that no patient was harmed by the drug experience.

As well as this uncontrolled research, the pilot phase of Kurland and Unger's evaluation of LSD in the treatment of alcoholism involved an attempt at a small controlled trial. Twenty-five of the psychedelic therapy patients were studied alongside another twenty-five similar alcoholic patients who were treated with only a limited amount of psychotherapy. However the study fell apart due to the high dropout rate in the psychotherapy only group. Both groups of patients had been in housed in the same ward, and the researchers concluded that the dropouts were due to feelings of rivalry from the psychotherapy only group towards the psychedelic patients, and their disappointment at missing out on the

27 Kurland et al. "Psychedelic Therapy," p. 1207
exciting new treatment for which they had volunteered. The difficulty in designing a control group that was both practicable and scientifically sound would be a problem that would plague the researchers throughout their attempts to evaluate the therapeutic usefulness of LSD.

Over the decade, the Spring Grove researchers would develop and refine their treatment method. Their focus on understanding, producing, and harnessing the psychedelic experience would distinguish them from other LSD researchers in the mid to late 1960s. The team would place particular emphasis on the importance of the preparatory psychotherapy, which would increase in duration to an average of twenty hours. While it was the psychedelic experience that could rapidly transform patients' attitudes and behaviours, the researchers believed that this was only possible “after the achievement of psychodynamic resolution and self understanding during the preparatory psychotherapy.” The drug session was then conceived of as “corrective and remedial” as opposed to uncovering,

the psychedelic procedure is designed to program and guide the evolving episodes of experience so as to regularly achieve meaningful catharsis, reciprocal inhibition of anxiety, conflict resolution, emotionally validated insight, attitude redirection, elevated self-esteem, and deepened philosophical perspective.

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30 Sanford Unger et al., "LSD-Type Drugs and Psychedelic Therapy," in Shlien (ed.), Research in Psychotherapy, p. 522.
The experience of psychedelic therapy for patients, and how it benefited them, will be explored throughout this chapter, through several case studies.

In the second half of 1964, the psychedelic research program at Spring Grove began to grow, in both staff and ambitions. A major addition to the team was Charles Savage. Since his previous LSD research at Spring Grove with Kurland in the mid-1950s, Savage had moved to California where he had been among the first in the US to explore the psychedelic therapy method developed in Canada: first at the Palo Alto Medical Research Foundation, then at the International Foundation for Advanced Study in Menlo Park. He would have a particular influence on the design of control treatments of the Spring Grove studies, bringing ideas which he had formulated at the International Foundation for Advanced Study, but which had not been implemented.

Savage’s main research innovation was the use of a low dose of LSD as an active placebo. His previous LSD research at Spring Grove had clearly demonstrated that a double-blind controlled comparison could not be maintained with an inert placebo. However this methodology was considered pre-eminent by both research experts and the FDA, therefore if they were ever to be convinced of the efficacy of psychedelic therapy, it could not be disregarded. Maintaining a double-blind would require an active placebo that mimicked the subjective effects of LSD, for both the patient and therapist, yet lacked its therapeutic properties. This was a complex proposition, as the therapeutic properties of LSD were believed not to be inherent in the drug, but rather in the psychedelic experience that the drug could produce. Psychedelic researchers generally
considered that a high dose of LSD, as well as the right “set and setting,” was necessary in order for a subject to attain this experience. Therefore, Savage theorised that the best active placebo for the psychedelic experience would be a non-psychedelic LSD experience, produced by a small dose of the drug. The low dose would leave the patient and therapist in no doubt that they had taken LSD, but would not have the same therapeutic effects as a high dose. This double-blind design would allow researchers to control for the therapeutic influence of the non-drug specific elements of psychedelic therapy—preparatory psychotherapy and a prolonged session with a therapist—as well as a placebo effect produced by the nonspecific factors involved in all drug treatments, such as expectation, suggestion, and enthusiasm.31

Two clinical trials were initially planned that would use this control design to test psychedelic therapy’s efficacy: an expanded alcoholic study, and a new study treating neurotic patients. Whilst psychedelic therapy had been developed and primarily researched in the treatment of alcoholics, several researchers had reported positive results with other categories of patients. Most notably, alongside their pioneering alcoholic work, Ross MacLean, Al Hubbard, and colleagues at Hollywood Hospital, Vancouver, had reported treating thirty-nine non-alcoholic patients, twenty-six of whom had a neurotic diagnosis. Of these patients, sixteen (61.5%) were considered “much improved” and seven (27%) “improved” after an average follow-up period of over six months, leaving only

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31 This method was first suggested in Charles Savage and Willis Harman, see “A Controlled Study of LSD-25 and Alcoholism,” draft application for research grant to the US Department of Health, Education, and Welfare, 27 December 1962, folder “LSD as Used by Various Therapists,” box Addition 1, Savage Papers.
three (11.5%) patients judged as unchanged.\textsuperscript{32} Savage himself had also been involved in psychedelic research with a variety of non-alcoholic patients at the International Foundation for Advanced Study, immediately prior to his arrival at Spring Grove. Positive results were found in a study of seventy-seven patients, two-thirds of who “resembled the typical case load of an out-patient psychiatric clinic,” and one-third of whom were considered “normal-depressives.”\textsuperscript{33} While clear diagnoses were not given for patients in the former group, it would have no doubt contained a large proportion of neurotics.

The Spring Grove researchers submitted a funding application for the neurotic study to the Department of Health, Education, and Welfare in August 1964, with Kurland as principal investigator and Savage as co-principal investigator. The study would begin in January 1965, and Savage would officially join the staff at Spring Grove in February.\textsuperscript{34} The trial aimed to evaluate the efficacy of psychedelic therapy in hospitalized “chronically-ill psychoneurotic patients.” The researchers recognized that this was a loose diagnostic category, representing a “heterogeneous group with a wide rand of pathology pictures.” However the patients shared predominant symptoms of “incapacitating depression, or chronic, pervasive anxiety.” Spring Grove admitted twenty to thirty such patients a month. They were considered poor candidates for treatment, and most had previously undergone hospital treatment for their condition. All newly admitted psychoneurotic patients would be screened for the study. Those with serious

\textsuperscript{34} Albert A. Kurland to Charles Savage, 28 September 1964, folder “Clippings, Correspondence, Reprints, Manuscripts,” box Addition 1, Savage Papers.
organic illness or “defective intelligence,” those outside the ages of twenty-one to forty, those unwilling to undergo treatment, and those for whom follow-up would be difficult, would be excluded.  

The trial design called for patients accepted into the study to be randomly assigned to one of four treatment groups. Group one was the baseline control group: patients underwent the hospital’s standard treatments for their condition. These treatments included tailored use of drug therapy, electroconvulsive therapy, group and individual psychotherapy, and participation in milieu programs. This control group would provide data on the efficacy of the hospital’s standard treatment procedure, against which the three experimental treatments could be compared. Groups two and three were then psychedelic therapy with a low or high dose of LSD: group two patients would receive 50 mcg of LSD, and group three patients would receive 400 mcg. Assignment to these two groups would be double-blind, and, other than dosage, they would be treated exactly alike. The fourth group, designated the “doctor’s choice” group, would also receive psychedelic therapy, however therapists would use their clinical judgement to determine the best treatment schedule for each patient. The therapist could vary the dosage, the timing for its administration, and administer repeat LSD session as desired. This tailored approach was designed to assess “whether or not a ‘no holds barred’ treatment effort would produce more impressive results” than the standard psychedelic therapy procedure.

36 Ibid., pp. 6-9.
All four treatments would last four weeks, after which the patients would be discharged from the hospital, unless this was considered clinically inappropriate. The researchers expected the treatment phase of the study to take two years, during which they planned to treat a minimum of forty patients for each group. Results would be assessed through a battery of psychological tests administered prior to treatment, prior to discharge, and then at six weeks, three months, six months, and one year after discharge. A close relative would also be interviewed prior to treatment and at the same post-discharge follow-up intervals. Research assistants who were not involved in the treatment of the patients would administer these tests.37

The initial design for the controlled alcoholic study was similar to that for the neurotic study. After consultation with the NIMH, the researchers planned to use two forms of control group. Firstly, patients accepted into the study would be randomly assigned to the experimental treatments or a waiting list. Patients in the waiting list would receive the same preparation for psychedelic therapy as those in the experimental group, and a “genuine effort would be made to help them.” However, after the preparation the patients would be discharged to wait six months for their LSD session. After six months they would be re-admitted and undergo their LSD session, discharged, and followed for a further six months. The researchers chose a waiting list control—a common form of control in psychotherapy research—due to their negative experience in implementing a no treatment control in the pilot phase of their research: as Savage explained, “the

37 Ibid., pp. 7-9
presence on the ward of a no treatment group provides an influence destructive to the morale of patients and staff alike.”

Patients assigned to the experimental group were then to be assigned on a double-blind, two-to-one basis to high-dose psychedelic therapy, or the second control group, low-dose psychedelic therapy. The researchers also decided to allow an optional repeat LSD session after six months for patients who needed it. Savage explained to Jonathan Cole that this was done partly for the sake of the therapists, who felt great pressure at only having one shot to deliver a therapeutic experience to their patients: “it is easier for a therapist to contemplate a ‘bad’ or ineffectual session, if he knows it can be made up at a later date.” He also felt that it would benefit some alcoholics who “do not quite make it after a single dose and need some kind of a booster.” Follow-up was planned as similar to that in the neurotic study.

By mid-1965, with the controlled trials with alcoholic and neurotic patients underway, the Spring Grove researchers began to explore a third indication for psychedelic therapy: pain and psychological distress associated with terminal illness. The impetus for this came from their desire to help an ill staff member. Sarah, a social worker in the hospital’s research department, was suffering from terminal breast cancer. Psychologist Sidney Wolf, a member of the Spring Grove psychedelic research team and a friend of Sarah’s, considered that

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38 Charles Savage to Jonathan Cole, 2 March 1965, folder 17, box Addition 2, Savage Papers.
39 Ibid.
40 The patient's name has been changed for confidentiality.
psychedelic therapy might benefit her.\textsuperscript{41} He believed that she had led an unhappy life, and that despite acting otherwise, was a “frightened, unstable individual.” He concluded that LSD therapy could help her to come to terms with her life and resolve inner conflicts, helping her to “gain the inner strength necessary to sustain her through her remaining days on earth,” so that she could “die with dignity.” Additionally, he hoped the psychedelic experience could help her “understand the purpose of life, love and death.” Wolf consulted with his colleagues and found they had all independently considered that LSD treatment might be appropriate for Sarah. He therefore offered the treatment to her, and found that she had also come to the idea herself. Although a member of the research department, Sarah had not been directly involved in the LSD research, and she had previously maintained a strongly sceptical attitude towards it. Nevertheless, she now believed that LSD could help her become more “acutely aware of the world” and make the most of her remaining life.\textsuperscript{42}

To prepare for her LSD session, Sarah underwent approximately thirty hours of intensive psychotherapy. During this therapy her low self-esteem and poor relationship with her mother and husband were deeply explored, and together Sarah and Wolf “began to expose unresolved conflicts, unfulfilled needs, crippling fears, and a psychological foundation that was shaky, hollow and rotten.” By the end of her preparation, Sarah had gained deep insight into herself and her past, and her relationships with her husband and children had greatly improved. She had also come to peace with her troubled relationship with her

\textsuperscript{42} “Post-Session Notes,” n.d., folder 37, box Addition 2, Savage Papers.
mother. Sarah’s husband and children met with Wolf and, after discussing their anxieties regarding the procedure, gave their full support.43

On 4 August 1965, Sarah underwent her LSD session. Having had extensive preparation, Sarah arrived at her session feeling confident, eager, and at peace. As the drug began to take effect, she reclined with eyeshades and headphones. Soon she began to feel “fused to the music” and was transported into experiences where her life, values, and concept of self were reassessed and a new perspective was discovered:

Mainly I remember two experiences. I was alone in a timeless world with no boundaries. There was no atmosphere; there was no color, no imagery, but there may have been light. I was in a kind of maelstrom, bodiless, lofted and buffeted. Suddenly, I recognized that I was a moment in time, created by those before me and in turn the creator of others. This was my moment and my major function had been completed at and by my birth. By being born, I had given meaning to my parents’ existence. Why then the rat race, the need to achieve, to attain the meaningless goals we spend our lives chasing?

Again in the void, alone without the time-space boundaries. Life reduced itself over and over again to the least common denominator. I cannot remember the logic of the experience, but I became poignantly aware that the core of life is love. At this moment I felt that I was reaching out to the world—to all people—but especially to those closest to me. I wept long for the wasted years, the search for identity in false places, the neglected opportunities, the emotional energy lost in basically meaningless pursuits.44

Writing two weeks after her session, Sarah felt that her psychedelic experience had had a profound positive effect on her mental state, her experience of her illness, and her relationships:

43 Ibid.
44 “My LSD Experience,” 19 August 1965, folder 37, box Addition 2, Savage Papers.
What has changed for me? I live a different value system. I am no longer on the merry-go-round chasing a tarnished brass ring. I am living now, and being. I can take it as it comes. Some of my physical symptoms are gone. The excessive fatigue, some of the pains. I still get irritated occasionally and yell. I am still me, but more at peace. My family senses this and we are closer. We no longer talk about the issues that were opened, but should we want to, the avenues of communication are open. All who know me well say this has been a good experience.\textsuperscript{45}

These positive results were supported by MMPI data, which was collected one week prior to her session, and two weeks after. Comparing the assessments showed a significant reduction in depression and a general lowering over several other ratings of pathology. Five weeks after her treatment, Sarah died after her condition suddenly worsened.\textsuperscript{46}

Following this positive experience, the Spring Grove researchers decided to begin systematically researching psychedelic therapy with terminally ill cancer patients. In February 1966, Kurland submitted a grant application to the Department of Health, Education, and Welfare for a controlled trial similar in design to alcoholic and neurotic trials. The application outlined the common experience of terminal cancer patients that the researchers hoped to improve. They considered that the modern “American Way of Death” was highly problematic: while modern medicine had developed many methods to prolong life, the quality of life for dying patients was very poor, with prolonged life often equalling prolonged suffering. The researchers wrote that with the increasing secularization of society death had taken on a different meaning for many. Where in more religious times death had been understood as God’s will, and belief in an

\textsuperscript{45} Ibid.

afterlife had provided comfort to both the dying and their loved ones, the secular perspective interpreted death as a “disease which ought to be eliminated...as a consequence of personal neglect or failure...something to be shunned and not openly discussed.” Denial was a common factor at the bedside, with all involved focusing on the hopes of a miraculous cure through herculean treatment instead of accepting death and preparing for it. This denial increased feelings of failure and defeat as the disease ultimately won out over treatment efforts. For the terminal cancer patient, the last stages of life were characterized by “increasing pain, increasing anxiety, increasing morphine, increasing addiction, increasing demandingness, with the ultimate disintegration and degradation of the personality.” With its focus on prolonging life at all costs, modern medicine left its patients “deprived of the opportunity to die with dignity.”

As well as justifying the trial on Wolf’s experience with Sarah, Kurland drew on the research of Eric Kast at the Chicago Medical School. Kast had been the first to treat cancer patients with LSD, with his initial results published in 1963. His intention had been to study the potential analgesic effects of LSD, however he had also found the drug to have a therapeutic effect on the patients’ attitudes towards their condition. Kast had theorized that LSD could have an analgesic effect due to its ability to produce profound distortions in an individual’s body image, and its effects on concentration. He considered that pathological pain was partly caused by an objective neurophysiological process, and partly by subjective psychological factors. The psychological element was primarily a conflict “between the desire to maintain bodily integrity and the wish to

47 Ibid, p. 3.
sequestrate the ailing part.” Therefore, if LSD could lessen a patient’s need to psychologically hold onto the pain producing parts of their body, they would become more dissociated from them, and thereby experience less pain. LSD also decreased subjects’ ability to maintain concentration on specific sensations: the focus of their attention shifted rapidly, and sensations that would usually dominate the mind, such as physical discomfort, no longer took such a priority. Therefore, Kast theorized that patients would no longer solely focus on their pain, whether it was of physical or psychological origin, as they would become distracted by the sensory and mental phenomena that the drug produced.

Kast tested his hypothesis by comparing LSD with two powerful opioid analgesics, meperidine and dihydromorphinone, in fifty patients who suffered from severe pain. Thirty-nine of the patients had a form of cancer. During the study, the patients received each of the three drugs at different times, following complaints of pain. They were subsequently monitored, with their degree of pain rated periodically. Kast found that although it took longer to have an effect, LSD had a significantly superior analgesic effect than either of the two opioids. With pain rated every twenty minutes, after LSD administration patients experienced an average of 95.6 of these time periods pain-free, compared to only 5.7 for meperidine and 8.4 for dihydromorphinone. As well as having an analgesic effect, Kast noticed that after LSD, “patients displayed a peculiar disregard for the gravity of their situations, and talked freely about their impending death with an affect considered inappropriate in our western civilization, but most beneficial to

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their own psychic states.” He interpreted patients’ accepting attitude towards their condition as related to meaningful experiences of beauty produced by LSD. The changed perspectives lasted even longer than the drug’s analgesic effects. Despite the positive effects of LSD, only twelve of the fifty patients wished for a repeat administration, which Kast believed was due to the experience being “hard work.”49

The stated aim of the Spring Grove trial was to cross-validate Kast’s research by testing two hypotheses: that LSD therapy could relieve pain and reduce the use of conventional analgesics in cancer patients, and that it could “reduce the depression and anxiety associated with impending death.” All participants in the study were to be cancer patients from Sinai Hospital, Baltimore. They were to have exhausted all conventional treatments, be functional enough to cooperate, be expected to live for at least one month, and not be in remission. Ninety willing patients would be randomly and equally assigned to one of three groups: high-dose (350 mcg) psychedelic therapy, low-dose (50 mcg) psychedelic therapy as an active placebo control, and conventional psychotherapy. Patients in the latter control group would receive the same amount of therapist contact as the LSD patients. The two LSD doses would be administered in a double-blind fashion, and no patient would be aware that they were part of a controlled trial that involved treatments other than what they received. The psychedelic therapy procedure delivered to these patients was the same as for the other Spring Grove studies. Evaluation would come from three sources: MMPI data; reports from the

patients, their relatives, and their physician; and morphine consumption. Data from these sources would be collected periodically for up to six months after admission into the study, as the patients’ condition permitted. Evaluative staff would be independent from therapy staff. The trial was planned to begin in September 1966 and take two years.\textsuperscript{50}

**Outside the Hospital**

By the mid-1960s, the psychedelic research program at Spring Grove State Hospital had developed into the largest such program in the country. The researchers were conducting two significant controlled clinical trials, and were planning for a third. Designed with both clinical needs and scientific rigour in mind, the trials promised to provide conclusive evidence of the efficacy of psychedelic therapy in treating alcoholism, neurosis, and pain and psychological distress associated with terminal cancer. At the same time, however, controversy over LSD’s non-medical use was an increasing social and political concern. It is important therefore to examine not only how research was progressing within the walls of Spring Grove, but also how the researchers were relating to the public, the research community, and politicians, and whether the controversy and increased regulation of drug research hampered their research.

\textsuperscript{50} Kurland, "LSD-Assisted Psychotherapy in Terminal Cancer," grant application MH CA 12916-01, pp. 4-5.
In 1965 the Spring Grove researchers collaborated with CBS News to create a television documentary that demonstrated their therapeutic use of LSD, and the results it could have. This was produced in the light of the national concern over LSD, as the public was frequently exposed to conflicting reports of the drug’s effects and dangers. By demonstrating their use of the drug, the researchers hoped to help educate the public not only on its therapeutic potential, but also how carefully it needed to be handled: it was a powerful drug that required expert preparation and supervision to be administered safely.\textsuperscript{51} As well as demonstrating the researchers’ efforts to offer the public a balanced perspective on LSD, the documentary offers a rare view of psychedelic therapy from the patients’ perspective.

Narrated by Charles Kuralt, the \textit{CBS Reports} documentary, “LSD: The Spring Grove Experiment,” followed alcoholic patient Arthur King, and neurotic patient Peg Meginnis, from their intake interview through to six months after discharge. In doing so it showed them going through the psychedelic therapy process, as well as exploring how it impacted their lives and how they interpreted its effects. The patients were shown first in preparatory psychotherapy, delving into their problematic attitudes and relationships with their family, and being told how to react to potentially frightening drug experiences. Their LSD sessions then took place in a dedicated room, made up as a comfortably furnished living room, with Unger as therapist. The patients were often reclining on a comfortable couch, wearing eyeshades and headphones, listening to emotive instrumental music. At other times they sat with Unger looking at family photographs, a rose, or a

\textsuperscript{51} \textit{Drug Safety}, p. 2270.
mirror. Unger directed them to observe how the objects or images changed as they thought about their problems: King saw the rose change from radiant to shrivelled and black when Unger suggested that they leave and go to a bar to have a drink. As they discovered insights into their behaviours and attitudes, the patients were overwhelmed with emotion, crying or laughing. King described one such profoundly emotional part of his experience:

> There was at one time a laughter that broke through and I think it was the best laugh I ever had in my life. It was just tremendous emotional release and I really felt wonderful at that time. I was just terrific just to laugh. At the end I felt a great weight had been taken off of me, instead of feeling it was the end of something, I felt like it was the beginning. Like it was something had opened up, and things could be seen in a different light.\(^{52}\)

Unger maintained supportive and comforting physical contact with the patients throughout the session.

At the six-month follow-up interview, both the patients reported dramatic improvements in their lives. Thirty-three year old King was now employed as an insurance examiner and was taking evening classes in accounting. He had completely abstained from alcohol, and reported no desire to drink. He explained this as being due to the resolution of internal conflicts that he had previously used alcohol to repress. These conflicts had concerned his inability to feel close to other people, regardless of his desire to. After treatment, King felt much less distant from his family and community. He also reported a significant rise in his self-esteem, optimism, and motivation. Instead of viewing his future pessimistically, only hoping that his children would do better than he had, King

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\(^{52}\) “LSD: The Spring Grove Experiment,” *CBS Reports*, with Dr. Sanford Unger, narrated by Charles Kuralt, 1967, folder 2, MSP 69, Sanford Unger Papers, Archives and Special Collections, Purdue University Libraries, West Lafayette, Indiana (hereafter Unger Papers).
now believed he had a future ahead of him, and the right to make the most of it, asking himself “What’s wrong with my becoming something? What’s wrong with my doing things? I feel that I’m a person too, that I got a life to lead and a long way to go yet.”

Meginnis, a housewife in her late forties, spoke even more dramatically of the changes in her attitudes and behaviours after LSD therapy. Meginnis’ husband had committed her to the hospital after she had suffered a mental breakdown. Over the previous years, Meginnis’ feelings of emptiness and estrangement from her somewhat distant husband had developed into increasingly paranoid beliefs about him: that he was having an affair, was a criminal, was severely ill, and was trying to murder her. Her fears escalated to the extent that she believed her husband was behind a local bank robbery. She reported him to the Federal Bureau of Investigation, which subsequently interrogated and released him. She later took him to a psychiatrist after seeing disturbing images in family photos that she believed he was responsible for. Much to her surprise, the psychiatrist recommended she, not her husband, be committed. After her LSD treatment, Meginnis had not only recovered from her delusional thinking, but had also reconnected with her husband and led a transformed life:

Before I went to the hospital I hadn’t slept inside my house a whole night. I slept outside on the lawn or in the car, because I thought I would be murdered if I slept inside. I spent every waking moment trying to solve this terrible agony. And I cut off all connections with humanity. And what is it compared to that now? Now I enjoy life the way I should. And life is, it’s so much fuller. I never dreamed, I didn’t have the conception, of what it was like to... receive love, and to give love, and to still be myself, and to not have to earn it. Life is fine now.53

53 Ibid.
When asked by Kuralt whether conventional psychotherapy could not have delivered the same results, Meginnis described how the drug experience transformed the power of psychotherapy:

Well, I was given the words before, and psychotherapy is verbal, understand? I was given the words, ‘you are a scared kid, you are really frightened inside, but you have taken a lifetime to build a wall around it.’ I listened to the words, see. Now with LSD, I experienced the words. I experienced it. All the fear that was trapped in me was released. It was hell, see, but I experienced it.54

Meginnis’ husband agreed that the value of the LSD experience was that insights actually led to change: “I think that somewhere along the line, before she even took LSD, she knew that she was sick. But this didn’t change what was going on in her mind about me, until after she took the LSD.” Psychedelic therapy did not simply lead to new insights; it transformed insights from theoretical knowledge to experiences. Experiencing insights meant that they were emotionally, rather than merely intellectually, validated. These insights were therefore more easily integrated into the patient’s personality.

Kurland also appeared in the documentary. He described how in all his years of research, the rapid effects of LSD on behaviour, thinking, and emotion, had “been one of the most dramatic experiences that I have ever observed.” However in assessing its therapeutic potential he remained a cautious scientist. He recognized that his enthusiasm for the drug could skew his impression of its efficacy, therefore he would remain “somewhat suspicious” until he had amassed

54 Ibid.
a lot more data. Unger, however, hinted at the difficulties researchers faced in obtaining such data that would satisfy the scientific community:

It's one thing to be a scientist, to be objective, detached. It's another thing to be a therapist. Psychotherapy is a human enterprise—it's in contact between humans. This is an intimate situation, one is exposed in a way that otherwise would never occur. There can’t be distance, or so-called objectivity. The commitment to patient is perhaps the prerequisite ingredient.55

While objective data on LSD psychotherapy’s efficacy was needed, psychedelic therapy could not be an objectively administered treatment. Indeed it required the active utilization of many of the subjective, nonspecific factors that controlled trials were designed to eliminate: primarily suggestion, empathic support, and enthusiasm. These nonspecific variables were used to craft and direct the psychedelic experience, yet they were also the basis of the placebo effect. Therefore researchers faced the difficult task of turning psychedelic therapy into a procedure that was standardized enough allow the use of controls and quantitative assessment, yet which maintained its personalized, subjective, intimate and variable nature enough to retain its therapeutic potential. This difficulty in balancing of scientific rigour with therapeutic method would be a defining issue in LSD psychotherapy research as it moved through the 1960s and early 1970s, and indeed would be the major factor to limit the success and influence of the Spring Grove research. At this stage, however, the documentary presented an optimistic picture of the future of LSD psychotherapy: that careful, sustained scientific research would ultimately reveal how to control and harness the drug’s effects for the good of humankind. While little information is available

55 Ibid.
on the reception of the documentary amongst the public and the scientific
community, in a 1966 letter to Ross MacLean, Savage stated that it “seems to
have been well received and has stimulated a number of inquires about LSD
treatment.”

The clinical trials underway at Spring Grove were also part of a still large and
dynamic field of LSD research in the mid-1960s. Indeed these years saw several
significant conferences in the United States that focused attention on LSD
research. Largest was the May 1965 “Second International Conference on the Use
of LSD in Psychotherapy and Alcoholism,” organized by psycholytic therapy
researcher Harold Abramson and held at South Oaks Psychiatric Hospital in
Amityville, New York. The conference featured thirty-six papers from LSD
researchers from across North America and Europe. In March 1966 the “Fifth
International Congress of the Collegium Internationale Neuro-Psycho-
Pharmacologicum,” held in Washington, DC, featured a panel on
“psychotomimetics as treatments in psychiatry” with eleven papers presented.
Also in May-June that year, the American Psychological Association’s third
“Research in Psychotherapy” conference featured papers grouped around three
themes, one of which was LSD. These last two conferences demonstrate that
LSD’s therapeutic potential was still of significant interest to mainstream mental
health professionals, rather than being an obscure niche field.

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56 Charles Savage to J. Ross MacLean, 24 May 1966, folder “Correspondence, Jan-Dec. 1966,” box
Addition 1, Savage Papers.
57 Harold A. Abramson (ed.), The Use of LSD in Psychotherapy and Alcoholism (Indianapolis:
Bobbs-Merrill Company, 1967); Brill (ed.), Neuro-Psycho-Pharmacology; Shlien (ed.), Research in
Psychotherapy.
The conferences each featured papers with a variety of focuses, from theoretical considerations to clinical trials, covering all forms of LSD psychotherapy. The general tone of the conferences was positive for the effectiveness of the various LSD therapies, and optimistic towards their future. The greatest debate surrounded the necessity and applicability of randomized controlled trial techniques in evaluating the outcome of treatment, as discussed in chapter three of this thesis. The Spring Grove researchers featured prominently in each of the conferences. Indeed Savage was the organizer of the LSD section of the American Psychological Association’s conference, reflecting his high esteem in the field. At the conferences the Spring Grove researchers reported details on their treatment method, trial designs, and positive preliminary results. Unfortunately, the proceedings feature little record of the participants’ reactions to their papers. How the various research programs active in this period differed in terms of treatment methods, trial designs, and results, and the role of these inconsistencies in the downfall of LSD psychotherapy, will be discussed in detail in the next chapter.

Outside of these conferences, the Spring Grove researchers maintained close relations with other LSD researchers, as well as others interested in the field. By 1966 Unger had not only visited all of the LSD researchers in the United States, but had twice toured Europe, visiting LSD psychotherapists in Norway, Denmark.

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Germany, Holland, and Czechoslovakia. Sandoz funded at least one of these trips, where Unger helped the European psycholytic therapists to set up psychedelic therapy programs. He had also travelled to Basel, Switzerland, to visit LSD’s inventor Albert Hofmann. During the mid to late 1960s, Spring Grove also hosted a constant stream of visitors interested in their psychedelic research. The visitors included numerous officials from the FDA, NIMH, state government, and even an official from the World Health Organization. Many visitors were physicians from hospitals and universities from across the country, as well as overseas. Amongst these were other LSD researchers, including prominent German psycholytic therapist Hanscarl Leuner, Kenneth Godfrey from the Topeka, Kansas, Veterans Administration Hospital, and John Lilly of the Communication Research Institute in Florida. Other visitors came from a background in religion, seeking to explore the religious implications of the psychedelic experience. These visitors included philosopher and populariser of Zen Buddhism Alan Watts; Walter Houston Clark, professor of psychology of religion at Andover Newton Theological School, Massachusetts; and Huston Smith, professor of comparative religion at Massachusetts Institute of Technology.

While LSD psychotherapy was still an active field of research in the mid-1960s, there is some evidence that the public controversy over the drug was having a negative effect on the conduct of some studies. In 1966, LSD researcher Charles Dahlberg and his colleagues conducted a survey of twenty-nine other

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researchers, inquiring whether the recent adverse publicity surrounding LSD had hindered their work. Many confirmed they were experiencing difficulties: volunteers were increasingly drug seekers considered to be inappropriate research subjects, patients and their families were more anxious about the drug, researchers and their colleagues were increasingly ambivalent and cautious in their attitudes towards LSD, and some projects had even been terminated.61 Savage, however, replied to Dahlberg that while the adverse publicity had had some effect, “I can’t say that this has been a major source of interference in our studies.” He explained that while pressure from anxious family members did lead to “occasional dropouts,” patient attitudes towards the drug were not easily influenced by the publicity: “The state hospital is a closed community and although patients do watch television and read the newspapers, they seem to be more susceptible to the propaganda from other patients who have been successfully treated.” More problematic were the normal difficulties of treatment and research, such as keeping alcoholics in hospital long enough to complete their course of therapy. Ultimately, he believed that “If we don’t complete the program, it will be the fault within us and not the publicity.”62 He did however recognize that this situation could change if the controversy continued to increase.

The LSD controversy also threatened the Spring Grove research by influencing Sandoz Pharmaceuticals to withdraw their sponsorship of LSD research on 11 April 1966, as discussed in chapter two. Since the passage of the Drug

62 Charles Savage to Charles Clay Dahlberg, 30 June 1966, folder “Correspondence, Jan-Dec. 1966,” box Addition 1, Savage Papers.
Amendments of 1962, the Spring Grove LSD research projects had operated under Sandoz’s Notice of Claimed Investigational Exemption for a New Drug (IND). As pre-market clinical research could only be conducted under an IND, and with Sandoz as the sole sponsor for LSD research, as well as its sole producer and distributor, the withdrawal of Sandoz’s IND meant that the Spring Grove researchers could no longer legally continue their research with the drug, and would have no access to further supplies.

On 14 April, Kurland wrote to Frances Kelsey at the IND Branch of the FDA in search of help in his predicament. He outlined the research underway at Spring Grove, which he reported as delivering very promising early results, and requested permission to submit an IND to continue this work. Kurland was particularly concerned about how to obtain additional supplies of LSD. He had enough stock of the drug to cover the present trials, however if these studies led to further research avenues (which he believed they would) he would require extra supplies. In a follow-up letter the next day, Kurland confirmed that Sandoz had given him permission to use the data contained in their IND to complete his own.

Another option for ensuring the continuation of the Spring Grove research was discussed by Savage in a May 1966 letter to Ross MacLean. Savage stated that it

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63 Kurland is listed among the first seventeen researchers included under Sandoz’s IND when submitted in 1963. See George P. Larrick to L. R. Fountain, 17 September 1963, box 3587, General Subject Files 1938-1974, Division of General Services, RG 88—Records of the Food and Drug Administration, National Archives at College Park, College Park, Maryland (hereafter RG 88).

64 Albert A. Kurland to Frances Kelsey, 14 April 1966, folder “Food and Drug Administration,” box 2, Savage Papers; Albert A. Kurland to Frances Kelsey, 15 April 1966, folder “Correspondence, Jan-Dec. 1966,” box Addition 1, Savage Papers.
had been suggested to him that the Spring Grove researchers should file a New Drug Application (NDA) for LSD, thus making it a restricted prescription drug “presumably somewhat on a par with morphine.” He wondered however whether this would increase the availability and misuse of the drug. On the other hand he considered that fear of malpractice suits and other “legal and social sanctions” would result in only those who were experienced using it. A perhaps more crucial problem was that processing a NDA apparently cost in the region of half a million dollars.65 Where this suggestion came from, and whether or not it was feasible, is not clear. The idea of giving LSD an effective NDA for restricted usage had been floated when representatives of Sandoz, the NIMH, and the FDA had met to discuss Sandoz’s potential withdrawal from LSD sponsorship in December 1965. Kelsey had seemed to support the idea; therefore from the perspective of the FDA it seems that an NDA was not out of the question.66

Even an effective NDA, however, would not have ensured a continued supply of LSD without a manufacturer or distributor. Ultimately, as previously discussed, this situation was resolved with the NIMH’s negotiation with Sandoz to take on their significant remaining stocks of LSD and act as the drug’s distributor. The FDA then helped to smooth the transition to independently sponsored research, by allowing researchers who were using LSD on a regular basis to temporarily continue doing so while they put together and submitted their own INDs.67

Whether due to cost or other factors, Kurland and colleagues went through with

65 Savage to MacLean, 24 May 1966.
66 Memorandum of conference between representatives of Sandoz Pharmaceuticals, NIMH, and FDA, 7 December 1965, folder 521.6-525.091, box 3758, RG 88.
67 Drug Safety, pp. 2135-2136; Organization and Coordination: LSD, p. 57. For more on the regulation of LSD in this period see chapter 2.
their submission of an IND rather than an NDA. Therefore, due to the assistance of the NIMH and FDA, LSD research at Spring Grove was not notably disrupted by Sandoz’s withdrawal from the field of LSD research.68

By mid-1966, Spring Grove State Hospital had become the site of the most extensive LSD research program in the United States. Reflecting this, in June the researchers were asked to testify before the “Drug Safety” congressional hearings held by the Intergovernmental Relations Subcommittee of the House Committee on Government Operations. The subcommittee had been examining the FDA’s implementation of the Drug Amendments of 1962 and the Drug Abuse Control Amendments of 1965, in light of its great concern over the widespread non-medical use of LSD. The congressmen, however, were also concerned that the government’s focus on LSD’s dangers and its regulation could hamper research and recognition of the drug’s legitimate uses. Therefore Kurland, Savage, and Unger were brought before the subcommittee to testify as to how research was progressing under the new regulations. The congressmen questioned the researchers respectfully as experts on the drug. They inquired about the researchers’ work and their opinions on various aspects of LSD’s use and misuse, without expressing disdain or scepticism. Overall, the researchers said nothing to suggest that their work had so far been hampered. Savage, however, was concerned that the potential future criminalization of personal

68 The continuation of the Spring Grove research clearly demonstrates that their IND was approved. However the exact nature of their IND and when it was approved is not clear. In June 1966 Kurland submitted to FDA commissioner James Goddard requested material supporting his IND application. The submission included an outline of their research programs, therapeutic method, current results, patient volunteer forms, curriculum vitae for all the researchers, and details on all assessment procedures. This may have satisfied the FDA. See Albert A. Kurland to James L. Goddard, 21 June 1966, folder “Project Reports,” box 2, Savage Papers.
possession could deter patients from volunteering for treatment, due to the increased stigma attached to the drug.\textsuperscript{69}

The subcommittee members questioned the researchers in great detail over the nature of their treatment and their results to date. Kurland, Savage, and Unger stressed that LSD’s medical use was very different from other drugs: it did not have any “inherent beneficial effects,” and was therefore not a chemotherapeutic agent, but a tool in a psychotherapeutic process. This characteristic, and the drugs dramatic subjective effects, had made it very difficult to design controlled studies, due to the difficulty in finding an adequate placebo treatment. Despite this, they were confident that their research efforts would provide a rigorous examination of the efficacy of psychedelic therapy. The Spring Grove researchers reported their impressive preliminary results with both alcoholic and neurotic patients. Indeed, Unger described the results to date from the controlled alcoholic study as “so good that I nearly don’t like to report it. I mean that. My feeling is that the present rate won’t, can’t continue.”\textsuperscript{70}

Questioned on the issue of LSD psychotherapy’s safety, the researchers testified to a remarkable absence of negative outcomes, which they believed was due to their rigorous preparation and screening. Indeed Kurland remarked that lack of “attempted suicides or psychotic reactions” was “puzzling,” as the severely alcoholic population they were treating frequently had other underlying psychiatric pathology, and traditionally had a high mortality rate after hospital

\textsuperscript{69} Drug Safety, p. 2268.
\textsuperscript{70} Ibid., p. 2213, 2216.
discharge. In the psychoneurotic study there had been two adverse events. The first was a psychotic episode in a patient not long after her LSD treatment. The patient had a history of these episodes and she recovered after conventional treatment. The second was an attempted suicide after discharge. The attempt was considered minor. Neither of these events could be conclusively tied to the LSD treatment, however the researchers recognized that this was a possibility. While attesting to LSD’s safety under their conditions, the researchers stressed that uncontrolled use was dangerous. The drug produced a period of intense emotionality, and there was no guarantee that these emotions would be positive. Without guidance, negative emotions could spiral out of control, leaving the user traumatized. In the worst-case scenario, this kind of reaction could lead to suicide.71

The subcommittee also questioned the researchers regarding how the non-medical use of LSD should be controlled. While they had little experience with the non-medical use of LSD, the researchers expressed doubt over whether further criminal sanctions would be effective. Unger was also concerned with the social ramifications of criminalizing users, who he believed were mostly college students who were by and large “not irresponsible people nor...particularly psychiatrically disturbed.”72 He suggested that the dangers associated with non-medical use of LSD could be minimized through the establishment of centres where interested individuals could experience LSD under appropriate supervision. Congressman John Dow expressed support for Unger’s idea in

71 Ibid., pp. 2240-2241, 2260-2262.  
72 Ibid., p. 2269.
theory, although he doubted that such centres would be effective in preventing uncontrolled use. However, Unger argued that the drug was not addictive, and that it was unlikely to be heavily abused except amongst a minority of already disturbed individuals. He felt that education was the only way to combat irresponsible use of LSD, and that further criminalization would merely fuel the public’s curiosity over the drug. The congressmen did not openly endorse nor oppose this view, although they did add that further criminal sanctions could make LSD more attractive to black marketeers, as increased risk raised prices.\(^\text{73}\)

In the mid-1960s, the psychedelic research program at Spring Grove was stable and well regarded. The researchers were not only active in the international research community, but took a role in educating the public on LSD, and their experience and expertise was respected by congressmen wary of the drug. While the public controversy over LSD had threatened the conduct and future of LSD research, so far its actual impact at Spring Grove had been minimal. From this position, the Spring Grove LSD program would continue to expand in scale, scope, and expertise.

**Further Expansion**

By the start of 1967, the Spring Grove researchers had developed enough confidence and support for their psychedelic therapy procedure with alcoholics to begin planning for its eventual integration into the standard treatment

\(^{73}\) Ibid., pp. 2268-2271.
procedure of the state's hospitals. The first external site to implement the Spring Grove program was to be Crownsville State Hospital, near Annapolis, Maryland. The researchers' plan was not to simply establish a psychedelic therapy unit at Crownsville, but to undertake a sophisticated study of the implementation of psychedelic therapy there that would act as a model for further expansion. The researchers conceived the “demonstration project” as a “sociological and social psychological” study, aiming to “document and assess the introduction, life history, usefulness, and success or failure of a new treatment form in a new environment.” Crownsville had the highest number of alcoholic admissions in the state, so it was a logical place to trial a new treatment. The researchers were careful not to represent their treatment program as a miracle cure, emphasizing that the introduction of psychedelic therapy to a hospital was not conceived as “capable of ‘transforming,’ nor even of radically affecting the rate of enduring treatment success.” Nevertheless they felt that a “substantial number” of patients who benefitted little from standard treatments would be “materially benefitted.” As well as its large alcoholic population, Crownsville did not have a strong tradition in research. Therefore, the site offered a good opportunity to test whether the positive atmosphere towards research in general at Spring Grove had influenced the success of their LSD treatment. Should the treatment be successfully adopted at Crownsville, the study would then aid other institutions in implementing their own psychedelic programs by helping them to anticipate the difficulties they might encounter.74

The researchers planned to commence the demonstration project after the completion of the controlled Spring Grove alcoholic study in 1969, dependent on positive final results in that study. Nevertheless, the researchers expected these positive results, and the plan had already met the approval of the Maryland commissioner of mental hygiene and the superintendent of Crownsville. State support for the project reflected not only the Spring Grove researchers’ positive preliminary results, but also the gravity of the problem of alcoholism, and Kurland’s place in Maryland’s psychiatric administration. Alcoholism was the leading cause of psychiatric hospital admissions in the state, amounting to two fifths of male admissions and one eighth of female admissions. The prognosis for these patients was poor, with a Spring Grove study finding less than 10 percent of patients maintaining sobriety one year after discharge following standard treatment. Kurland, as director of research for the state’s Department of Mental Hygiene, was responsible for finding new treatments to alleviate this situation. He had initiated the Spring Grove LSD studies for this reason. It was therefore the department’s responsibility to use the results of his research endeavours to better the situation of its psychiatric patients. The department’s commissioner, Isadore Tuerk, had been the superintendent of Spring Grove State Hospital in the 1950s when Kurland had joined the staff and began his research career. Tuerk was most likely responsible for installing Kurland as director of research for the Department of Mental Hygiene, just as he had installed him in the same position at Spring Grove. While Tuerk’s personal opinion of LSD therapy is not clear, his

75 Ibid.

76 Tuerk’s positions at Spring Grove and in the Maryland Department of Mental Hygiene are acknowledged in Albert A. Kurland, "Psychiatric Research in a State Psychiatric Hospital," *Maryland State Medical Journal* 3, no. 11 (1954), p. 611; and Albert A. Kurland et al., "Comparative Studies of the Phenothiazine Tranquilizers: Methodological and Logistical
long and close relationship with Kurland strongly suggests that he had great faith in his integrity, abilities, and ambitions. Therefore, he supported, or at least did not thwart, Kurland’s plans to expand LSD research in the state.

The same year, the addition of two significant new staff members bolstered the Spring Grove research team. They came from diverse backgrounds, in terms of qualifications and experience, and their academic and clinical interests would help further expand the scope and sophistication of the Spring Grove research. Psychiatrist Stanislav Grof, from Czechoslovakia, was one of Europe’s most prominent and experienced LSD psychotherapists. His research had begun in 1956 when he ingested LSD while a student volunteer in the psychiatry department of the Charles University School of Medicine in Prague. The profound experience that ensued left Grof in no doubt that the drug had great implications for psychiatry. Having completed his medical degree that same year, Grof joined a research team at the Psychiatric Research Institute to further investigate the drug. There he spent several years employing LSD and similar drugs as psychotomimetics, to study the possible biochemical origins of psychoses. At the same time Grof had been training in psychoanalysis, leading him to decide that the experiences of his LSD subjects were revealing psychodynamic processes, rather than representing model psychoses. He therefore began exploring psycholytic therapy. Grof first travelled to the United States in 1965 to present his research at the “Second International Conference on the Use of LSD in

Considerations,” *Journal of Nervous and Mental Disease* 132, no. 1 (1961), p. 61. The date of Tuerk’s appointment as commissioner of Mental Hygiene, as well as the details of Kurland’s appointment as director of research in the department, are not clear. However, as Kurland took up his position in 1960, and Tuerk was in his role by 1961, it seems likely that Tuerk would have taken Kurland with him into the department.
Psychotherapy.” This resulted in him being offered a fellowship from the Foundations’ Fund for Research in Psychiatry, of New Haven, Connecticut, which saw him take-up the position of clinical and research fellow in the Department of Psychiatry and Behavioral Sciences of Johns Hopkins University in 1967. At the time, this department had a close relationship with the LSD researchers at Spring Grove, so Grof began collaborating with them.77 Adopting the psychedelic method, Grof would become a senior member of the Spring Grove team, taking leading roles in both the conduct of the clinical trials, and the administration of the research program. He would later publish numerous monographs from his experiences in LSD research, cementing his place as an international authority on psychedelics.78

Psychiatrist Walter Pahnke made a significant and immediate contribution to the sophistication of the research program at Spring Grove. Pahnke came from a background in both medicine and religion. His prior research had focused on the religious implications of psychedelic drugs, particularly on the relationship between the psychedelic experience and the spontaneously occurring mystical states of consciousness considered divine in many religions. Based on this research, Pahnke categorized the typical elements of mystical experiences, developing a model that could be applied to psychedelic experiences. When


brought to Spring Grove, this model helped the researchers to better conceptualize the therapeutic experiences of their patients. While the team had long considered the mystical LSD experience the most beneficial, Pahnke’s research helped them to better define and understand this reaction, improving the precision of their therapy and research.

Born in Harvey, Illinois, in 1931, Pahnke’s initial research with psychedelics had been undertaken for his PhD in History and Philosophy of Religion at Harvard University, awarded in 1964. He had already earned a Bachelor of Arts degree from Carleton College, and Doctor of Medicine and Bachelor of Divinity degrees from Harvard. Pahnke’s PhD centred around a study often referred to as the “Good Friday Experiment,” or the “Miracle at Marsh Chapel.” The experiment compared the experiences of volunteers administered psilocybin or a placebo, in a double-blind fashion, against a typology of mystical experience. The aim was to examine the similarities and differences between the psychedelic experience and naturally occurring mystical states, while controlling for the role of extrapharmacological factors in producing the experimental mystical state. The study was stimulated by both the increasing reports of mystical states resulting from psychedelic drugs, and the traditional use of psychoactive plants, such as the peyote cactus, in many of the world’s religions, particularly those of native peoples of the Americas.

The first stage in Pahnke’s research was to develop a typology of the “genuine” mystical experience. This typology presupposed that mystical experiences had certain core characteristics that were universal, irrespective of a person’s religion and culture, or the setting or time period they took place in. Where mystical states gained their significance to a specific religion was in their interpretation, rather than in the basic types of experience they were composed of. For this argument, and the categorization of the elements of the mystical experience, Pahnke drew on the work of scholars of mysticism such as William James, James B. Pratt, Richard M. Bucke, Walter H. Clark, and Walter T. Stace. As the research would confirm the high degree of similarity between psychedelic and mystical states, considering Pahnke’s typology in detail gives insight into the kinds of experiences that patients commonly encountered in their psychedelic therapy sessions.

The first, and most important, of nine universal characteristics of mystical experiences Pahnke named “unity.” This was then further divided into “internal unity” and “external unity.” Internal unity was the experience of an “undifferentiated unity,” characterized by the loss of the usual sense of self, or ego—a “fading or melting away into pure awareness.” In this state, awareness no longer revolved around the senses. Despite the dissolution of the ego and loss of sense impressions, consciousness and the ability to experience these phenomena were retained: the subject experienced “no empirical distinctions or particular content except the awareness of the unity itself.” External unity saw retention of the senses but an experience of “oneness” with all animate and inanimate objects.

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81 Ibid., pp. 27-47.
in the external world: “The subject feels a sense of oneness with these objects, because he ‘sees’ that at the most basic level all are part of a single unity.” This feeling of “all is one,” however, did not override all normal understanding of the separation between subject and object, but instead operated on a different level of consciousness: “the essences of objects are experienced intuitively while their outward forms are experienced through the senses.”

The second universal characteristic of mystical experiences was a “transcendence of time and space.” This was often described as a feeling of “eternity” or “infinity,” where not only the experience’s relation to clock time was lost, but also “one’s personal sense of his past, present and future.” The next characteristic was a “deeply felt positive mood.” Subjects often described these intense, overwhelming, feelings of “joy, blessedness, and peace” with terms such as “ecstasy,” “beatitude,” “bliss,” and “rapture.” The fourth characteristic was a “sense of sacredness” regarding the experience—feelings of “awe and wonder” and “profound humility before the overpowering majesty of what is felt to be holy.” The fifth characteristic, “objectivity and reality,” encompassed the experience of intuitive, insightful, knowledge. This knowledge was not factual, but had the quality of illumination, or a profound sense of understanding, achieved through transcendence into an “ultimate reality” that existed at a higher level of consciousness than “ordinary reality.” To the subject, this knowledge was inherently authoritative, as it was directly experienced rather than conveyed to them.

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82 Ibid., p. 47, 58, 60.
83 Ibid., pp. 60-62, 64, 67.
The sixth characteristic of “paradoxicality” referred to the tendency for mystics to describe many of their experiences in paradoxical terms. For example, internal unity was often described by the same mystic as both feeling both “empty” and “full,” and subjects’ awareness of their ego dissolution was dependent on the retention of a self that experiences it. Mystics also typically claimed that words were inadequate to describe their experiences. While they obviously did write impressive accounts of their experiences, this characteristic of “alleged ineffability” can be seen in the difficulty of effectively communicating elements that seem paradoxical, as well as profound intuitive knowledge that is not, and can not be, conveyed. The eighth characteristic was that the mystical experience was by its nature transitory. Whatever lasting effects they had, such experiences as unitary consciousness could not be indefinitely maintained. The final characteristic was that the mystical experience resulted in “persisting positive change in attitude and/or behavior” in the subject. These positive changes could be in the mystic’s personality structure, or their outlook towards, and relation to, others, life in general, or mysticism itself. These changes often constituted a profound transformation of the mystic’s outlook on life, towards greater love, tolerance, understanding, optimism, and appreciation of life in general.84

Having constructed this typology, Pahnke set out to use it to assess psychedelic experiences as mystical states of consciousness. The experiment saw twenty Christian theological students attend a two and a half hour Good Friday service in a private chapel. Prior to the service half of the students had been

84 Ibid., pp. 70-81
administered psilocybin and the other half nicotinic acid as an active placebo, in a randomized double-blind fashion. Theological students, and the stirring religious setting, were chosen to help “maximize the possibility that mystical phenomena would occur.” The placebo, which produced a tingling sensation and relaxation, controlled for whether or not any mystical phenomena were a result of this suggestive set and setting alone. The students were given preparation for the experience, however neither they nor the experimenter had had prior personal experience with psychedelic drugs. Pahnke then used independent judges, who were ignorant of the nature of the experiment, to rate the correlation between the subjects’ written accounts of their experiences and the typology of mystical experience. Analysing these ratings—as well as data from additional questionnaires and interviews with the subjects—revealed that the experiences of the psilocybin subjects correlated more closely with the mystical typology than those of the placebo subjects, to a statistically significant degree.85 The results led Pahnke to conclude that,

the experimental evidence has strongly suggested that under the conditions described psilocybin can induce states of consciousness which are apparently indistinguishable from, if not identical with, those experienced by mystics, according to their own descriptions.86

While completing his PhD, Pahnke was awarded the Sheldon Travelling Fellowship from Harvard, which allowed him to travel Europe to observe and participate in LSD research being undertaken there. During the trip he received training in LSD psychotherapy from Hanscarl Leuner, at Georg-August University

in Göttingen, Germany. On his return to the US in 1964, Pahnke undertook his psychiatric residency at the Massachusetts Mental Health Center, Boston, where he continued to explore using psilocybin with non-psychiatric volunteers. In 1966 he began training in psychedelic therapy at Spring Grove State Hospital, and joined the team there as a research psychiatrist upon completing his residency in 1967. Once there, Pahnke took over directorship of the study of psychedelic therapy in the treatment of terminal cancer patients. His typology of the mystical experience was simplified and used to classify the “psychedelic peak experience.” The criteria were,

1. Sense of unity and oneness: (positive ego transcendence, loss of usual sense of self without loss of consciousness). (2) Transcendence of time and space. (3) Deeply felt positive mood (joy, peace, and love). (4) Sense of awesomeness and reverence. (5) Meaningfulness of psychological and/or philosophical insight. (6) Ineffability (sense of difficulty in communicating the experience by verbal expression).

By this stage the Spring Grove researchers had renamed their therapeutic method “psychedelic peak therapy.” This name re-emphasized that their treatment was defined by the kind of experience it utilized, rather than simply the category of drug involved. While this kind of LSD reaction had been the central characteristic of psychedelic therapy since its development, increasingly the term “psychedelic” had become more generalized: other researchers, such as Arnold Ludwig and Jerome Levine, as well as Leo Hollister, had been conducting

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87 “Curriculum Vita of Walter Norman Pahnke.”
89 Walter N. Pahnke et al, “LSD-Assisted Psychotherapy with Terminal Cancer Patients,” in Hicks and Fink (eds.), Psychedelic Drugs, p. 34.
high-dose treatments without the mystical framework, and many recreational users of LSD had adopted the term.\textsuperscript{90}

As well as expanding in staff and scope, the Spring Grove research program also upgraded its facilities in the late 1960s. Until late 1968, the psychedelic research had been conducted in a modest, two storeyed cottage—cottage thirteen—on the hospital’s grounds.\textsuperscript{91} Since 1959, Kurland had been in negotiations with the state and federal government to establish a dedicated psychiatric research facility for Maryland. After delays due to budgetary and planning issues, the Maryland Psychiatric Research Center (MPRC) was opened in late 1968. The MPRC was designed as an interdisciplinary facility for clinical, psychological, biological, chemical, and psychosocial research focusing on the causes, manifestations, and treatment of mental illnesses.\textsuperscript{92} Located on the Spring Grove grounds, the three-storeyed, 40,000 square foot, air-conditioned building housed extensive laboratory, data processing, and clinical facilities. For psychedelic research, the MPRC included two purpose-built treatment suites that included homely furnishings, overnight facilities, private bathrooms and kitchens, and closed-circuit television monitoring from a nearby conference room.\textsuperscript{93}


\textsuperscript{91} Yensen and Dryer, "Thirty Years of Psychedelic Research," p. 76.

\textsuperscript{92} Albert A. Kurland to John Walton, 18 December 1964, folder "W—Misc," box 2, Savage Papers; Description of proposed Maryland Psychiatric Research Centre, n.d., folder 6, box Addition 2, Savage Papers.

\textsuperscript{93} Description of Facilities," n.d., folder, "P.R.C. Present Facilities," box 1, Savage Papers; Yensen and Dryer, "Thirty Years of Psychedelic Research," p. 84.
The Spring Grove LSD researchers took leading roles in the MPRC's administration, with Kurland appointed as superintendent, and Savage as associate director. In the Clinical Sciences Division, which housed the psychedelic program, Pahnke was appointed chief of psychiatric research, and Unger chief of psychological research. In 1969 Pahnke was promoted to director of clinical sciences research, and Grof took his place as chief of psychiatric research. The important role of the Spring Grove psychedelic research staff, and their work, in the establishment and administration of the MPRC reflected the respect that they had garnered at both the state and federal level. Rather than fringe workers in a controversial field, they were government-funded scientists at the forefront of psychiatric research in Maryland.

As well as the new premises, 1968 also saw the Spring Grove researchers commence their fourth psychedelic research program: the treatment of narcotic (heroin) addiction. This was the final clinical indication into which the team would expand their psychedelic research. The trial was a natural progression from the alcoholic study, based on the assumption that if psychedelic therapy could help treat addiction to one drug, it would most likely help those addicted to others. Narcotic addiction was generally considered to be even more highly

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95 In a 1968 document outlining the proposed study, the researchers only used the term “narcotic” when referring to the drugs that patients were addicted to. See, “Narcotic Addiction—Psychedelic Therapy: Research Program,” November 1968, folder “Coleridge House,” box 1, Savage Papers. Narcotic is a somewhat ambiguous term, as what drugs are considered narcotics can vary depending on the context of the term’s use (medical or legal) as well as the historical period of its use. However from later reports on the study, it is clear the Spring Grove researchers used the term to refer specifically to heroin. See, Savage Charles and O. Lee McCabe, ”Residential Psychedelic (LSD) Therapy for the Narcotic Addict: A Controlled Study,” Archives of General Psychiatry 28 (June 1973), p. 808.
resistant to treatment than alcoholism: the researchers cited one study from the Public Health Service Hospital at Lexington, Kentucky, which specialized in treating narcotic addicts, that found a 94 to 97 percent relapse rate among its patients. However they noted that another Lexington study, conducted by Arnold Ludwig and Jerome Levine, had found success treating narcotic addicts with a unique treatment combining LSD with hypnosis and psychotherapy. This study, however, had been on inpatients; therefore it had not tested for long-term abstinence or social adjustment, but changes in ratings of psychopathology. Therefore at Spring Grove the researchers planned to expand on this work by evaluating LSD’s effectiveness in promoting long-term narcotic abstinence, using the psychedelic therapy method that they were finding successful with alcoholics.96

The Spring Grove researchers designed their NIMH funded study to include 144 male narcotic addict inmates from Maryland correctional institutions, who would be paroled early in order to participate. The inmates would be randomly assigned to either the treatment or control group. Members of the control group would be enrolled as outpatients at the Narcotic Clinic in Baltimore, also known as Coleridge House. There they would undergo an existing program for paroled narcotic addicts in Maryland that involved daily monitoring of urine for drug use, weekly group psychotherapy sessions, and close parole supervision. Patients in the treatment group would be admitted to the same clinic as inpatients for four to six weeks while they underwent psychedelic therapy. The actual treatment,

including all associated psychotherapy, would take place the MPRC. Like the outpatients, the inpatients would have their urine monitored daily. After treatment they would be discharged to the same outpatient care as the control group. Participation in the program was a condition of the patient’s parole, therefore repeated drug use or failure to attend the clinic, as well other normal parole violations, would result in re-imprisonment. A low-dose LSD control group was not utilized in this trial, as the researchers expected that its inclusion in their other clinical trials would clarify the role of the psychedelic experience in the overall psychedelic treatment procedure. Therefore, in this case, psychedelic therapy simply needed to be compared to an alternative treatment.

Psychologist Oliver Lee McCabe, who had been part of the Spring Grove LSD team since 1965, was responsible for the inpatient phase of the study and was chief psychotherapist. Savage was principal investigator, while Kurland was co-principal investigator. Follow-up assessments would occur at six and twelve months, and would include psychological testing similar to that conducted in the other psychedelic therapy trials. These results would be compared to scores patients received on the same tests prior to treatment. Additionally, data from the patients’ urine monitoring, and their cooperation with the clinic’s program, would take a major role in helping the researchers to evaluate the comparative effectiveness of the experimental and control conditions.

97 “Narcotic Addiction—Psychedelic Therapy.”
99 “Narcotic Addiction—Psychedelic Therapy.”
As their fourth clinical trial was getting underway, the Spring Grove researchers began to present preliminary results from their other three trials. Whilst it was still too early to draw firm conclusions, results to date suggested that high-dose psychedelic peak therapy was significantly benefiting their patients. In November 1968, the researchers presented results for the neurotic and cancer studies at the “Psychedelic Drugs” symposium hosted by the Department of Psychiatry of Hahnemann Medical College, Philadelphia. For the neurotic study, eighty-five patients had undergone either high or low-dose psychedelic therapy, or group therapy. The researchers compared the results of a battery of psychological tests administered to patients prior to treatment and shortly afterwards, a time span of six to eight weeks. While precise figures were not given, the researchers reported that, “all treatment-specific effects are in favor of psychedelic therapy, in general, and high-dose psychedelic therapy in particular.” These areas of improvement included scores of depression, obsessive-compulsive syndrome, introversion, neuroticism, and anxiety. As well as decreases in pathological ratings, patients showed improvements in measures of positive mental health, such as ego strength, spontaneity, self-regard, and “self-actualized values.”

The study with patients suffering from terminal cancer was still in the pilot phase, therefore no data from low-dose LSD, or non-drug control treatments were available. Nevertheless, the data from pre and post-treatment assessments of twenty-two patients who had undergone high-dose therapy were impressive:

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100 Charles Savage et al., “Research with Psychedelic Drugs,” in Hicks and Fink, Psychedelic Drugs, pp. 18-19.
27 percent of the patients showed “dramatic” positive change, while another 36 percent showed “meaningful” change. The positive changes were in ratings of “depression, anxiety, emotional tension, psychological isolation, fear of death, and the amount of pain medication required.” The researchers’ hypothesis that the peak experience was most conducive to positive change was supported by the observation that of the six patients that had the most intense peak experience, five were also considered to have experienced the greatest post-treatment improvement. They also observed that patients who were in the earlier stages of their illness improved the most.

More detailed data was available for the preliminary results of the alcoholic study. In July 1969, the Spring Grove researchers presented the results of treatment at the six-month follow-up point to a symposium on psychedelic drugs at the annual convention of the American Medical Association in New York. One hundred and thirty-five alcoholic patients had undergone treatment, two-thirds of whom had been blindly assigned to the experimental high-dose group, while the rest were in the low-dose control group. The study’s design had allowed for up to three LSD sessions, however this had only occurred with eighteen patients. A further thirteen patients could not be reached for follow-up at the six-month point. Therefore in the interests of uniformity, only the 104 locatable patients who received one dose were considered in the analysis of results. The ratio of high to low-dose patients was maintained during these reductions in the total sample size. At the six-month follow-up point the high-dose treatment showed a statistically significant advantage over the low-dose, with 53 percent of high-

dose patients, compared to 33 percent of low-dose patients, considered “essentially rehabilitated” in terms of drinking behaviour, and 44 percent compared to 25 percent in terms of global adjustment (which included factors such as employment and interpersonal relationships). The team also analysed the results in relation to the nature of patients’ subjective drug experiences, labelled “psychedelic reactivity,” regardless of dose. This was to test the hypothesis that it was the profound peak experience that was most therapeutically beneficial. The results were statistically significant in favour of the more profound reactions for global adjustment. Drinking behaviour results displayed a similar trend although they were not statistically significant. These results prompted the researchers to put forward a modest claim of efficacy: “in practical terms, we can say that a given alcoholic patient receiving a single high dose of LSD in the context of psychedelic-peak psychotherapy and experiencing a profound psychedelic-peak reaction has the best likelihood for improvement six months later.”

While these results were very positive, they would not go unchallenged. Reactions to the Spring Grove research tended to focus on critiquing the design of the clinical trials, with researchers and officials questioning whether the intended high level of control had been realized. These critiques will be considered in the next chapter, as the Spring Grove research is contextualized.

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102 Walter N. Pahnke et al., "The Experimental Use of Psychedelic (LSD) Psychotherapy," *JAMA: The Journal of the American Medical Association* 212, no. 11 (1970), pp. 1859-1860. Statistical significance was at the level of p 0.05 (results would be produced by chance alone five times out of one hundred) for both drinking behaviour and global adjustment in the high versus low dose comparison. For psychedelic reactivity, patients’ drug reactions were classed as “profound,” “marked,” or “minimal” with the percentage of patients “essentially rehabilitated” in each of these categories tabulated. For global adjustment percentage scores for these categories were 61, 39 and 24, respectively, and for drinking behaviour were 61, 48 and 36. For global adjustment the statistical significance was at the level of p 0.025.
within the greater field of LSD therapy research in the mid to late 1960s. Methodological conflicts would ultimately undermine the significance of the Spring Grove research; nevertheless this was not yet apparent in the late 1960s.

Buoyed by their positive preliminary results, and reflecting their expertise in LSD administration, in 1969 the Spring Grove researchers applied to the FDA to have their IND amended to allow them to administer LSD to mental health professionals and scientists for training purposes. The researchers had long allowed their own staff to have a personal LSD session in order to familiarize them with the treatment process.\(^{103}\) The new program would make Spring Grove a national centre for such training. The program was a response to frequent requests from mental health professionals for an LSD session to aid them in their own work, which they were usually forced to decline. The researchers proposed that acceptable reasons for requesting a session would include training for independent psychedelic research, a desire to better understand the symptoms of schizophrenia or the problems of youth drug abuse, or for psychotherapists to develop their skills by increasing their self-understanding and insight.

Candidates would go through similar screening, preparation, session, and aftercare procedures as patients. The program was designed as a study, with forty candidates receiving LSD over two years, and data collected to assess how the LSD session impacted them both professionally and personally.\(^{104}\) However,

\(^{103}\) "A Policy Statement Covering the Conduct of Psychedelic Research Within the Department of Medical Research at Spring Grove State Hospital," 1965, folder "Psychedelic Research Staff Meetings," box 1, Savage Papers.

\(^{104}\) Albert A. Kurland, "Application to Amend IND-3250 for the Administration of LSD for Training Purposes," 7 March 1969, folder 9, box 1, MSP 1, Stanislav Grof Papers, Archives and Special Collections, Purdue University Libraries, West Lafayette, Indiana.
the program continued beyond this plan, and by 1976, 203 mental health professionals had received a training session of LSD.105

As well as expanding the scope of the LSD research programs, the Spring Grove researchers continued to work to improve their psychedelic peak therapy treatment method. Since the inception of the Spring Grove psychedelic research program, music had been used extensively in LSD sessions to help guide patients’ experiences. In 1969, music therapist Helen Bonny joined the team in order to perform research that would deepen their understanding of the role of music in psychedelic therapy.106 In 1972 she published a paper with Pahnke in the Journal of Music Therapy discussing in detail how music was of benefit in LSD sessions. They summarised that music facilitated therapy in five ways:

1) by helping the patient relinquish usual controls and enter more fully into his inner world of experience; 2) by facilitating the release of intense emotionality; 3) by contributing toward a peak experience; 4) by providing continuity in an experience of timelessness; 5) by directing and structuring the experience.107

They then outlined how specific kinds of music were used during the different phases of LSD’s effects in order to direct patients’ reactions. During the onset of the drug’s effects, pleasant, calm music would be played in order to relax and reassure the patient. As the effects intensified more rhythmic and dynamic music was used to provide “an undercurrent of support and forward movement,”

105 Yensen and Dryer, “Thirty Years of Psychedelic Research,” p. 87.
helping to draw the patient into the drug experience.\textsuperscript{108} During the height of the drug's effects, powerful, inspiring music was used to help bring the patient to the peak experience. As the drug's effects diminished, the music would return to a quieter, calming tone. During the early and later periods of the session, music of various genres was played, including the patients' own selections. In the periods of greater drug intensity the music was either instrumental or included vocals in language the patient could not understand. This was to prevent patients from engaging intellectually with the lyrics, as this would prevent them from “letting go” to achieve the higher peak experience.\textsuperscript{109}

\section*{Conclusion}

By all appearances, at the close of the 1960s the Spring Grove LSD researchers had every reason to be optimistic. Over the decade, despite the increasing controversy surrounding LSD, their research program had continuously expanded. Not only had their research program grown in scope and staff, but their expertise had been recognized by continued federal funding, their consultation by a congressional investigation of LSD, state support for expansion of their programs into other hospitals, and appointment to leadership roles in the Kurland initiated Maryland Psychiatric Research Center. The Spring Grove researchers had developed the most advanced program for evaluating psychedelic therapy ever to be instituted in the United States. For each trial they

\textsuperscript{108} Ibid., p. 79.
initiated, the researchers had focused on carefully balancing the clinical requirements of psychedelic therapy with the need for scientific rigour in efficacy evaluation. Their method of psychedelic peak therapy involved the subjective manipulation of extrapharmacological treatment-impacting variables; however the researchers recognized that objectivity was needed to properly assess its effectiveness. They therefore cleverly devised the low-dose LSD control group that would theoretically allow double-blind treatment administration without compromising their therapeutic method. They also designed their trials with an extra non-drug control group to provide a baseline against which the untested low-dose psychedelic treatment could be compared. Their sophisticated use of independent treatment assessment teams, using established psychological tests, provided an objective assessment of results for all treatments. By the end of the decade positive preliminary results were beginning to emerge from the clinical trials, and all evidence suggested that final results would confirm treatment efficacy.

Yet, ultimately, in the 1970s no consensus would emerge on the efficacy of any form of LSD psychotherapy for any indication. Over the decade LSD psychotherapy research would slowly diminish until it came to a complete halt. The research that had been conducted would have little impact on mainstream psychiatric theory or practice, despite the continued absence of effective treatments for alcoholism, narcotic addiction, or end of life anxiety. The Spring Grove LSD research would be largely forgotten. Examining why the early promise of the Spring Grove program failed to lead to a consensus on psychedelic therapy’s efficacy reveals how deeply problematic it was to perform controlled
trials with LSD. The final results of the Spring Grove trials were partially compromised by difficulties in maintaining their original design, and further undermined by the results from other research groups that compromised therapeutic method for scientific rigour.
5. Elusive Efficacy: The Undermining of the Spring Grove Psychedelic Research

After a period of almost constant success and growth during the 1960s, in the early 1970s the Spring Grove psychedelic researchers began to face challenges that undermined the significance of their work. These challenges would lead to their research having little impact on psychiatry, as they failed to establish the efficacy of psychedelic therapy for any indication. The researchers would continue working with LSD and other psychedelics at the Maryland Psychiatric Research Center (MPRC) until 1976. However, from the early 1970s the research program would operate at a diminishing influence and scale. In those years it would be the only active LSD research program in the United States. Examining why the Spring Grove LSD program failed to live up to its potential, as well as exploring the fate of LSD research more generally, therefore requires closely examining the challenges that those researchers faced. These challenges were both internal and external.

Internally, as final results for the Spring Grove clinical trials took shape, problems emerged in their design. While the researchers had gone to great lengths to design trials that balanced clinical needs with scientific rigour, the planned level of control could not always be implemented. Additionally, low-dose psychedelic therapy turned out to be a more effective treatment than the
researchers had assumed, making it an inadequate active placebo control. These and other problems influenced often lacklustre and inconclusive results. They also left the researchers open to critiques that could undermine positive elements in their results. External challenges came from other researchers conducting concurrent clinical trials of LSD in the treatment of alcoholism. These researchers all reported a lack of efficacy for their treatments. This further diminished the significance of the Spring Grove research, as any positive results appeared unconvincing in the face of the greater volume of negative results. Closely examining those clinical trials, however, will reveal that the researchers utilized treatment methods that deviated significantly from psychedelic therapy, making positive results unlikely.

Examining the internal and external challenges that the Spring Grove researchers faced sheds light not only on the fate of LSD psychotherapy, but on the problematic complexity of controlled clinical trials. Each research group claimed that the randomized controlled trial methodology would provide objective data on the efficacy of psychedelic therapy. Yet they designed their therapeutic methods and control groups in widely divergent ways based on their own biases and assumptions, which their final results ultimately reflected. Their use of the randomized controlled trial methodology therefore obscured rather than clarified the efficacy of psychedelic therapy. Rather than neutralizing bias, the method hid it behind a veil of objectivity.
Internal Challenges

The Spring Grove researchers reported the final results for their alcoholic study in 1970, at the seventh international congress of the Collegium Internationale Neuro-Psycho-Pharmacologicum, held in Prague, Czechoslovakia. Their report was published the following year in *Pharmakopsychiatrie-Neuro-Psychopharmakologie*. After the statistically significant results in favour of the high-dose group at the six-month follow-up point, at the twelve and eighteen-month points there were no significant differences between the results of the high and low-dose groups. The positive results for the high-dose group had not been lost, in fact they had either remained steady or improved: for drinking behaviour the results had remained essentially unchanged, with 53 percent of patients essentially rehabilitated at six months, and 54 percent at eighteen months, while for global adjustment the rate had risen from 44 to 53 percent. However, the rate of treatment success in the low-dose group had risen significantly, from 33 to 47 percent for drinking behaviour, and from 25 to 41 percent for global adjustment.¹ Therefore the difference between the results for the two groups was no longer significant.

Additionally, removing the double-blind had revealed that randomization of patients between the low and high-dose groups had failed to provide an even distribution of demographic factors that could influence treatment success: the

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¹ A. Kurland et al., "LSD in the Treatment of Alcoholics," *Pharmakopsychiatrie-Neuro-Psychopharmakologie* 4, no. 2 (1971), pp. 90-91. The successful follow-up rate, although considered very good, inevitably dropped over the study: from 89 percent at six-months, to 78 percent at eighteen months. This further decreased the statistical significance of the results.
high-dose group had a significantly greater number of patients who were married, and who had completed high school, while the low-dose group had more patients with five or more hospital admissions. These factors had the potential to bias the high-dose group in favour of positive results. The results were obviously disappointing, as clinical impressions as well as early results had suggested that the treatment was very effective. The final results, however, suggested that any advantages of high-dose psychedelic therapy were short-lived, and the uneven demographic factors in the treatment and control groups called into question the validity of even this short-term advantage. While on the surface these results appear to demonstrate that psychedelic therapy was at best of only limited efficacy, a deeper analysis reveal that flaws in the design and conduct of the trial undermined the significance of the results.

Reflecting on the alcoholic trial some years after its conclusion, Charles Savage discussed some of the problems in the study. He wrote that at the time of its conclusion, he had been “not unhappy with the results.” He had been disappointed that the positive results at six months had only been at a p 0.05 level of statistical significance (results would be produced by chance alone five times out of one hundred), and that this advantage had not been maintained beyond that follow-up point. Savage’s dissatisfaction with a p 0.05 level of statistical significance demonstrates his highly rigorous scientific standards, as drug researchers commonly used this level as a standard for determining significant results. Nevertheless he considered that “a 54% recovery rate

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2 Ibid., p. 85.
3 Daniel Carpenter, Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA (Princeton: Princeton University Press, 2010), p. 518. This standard was used in
seemed hardly nugatory,” and furthermore he had “optimistically assumed that a greater N [number of patients] would lead to higher levels of significance.” The study, however, never achieved a greater sample size, as it was “abruptly stopped after 135 patients.” According to Savage the trial was halted “for no very good reason except that the therapists were tired of working with a high-low dose LSD comparison in a double blind study and preferred to turn their attention to a new compound, dipropyltryptamine [DPT].” DPT was a shorter acting psychedelic compound, which the Spring Grove researchers began working with in the 1970s.

That the trial stopped due to therapist fatigue provides two important insights into LSD research at Spring Grove. Firstly it shows how taxing the psychedelic therapy procedure was for the therapists. The procedure was inherently demanding, as it involved a marathon ten to twelve hour therapy session, during which the therapist had to provide effective support and guidance to a patient undergoing a dramatic and variable emotional experience. However, performing this, as well as the intensive preparation, was made even more taxing by knowing that one-third of the patients—those in the low-dose group—were not expected to benefit greatly from their efforts. While ideal from a scientific point of view, the double-blind controlled trial form of research was a disheartening prospect for therapists whose main goal was to deliver an effective treatment to significant trials such as the landmark 1960 Veterans Administration multi-hospital study of the efficacy of chlorpromazine. See Jesse F. Casey et al., “Drug Therapy in Schizophrenia: A Controlled Study of the Relative Effectiveness of Chlorpromazine, Promazine, Phenobarbital, and Placebo,” A.M.A. Archives of General Psychiatry 2, no. 2 (1960), pp. 210-220.

[Charles Savage], untitled manuscript, n.d., folder 33, box Addition 2, MSP 70, Charles Savage Papers, Archives and Special Collections, Purdue University Libraries, West Lafayette, Indiana (hereafter Savage Papers), p. 9.
each patient. The second insight into research at Spring Grove is that the design and conduct of their research was not shaped purely with scientific rigour in mind, but was heavily influenced by therapeutic demands. This is further supported by Savage’s comment that the assignment of patients between high and low-dose on a two-to-one, rather than equal, basis was done in order to “placate the therapists.”

Further reflecting on the disappointing results of the study, Savage realized that the sample size was not the major factor limiting the potential significance of results: he now believed that “prolongation of the studies would have made no difference, because everyone got LSD.” The original design for the alcoholic study included two control groups. As well as low-dose psychedelic therapy control, patients in a second control group would be assigned to a six-month waiting list after the completion of their preparatory psychotherapy, after which they would be re-admitted to the hospital to receive their LSD session. The progress of these patients over the waiting list period would provide data on the effectiveness of the preparatory psychotherapy alone, against which the two LSD treatments could be compared. However, for reasons that are not clear, this second control condition was never implemented. This became problematic, as results for low-dose psychedelic therapy suggested that it was a more effective treatment than they had expected.

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5 Ibid., p. 9.
6 Ibid., p. 9. Emphasis original.
7 Charles Savage to Jonathan Cole, 2 March 1965, folder 17, box Addition 2, Savage Papers.
8 Kurland et al., “LSD in the Treatment of Alcoholics,” p. 91
Although designed as an active placebo treatment, the efficacy of low-dose psychedelic therapy had not previously been tested. Instead its use was based on the theory that the low dose would be insufficient to produce a psychedelic experience, and that this reaction was necessary for treatment effectiveness. As previously discussed, at the six-month follow-up point the researchers’ analysis of results in terms of “psychedelic reactivity,” regardless of dose, had provided some evidence that the more profound psychedelic experiences were most beneficial to patients.\(^9\) However, by eighteen months the researchers concluded that for a “considerable number of patients” the “considerable abreaction and catharsis of psychodynamically charged material” that occurred frequently in low-dose sessions was “quite helpful.”\(^10\) Therefore it appears that low-dose psychedelic therapy was not a placebo condition, but a somewhat effective treatment in its own right. As Savage commented, the study was therefore “not a controlled study but a dose response curve study”: rather than providing data on the efficacy of psychedelic therapy, it provided data on the comparative efficacy of two forms of psychedelic therapy.\(^11\)

Regarding the planned second waiting list control group, Savage commented only that it was “Unaccountably...eliminated from the study.”\(^12\) Considering that the design and conduct of the study had been strongly influenced by therapeutic demands, therapists may have protested against discharging patients to fend for themselves for six-months before treatment. As previously

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\(^11\) [Savage], untitled manuscript, p. 9.

\(^12\) Ibid., p. 9.
discussed, in the pilot alcoholic trial an attempt to implement a non-drug control group had failed due to low morale, as these patients were housed on the same ward as the LSD patients. The waiting list control was designed to remedy this situation, by guaranteeing that everyone eventually got LSD, and keeping the waiting list patients separate from those who immediately underwent treatment. However, it is still possible that therapists’ belief in psychedelic therapy’s effectiveness left them unwilling to knowingly delay treatment to a patient in need. Although with the low-dose treatment the therapists were also delivering a treatment that they did not expect to be effective, in this case the double-blind psychologically shielded both therapists and patients from this knowledge, making the design easier to implement. Other possible explanations include simply insufficient funding, staff, or time to treat and follow a third group of patients.

Despite the difficulties and disappointments in their alcoholic study, the Spring Grove researchers still found some significance in their results. While the unexpectedly positive results for the low-dose group made the evaluation of the efficacy of the high-dose treatment problematic, these results also suggested that the uneven demographic factors between the treatment groups had not significantly skewed favour towards the high dose. The researchers recognized that the inclusion of a non-drug control group would have provided a much clearer picture of overall treatment efficacy. Nevertheless, the positive results for both groups compared to existing data for the hospital’s standard treatment suggested that psychedelic therapy was effective: a previous study at Spring Grove, with comparable alcoholics, found a 12 percent recovery rate at eighteen
months, compared to 54 percent at the same point for high-dose patients in the LSD study. As significant as this was, as it was not part of the same study, it could not be formally considered in determining proof of efficacy. Overall, the researchers concluded that the “clinical achievements of only one psychedelic peak experience and its maintenance for a period of several months in these types of patients is an observation that cannot be discounted.”\textsuperscript{13} They proposed further research in order to learn how to “sustain and maximize” these positive results.

Final results for the Spring Grove study of psychedelic therapy in the treatment of neurotic patients were published in 1973, in the \textit{Journal of Altered States of Consciousness}. For this trial, the researchers implemented the non-LSD control group as planned. Results, however, were even more disappointing than those for the alcoholic study. Ninety-six patients were assigned to either high-dose psychedelic therapy, low-dose psychedelic therapy, or the hospital’s conventional treatment program with additional group therapy. The researchers performed an initial analysis of treatment effectiveness at the completion of the six to eight week treatment program. They compared results from psychological tests administered before treatment to those administered after, which provided an assessment of the immediate impact of treatment. At this point, results demonstrated a superior efficacy for high-dose psychedelic therapy over conventional therapy, to a statistically significant degree, on nineteen of fifty ratings of both psychopathology and positive aspects of mental health. Low-dose psychedelic therapy was significantly superior to conventional treatment on

\textsuperscript{13} Kurland et al., "LSD in the Treatment of Alcoholics," pp. 91-92.
eleven ratings. There was little significant difference between the high and low-dose treatments. Despite these positive early results, at the six-month follow-up point, a more limited battery of tests failed to find any significant difference between the three groups. At the twelve-month follow-up there was some indication of superior efficacy for high-dose psychedelic therapy, however a high dropout rate had left the sample unrepresentative of the original population. Therefore the results could not be considered accurate. At eighteen months there were again no significant differences between the three groups.14

The inclusion of the non-LSD control group in this trial suggests that the negative results attained were due simply to the lack of efficacy for psychedelic therapy in the treatment of patients suffering from chronic, severe, psychoneuroses. However, despite the superiority of the neurotic trial’s design compared to the alcoholic trial, the Spring Grove researchers still questioned whether flaws in the study diminished the significance of results. As had happened in the alcoholic study, randomization had failed to equally distribute demographic variables between the treatments. Where the alcoholic study had only included male patients, the neurotic study included both male and female patients. Random allocation of patients had resulted in a disproportionately high number of females in the high-dose LSD group. This was significant, as an analysis of results in terms of gender suggested that females improved most with the low-dose treatment, while male patients improved most with the high-dose.15


15 This dose-response relationship was statistically significant at the level of 0.10 at the six-month follow-up point. This was below the standard significance level of p 0.05. The analysis therefore simply indicated a trend, and further proof would be needed to prove the dose-
The researchers theorized that differences in dose-response between males and females could be due to both differences in their illness, and in the support they received in the home and community after discharge. Since the study's inception the researchers had acknowledged that the psychoneurotic diagnosis encompassed patients with wide variations in pathology, even if their chief complaints were consistently depression and anxiety. The researchers found that females in the study “tended to be ‘anxiety reactions’ and ‘hysterical depressives’ who were unable to cope with marital and/or home problems.” These patients often found the high-dose LSD session too confronting, and any improvement was frequently undone on their return home: instead of any finding “rewards for becoming less depressed...her husband and children may increase their demands on her.” Males were found to be more often suffering from “character problems,” and had psychological defences that were “generally conceded to be refractory to conventional therapeutic intervention.”\(^{16}\) For these patients the intense high-dose LSD session was particularly useful, as it could break through these defences. They also found that with males, improvement met with great community support in the form of new employment opportunities.

The researchers’ analysis of results in terms of gendered dose-response had not been part of the original trial design, but had instead been conducted post hoc. Therefore they considered these results as only speculative trends. Nevertheless, response relationship. At eighteen months the trend continued but its significance had dropped further. Nevertheless, there was some significant corroborating evidence: female patients in the low-dose group improved more than those in the conventional treatment group to the level of \(p = 0.05\), while there was no significant advantage for high-dose therapy for women. Ibid., pp. 38, 41-44.

\(^{16}\) Ibid., p. 43.
if they were accurate, then the failure of randomization had undermined the efficacy of high-dose psychedelic therapy, as the patient population in that treatment group was biased in favour of non-responders. Ultimately, the results of the Spring Grove neurotic trial were discouraging if not conclusive. Nevertheless, they were not damning to the Spring Grove psychedelic research program as whole. While there had been some history of claims of efficacy for psychedelic therapy for patients with neurotic illnesses, alcoholism had always been its primary indication. Alcoholism, or more generally addiction, was a distinctly different illness to psychoneurosis; therefore the results of this trial could not indicate a lack of efficacy for psychedelic therapy in the treatment of alcoholism or other addictions.

Significant challenges also faced the Spring Grove study of psychedelic therapy in the treatment of emotional distress and physical pain associated with terminal cancer. While the researchers had planned a controlled study for this indication, similar in design to the alcoholic and neurotic studies, a lack of funding left them unable to implement it. Despite early indications of the effectiveness of the treatment, funding applications to the Public Health Service (PHS) and National Cancer Institute were unsuccessful. Research did continue, using limited funds from the Maryland Department of Health and Mental Hygiene, and an all-purpose grant from the PHS, as well as some specific funding from the private Mary Reynolds Babcock Foundation. However this funding was not adequate to

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17 William Richards, email to author, 18 February 2013; S. Grof et al., "LSD-Assisted Psychotherapy in Patients with Terminal Cancer," International Pharmacopsychiatry 8 (1973), p. 144. The researchers received $40,000 from the Mary Reynolds Babcock Foundation, however in the original application for PHS funding the trial had been costed at $119,437. Albert A. Kurland, "LSD-Assisted Psychotherapy in Terminal Cancer," application for research grant to Department
launch the controlled trial, therefore research stayed in the uncontrolled pilot phase. Why the PHS did not award specific funding for this trial, when it did for the other three Spring Grove LSD clinical trials, is not clear. It was most likely not due to any significant flaw in its design, nor a more fundamental opposition to the research, but simply to a lack of funds to cover all worthy research applications. PHS officials likely considered the public health implications of this work as less significant than that of finding a successful treatment for alcoholism, chronic psychoneuroses, or narcotic addiction. While the emotional distress of the dying patient was of significant personal cost to the patient and their loved-ones, it did not represent a major financial burden to the government.

Nevertheless, the Spring Grove researchers continued to publish positive results from their uncontrolled pilot research of LSD therapy with cancer patients. Their final report, published in 1973 in *International Pharmacopsychiatry*, assessed the treatment’s effects in thirty-one patients. The researchers compared pre and post-treatment ratings of patients’ degree of depression, anxiety, experience of pain, fear of death, psychological isolation, and difficulty of management, as well as narcotic use, using ratings by members of the research team, the patient’s family, and an independent observer. Averages were then made by pooling the scores for all of the patients in each rating category. Comparing these averages pre and post-treatment revealed a statistically significant improvement for all categories, to the level of p 0.001. The researchers reported that 29 percent of the patients were “dramatically improved,” while 41.9 percent were “moderately

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improved.” Only two patients (6.4%) worsened over the treatment period, even though the degenerative nature of the patients’ illnesses would have predisposed all of them towards a worsening disposition. Despite the significant reduction in patients’ experience of pain, narcotic use did not decrease to a statistically significant degree. The researchers suggested that LSD treatment made many patients more comfortable on their standard regimen of narcotic pain relief, but did not go so far as to remove the need for narcotics. Other patients may have continued their narcotic use out of habituation or addiction.\textsuperscript{18} Despite the highly positive nature of these results, and the careful manner in which they had been collated and analysed, without a control group they did not provide convincing evidence of efficacy.

The Spring Grove researchers found their most clearly positive results for the efficacy of psychedelic therapy in their study of the treatment of heroin addicts, published in 1973 in \textit{Archives of General Psychiatry}. Seventy-four paroled inmates took part in the study, which compared the progress of patients who underwent either the standard program of an established outpatient narcotic clinic, or a four to six week inpatient psychedelic therapy program followed by the same outpatient treatment. In this trial, random allocation had successfully insured an even distribution of potential treatment impacting demographic variables between the treatment and control groups. Results were analysed in terms of abstinence from narcotics, and global adjustment, for the first twelve months.

\textsuperscript{18} Grof et al., “LSD-Assisted Psychotherapy,” pp. 136-143. In the original design, results were to be assessed through the same sophisticated psychological tests used in the other Spring Grove studies, such as the Minnesota Multiphasic Personality Inventory. However, undergoing these tests proved to be too taxing for the severely ill cancer patients. Therefore a simpler rating scale was devised that relied on the subjective judgement of observers.
months of patients’ participation in the outpatient program. Abstinence could be evaluated accurately due to the clinic’s daily monitoring of patients’ urine for opiates. These results revealed that 25 percent of the psychedelic therapy patients maintained complete abstinence over this period, compared to just 5 percent of the control group. This result was statistically significant to the level of $p < 0.05$. A further three LSD patients maintained complete abstinence for over a year following a brief relapse on their entry into the outpatient program. Including these patients raised the abstinence rate up to one-third.\(^{19}\)

Global adjustment scores were rated by independent assessors. Despite ratings trending in favour of psychedelic therapy at twelve months, there was no statistically significant difference between the average scores of the two groups. Comparing individual scores, however, revealed that four times more LSD patients received the top global adjustment score than control patients. Therefore, while the treatment seemed to have had little impact on the global adjustment scores of the majority of patients, those patients who did react to treatment seemed to benefit maximally. Twelve of the thirteen LSD patients who received the maximum adjustment score were also among those judged to have achieved the “psychedelic peak experience” in their LSD session. Therefore the researchers concluded that “the peak experience is a facilitative, but hardly an essential or sufficient ingredient for behavior change.”\(^{20}\)

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\(^{20}\) Ibid., p. 813. Twenty-nine of the thirty-six LSD patients (80%) achieved the psychedelic peak experience.
Therefore, although the majority of narcotic addict patients did not remain abstinent following psychedelic therapy, the treatment was significantly more successful than the standard outpatient treatment. Heroin addicts were notoriously difficult to treat. The researchers highlighted that the patients had been unmotivated for treatment, with all admitting that they had volunteered solely in the hope of obtaining early prison release. The researchers also found that “a tremendous socio-cultural gulf between the patients and the therapists” made establishing rapport and trust difficult:

The modal therapist was white, Anglo-Saxon, Protestant, and from the upper middle class; the typical addict was a ghetto-raised Negro with an 8th grade education. One therapist, attempting to assert his legitimacy, pointed out that he had once actively done physical labor but literally brought down the house when under cross examination he admitted that he had been the manager of a supermarket. The addict’s view was, “Doc, if you haven’t lived in the street, you don’t know what it’s like.”

The researchers felt that they generally did manage to adequately overcome this gulf, and that “Even the racial problem was contained either out of mutual denial or respect.” Nevertheless, they suggested that black therapists could be more effective. Given these difficulties, even the modest abstinent rates achieved could be considered significant. As the control condition was not a placebo treatment, the researchers conceded that the trial did not delineate whether it was the LSD session, or other components of the overall psychedelic therapy procedure, that was behind any treatment effects. The researchers had intended to clarify the role of the psychedelic experience in psychedelic therapy in the alcoholic and neurotic trials, through the low-dose LSD control treatment. However, as we

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22 Ibid., p. 4.
have seen, this question had remained unanswered, as in those trials the low
dose of LSD produced a more therapeutic experience than the researchers had
expected, making it an alternative, rather than a placebo, treatment. Countering
this potential critique, they pointed out that it was unlikely that non-drug
elements in the treatment condition were solely responsible for treatment
effectiveness, as “no consistently positive claims have ever been associated with
individual psychotherapy and/or brief residential treatment for chronic heroin
abusers.”

The internal challenges faced by the Spring Grove researchers in conducting
their clinical trials therefore left them with results that were largely both
disappointing and inconclusive. This circumstance was most evident in the
alcoholic trial, where the low-dose LSD treatment failed to act as an adequate
control group. Due to the absence of the originally planned non-LSD control
group, this problem left the trial unable to demonstrate the efficacy of
psychedelic therapy. Not only were these results inconclusive, but on the surface
they also appeared largely negative, at least in terms of long-term efficacy. While
the researchers implemented the neurotic study as planned, the failure of
randomization may have skewed the trial in favour of the null hypothesis.
Randomization had failed to ensure an equal distribution of potential treatment-
impacting variables in both the alcoholic and neurotic trials. This demonstrated
that rather than the solution to the problem of bias in the assignment of patients
to treatment groups, the method simply ensured that the researchers themselves
could not be blamed for any unequal variables between the groups.

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The two trials that had the most clearly positive results were the two that were the least impressive methodologically. Funding difficulties had left the cancer study in the uncontrolled pilot phase of research. Therefore despite their impressive nature, the results could only be considered as indicating, rather than proving, efficacy for the treatment. The narcotic study was the most successful of the four trials. It was implemented as planned and returned positive results. It was less methodologically sophisticated than the alcoholic or neurotic studies, as it did not incorporate a double-blind placebo control condition. Nevertheless, the researchers made every effort to minimize bias: outside of the experimental treatment phase the two treatment groups were treated as identically as possible, the control condition was a commonly used treatment that experience had proven to have very limited effectiveness, and outcome was based on objective measures of drug use, as well as ratings by independent assessors.

The Spring Grove researchers had therefore found their best success when they focused on providing a clear comparison between two distinct treatments, rather than on achieving a double-blind condition. Achieving a double-blind had only obscured the efficacy of psychedelic therapy, as it required using a control condition of unknown efficacy. Overall the results of the Spring Grove studies were underwhelming and inconclusive, however they were not disastrous. Despite the disappointments in the alcoholic trial there were still clear indications of effectiveness, therefore further research with a different control condition was fully justified. Psychedelic therapy for terminally ill cancer patients remained a treatment deserving controlled research. Further
understanding why little came from the Spring Grove research therefore requires contextualizing their work within the greater field of LSD therapy research in the late 1960s and early 1970s.

**External Challenges**

The researchers at Spring Grove formed only one of a number of LSD research groups active in the United States in the years after the Drug Amendments of 1962. In fact, between 1967 and 1970 the results from six other clinical investigations of the efficacy of LSD in the treatment of alcoholism were published. These trials were led by Leo Hollister at the Palo Alto Veterans Administration Hospital, California; Keith Ditman of the University of California, Los Angeles; William Bowen at the Veterans Administration Hospital in Topeka, Kansas; Milan Tomsovic at the Veterans Administration Hospital in Sheridan, Wyoming; Wilson Van Dusen at Mendocino State Hospital, California; and Arnold Ludwig and Jerome Levine at Mendota State Hospital, Wisconsin. By the mid-1960s, alcoholism was by far the primary indication for LSD therapy research. Several factors influenced this. Firstly, the early, uncontrolled psychedelic therapy research had produced remarkable and unprecedented results that had garnered much attention in the psychiatric research community. Alcoholism was a major public health problem, with no significantly effective treatment options. Extensive further research was therefore unsurprising. Secondly, while it was difficult to establish a double-blind in any form of LSD research, several features of psychedelic therapy made it better suited for controlled research than
psycholytic therapy. Psycholytic therapy was simply a modified form of psychodynamic therapy. Therefore it had no standardised indication, goal, treatment course, or outcome criteria. While the therapeutic method utilized by researchers of psychedelic therapy would vary widely, several significant aspects of treatment were ideal for controlled research: alcoholism was a clear indication, drinking behaviour was an objective outcome measure, and the early researchers had established the treatment as running a short course with a limited number of drug sessions. Therefore psychedelic therapy was both the most desirable and seemingly simple LSD therapy to research in the years after the 1962 amendments.

Like Kurland and Unger had, the other researchers of LSD therapy for alcoholism in the late 1960s had all initiated their research after reading the reports of dramatic recovery amongst alcoholics following psychedelic therapy. While intrigued by these results, the researchers were all highly critical of the uncontrolled research that had produced them, and therefore decided to put the treatment under scientific examination. The clinical trials that resulted were all conducted in hospital settings, and were funded by the federal or state governments. With varying degrees of sophistication and success, they all designed their studies with substantial numbers of patients, control groups, blinding procedures, long follow-up periods, and statistical evaluations of the

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24 Some limited psycholytic therapy research was conducted in the United States after the Drug Amendments of 1962. This was process rather than outcome research: it measured how LSD altered psychotherapy, rather than whether or not treatment was effective. See J. Jaffe et al., "Speech Rhythms in Patient Monologues: The Influence of LSD-25 and Dextroamphetamine," *Biological Psychiatry* 4, no. 3 (1972), pp. 243-246.
significance of results. The trials therefore all conformed to the formalized mode of pharmaceutical research encouraged under the Drug Amendments of 1962.

With seven independent controlled clinical trials of LSD in the treatment of alcoholism being conducted in the mid to late 1960s, it could have been expected that a clear consensus on treatment efficacy would emerge. If the results of all the trials were comparable, this would theoretically provide overwhelming evidence for or against efficacy, as inevitable variations in the design and research environment of each trial would provide protection against the influence of hidden bias in any single study. Indeed, multi-hospital controlled trials were the ultimate form of controlled trial design. The comparative results of the seven studies did, in fact, approach consensus: on the surface the Spring Grove results appeared negative, while five of the other trials reported firmly negative results, and one reported results that were somewhat ambiguous, though largely negative. However, the uniformity in both the aim and outcome of these clinical trials hid a great variation in the most fundamental element of a clinical trial’s design: the therapeutic method being evaluated. While the original claims for LSD’s effectiveness in treating alcoholism had been made for its use in specific treatment method—psychedelic therapy—only the Spring Grove researchers actually utilized this method.

Instead of replicating the psychedelic therapy method as developed in Canada, each of the six non-Spring Grove research teams devised their own treatment that resembled it, but also differed from it in critical ways. Essentially the only constant characteristic of the tested treatments was that they involved no more
than three LSD sessions. Otherwise, each study evaluated the efficacy of a unique treatment that incorporated selected aspects of psychedelic therapy. While several of the six studies adequately provided their patients with a psychedelic setting, and some specific preparation for the session, none of the tested treatments involved extensive preparatory psychotherapy. One study did involve psychotherapy during the LSD session, however it was in a form completely at odds with the established techniques of psychedelic therapy. Therefore, analysing the therapeutic methods of these trials calls into question whether they can be fairly used in an evaluation of psychedelic therapy in the treatment of alcoholism.

Amongst the researchers, Leo Hollister and colleagues at the Palo Alto Veterans Administration Hospital utilized a therapeutic method that most starkly contrasted to that of psychedelic therapy. The method tested not only involved no psychotherapy, but also minimal preparation and session guidance. In fact, the method equated to little more than the administration of a high dose of LSD. By the mid-1960s, Hollister was a prominent psychopharmacologist, who had been at the forefront of research methodology for over a decade. His prior research had been largely biologically orientated, and this likely influenced how he approached LSD therapy. Exploring Hollister's clinical trial in the light of his research background helps to illustrate how mainstream psychopharmacologists struggled to appreciate how psychedelic therapy fundamentally differed from their established “magic bullet” mode of drug treatment.
Hollister had not entered the field of psychiatry and psychopharmacology deliberately. After training in internal medicine, in the early 1950s Hollister took up a position at the Veterans Administration Hospital in Menlo Park, California, which mainly treated psychiatric patients. In his medical role there, in 1953 he began researching reserpine as a treatment for hypertension. Soon afterwards a representative of the drug’s manufacturer informed him that the drug might also be useful for psychiatric patients. Therefore, Hollister began collaborating with some of his psychiatrist colleagues to test the drug’s effectiveness in treating schizophrenia. Having had some experience with the placebo-controlled double-blind method of drug evaluation, he conducted the research in this manner.

According to Hollister, this was the first time that a parallel-group, double-blind placebo-controlled trial had been conducted with schizophrenic patients. Finding the treatment successful, Hollister expanded his research to controlled trials of chlorpromazine in 1954, after finding research suggesting that it had similar antipsychotic effects. He then collaborated on the most sophisticated clinical trial to have yet been undertaken in the field of psychopharmacology: a large-scale, multi-hospital, randomized, double-blind, placebo-controlled study of the efficacy of chlorpromazine in schizophrenia. The trial, reported in 1960, confirmed the drug’s efficacy. Therefore, by the start of the 1960s, despite

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26 Casey et al., “Drug Therapy in Schizophrenia,” pp. 210-20. The trial involved 692 patients from thirty-seven Veterans Administration hospitals. The study compared the efficacy of two experimental drugs, chlorpromazine and promazine, with two control treatments, phenobarbital as an active control, and an inert placebo.
having no formal training in psychiatry, Hollister found himself at the very forefront of psychopharmacology.

In 1962, Hollister published two reports on his initial research with psychedelics. The first was a comparison of the state produced by various psychedelic drugs to the schizophrenic state, which found distinct differences. This finding undermined the value of using the drugs to study the origins and manifestations of psychotic illnesses. His second report concerned a small-scale attempt to evaluate the effect of psychedelics on conventional psychotherapeutic interviews. Hollister and his colleagues found that the drugs did produce some improvement in their psychotherapy sessions, however they stressed that the small sample, as well as limitations in their research design, precluded them from reaching any convincing conclusions.

Hollister was highly sceptical regarding the claims of effectiveness for the various forms of LSD psychotherapy that had been reported since the early 1950s. Primarily, he was critical of the lack of scientific rigour behind these claims, writing in his 1968 monograph *Chemical Psychoses: LSD and Related Drugs* that “not one single report...meets the criteria for an adequate evaluation by modern standards of clinical pharmacology,” due to the “absence of controls or random assignment to comparison treatment, failure to use blind techniques,

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28 Leo E. Hollister et al., “An Experimental Approach to Facilitation of Psychotherapy by Psychotomimetic Drugs,” *Journal of Mental Science* 108 (1962), pp. 99-100. A total of twenty-two patients were administered LSD, psilocybin, mescaline, or a placebo during psychotherapy sessions. These sessions were then compared with control interviews with the same subjects, with ratings made of any changes that occurred in therapeutically desirable aspects of the interview, such as increased or decreased insight or rapport.
failure to account for nonspecific factors in treatment programs, and inadequate follow-up procedures.\textsuperscript{29} His criticism went beyond the role of LSD in therapy, to the lack of evidence for the efficacy of the forms of psychotherapy that LSD was supposed to facilitate, such as abreactive or group therapy. Hollister conceded that controlled trials, particularly double-blind trials, were difficult to perform with LSD. Nevertheless, he argued that methodologically sound studies were possible. He also drew attention to the “curious” situation where few LSD psychotherapy researchers had experience evaluating conventional psychopharmacological treatments, commenting, “One might be more inclined to believe claims made by anyone of demonstrated reliability in other areas of clinical psychopharmacology.”\textsuperscript{30} In this judgement, however, he overlooked the fact that as researchers used LSD in a form of psychotherapy, many of them came to the field from backgrounds of psychodynamic, rather than biological, psychiatry. For this reason it is not surprising that they may not have conducted prior drug research.

Hollister and his colleagues set out to bring scientific rigour to the evaluation of LSD in the treatment of alcoholism. However, in doing so they adopted what they described as a “medical” form of treatment, one that apparently assumed any beneficial effects of LSD were inherent in the drug’s action. Seventy-two alcoholics were treated in the randomized double-blind trial, which compared a large 600 microgram (mcg) dose of LSD against the stimulant dextroamphetamine as an active placebo. Results were published in 1969.

\textsuperscript{30} Ibid., pp. 124-125.
Rather than the extensive preparation typical of psychedelic therapy, prior to treatment the patient simply had a discussion with their psychiatrist regarding their drinking problem, designed to minimize guilt over their condition: they were told that their alcoholism was not the result of any “psychological weakness,” but simply that they had “been hooked by an addicting drug.” Following this perspective, the treatment was not conceived as an attempt to address personality problems, but was to be used simply as an “introspective experience.” A rationale for how this experience could aid the alcoholic was not given. Specific preparation for receiving LSD was also almost nonexistent: as the researchers wrote “Within the bounds of medical ethics, patients were given as little concrete information as possible about the drugs to be tested.” In fact, they were not even named.31

The treatment then consisted of merely administering the drugs in a comfortable room, with brief reassurance provided by an attending research assistant when needed. Music was available; however the research assistant made no attempt to guide the session, other than to emphasize that it was for self-examination. At no point—neither in the experiment’s preparation or treatment, nor as part of the general ward procedure—was any psychotherapy given. The whole treatment program was remarkably brief, lasting less than one and one-half weeks from hospital admission to discharge. This time period included all necessary medical detoxification as well as the experimental treatment.32 By comparison, the treatment period in the Spring Grove alcoholism study lasted an average of seven

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32 Ibid., p. 1353.
weeks. With the lack of any active form of therapy in the treatment, it is unsurprising that negative results were found. At the two-month follow-up the LSD patients actually had a significantly greater rate of improvement than the dextroamphetamine patients. However, by the six-month follow-up there was no significant difference between the two groups. A significant dropout rate prevented a fair analysis of results at the twelve-month follow-up point. The researchers interpreted the results as demonstrating the lack of efficacy of this form of treatment.

Hollister and his colleagues did place a caveat on the significance of their findings: they emphasized that the results were only relevant to the treatment method that they tested. Indeed they acknowledged that the concurrent research at Spring Grove involved preparatory psychotherapy and a “therapeutic intervention” during the drug session, which could have an impact on treatment effectiveness. However, they defended their therapeutic method by claiming that they were testing the “original contention” that LSD administration with “little or no specific psychotherapy” could benefit alcoholics. This statement is highly misleading, as the original reports they cite did clearly outline the use of both psychotherapy and guidance during the drug session as important components of treatment. In fact, Hollister and his colleagues even mention this when first

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citing these studies. Therefore, their later claim that the original studies involved "little or no" psychotherapy is completely unsupported. This contradiction is highly problematic, as the later claim makes the report appear deceptive: Hollister and colleagues suggest that their research has disproven the work of the previous researchers, where in fact they tested an entirely different treatment. Whether this was intentional or not, it appears that rather than improving his objectivity, Hollister’s prior experience evaluating conventional psychiatric drugs biased him towards viewing drugs as magic bullet treatments.

Although Hollister’s therapeutic method seems an obvious departure from the established method of psychedelic therapy, treating LSD as a magic bullet treatment was not uncommon: two other clinical trials of LSD in the treatment of alcoholism conducted in the second half of the 1960s also involved no psychotherapy. These trials somewhat more closely resembled psychedelic therapy, as patients received better preparation for their drug session, and the conduct of the sessions was less austere. However, without the critical framework of psychotherapy, these trials can still not be considered as a fair evaluation of the efficacy of psychedelic therapy.

Keith Ditman had been researching LSD since the mid-1950s. His earliest study was a comparison of the effects of LSD with the experience of delirium tremens, which found significant differences.\(^{37}\) Despite this study not being a therapeutic

trial, many of the subjects given LSD reported beneficial effects.\textsuperscript{38} As well as this research, throughout the 1960s Ditman published critiques of LSD psychotherapy research, highlighting the lack of controlled trials, and studied the harmful effects of the non-medical use of LSD.\textsuperscript{39} Ditman and colleagues' LSD and alcoholism trial, reported in 1969, paid some attention to set and setting, with the experiment taking place in an "LSD setting," although the researchers did not explain exactly what this meant. In the double-blind experiment, all patients were expecting to receive LSD, but some instead received the stimulant methylphenidate, or the minor tranquilizer chlordiazepoxide. Results were not measured in terms of the treatments' effects on long term drinking behaviour, but on an analysis of patients' drug sessions for the prevalence of experiences usually deemed therapeutic, such as increased self-understanding. The study found LSD to be no more therapeutic than the two control drugs.\textsuperscript{40}

At the Topeka Veterans Administration Hospital, Kenneth Godfrey had been conducting research with LSD and alcoholics since 1963. Over the mid-1960s Godfrey's method of administering the drug had evolved considerably, as he attempted to find a way to reliably produce a psychedelic reaction. Originally, he administered LSD in a highly clinical fashion: alone, except for a technician, patients were observed through one-way glass while being subjected to


psychological tests. This method resulted in only psychotomimetic reactions. In light of this, Godfrey began to administer the drug in a more comfortable environment, with more supportive company and some music. On the advice of Abram Hoffer, he visited both Sanford Unger at Spring Grove, and Humphry Osmond, by then at the New Jersey Neuropsychiatric Institute, to learn more about their psychedelic therapy method. Following this he gradually adopted the psychedelic method of LSD administration, with patients undergoing their session in a private home-like room, with constant supervision from a supportive nursing assistant, and with music as well as flowers, pictures, and mirrors used to manifest emotive and symbolic experiences. With this method patients consistently achieved the psychedelic experience.41

Despite Godfrey’s clearly psychedelic goal for LSD administration, and his consultation with Unger, Hoffer, and Osmond, his method did not utilize psychotherapy. Regarding psychotherapy, he only mentioned that he had found that classical psychoanalytical interpretations given to patients during their session “fell on deaf ears.” However he found more broadly symbolic interpretations could be helpful. Godfrey gave a passing mention to patients receiving group psychotherapy as part of their background ward treatment, however he did not discuss it as an important part of the LSD treatment. Nevertheless, the results from Godfrey’s research were very promising, although it was uncontrolled, and the results were largely based on subjective impressions from the treatment staff, the patients, and their families. From his enthusiastic

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descriptions of the insights and changes in patients produced by LSD, it is clear that Godfrey was convinced of the effectiveness of psychedelic therapy. While recognizing that more research was necessary, he showed an appreciation for the need to balance rigour with therapeutic method, stating, "The design for such research must be as scientifically precise as possible, but at the same time clinically tenable."\(^{42}\)

Results from a controlled trial of psychedelic therapy at the Topeka Veterans Administration Hospital were published in 1970. While the research was performed at the same location and using the same therapeutic method that Godfrey had developed, his name does not appear on the paper. Instead, William Bowen was listed as the lead author. Two clinical trials were conducted. For the first, forty-one male alcoholic subjects treated with high-dose (500 mcg) LSD therapy were compared with forty patients who underwent only the hospital's standard alcoholic treatment program, which the LSD subjects also underwent. The second trial was similar in design to the Spring Grove studies, with forty-four patients randomly assigned in a double-blind fashion to receive either the high or a low (25 mcg) dose of LSD.\(^{43}\)

The therapeutic method for both trials was the same. Patients were prepared for their LSD session through group lectures, where they were instructed to "go

\(^{42}\) Godfrey, "Metamorphosis of an LSD Psychotherapist," p. 460, 469; Kenneth E. Godfrey, "Evaluation of Psychedelic Drugs as Therapeutic Agents," in Richard E. Hicks and Paul Jay Fink (eds.), Psychedelic Drugs (New York: Grune and Stratton, 1969), pp. 226-233. Over the same years Godfrey was also conducting limited psycholytic therapy research with LSD. This, by its nature, involved extensive psychotherapy, however he does not discuss psychotherapy being a part of his psychedelic therapy research.

along” with the drug's effects, and positive expectations for the treatment were emphasized. A nursing assistant trained for the task supervised the drug sessions. They were there primarily to give intensive support to the patient, and to provide encouragement that they could harness their experience for positive change in their lives. This form of guidance, while more involved than that employed in Hollister's research, still appears to be much less directive than the method employed at Spring Grove, where the therapist more actively worked to shape the patient’s experience. The background ward treatment was composed of lectures, exercises, and other activities designed primarily to improve interpersonal problem-solving skills. No form of psychotherapy was given to the patients in either the LSD or ward treatments, apparently due to “limitations on staff time.” 44 No significant differences were found between the results for the experimental or control groups in either study at the one-year follow-up point. Combining the data from the two studies did not reveal any significant differences between the high-dose patients and either of the two control groups.

Discussing their poor results, Bowen and colleagues recognized that the attitudes of the researchers could have a profound influence on the success of psychedelic therapy. However they felt that it was unlikely that researcher attitudes had negatively affected their results, as they not only were experienced with LSD, but also had held a “favorable view of its value in the treatment of alcoholism.” 45 They now believed that past impressions of effectiveness were due to dramatic personality changes that frequently did appear in patients, but which could

44 Ibid., p. 113.
45 Ibid., p. 117.
ultimately not be maintained after discharge when patients were exposed to the stresses of life. Godfrey certainly had been convinced of LSD therapy’s effectiveness. Whether he took part in this research, and why he was not credited for his part in establishing LSD research at the hospital is not clear. However whether or not this signals any change in the research environment or therapeutic method at the Topeka hospital, it is clear that psychotherapy was never a major element of treatment. Therefore, the results have little relevance in establishing the efficacy of psychedelic therapy.

The clinical trials of LSD therapy for alcoholism led by Milan Tomsovic and Wilson Van Dusen may have involved a limited amount of psychotherapy. Nevertheless, from the limited discussion of this aspect of treatment in their reports, it appears that the researchers did not consider psychotherapy an integral part of treatment. Tomsovic’s study at the Sheridan Veterans Administration Hospital, Wyoming, was the only non Spring Grove trial to return a somewhat ambiguous result. Patients in the study were prepared for LSD treatment through a lecture and readings designed to reduce apprehension. The treatment then consisted of a single 500 mcg LSD session, administered in a comfortable room with music and visual stimuli available. A nurse was present during the session, however they did not attempt to direct the patient’s experience, but instead simply provided support when needed. The day after their treatment the patient spent one hour discussing their experience in their “regular therapy group.” 46 The study compared the results for 52 volunteers for

LSD therapy from the hospital’s Alcoholic Rehabilitation Program, against the results from two control groups: a further 45 patients who also volunteered for LSD, but were later randomly assigned to undergo only the unit’s standard treatment program, and data for 123 patients from a separate ongoing follow-up study of the success of the Alcoholic Rehabilitation Program. Despite the mention of patients having a regular therapy group, it is not clear to what extent any patients in the study received psychotherapy.47

The researchers conducted follow-up evaluations at three, six, and twelve months after discharge. At each point, results trended in favour of LSD therapy in terms of patients’ drinking behaviour. However, the results were only statistically significant at twelve months, and then only between the LSD treatment group and the LSD volunteer control group. This result was significant at the high p 0.01 level of significance. However, as the results for patients who underwent the hospital’s standard alcoholic treatment program after volunteering for LSD were significantly worse than those for patients who routinely went through that same program, the researchers concluded that being offered and then denied LSD had a detrimental effect on the patients. On this basis, patients denied LSD after volunteering did not represent a fair control group, and the results of treatment were best compared with the study of the program’s normal effectiveness. Here the results were not statistically significant. The researchers did propose an alternative interpretation: those who volunteered for LSD may have been patients who were best suited for drug

47 Ibid., pp. 935-937. The standard treatment routine of the hospital’s Alcoholic Rehabilitation Program is not described in the report. It was likely similar to the milieu treatment programs that were the background ward conditions in many of the other studies, as described in this chapter.
treatment. The volunteers were observed as engaging poorly with the routine treatment program, as they were holding out for LSD. Therefore, the significant difference between the results for the LSD patients and volunteer controls may have shown efficacy within a specific subgroup of patients, with the background treatment program having little influence on their rates of improvement. Nevertheless, the researchers appeared to favour the former analysis.48

Psychologist Wilson Van Dusen and colleagues at the Mendocino State Hospital, conducted a clinical trial that tested a therapeutic method that most closely resembled the psychedelic therapy method of the Spring Grove and original Canadian researchers. The California Department of Mental Hygiene funded the trial, and results were published in 1967. Van Dusen was familiar with the psychedelic experience. In 1961 he had published an account of his exploratory research with LSD in Psychologia, entitled “LSD and the Enlightenment of Zen,” in which he compared the experiences of some LSD subjects to the state of satori in Zen Buddhism. He described this state as a “central human experience” that could forever alter the subject’s life, as it deepened the “very root of human identity.” Van Dusen had himself had this experience under LSD, and he described soaring “into paradise” where he saw the “structure of the whole of things...beyond time and space to the eternal unchanging One who was at the same time the whole of changing creation.” He had found that it normally took several LSD sessions for a subject to reach satori, and that it usually emerged

48 Ibid., pp. 941-948. At twelve months 44 percent of the LSD patients were completely abstinent, compared to 11 percent of the volunteer controls, and 31 percent of the standard treatment controls. These results were for nonschizophrenic patients. Schizophrenic patients who were not acutely psychotic had not initially been excluded from the study. However the researchers soon found that LSD therapy had a negative effect on these patients, therefore they considered the results for nonschizophrenic patients separately.
after the “individual finds the core of his identity and finds he can afford to give it up in psychological death.”

Van Dusen’s clinical trial of LSD in the treatment of alcoholism was an attempt to confirm the positive results of Canadian researchers Ross MacLean and Colin Smith. As well as criticising the lack of controls in their research, Van Dusen and his colleagues expressed scepticism of the role of the LSD session in the impressive results of MacLean’s study: those patients had apparently been chosen for their good motivation and support networks, and were given extensive social and vocational support outside of the reported treatment framework. Van Dusen and colleagues had learned this from personal communication with MacLean’s colleague Alfred Hubbard. The Mendocino trial was originally designed as double-blind, with scopolamine as an active placebo. However, the blind had proved impossible to maintain, therefore the researchers abandoned this design. Instead, results for the LSD patients were compared with those for patients who had undergone the hospital’s standard alcoholic treatment program just prior to the beginning of the experiment. All patients were female. The average dose of LSD used was 400 mcg. Before treatment, patients were rated as to their prognosis, based on factors such as marital status, motivation, and economic resources, and assigned to one, two, or three LSD

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sessions, with a poorer prognosis resulting in more sessions. A total of seventy-one patients went through the LSD treatment.

Few details of the therapeutic framework surrounding the LSD sessions appear in Van Dusen’s report. The patients resided in the hospital’s alcoholic unit, described as a “small therapeutic-community-like setting” with “various social activities” and work assignment. Patients were also assigned, or often chose, a staff member who “worked with them before, during and after the experience.” These staff members were male psychotherapists and female psychiatric technicians. The nature and extent of the “work” that these staff members did with the patients is not described; therefore it is not entirely clear whether or not the patients received psychotherapy. However, the lack of discussion of this aspect of treatment strongly suggests that if there was any psychotherapy, it was not extensive and the researchers did not consider it critical to the LSD treatment process. Preparation for the LSD session was both informal and formal: patients learned what to expect from other patients who had already undergone treatment, as well as from the investigators. They were “vigorously counselled to cooperate with the experience,” rather than try to resist the drug’s effects. The researchers recognized that “the subject’s emotional state and the setting of his experience is a critical factor in outcome,” and claimed to use the drug “as a facilitating agent in a therapeutic setting.” Therefore, it seems that the researchers understood some of the unique aspects of psychedelic therapy, yet still viewed it as a magic bullet treatment: they realized that it was a

52 Ibid., p. 297, 296.
particular drug experience, rather than merely the drug’s administration, that could be therapeutic, however they still assumed that this experience was therapeutic in itself, rather than as part of a psychotherapeutic treatment.

The LSD sessions were conducted with groups of up to four patients. The researchers chose this format for pragmatic reasons: Mendocino State Hospital admitted 1600 alcoholic patients annually, therefore time-consuming individual treatment was not practical. While more than one patient was present in the treatment room, each patient had their own therapist and some privacy was provided by cloth room dividers. The setting was typical of psychedelic therapy: a comfortable, dedicated room, with visual and auditory stimuli. Where the treatment session varied most from psychedelic therapy was in its conduct: rather than the experience being carefully guided by the therapists, “The day belonged to the subjects” who were free to spend their time how they wished. The therapists only interacted with the patients when requested to. Although music was played during the session, from the report it appears that it was merely in the background, rather than carefully and individually tailored to heighten and direct the experience. The researchers reported that the subjects spent most of their time in quiet contemplation. Some dwelt on issues such as relationships and the meaning of life, however “Rarely did they examine drinking.” In the days following the session, the patients “worked through” their experience with their therapist.53

53 Ibid., p. 299.
Van Dusen did not provide a therapeutic rationale for the conduct of the LSD sessions in his clinical trial. However, in his previous report of using the drug with experimental subjects, he had expressed his opinion that the LSD reaction was best left to guide itself, stating that there “is an inner wisdom to the LSD reaction that is better without my intervention...this way subjects learn along their own lines at their own pace.” It would seem that he carried this view over into the drug’s therapeutic use, believing that with some preparation and a comfortable setting, the drug could produce an experience that was intrinsically therapeutic.

After treatment, the LSD patients were rated as to their drinking behaviour and social adjustment at six, twelve, and eighteen-month follow-up points. Follow-up for the control patients was only conducted at eighteen months; therefore results were not available at the six-month point, at which the Spring Grove researchers had had their greatest success. At eighteen months there were no significant differences between the LSD and control groups on ratings of drinking behaviour or social adjustment. Pre-treatment ratings of prognosis, the number of LSD sessions administered, measured demographic factors (such as age and duration of alcoholism), and ratings of the nature of the patients’ drug experiences, also appeared to have had no influence on results.

Analysing the significance of these results requires taking into account further considerations. Controlled trials test whether the apparent benefits of a

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54 Van Dusen, "LSD and the Enlightenment of Zen," p. 11.
55 Van Dusen et al., "Treatment of Alcoholism with Lysergide," pp. 300-301.
treatment are indeed due to the treatment, or whether they are merely produced by chance or a placebo effect. The statistical significance of results does not reveal how effective a treatment is, but merely whether any benefits are genuine. Therefore, it is important to consider not only the comparative efficacy of the treatment and control conditions, but the degree to which patients were actually benefiting from treatment, regardless of what caused this benefit. Unfortunately detailed results were not provided in Van Dusen’s report, however average improvement rates for the LSD group appear to have been low. At each follow-up point, patients were rated as to changes in their drinking behaviour on a scale where a score of three indicated no change, and a score of four indicated improvement. These scores were then averaged for the group. The score for the LSD group reached its highest level at the eighteen-month follow-up, however it was still only 3.97—trending towards improvement, but on average insufficient to be classified as improved.56 While it is difficult to accurately compare these results to those from other studies, given the different rating systems, a superficial comparison with the average improvement rates from the Spring Grove alcoholic study suggests those patients benefited much more significantly: on a drinking behaviour rating scale from one to ten, with a score of one signalling daily drinking, and ten signalling total abstinence, high-dose LSD patients had improved an average of 3.82 points at the eighteen-month follow-up.57 Van Dusen’s averaged results do not mean that no patients improved: such a middling average score could result from individual scores ranging widely from worsened (as score of two), to much improved (a score of five). However the fact

56 Ibid., p. 300.
that the researchers only expressed their results in this manner suggests that they saw no significance in the variation of individual scores, or the totals for each category of results.

The researchers recognized that their treatment results were not as positive as those of the original Canadian researchers. They suggested that this could have been because “we were already so successful with these women that there was no room for improvement.” However this does not seem to be a convincing explanation: at eighteen months the control group was only just rated as improved, with an averaged score of 4.03. Furthermore, the whole reason that psychedelic therapy had seemed remarkable to researchers was that there was no particularly effective treatment for alcoholism. If the Mendocino researchers had developed a successful milieu treatment for alcoholism, it surely would have seemed unfair to not only use this as a control treatment, but as the backdrop to the experimental treatment. Ultimately, whether the poor results were due to the lesser emphasis on preparatory psychotherapy, the lack of guidance during the LSD session, or some unknown factor in the backdrop or conduct of the study, is not clear. Nevertheless, the results suggest that differences in the treatment method utilized in the Van Dusen study, compared to those used in the studies of Kurland and the original Canadian researchers, had a significant impact on uncontrolled ratings of treatment effectiveness. Van Dusen and his colleagues seem to have used the controlled trial methodology to demonstrate that an apparently ineffective treatment was indeed ineffective.

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The foremost challenge to the significance of the Spring Grove research came from a clinical trial of LSD in the treatment of alcoholism conducted by Arnold Ludwig and Jerome Levine, at the Mendota State Hospital, Wisconsin. This trial was particularly important for several reasons: it was the only trial to expressly use psychotherapy as part of the tested treatment, it had the most sophisticated design and the largest number of patients, results were extensively analysed and published in a significant monograph, and it received a major award from the American Psychiatric Association. Also of great significance was the fact that since 1964, Levine, when not conducting his own research, had been employed by the National Institute of Mental Health's (NIMH) Psychopharmacology Service Center to oversee LSD research in the nation. By the time of the publication of Ludwig and Levine’s final results in 1970, Levine had taken over as chief of the NIMH psychopharmacology unit, now renamed the Psychopharmacology Research Branch. Therefore, the attitudes towards LSD therapy and research expressed in Ludwig and Levine’s reflected the official outlook of the NIMH.

Ludwig and Levine were highly sceptical of the positive reports of psychedelic therapy's efficacy from uncontrolled studies, so they attempted to evaluate the claims in a scientifically rigorous manner. However, although their therapeutic method involved psychotherapy, it still differed significantly from the psychedelic therapy method. The researchers invented a new and unique LSD therapy, which under scrutiny showed negative results. That the NIMH official responsible for LSD research could not appreciate the importance of exactly

replicating the therapeutic method of psychedelic therapy for an accurate
evaluation of its efficacy, strongly suggests that the Spring Grove researchers had
little hope in distinguishing their studies from those with different methods.
Given the great significance of this research, a detailed analysis of its
development, design, and results is necessary.

Ludwig and Levine had first begun working with LSD in 1962, at the US Public
Health Service Hospital for narcotic drug addicts in Lexington, Kentucky. There
they developed a treatment combining LSD with hypnosis—”hypnodelic
therapy”—to treat narcotics addicts, and later, alcoholics. Their impetus for
investigating LSD came through frustration at the ineffectiveness of the
hospital’s normal psychotherapeutic treatment, and anecdotal reports from
colleagues that a few patients who had been given the drug in a non-therapeutic
experiment had claimed the experience changed their outlook on life and values
in a positive direction, away from drugs. A literature review confirmed that many
researchers had claimed this kind of therapeutic effect for LSD. Ludwig and
Levine therefore decided to systematically investigate whether the drug could
benefit their patients. However in doing so, the researchers did not model their
therapeutic method on that of the researchers who had claimed success in
treating alcoholics, such as Hoffer and Osmond, and MacLean and Hubbard.
Instead they developed their therapy based on their own conceptions of how
addiction could be treated. Indeed they founded their method on a dismissal of
the role of the psychedelic experience in therapy: “we could not see much
therapeutic benefit being derived from the illusions, hallucinations, or nirvana-
like feelings which frequently accompany administration of the drug.” Instead, the researchers believed that in order for a treatment to be effective,

> it would be necessary to control the LSD experience and divert or channel whatever therapeutic potential it might possess toward the more conventional notions of psychological therapy, such as directing the patient’s attention to his present problems and trying to get him to understand them in terms of his previous conflicts.\(^\text{60}\)

Ludwig had been experimenting with hypnosis, and he considered that it could be a good tool for directing the LSD experience in such a way.\(^\text{61}\)

Hypnodelic therapy involved hypnotising the patient in the period between LSD administration and the onset of its effects. During this stage the therapist established a stronger than usual bond with the patient, and gave suggestions that the treatment provided a new chance for insight and improvement. Once the patient was under the effects of the drug, the therapist conducted a two-hour session along the lines of conventional psychodynamic therapy, but with increased depth, suggestibility, and intensity. Emphasis was placed on recalling and reliving past traumatic events, and comprehending negative dynamic processes. After the session the therapist lifted the hypnotic trance and transferred the patient to an overnight room. There patient remained there alone, except for periodic checks by a nurse, for the rest of the drug’s period of action (another eight to ten hours). The therapist encouraged the patient to use

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61 Ibid., pp. 130-131.
this time further think through the issues discussed during the session and possibly write up the experience.\textsuperscript{62}

In 1965 Ludwig and Levine published the results of a controlled pilot study of hypnodelic therapy in the treatment of narcotics addiction. The trial was not double-blind, but randomly assigned seventy patients between five treatment groups: brief psychotherapy, hypnotherapy, hypnodelic therapy, LSD administration plus psychotherapy, or LSD administration without psychotherapy.\textsuperscript{63} Results revealed that hypnodelic therapy was significantly more successful than the other treatments. However, as the follow-up tests were performed while the patients were still hospitalized, they did not test abstinence from drugs or life adjustment, but therapeutic effect on psychopathology.\textsuperscript{64} This trial provided the formula for the later alcoholic trial: a controlled comparison of various combinations of LSD, hypnosis, and psychotherapy. The major changes lay in the population, follow-up period, and sophistication in testing for therapeutic result.

Ludwig and Levine had both been working at the Lexington Public Health Service hospital as part of a draft deferment scheme that saw them owe two years of service to the PHS on the conclusion of their medical residency. At the end of Levine’s service in 1964, Jonathan Cole of the NIMH’s Psychopharmacology Service Center hired him for the task of “stimulating, supporting and consulting

\textsuperscript{62} Ibid., pp. 134-135
\textsuperscript{63} Arnold M. Ludwig and Jerome Levine, "A Controlled Comparison of Five Brief Treatment Techniques Employing LSD, Hypnosis, and Psychotherapy," \textit{American Journal of Psychotherapy} 19 (1965), pp. 423-424. On volunteering for the trial patients were told they might receive an “experimental” drug but were not given its name nor told its effects.
\textsuperscript{64} Ibid., pp. 431-434
on the development of studies which would evaluate the usefulness of LSD or LSD-like agents as treatments in psychiatry.” Cole had been under increasing pressure to assess whether or not there was any truth to the claims from various researchers that LSD was therapeutically useful. Levine’s experience, as well as his interests in both chemistry and psychology, made him appear ideal for the task. As well as consulting with LSD researchers such as those at Spring Grove, Levine fulfilled his role by continuing his collaboration with Ludwig, who had moved to Mendota State Hospital. There they had the opportunity to more thoroughly explore the efficacy of their therapeutic techniques with alcoholic patients.

Ludwig and Levine, joined by research analyst Louis H. Stark, approached the task of assessing the efficacy of LSD psychotherapy with great scepticism of all the research that had gone before them. Like Kurland and Unger had, they drew attention to the lack of sophistication in the design of clinical trials that reported on LSD’s therapeutic effectiveness, describing them as “poorly controlled and lacking in scientific rigor.” As well as the absence of control treatments, they judged previous trials as inadequate to assess efficacy due to their small patient samples, and short follow-up periods. Furthermore, the Mendota researchers expressed suspicion over the objectivity of those researchers who had claimed successful treatment with the drug, commenting that “therapeutic claims for this drug have been more of the nature of religious testimonials or statements of

clinical conviction than cautious scientific observations and interpretations.”

However, they claimed to maintain a balanced perspective, recognizing that a poorly designed trial did not equate to a poor treatment: while a “sceptical attitude was justified,”

Given the impotency of current treatment procedures for alcoholics and the magnitude of the problem, it seemed wise to pursue and investigate any treatment approach which might offer help, even though the approach be viewed as radical, unconventional or untested.

The researchers set out to right the wrongs of previous studies. The stakes were high as “If the glowing claims for LSD could be substantiated, the drug would indeed revolutionize psychiatric treatment,” but the “proof will only be forthcoming through an impartial arbitor, known as scientific method, which makes no compromise with bias, regardless of its source.”

The study took place in the Alcoholic Treatment Center of the Mendota State Hospital over four years, with results published in 1970. The experimental treatments were given against a background of the centre’s normal procedure: after having recovered from withdrawal at the hospital, patients were admitted for thirty days where they underwent “milieu therapy” consisting of “five community-therapy meetings per week, group counseling, instructional lectures and films, Alcoholics Anonymous meetings, and opportunities for individual counseling.”

A total of 176 male patients took part in the study. The researchers reasonably concluded that a double-blind trial was impractical with

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68 Ibid., p.5
70 Ibid., p.71
LSD, so again decided on a controlled comparison method. Patients were randomly assigned to one of four treatments, with an equal number of patients in each treatment; half of each treatment group was also randomly assigned to receive Antabuse on discharge, a drug that causes severe nausea when alcohol is consumed. Thirteen psychiatrists administered the treatments, seven of whom were second or third year psychiatric residents. All were volunteers who were trained in hypnosis and LSD administration by Ludwig through “extensive reading material” and “demonstration sessions.”

In lieu of the double-blind, the researchers attempted to minimize a bias towards the experimental treatments by withholding information regarding the nature of the trial. They told patients that they would receive one of four treatments involving, either alone or in combination, LSD, hypnosis, a “contemplative session,” and Antabuse. However, they were not told that it was an experimental comparison, but instead that the most appropriate treatment for their condition would be chosen. The researchers provided the patients with only basic information regarding LSD, and neither the patient nor psychiatrist knew which treatment was going to be used until just prior to the session. In order to control for therapist skill, psychiatrists were given an equal number of patients from each treatment group.

The four tested treatments were hypnodelic therapy, psychedelic therapy, drug therapy, and milieu therapy. The Wisconsin researchers’ form of psychedelic

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71 Ibid., pp. 84-85, 80.
72 Ibid., pp. 74-76, 87, 164.
therapy was essentially the same as hypnotelic therapy, but without hypnosis: LSD plus conventional psychotherapy focusing on the patients’ major problems.

The other two treatments were different forms of control treatments. Drug therapy was the administration of LSD without psychotherapy. This controlled for the role that psychotherapy played in the effectiveness of either of the two LSD psychotherapy treatments. Milieu therapy involved no drugs or psychotherapy, but a period of “contemplation and meditation” alone, where the patient was told to think hard about their problems and make plans for the future. This gave a baseline assessment of the efficacy of the hospital’s standard treatment procedure, against which the results of the experimental treatments could be compared. All treatments took place in an “ordinary clinical office setting” and lasted approximately three hours, after which the patient was placed in an observation room overnight. The dose of LSD for the three drug treatments was 3 mcg per kilogram of body weight.\textsuperscript{73}

Prior to all treatments, patients went through a two-hour psychiatric interview with their assigned therapist in order to gather personal information on which to base any psychotherapy. This brief preparation contrasts significantly with the established technique of psychedelic therapy, where weeks of psychotherapy prepared the patient for the drug session. Therefore, although two of the tested treatments involved LSD and psychotherapy, they had little in common with the psychedelic therapy method established in the 1950s, which focused on attaining the psychedelic experience through the manipulation of the patient’s “set and

\textsuperscript{73} Ibid., pp. 46, 87-89.
setting” by the therapist, who acted as a supportive guide throughout the entirety of the drug’s period of action.

Social workers blind to the patients’ treatments performed the patient evaluations. They assessed patients with a battery of tests—a total of five used in different combinations at different times—prior to the first therapist meeting and prior to discharge, and then at three, six, nine, and twelve months after discharge. The tests rated patients on aspects of personality, psychological health, drinking behaviour, and social adjustment. They also interviewed a relative of each patient prior to treatment and at six and twelve months. The successful follow-up rate was remarkably high for this category of patients—ranging between 88 and 96 percent, with the highest rate achieved at twelve months.74

Ludwig, Levine, and Stark extensively analysed the data from the follow-up assessments to determine any statistical significance in the improvement rates of the four treatments. They found that although all four groups showed significant improvement in most areas of assessment, none of the LSD treatments produced significantly different results than the control treatment. They also analysed the influence of thirty-six different variables on the success of treatment. These variables included the patients’ marital status, age, whether or not their therapist had finished residency, motivation for improvement, pre-treatment personality assessment, and number of admissions to the hospital. The variables seemed to

74 Ibid., pp. 81, 90-96
have no significant impact on results. Antabuse was also judged as ineffective.\textsuperscript{75}

Lastly, the researchers took into account how treatment success related to patients’ subjective experience of their LSD session. Reports showed that, among other measures, 65.6 percent enjoyed the experience, 8.4 percent had a “mystico-religious” experience, and 47.3 percent reported positive benefits. No statistically significant variation was found in the distribution of these factors between the treatments, and they appeared to have no significant influence on treatment outcome.\textsuperscript{76} The researchers were confident enough in their methodology and the comprehensiveness of their study to state that their negative results produced such “inescapable conclusions about the purported efficacy of LSD for the treatment of alcoholism as to preclude any further investigation, at least as far as evaluating the usefulness of the particular techniques used in this study.”\textsuperscript{77}

\textbf{Debating Design: Scientific Rigour and Therapeutic Method}

Assessing the variety of LSD psychotherapy research being conducted in the United States in the late 1960s, the Spring Grove researchers emphasized the critical significance of therapeutic method to results. In reporting on the results of their alcoholic trial, the researchers dismissively categorized the method of Hollister as “psychedelic chemotherapy,” a treatment with minimal psychotherapy where “the major emphasis was on the administration of the drug

\textsuperscript{75} Ibid., pp. 128-145
\textsuperscript{76} Ibid., pp. 101, 142.
\textsuperscript{77} Ibid., p. 9.
itself.” The report did not mention Ditman and Bowen's work, but their methods could easily have been included under the same rubric. The Spring Grove researchers’ emphasis on achieving the peak experience and the importance of psychotherapy made their method so “distinctly different” that the consistently negative results of psychedelic chemotherapy were irrelevant. In this published report, they made only passing mention of Ludwig, Levine, and Stark’s research, discounting it as simply a modification of psychedelic chemotherapy. While this appears to be the Spring Grove researchers only published critique of the other clinical trials, in an unpublished review from 1971, Charles Savage gave a detailed, scathing account of the Mendota research, based on its deviation from the theory and method of psychedelic therapy. Who this review was distributed to, and why it was not published is not clear. However, it is clear that by this time the Spring Grove researchers had come to see Ludwig, Levine, and Stark’s research as a great threat to the significance of their own results, and to the future of LSD psychotherapy research. Savage described Ludwig, Levine, and Stark’s research as a “disservice to science and the alcoholic.” Instead of establishing the scientific method as an “impartial arbiter,” Savage saw the clinical trial as representing “bias in, bias out,”

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78 Kurland et al., "LSD in the Treatment of Alcoholics,” p. 84. The Spring Grove researchers also described the work of Canadian researchers Reginald Smart and F. Gordon Johnson as psychedelic chemotherapy. Like their counterparts in the United States, in the mid-1960s these researchers challenged the work of the early Canadian psychedelic therapy researchers by performing controlled trials of a treatment method that differed significantly from psychedelic therapy. As well as incorporating little or no psychotherapy, these researchers restrained their patients to their beds. See R. G. Smart et al., *Lysergic Acid Diethylamide (LSD) in the Treatment of Alcoholism: An Investigation of Its Effects on Drinking Behaviour, Personality Structure and Social Functioning* (Toronto: University of Toronto Press, 1967); F. Gordon Johnson, "LSD in the Treatment of Alcoholism," *American Journal of Psychiatry* 126, no. 4 (October 1969), pp. 481-87. Unfortunately, the Spring Grove reports did not comment on the research of Van Dusen and colleagues, whose therapeutic method most closely resembled their own.

79 Kurland et al., "LSD in the Treatment of Alcoholics,” p. 84.
What makes the work unscientific is that they make not the slightest effort to replicate the works that they are attacking except by employing the same name, psychedelic...The point is not whether or not the psychedelic hypothesis is correct, but that they made no effort to test it.\textsuperscript{80}

Savage emphasized that Ludwig, Levine, and Stark had shown a firm understanding of the theory and method of psychedelic therapy in their review of previous research. They had described its goal of producing a transcendental experience through intensive patient preparation and the use of visual and auditory stimuli, which could promote positive changes in the patient in a similar manner to a conversion experience. Yet their form of psychedelic therapy employed minimal preparation, a brief, conventional, insight orientated psychotherapy session, little regard to “set and setting” and an anti-mystical focus. Hypnodelic therapy used hypnosis to improve control over the LSD session, but did not fundamentally alter the treatment. In essence both treatments involved a single session of psycholytic therapy. However that form of therapy usually involved numerous LSD sessions over a extended period of time, and, as Savage stated, “I know of no one who has ever claimed that a single psycholytic session was curative of anything, least of all alcoholism.” It is questionable whether Ludwig, Levine, and Stark could have themselves expected their treatment to be successful: Savage quoted their statement that with alcoholism, “All forms of insight orientated therapies ...have been employed with equivocal or inconclusive results being obtained at best.” In their monograph, the Wisconsin researcher even acknowledged—although only in passing—that their form of psychedelic therapy was not the mystically orientated treatment that the

name usually referred to. They explained that their use of the term was "primarily for convenience." This led Savage to accuse the researchers of designing an intentionally deceptive clinical trial: "It is apparent that they rejected the psychedelic model on moral grounds while pretending to test it." Savage argued that in addition to being misleading and ineffective, the Mendota researchers’ therapeutic method was intentionally antitherapeutic. He believed that after their early positive research, as "LSD fell out of favor and positive results [became] politically unwise," they “loaded the dice in favour of the null hypothesis.” Where they had originally found success performing the therapy themselves, after having a personal training session with LSD, they now used inexperienced therapists who were denied a personal experience with the drug. Furthermore, Savage argued that elements of the researchers’ therapeutic method seemed deliberately unpleasant. He highlighted that the Mendota researchers’ practice of placing patients alone in an observation room for the majority of the drug’s period of action was “considered contraindicated and antitherapeutic by most other workers in psychedelic research.” At the American Psychological Association’s third “Research in Psychotherapy” conference in 1966, Ludwig had described this post-therapy observation room as the “cooker,” which had led Savage to comment that the treatment “was not an experience that I suspect he would care to have had himself.”

83 Savage recounts Ludwig’s description of his method at this conference in, Hicks and Fink (eds.), *Psychedelic Drugs*, p. 51. The description is not included in the Ludwig’s paper in the conference proceedings, see Arnold M. Ludwig, "Relationship of Attitude to Behavior: Preliminary Results and Implications for Treatment Evaluation Studies," in John M. Shlien (ed.), *Research in*
reported that two-thirds of their patients had “pleasant reactions,” and that 47 percent claimed that the experience had been beneficial. However the researchers also commented on a peculiar finding in their analysis of readmission rates for the study participants: while proportionately fewer LSD patients than milieu treatment patients were readmitted to Mendota State Hospital during the follow-up period, when other local institutions were included the total number of readmissions were equivalent for the two groups. They concluded that “patients may have avoided Mendota State Hospital to preclude the possibility of additional therapy with LSD.”

Ultimately, Savage argued that the antitherapeutic nature of the Mendota researchers’ treatment was evident in their results:

What is striking about the study is not the low incidence of mystical experience since the very nature of the design programmed them out, but the appallingly low remission rate in all categories. By 6 months, between 70 and 80% of their patients in all categories were drinking, and by a year, between 80 and 90%. One would have expected from the Hawthorne effect alone that the result would have been a little better than that. One can only conclude with the Truax that therapy is for better or worse and that at Mendota State Hospital it is by and large for worse.

In another unpublished review of Ludwig, Levine, and Stark’s study, the Spring Grove researchers contrasted the eighteen-month results in the two trials: 22.2 percent of the Spring Grove high-dose LSD patients had maintained complete sobriety, compared to only 6.8 percent for the Mendota patients. They also

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emphasized that “morale at Spring Grove was (and is) enthusiastic and each patient looked forward to his treatment; in addition, most patients have stated a willingness for a repeat session if indicated.”

In an attempt to pre-empt critiques of their therapeutic method, Ludwig, Levine, and Stark had argued that although only 8.4 percent of their patients had a mystical experience, their data showed that there was no significant correlation between the “peak” response and therapeutic outcome. They had also defended their minimal patient preparation on the basis that “virtually all patients seemed sufficiently prepared so as to experience the panoramic, spectacular effects of this drug without marked adverse reactions,” and on the positiveness of patients’ accounts of their experiences. However Savage pointed out the false logic in this assertion, comparing it to “justifying surgery on the basis that the patients did not bleed to death.”

Ludwig and his colleagues responded in kind, although their criticisms targeted only the Spring Grove alcoholism study. Despite the Spring Grove researchers’ attempt to design an adequately controlled clinical trial that appreciated the unique theory and method of psychedelic therapy, the Mendota researchers questioned their evaluative method: Ludwig and his team criticised their lack of

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87 Walter Pahnke et al., untitled manuscript, 22 June 1971, folder 25, box Addition 2, Savage Papers. Nine members of the MPRC psychedelic research team signed this review, and while essentially covering the same critique, it was written in a much more restrained tone to Savage’s review. This suggests that it could have been intended for publication, however again there is no evidence of its actual or intended dissemination.


a non-drug control, and also a possible non-therapy drug control. During the course of the Spring Grove trial, Levine had frequently visited the researchers as chief of the Psychopharmacology Research Branch of the NIMH, and in retrospect Savage wondered, “why he permitted some of the now obvious defects to remain uncorrected, unless he wished to give us plenty of rope.” In their final report, the Spring Grove researchers recognized that a non-drug control would have been useful. However, including a non-therapy drug control was a more complex issue. As public policy scholar Rick Doblin has argued, if Kurland and colleagues believed that their patient preparation and extensive psychotherapy was necessary to ensure safety and efficacy when administering LSD, giving the drug without these measures would be unethical.

Ludwig, Levine, and Stark were also dismissive of the Spring Grove results, stating that, “At the six-month evaluation, high-dose patients did not show significantly different amounts of drinking than low-dose patients when differences in other prognostic factors such as marital status were taken into account.” This opinion, apparently based on “currently reported results and informal communications,” seems very unfair, if not misleading. In their final 1971 report, Kurland and colleagues had acknowledged that randomization had failed to control some important variables, however they also stressed that the groups were matched on “IQ, age, occupational status, and most importantly, on

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91 [Savage], unpublished manuscript, p. 10.
92 Richard Elliot Doblin, “Regulation of the Medical Use of Psychedelics and Marijuana,” (PhD diss., Harvard University, 2000), p. 244.
the pre-treatment rating of abstinence.” They also emphasized that the great success of the low-dose group suggested that this group’s patients had not been predisposed towards treatment failure. Therefore, although they took the idea into account, the Spring Grove researchers did not decide that the uneven variables, such as marital status, accounted for the significant difference in drinking behaviour at six months. Nor did they have the data needed to thoroughly assess this proposition.

Ludwig, Levine and Stark were not the only critics of the Spring Grove research. At Hahnemann Medical College’s 1968 Psychedelic Drugs conference, Carl Salzman, of the Early Clinical Drug Evaluation Unit of the NIMH’s Psychopharmacology Research Branch, had presented a critique of controlled research with psychedelic drugs. His critique of the Spring Grove alcoholic trial, based on preliminary results, focused on flaws in the design of its control condition. Salzman recognized that the low-dose LSD treatment may have been an unintentionally effective treatment, and that without a second non-LSD control treatment the efficacy of neither high nor low-dose treatments could be properly assessed. However he also downplayed the positive elements of the results:

These results are further corroboration of earlier efforts: all patients in an LSD treatment program initially improved when compared on pre-post [treatment] measurements, and no differences were ultimately observed between treatment and control groups.  

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95 Carl Salzman, "Controlled Therapy Research with Psychedelic Drugs: A Critique," in Hicks and Fink (eds.), Psychedelic Drugs, p. 28.
Salzman then criticised the design of the Spring Grove researchers’ analysis of the relationship between profoundness of drug reaction and treatment results, regardless of dosage. He described the use of therapist ratings to assess the intensity of patients’ experiences as a “serious methodological problem,” arguing that this introduced the potential for biased ratings, and that objective observers should have been used instead. Savage strongly objected to this critique, arguing that this was a simple assessment where there was minimal risk of bias creeping in. Salzman, however, was not convinced.96

Discussing a number of other LSD therapy trials, Salzman’s analysis continued to focus on scientific design. While he gave limited descriptions of the treatment methods tested in the trials, he did not speculate on how extrapharmacological factors may have influenced outcome. He described Ludwig and Levine’s trials as “well designed” and as representing “further progression along the controlled psychedelic treatment scale.”97 In fact, seemingly supporting their treatment method, he praised their incorporation of patient preparation, the suggestions for positive expectations of outcome given to patients, and the central place of the patient-therapist interaction in the study. Summing up the results of all research conducted so far, Salzman concluded that the specific efficacy of LSD therapy had not been established. Salzman claimed that his critique represented his views as a psychiatrist and researcher, rather than as a NIMH official. However, with his critique so closely aligned with Levine’s, it is clear that at the

96 Hicks and Fink (eds.), *Psychedelic Drugs*, pp. 43-44.
NIMH issues of research methodology took precedence over issues of treatment methodology in clinical trials.

Despite the significant flaws in Ludwig, Levine, and Stark’s therapeutic method, the wider psychiatric community judged the trial on the scientific rigour of its design. In 1970 the American Psychiatric Association granted the study the prestigious Hofheimer Award, for “developing a technique for administering a complex but precisely defined schedule for LSD treatment of chronic alcoholic patients, a method for studying it under controlled conditions, and for evaluating the clinical outcome in both qualitative and quantitative terms.”

For psychiatrists who were not sensitive to the unique theories of psychedelic therapy, the Mendota researchers’ method would have indeed seemed watertight, and the inadequacies in therapeutic method would have gone unnoticed. In addition, in a discipline that was striving to solidify its scientific basis, a critique based on a lack of mystical focus would have seemed absurd. Although the Spring Grove research was also performed on a large scale and attempted to provide a sophisticated controlled analysis of efficacy, it could more easily be ignored as it provided only inconclusive results that on the surface suggested a lack of long-term effectiveness. The problems with the trial’s design that led to this situation could easily be overlooked.

In the mid-1960s, six research groups had set out to systematically evaluate claims of the effectiveness of psychedelic therapy in the treatment of alcoholism. For the Mendota researchers, whether or not elements of their trial were

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intentionally antitherapeutic, it seems that their biases against the theory of psychedelic therapy left them unwilling adopt its method. They instead favoured a method that clung to traditional forms of psychotherapy. Hollister's research seems similarly shaped by his biases. His experience in psychiatric research had been biologically orientated, as he had primarily evaluated the efficacy of chemotherapeutic agents. He therefore treated LSD as a similar magic bullet drug, assuming that its therapeutic effect was inherent in its action.

Why the research led by Ditman, Bowen, Tomsovic, and Van Dusen took the direction it did is less clear. Bowen cited a lack of staff time for the absence of psychotherapy in his study. This may have been a factor in the other studies. Psychedelic therapy was a very labour intensive treatment, and it may have been that the other researchers simply did not have the resources to implement the psychotherapy component of treatment. However, given that these researchers did not acknowledge how their treatment deviated from psychedelic therapy in this manner—even Bowen only gave the lack of psychotherapy passing mention—it seems more likely that they simply failed to grasp the importance of this element in the psychedelic therapy method. Their treatments focused on brief instructive preparation, followed by administration of the drug in a standardized setting. This format more closely resembled a standard drug treatment than a form of psychotherapy, and its standardized nature made objective testing easier. Therefore psychedelic chemotherapy may have been popular because it fit psychiatrists’ perceptions of both how drug treatments functioned, and how drug efficacy should be tested.
Conclusion

Analysing the internal and external challenges that faced the Spring Grove psychedelic researchers gives insight into both the downfall of psychedelic therapy in the United States, and the complex relationship between the randomized controlled trial research methodology and researcher bias. The Spring Grove researchers faced internal challenges that left their research unable to establish the efficacy of psychedelic therapy. These challenges included finding a placebo treatment that could sustain a double-blind while remaining therapeutically neutral, the failure of randomization to deliver an even distribution of treatment impacting variables between treatment and control groups, and the inability to obtain the necessary funding to undertake all their planned trials. The significance of any positive results they reported was then overshadowed by the negative reports of LSD’s efficacy in treating alcoholism reported from six other concurrent clinical trials. While none of these trials actually tested psychedelic therapy, this fact was obscured by their failure to clearly acknowledge it, and their emphasis on research methodology as the signifier of a clinical trial’s value. Their focus on chemotherapeutic treatments and objective research methodology reflected the increasingly biological focus of mainstream psychiatry. Therefore the deficiencies in their treatment methods were unlikely to be picked up by the wider psychiatric community.

The seven controlled trials of LSD therapy for alcoholism conducted in the late 1960s obscured rather than clarified the efficacy of psychedelic therapy. Each
research group promoted the randomized controlled trial methodology as the only reliable tool for obtaining objective data on the efficacy of treatment, due to its ability to eliminate bias from research. Yet the methodology could not account for bias in the design of the treatment, only in the evaluation of its effects. In the six non-Spring Grove trials, the randomized controlled trials did in fact provide an objective appraisal of the researchers’ treatments. The problem was that the researchers had expressed their bias when designing their treatments; therefore their bias was built into the clinical trials, and the negative results were essentially foregone conclusions. For the Spring Grove researchers the problem was almost opposite: rather that hiding their bias, the methodology hid their treatment’s potential efficacy due to their poorly designed control condition. Therefore in each study the controlled trial methodology gave the appearance of objectivity while hiding the design flaws that ultimately shaped the results. Faith in the methodology was so high amongst scientists that its employment gave the results authority, and the therapeutic methods utilized were not scrutinized. With studies appearing to show a consensus that psychedelic therapy was ineffective, research would dwindle before dying out entirely.
The results of the seven controlled trials of LSD therapy in the treatment of alcoholism reported between 1967 and 1971 appeared to many to clearly demonstrate a lack of efficacy. While flawed treatment methods and problematic control conditions led to the negative or underwhelming results, scientific authorities failed to acknowledge this. In 1970, the Controlled Substances Act listed LSD and other psychedelics in the schedule for drugs with “no currently accepted medical use.”¹ This resulted in increased regulation over LSD research. In 1972, Jerome Levine, in his position as chief of the Psychopharmacology Research Branch of the National Institute of Mental Health (NIMH), commented that studies had shown that LSD therapy was “no better than other therapies.” His predecessor Jonathan Cole, who had helped to initiate many of the studies, also described the treatment as “mostly a bomb.”² In 1974 an NIMH Research Task Force conducted a review of LSD research. It concluded that studies had “contributed little to our understanding of the bizarre and potent effects of this drug” and had “not clearly defined a therapeutic use.”³ Consequently, the NIMH ceased funding LSD research. With no federal funding and increased regulation, psychedelic research faced a bleak future. Examining the provisions of the Controlled Substances Act, and following the final years of research at the Maryland Psychiatric Research Center (MPRC), reveals, however, that neither of

these developments immediately terminated research. In fact, psychedelic research continued at the MPRC until 1976, and it finally came to a close due to a change in the management of the centre, rather than problems with regulation, funding, or controversy over LSD. Nevertheless, the fate of LSD psychotherapy research was set long before it ended, due to the failure of researchers to clearly demonstrate its efficacy through randomized controlled trials.

While this analysis accounts for the demise of LSD psychotherapy research in the mid-1970s, it was not the only factor that held LSD back from becoming an approved tool of psychiatric therapy. Turning a drug into an approved medicine requires both research and development. Whilst complimentary, and usually closely intertwined, research and development are ultimately distinct undertakings. Research is the domain of scientists; development is normally the responsibility of pharmaceutical firms. Much research was conducted with LSD in the United States between 1949 and 1976, however the drug underwent very little development. Sandoz Pharmaceuticals withdrew its sponsorship of LSD research in 1966, and even earlier the company appeared to do little to direct research towards the goal of submitting a New Drug Application (NDA) to the FDA. The case of LSD research therefore raises questions over the significance

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4 Other histories of LSD have included the Controlled Substances Act in the series of restrictive regulations that terminated research, starting with the Drug Amendments of 1962. The legislation has not, however, received significant attention, as many authors regard LSD research as already having come to an end by the mid to late 1960s. For works that briefly mention the Controlled Substances Act, see Lester Grinspoon and James B. Bakalar, *Psychedelic Drugs Reconsidered* (New York: The Lindesmith Center, 1997), pp. 309-311; Richard Elliot Doblin, “Regulation of the Medical Use of Psychedelics and Marijuana,” (PhD diss., Harvard University, 2000), pp. 48-50; and Kimberly Allyn Hewitt, “Psychedelics and Psychosis: LSD and Changing Ideas of Mental Illness, 1943-1966,” (PhD diss., University of Texas, 2002), pp. 3, 216-217. For works that represent LSD research as ending before 1970 see, Jay Stevens, *Storming Heaven: LSD and the American Dream* (London: Heinemann, 1987); Martin A. Lee and Bruce Shlain, *Acid Dreams. The Complete Social History of LSD: The CIA, the Sixties, and Beyond* (New York: Grove Press, 1985); and Hewitt, "Psychedelics and Psychosis," p. 294.
and prospects of clinical drug research without the backing of a pharmaceutical company. If the results from the clinical trials of LSD therapy of the 1960s had clearly demonstrated its efficacy and safety in treating alcoholism, would that have resulted in the drug becoming an approved tool of psychiatry?

**LSD under the Controlled Substances Act**

In 1970, LSD research became subject to new regulations under the Controlled Substances Act. While this act was designed to tackle drug abuse, it had the potential to discourage or even disable psychedelic research, since gaining approval to conduct research became more complex. Part of the Comprehensive Drug Abuse Prevention and Control Act of 1970, the Controlled Substances Act reformed the complex set of federal laws that controlled drugs of abuse. The previous laws—notably the 1914 Harrison Narcotic Act, the 1937 Marijuana Tax Act, and the 1965 Drug Abuse Control Amendments—had each controlled different categories of drugs, in different ways, and through different agencies: the Treasury Department’s Federal Bureau of Narcotics controlled opiates, cocaine, and marijuana through taxation, while the Department of Health, Education, and Welfare’s Bureau of Drug Abuse Control controlled depressants, stimulants, and hallucinogens through regulating interstate commerce. This complex regulatory system caused significant jurisdictional difficulties for enforcers when, for example, drug traffickers were caught with both heroin and barbiturates. In 1968 this problem was partly solved through the merger of the Federal Bureau of Narcotics and the Bureau of Drug Abuse Control into the
Bureau of Narcotics and Dangerous Drugs, under the Department of Justice. However, while the new agency had jurisdiction over all drugs of abuse, enforcement was still complicated by the different regulations and penalty structures for different drugs. The Controlled Substances Act remedied this situation by bringing all drugs of abuse under one regulatory framework, administered and enforced by the Department of Justice.¹

The Controlled Substances Act created five schedules for drugs, each denoting a different level of regulation. Inclusion in a schedule was dependent on the drug’s potential for abuse, the likelihood of use leading to physical or psychological dependence, and whether or not it had a legitimate medical use. The legislation listed the drugs to be included in each schedule. Future additions and changes in scheduling were the responsibility of the attorney general, however he or she was required to solicit the advice of the secretary of health, education, and welfare on determinations related to medical and scientific criteria, and such advice would be binding. LSD, along with other psychedelics such as mescaline and psilocybin, was listed in Schedule I. This was the most prohibitive schedule, under which heroin and marijuana were also listed. The criteria for inclusion in Schedule I were:

(A) The drug or other substance has a high potential for abuse.
(B) The drug or other substance has no currently accepted medical use in treatment in the United States.

There is a lack of accepted safety for use of the drug or other substance under medical supervision.\(^6\)

The last criterion seems to contradict scientific experience with LSD, as the safety record for all forms of LSD psychotherapy had been exemplary when performed under medical supervision.\(^7\) However, from congressional hearings on the legislation, it is clear that officials in the Bureau of Narcotics and Dangerous Drugs considered that determining whether or not a drug was safe, or had a medical use, did not require lengthy deliberation, but simply a checking of the drug’s official status with health authorities.\(^8\) A drug’s medical use and safety under medical supervision were established officially in the United States through the FDA’s approval of an NDA. The criteria for Schedule I therefore simply meant that a drug had a high potential for abuse and did not have an approved NDA. In fact, as Schedule I was the only schedule for drugs without an accepted medical use, any drug with an abuse potential but without an approved NDA would be placed in that schedule. LSD clearly met these criteria.

The regulation of Schedule I drugs equated essentially to total prohibition of their manufacture, distribution, administration, and possession. However, as with previous laws, there was an exemption for legitimate scientific research: medical practitioners could use a Schedule I drug in research after obtaining

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\(^6\) *Controlled Substances Act, Sec. 202, (b), (1).*

\(^7\) Sidney Cohen’s 1960 survey of LSD researchers for adverse reactions in treatment found that prolonged and serious adverse reactions were rare. See Sidney Cohen, "Lysergic Acid Diethylamide: Side Effects and Complications," *Journal of Nervous and Mental Disease* 130 (1960), pp. 30-40. Furthermore, no prolonged adverse reactions were found in the Spring Grove/ MPRC research, or reported in the other clinical trials discussed in the previous chapter.

registration to do so from the attorney general. This registration requirement was in addition to the standard FDA approval process to conduct research with an investigational drug. While this provision appears to have put the ultimate control of research in the hands of the Department of Justice, the attorney general’s powers to deny registration were in fact very limited. On receiving an application for registration, the attorney general was required to refer it to the secretary of health, education, and welfare, who judged the adequacy of the researcher’s qualifications and the merits of their research proposal. The secretary was also required to consult with the attorney general over the adequacy of measures to prevent diversion of drug supplies to illegitimate channels. If the secretary then recommended registration, the attorney general was only permitted to deny it if he or she found that the applicant had falsified information in their application, had been convicted of a felony related to a controlled substance, or had had their licence to practice medicine revoked.\(^9\)

Despite the attorney general’s limited powers to deny registration for legitimate research with Schedule I drugs, the intrusion of the Department of Justice into medical research was highly controversial. At congressional hearings considering the proposed legislation, several prominent figures in psychopharmacology research, including Jonathan Cole, Nathan Kline, and Daniel Freedman, as well an official from the American Psychiatric Association, spoke out against the provisions. They argued that registration would seriously impede research by slowing down the approval process, discouraging researchers from

\(^9\) *Controlled Substances Act*, Sec. 303, (f); Sec. 304, (a).
investigating Schedule I drugs. They also feared that the Department of Justice might take a harder line in regulating research than intended in the legislation.\textsuperscript{10}

Whether or not the registration requirements of the Controlled Substances Act did indeed impede research in the case of LSD is not easy to determine. As will be explored below, LSD research at the MPRC did not come to a close until 1976, and then for reasons unrelated to LSD per se. Although the legislation did not immediately terminate LSD research, from the start of the 1970s research was clearly in decline, and it had faded away to almost nothing before its eventual demise. Difficulties in gaining and maintaining approval for research could have influenced this. A 1972 survey of researchers interested in psychedelics found that 81 percent of respondents rated governmental red tape as a “large” obstacle for research with the drugs.\textsuperscript{11} FDA officials responded to claims of prohibitive regulations by arguing that they received few applications for psychedelic research, which they put down to disillusionment with the drugs. They also argued that widespread research with marijuana suggested that registration requirements did not prevent access to Schedule I drugs.\textsuperscript{12} Ultimately, although the increased regulation may have had some impact, the decline in LSD research in the 1970s can be more convincingly explained through the outcome of the clinical trials of the late 1960s, as discussed in the previous chapter. The difficulties of evaluating psychedelic therapy through the randomized controlled trial methodology left researchers with negative or underwhelming results, leading many researchers, regulators, and funders to conclude that LSD therapy

\textsuperscript{10} See \textit{Drug Abuse Control Amendments}, Hearings, pp. 195, 277, 313, 394-395, 423, 441, 455.
\textsuperscript{12} Asher, "Psychedelic Research," p. 5.
was ineffective. With little subsequent encouragement from the scientific community and funding bodies, research dwindled.

The Later Years of Psychedelic Research at the Maryland Psychiatric Research Center

As the controlled trials of LSD therapy initiated in the 1960s came to a close in the early 1970s, clinical LSD research in the United States declined. For most of the researchers, the results of their trials had shown that their form of LSD therapy was ineffective; therefore they withdrew from the field. In 1975, the FDA listed five medical institutions as still authorized to conduct research programs involving LSD administration to human subjects. As well as approved programs at the MPRC, research with LSD and alcoholism was still authorized at the Veterans Administration Hospital in Topeka, Kansas, where Kenneth Godfrey and William Bowen had conducted research, and at the Vista Hill Psychiatric Foundation, through which University of California, Los Angeles researcher Keith Ditman had conducted his trial. Additionally, research with psychotic patients was allowed at the Medical College of Birmingham, Alabama, as well as research involving psychotherapy with chronic LSD users at the Langley Porter Neuropsychiatric Institute, California.\(^{13}\) Whilst LSD research was still permitted at these institutions, it is not clear whether or not it was actually taking place. In 1975, Levine commented that Godfrey still occasionally administered LSD "even

\(^{13}\) Food and Drug Administration, "FDA Lists Approved LSD Research Projects," *FDA Consumer* (September 1975), pp. 24-25.
though his own previous studies don’t support it.”¹⁴ The other programs were most likely inactive.¹⁵ The MPRC was certainly the only institution from which published reports of systematic studies were still emanating.

At the MPRC, psychedelic research continued despite new internal obstacles, as well as the new registration requirements of the Controlled Substances Act. In the early 1970s, as the results were being published for the four original Spring Grove trials of psychedelic therapy, essentially the entire senior psychedelic research team departed the MPRC. In July 1971, Walter Pahnke drowned while scuba diving in Maine. Sanford Unger, whose name last appeared on a MPRC publication in 1972, left due to medical reasons. Charles Savage left the MPRC around 1973, taking up the positions of chief of psychiatry and director of drug abuse programs at the Baltimore Veterans Administration Hospital. He was also by then associate professor of psychiatry at the University of Maryland.¹⁶ Why Savage left the MPRC, and in doing so ended his long career with psychedelics, is not clear. Stanislav Grof also left the MPRC in 1973, motivated by difficulties in obtaining support for new research, disagreements with MPRC management, and a lack of employment opportunities for his wife in Baltimore. With extensive unanalysed data from his years of research, and book offers from various

¹⁵ See Doblin, “Regulation of the Medical Use of Psychedelics and Marijuana,” p. 54 n. 312.
publishers, Grof relocated to the Esalen Institute in California to write several monographs on his work.\textsuperscript{17}

The loss of these researchers presented a threat to the future of psychedelic research at the MPRC. Not only had they been critical for the initiation, design, and conduct of the Spring Grove and MPRC clinical trials, but they also held many positions of authority in the MPRC. However, Kurland remained superintendent of the centre, and he continued to focus much of its research on psychedelics. Additionally, by the early 1970s many of the originally more junior members of the MPRC psychedelic research team, such as psychologist William Richards, were highly experienced in psychedelic research, and were able to take over conduct of the program. Richards, who held masters degrees in psychology and divinity, had joined the Spring Grove research team as a therapist in 1967. In prior years he had also studied under renowned psycholytic therapist Hanscarl Leuner at Georg-August University in Germany, and worked as a research assistant to prominent humanistic psychologist Abraham Maslow.\textsuperscript{18} At the MPRC Richards had been heavily involved in the research treating terminally ill cancer patients, and he led this research after the senior researchers departed.\textsuperscript{19}


The later years of psychedelic research at the MPRC were characterized by experimentation with new forms of psychedelic therapy. The focus of research changed from LSD to the shorter-acting psychedelic dipropyltryptamine (DPT). This move was not prompted by either disappointment in the results of their previous studies on LSD, or overwhelming controversy over the drug, but was instead a long planned evolution of the research program. As early as 1966, Kurland had stated that if he found positive results for psychedelic therapy with LSD, then he would look for a shorter acting psychedelic drug that would render treatment more practical as a routine therapy.\footnote{Drug Safety (Part 5, Appendices, and Index), Hearings before a Subcommittee on Government Operations, House of Representatives, 89th Congress, 2nd Session, March 9, 10; May 25, 26; June 7, 8, and 9, 1966 (Washington: U.S. Government Printing Office, 1966), p. 2267.} The researchers began experimenting with DPT in the early 1970s, and found it to have similar subjective effects to LSD, but with a four to six hour period of action (half that of LSD), and a quicker transition back to normal consciousness. If psychedelic therapy with DPT could be as effective as with LSD, then the drug's shorter period of action would make treatment much easier for both therapists and patients, making it a more attractive treatment. While it was not the primary reason to switch drugs, the researchers did also consider the lack of stigma around the drug, which was barely known outside of medicine, as an added benefit.\footnote{S. Grof et al., "DPT as an Adjunct in Psychotherapy of Alcoholics," \textit{International Pharmacopsychiatry} 8 (1973), p. 106, 108; Robert A. Soskin, Stanislav Grof, and William A. Richards, "Low Doses of Dipropyltryptamine in Psychotherapy," \textit{Archives of General Psychiatry} 28, no. 6 (1973), p. 817. DPT was not scheduled under the Controlled Substances Act, and this could have influenced the researchers' decision to employ it. However, given that its effects fit with their long-held research plans, and that as well as continuing to use LSD they also initiated studies with another Schedule I drug (methyleneoxyamphetamine), it seems unlikely that this patients at the MPRC to earn his PhD. William A. Richards, "Counseling, Peak Experiences and the Human Encounter With Death (PhD diss., Catholic University, 1975).}
The MPRC researchers used DPT in a number of studies, some of which were closely related to their previous LSD trials, and some of which explored other forms of therapy. In 1973 the researchers published results from an uncontrolled pilot study of psychedelic therapy with DPT in the treatment of fifty-one alcoholic patients. The form of treatment employed was essentially the same as in the LSD study, except that patients received up to six drug sessions, with an average of 1.86. Positive results were found, closely mirroring the rate of success for high-dose LSD therapy.\(^{22}\) Another uncontrolled pilot study, published in 1979, also essentially confirmed that DPT could have a similar therapeutic effect to LSD: thirty cancer patients received a single DPT session in a psychedelic therapy framework, with a comparison of pre and post-treatment tests showing significant improvements in their psychological states.\(^{23}\)

As well as this psychedelic research with DPT, the MPRC researchers explored using the drug in psycholytic therapy. Psycholytic therapy had not previously been employed at Spring Grove State Hospital or the MPRC, and it had not been popular in the United States since the start of the 1960s. Nevertheless, it had remained popular in Europe throughout that decade, and Grof was highly experienced with the treatment from his previous research in Czechoslovakia. Before he left the MPRC, Grof influenced the research team to take a greater interest in using psychedelics to aid conventional forms of psychotherapy.\(^{24}\) In


\(^{24}\) Richard Yensen and Donna Dryer, "Thirty Years of Psychedelic Research: The Spring Grove Experiment and its Sequels," *Jahrbuch des Europäischen Collegiums für Bewußtseinsstudien/
1973, the team published results from a partially controlled study of DPT-assisted psychotherapy with eighteen alcoholic patients. After one or two drug-free psychotherapy sessions, the patients underwent six to eight further sessions where they received either a low dose of DPT or an inert placebo, on a randomized double-blind basis. The low dose attenuated both the intensity and the duration of the drug’s effects; the sessions lasted just 1.5 to 2 hours. Based on post-session ratings made by both therapists and patients, the researchers found that DPT significantly enhanced recall of memories, emotional expressiveness, self-exploration, and psychodynamic resolution in psychotherapy sessions.25

The researchers also conducted a small pilot study of methylene-dioxyamphetamine (MDA) assisted psychotherapy with ten outpatient neurotics. MDA, chemically related to amphetamine, produced milder effects than psychedelics such as LSD or DPT. It produced therapeutically useful effects such as increased insight, empathy, and openness, but with less perceptual changes, visions, and peak experiences. The tested treatment saw patients undergo two to four MDA sessions, as part of a two to six month course of psychotherapy. The conduct of the drug sessions incorporated elements of both psychedelic and psycholytic therapy. The researchers reported in 1976 that the treatment significantly benefited their patients.26 Another study saw patients who were

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25 Soskin, "Dipropyltryptamine in Psychotherapy," pp. 817-821. The sessions were not run according to a specific form of psychotherapy. The researchers described that the therapists focused on establishing a good therapeutic relationship, and explored patients’ past and present maladaptive behaviours and patterns of thinking, as well as their life philosophy, hierarchy of values, and religious beliefs. Despite the double-blind, therapists were usually able to correctly identify when patients received DPT.

undergoing private psychotherapy referred to the MPRC for the full psychedelic therapy procedure (with LSD or DPT), in order to study whether it could significantly progress their ongoing therapy. Based on clinical impressions, psychoanalytically orientated psychiatrist Margret Berendes reported that the treatment greatly benefited her patients.27

The last major controlled study using psychedelics at the MPRC tested the efficacy of DPT therapy in the treatment of alcoholism. Reported in 1977, the researchers attempted to learn from their past research by using both a modified treatment technique, and a clearer control condition than low-dose psychedelic therapy. Nevertheless, problems again emerged in the conduct of the trial that led to insignificant results. The trial’s design saw 174 patients randomly assigned to one of three treatment groups: routine hospital treatment, or routine hospital treatment plus either DPT therapy or individual psychotherapy. This design had the advantage of providing a clear baseline control group in the form of the routine hospital treatment group, and a control for the psychotherapy element of DPT therapy in the individual psychotherapy group. With such distinct comparative treatments, blind administration could not be achieved. However, as in the previous trials, the researchers ensured objective ratings of outcome by having social workers that were blind to patients’ treatment groups perform


follow-up assessments with standardized psychological tests. Patients in the DPT group received up to six drug sessions at the therapist’s discretion. After several preparatory drug-free psychotherapy interviews, patients underwent at least one session of psycholytic therapy with a low dose of DPT. As well as being therapeutic, the researchers considered these sessions as further preparation for later high-dose sessions. These sessions were interspersed with further drug-free interviews. When the therapist deemed them ready, patients then received at least one high-dose psychedelic therapy session.28

At the six-month follow-up point, the researchers found no significant differences in the results between the three treatment groups. At twelve months, results for occupational adjustment and sobriety significantly favoured individual psychotherapy. Although this trial’s design had seemed elegant, the researchers argued that its open nature influenced the insignificant results.

Before entering the study, patients were fully informed of the three treatment groups, and the fact that they would be randomly allocated to one. This resulted in high and varied dropout rates between the three treatments groups, as patients who signed-up hoping for one treatment were assigned to another. After the dropouts, each treatment group’s population was no longer a representative sample of the original total pool of patients, but a self-selected group of those most motivated for each treatment; the higher the dropout rate in a group, the more refined the population, and therefore the greater the bias towards treatment success. At the twelve-month follow-up point, the individual

psychotherapy group had the highest dropout rate, while the DPT group had the lowest. Therefore, the positive results in favour of individual psychotherapy at that point may not have reflected the actual superiority of that treatment, but instead that the group’s population was ideally suited for that treatment.29

The End of Psychedelic Research

Psychedelic research at the MPRC finally came to a close in 1976 for reasons essentially unrelated to LSD. Over the 1960s, LSD research had flourished in Maryland partly because Kurland had been able to facilitate it through his roles as director of research for both Spring Grove State Hospital and the state Department of Mental Hygiene, as well as superintendent of the MPRC. However, in 1973 a controversy began over the apparently poor management of the MPRC under Kurland and the Maryland Department of Health and Mental Hygiene. Over the next three years prolonged disputes over the MPRC raged in public, judicial, and legislative arenas, eventually resulting in the transfer of its management from the Department of Health and Mental Hygiene to the University of Maryland. In this transfer, the MPRC was reorganized, Kurland and many other staff members were replaced, the research focus of the centre changed, and psychedelic research was terminated. Following this dispute, as it unfolded in the *Baltimore Sun*, confirms that the ultimate demise of LSD psychotherapy research in the United States was not a result of either the government restricting research, or the controversy over LSD’s non-medical use.

Instead, after the disappointments of the controlled clinical trials of LSD psychotherapy, research survived at a diminished scale purely due to the continued enthusiasm of researchers such as Kurland. With the lack of wider interest and support, the future of LSD research was essentially tied to the careers of its champions.

Kurland first became the subject of controversy in January 1973, as part of a state audit of Friends Medical Science Research Center, a private non-profit organization that administered funding for psychiatric research in Maryland. Kurland, with the support of the state, had founded the organization (commonly referred to simply as Friends) in 1955 for the purpose of obtaining and administering federal and private funding for psychiatric research. By the early 1970s, Friends handled all federal research grants for Maryland’s state hospitals, as well as private and state grants, employed 150 professional staff, and ran a neurological laboratory, group homes, and clinics. Kurland retained the position of director of research in the organization, and was a member of its board of directors, and central research authority. As reported in the Baltimore Sun, state legislative auditor Pierce J. Lambdin criticised many aspects of Friends’ management of state funds, including failure to account for how funds were spent, running at a significant cash deficit, and making large payouts to state employees. The report singled out a payment of $14,000 to Kurland, who was also receiving a salary from the state as superintendent of the MPRC. Lambdin’s report criticised the relationship between Friends and state employees for being so confused that it was impossible to tell whether state employees such as Kurland were performing work for Friends on the state’s time. The executive
director of Friends defended the organization’s financial practices, and stated that Kurland had been made director of research at the insistence of the state Health Department, however Kurland was forced to resign from his positions at Friends.\(^{30}\)

Four months later, criticism against Kurland was again reported in the *Baltimore Sun*, however this time it was over the management of the MPRC. The state commissioner of mental health, Bertram Pepper, was preparing to investigate the management of the MPRC, after having received a letter from former MPRC medicinal chemist Reuben Sawdaye accusing Kurland and the director of the MPRC’s biochemistry department, Richard Von Korff, of “mismanagement of state funds and mistreatment of employees.” Specifically, Sawdaye made complaints regarding management’s purchase of expensive, unnecessary equipment, the poor management and lack of productivity in the biochemistry department, Kurland’s censorship of all staff communication with the outside world, the close relationship between the MPRC and Friends, and the treatment of staff under Von Korff, stating, “never during my scientific career have I seen such lack of co-operation between departments and individuals, and so much suspicion and distrust.” Kurland had recently fired Sawdaye from the MPRC, which Sawdaye believed had been done to make way for a Friends scientist. He had subsequently filed a complaint with the state Department of Personnel complaining that the firing was “arbitrary, capricious, unlawful and personally

motivated.”31 Soon after Sawdaye, MPRC educational psychologist John Lenox also wrote to the commissioner of mental health accusing Kurland of wasting taxpayers’ money. Like with Sawdaye, Kurland had recently dismissed Lenox from the centre. Lenox criticised Kurland’s dismantling of a recently completed $80,000 physiology laboratory because he had “lost interest” in it, as well as his “devoting most of his energies to promoting ‘a dream of a $10 million cancer project in which psychedelics are given to cancer patients.’”32 Significantly, this was the only time that psychedelic research at the MPRC was mentioned in the Baltimore Sun’s extensive coverage of the centre’s management controversy.

As a result of these disputes, in June 1973 an MPRC management committee fired Von Korff. The state health department also conducted an investigation into the centre that resulted in Sawdaye and Lenox’s reinstatement, and a limited reorganization of management. However, these developments did not settle the matter, and in March 1974 MPRC researchers began again voicing complaints. In May, Kurland fired Sawdaye, Lenox, biochemist Mishrilal Jain, and psychologist Lawrence Gaines, shortly after they had called for the replacement of both Kurland and the MPRC’s associate director, T. Glyne Williams, publicly and in writing to the state secretary of health and mental hygiene, Neil Solomon. In terminating their employment, Kurland cited poor performance and “taking public actions which were not in the best interest of the center.” Throughout the controversy, Kurland declined to publicly defend his management of the MPRC.

While the researchers complained that their dismissals were simply a “reprisal”

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for their criticism, Solomon backed Kurland’s decision. Robert Campbell, the health department’s coordinator of psychological services and research, also defended the management of the centre. In response to their firings, the four MPRC scientists filed a federal lawsuit for reinstatement and damages, with Kurland, Solomon, and Campbell named as defendants. The lawsuit would not be settled until August 1975, when an arbiter ordered that Jain, Sawdaye, and Lenox be reinstated to their positions at the MPRC.33

In the intervening period, the state House Appropriations Subcommittee on Health and Education responded to the controversy by ordering an audit of the MPRC. In March 1975, auditor Lambdin, who had performed the 1973 audit of Friends, reported that the centre’s management was “inadequate,” and had resulted in low staff morale. He criticised the close relationship between the centre and Friends, and argued that the Health Department’s attempts to remedy the problems at the centre had been ineffective. Lambdin recommended that control of the MPRC be transferred from the Department of Health and Mental Hygiene to the University of Maryland School of Medicine, and that “a clear separation” be made between the centre and Friends.34

Despite protests from Campbell and Solomon, the state legislature went through with the recommendations, transferring control of the MPRC over to the

University of Maryland in 1976, as well as ordering the new management to focus the centre’s research on schizophrenia—a recommendation that had come from the American Psychiatric Association.\textsuperscript{35} In the transition, Kurland was replaced, and the new management dismissed many of the MPRC’s staff members, on the basis that “The expertise of the men was not appropriate for the new goals of the center.”\textsuperscript{36} A committee of the University of Maryland School of Medicine terminated the centre’s psychedelic research program, and the clinical sciences department (which oversaw psychedelic research) was disbanded. William Richards was the last member of the psychedelic research team to leave the MPRC. He left in 1977, after being invited to stay on part-time for one year so that he could retain his health insurance benefits, as his wife had recently been diagnosed with cancer. Even at the end, Richards maintained FDA approval to conduct psychedelic research at the centre, however the lack of funding and institutional support prevented it.\textsuperscript{37}

The University of Maryland School of Medicine’s termination of the MPRC psychedelic research program may have been influenced by a controversy over clandestine army and Central Intelligence Agency (CIA) LSD research that erupted in the press in 1975. Reports accused the School of Medicine of participating in army LSD research in the 1950s, where the drug had been given to subjects without their knowledge.\textsuperscript{38} Therefore, the medical school may have


\textsuperscript{36} “No Retaliation in Dismissal,” p. B2.

\textsuperscript{37} William Richards, email to author, 18 February 2013; William Richards, email to author, 13 September 2012.

\textsuperscript{38} "UM Tied to LSD Testing," \textit{Baltimore Sun}, 17 July 1975, p. C1, C2. See also "The CIA’s Shocking
wished to distance itself from the drug. However, reports in the *Baltimore Sun* had been careful to distinguish between the unethical forms of research conducted by the army and CIA, and legitimate medical research. Reports contrasted the murky motives and lack of informed consent in the CIA and army research, with the admirable motives, careful attention to informed consent, and extensive patient preparation and support in the MPRC research: as one reporter commented, “That federal institutions have sponsored LSD experiments is not a scandal, but the circumstances of some experiments might be.”39 Indeed the paper continued to publish reports on the MPRC research that not only presented it in a positive or neutral light, but which lamented its demise: one reporter commented that results so far suggested that “research not only should not be halted but should be expanded.”40 Whether or not this controversy played a role in the School of Medicine’s decision to terminate psychedelic research at the MPRC, LSD research was ultimately unlikely to survive the change in the centre’s management, due to the general declining prospects of psychedelic research, the absence of a strong champion in Kurland, and the mandate to overhaul the centre and focus on schizophrenia.

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Pschedelic Research and Development

As this thesis has established, the difficulties in establishing LSD psychotherapy’s efficacy through randomized controlled trials, as required under the Drug Amendments of 1962, was the primary issue that frustrated research and led to its demise. Without proof of efficacy, LSD could not be become an approved tool of psychiatry. However, proof of efficacy would still not have automatically resulted in LSD becoming a marketable pharmaceutical—a sponsor was still needed who would collate all the necessary data on the drug’s safety and efficacy for a specific indication, and submit it to the FDA in the form of a New Drug Application. As well as research, LSD needed development. A developer’s role was not only turning the results of scientists’ research into an NDA, but also directing and coordinating research towards that goal. The case of LSD research highlights the distinctions between the usually intertwined processes of drug research and development.

Since LSD research began in the United States in 1949, it had progressed with little developmental oversight. Prior to 1962, Sandoz had distributed the drug widely and free of charge to interested researchers, with recommendations that it be explored as a tool to facilitate psychotherapy, and to study psychoses. Other than this, it appears the company’s only effort to stimulate research was providing some funding for conferences. Sandoz did not submit an NDA for

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LSD, despite only needed to supply proof of safety when used as directed on the labelling. After the passage of the Drug Amendments of 1962, Sandoz took a somewhat more active approach in overseeing LSD research, by formally acting as the drug’s sponsor and voluntarily restricting research to hospital based studies, funded or approved by federal or state agencies. While the field of LSD research became more organized in the mid-1960s, with numerous researchers conducting controlled trials of LSD therapy with alcoholics, this does not appear to be primarily a result of Sandoz’s influence. Instead, independent researchers initiated the studies on the basis of the great scientific and medical significance of the claims of effectiveness reported from earlier uncontrolled research. That the new research took the form of larger-scale controlled trials appears symptomatic of the formalization of pharmaceutical research under the 1962 amendments, rather than as a result of Sandoz’s sponsorship. Sandoz withdrew its sponsorship of LSD research before these studies concluded, due to the negative publicity surrounding the drug. It is therefore difficult to determine what intentions the company had for LSD, if any.

In the absence of evidence, it can be reasoned that commercial as well as scientific factors would have influenced Sandoz to take a backseat role in LSD’s development. While there was much scientific and clinical interest in LSD as a potential tool in psychiatry, its effects were clearly unconventional. There were precedents for drug-assisted psychotherapy, however the barbiturates and amphetamines used in those treatments had been established in the market on the basis of their other conventional uses. There was therefore no precedent for

developing a drug through FDA approval on the basis of its variable subjective effects. Even if Sandoz had successfully developed LSD into an approved pharmaceutical, it was unlikely to be a hugely profitable product for the company. Psychedelic therapy usually involved only one administration of LSD. Psycholytic therapy involved a greater number of drug sessions; however the number was still relatively small, typically fewer than fifty. The commercial potential of LSD therefore paled in comparison to tranquilizers, antidepressants, and anxiolytics that were commonly taken every day for extended periods of time. After Sandoz’s patent for LSD expired in 1963, there was even less financial incentive for developing the drug, as generic manufacturers could reap the profits of their investment.

Ultimately, LSD’s potential in psychiatry was of greater medical and scientific significance than commercial. Faced with an unconventional drug with a difficult development path, and limited potential profitability, the prudent approach was to release it to the scientific community and see whether a marketable use for it emerged. If so, then a more limited investment could turn the independent researchers’ work into an NDA. Officials at Sandoz must not have believed this point was reached, at least not before the controversy over LSD’s non-medical use made the drug’s commercial potential even less worth chasing. While this thesis has demonstrated how the public controversy over the drug did not end clinical LSD research in the United States, by influencing Sandoz to withdraw

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42 For the patent expiration date see Albert Hofmann, LSD: My Problem Child. Reflections of Sacred Drugs, Mysticism and Science, trans. Jonathan Ott (Santa Cruz: The Multidisciplinary Association for Psychedelic Studies, 2009), p. 86.
from the field, it did make the drug’s development into an approved pharmaceutical much less likely.

The importance of a pharmaceutical firm’s role in developing an experimental drug into an approved medicine went beyond sponsoring research and collating the results into an NDA, to determining how efficacy should be conceptualized for that specific drug. The Drug Amendments of 1962 required that an NDA contain “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.” Therefore, how the drug was to be labelled defined the kind of treatment effect that needed to be demonstrated through controlled trials. As historian Peter Temin has explained, this had profound implications for drug development: “experts, by insisting on changes in the drug’s label, can change the effectiveness of that drug... If a drug has any desirable effect at all, the process of getting FDA approval will be centered on the label.”

Of the post-1962 controlled trials of LSD therapy with alcoholics, all except Keith Ditman's evaluated the long-term effects of treatment on drinking behaviour, and often aspects of psychopathology and social adjustment—their research questions all essentially equated to “does LSD therapy cure alcoholism?” This

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43 Drug Amendments of 1962, 87 P.L. 781; 76 Stat. 780, 10 October 1962, Title 1, Part A, Sec. 102, (c).
45 As discussed in chapter five, outcome was assessed in Ditman’s trial through a comparison of LSD and active placebo sessions for experiences usually deemed therapeutic, such as the patient having increased insight. The trial found LSD no more therapeutic than the control drugs,
may have been the most medically significant question, however it was only necessary to establish such an ambitious effect if that was the claim to be made on the labelling. This is illustrated in the case of Antabuse (disulfiram), another drug used to treat alcoholism. Ludwig, Levine, and Stark had tested the efficacy of Antabuse as well as LSD in their clinical trial. They found that it was also an ineffective treatment for alcoholism. The drug was, however, unquestionably effective at causing alcohol consumption to produce severely unpleasant physical effects in patients. This effect was useful in helping alcoholics to abstain from drinking, but only insofar as they were motivated to stay on the drug. Ayerst Laboratories therefore labelled Antabuse as “an aid in the management of selected chronic alcoholic patients,” rather than as a cure for alcoholism. Indeed, the labelling explicitly stated the drug’s limitations in treatment: “used alone, without proper motivation and without supportive therapy, it is not a cure for alcoholism, and it is unlikely that it will have more than a brief effect on the drinking pattern of the chronic alcoholic.” Reviewing the drug’s efficacy in 1969, the FDA concluded that Antabuse was “an effective adjunct in the management of selected chronic alcoholic patients.”

Therefore, by promoting the drug as simply an “aid in management,” the drug was approved despite its very limited

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however the significance of this result was undermined by apparent lack of psychotherapy in Ditman’s LSD therapy method. See, Keith S. Ditman et al., "Dimensions of the LSD, Methylphenidate and Chlordiazepoxide Experiences," *Psychopharmacologia* 14, no. 1 (1969), pp. 1-11.

46 Herbert L. Ley, "Disulfiram: Drugs for Human Use; Drug Efficacy Study Implementation," *Federal Register* 34, no. 175 (12 September 1969), p. 14340. Antabuse was originally approved in 1951, before proof of efficacy was required in a New Drug Application. The quoted labeling and efficacy determination were the result of the drug’s efficacy review as part of the FDA’s Drug Efficacy Study, which brought drugs approved between 1938 and 1962 into line with the new regulatory requirements. For the date of its original approval see, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchOverview&DrugName=ANTABUSE&CFID=19958764&CFTOKEN=338372c78d9f2ba2-9A55C280-CCB-6C5E-598A32448DB50679 > viewed 30 December 2013.
efficacy as an actual treatment. Physicians were then left to decide for themselves how useful it ultimately was.

Such a tactic may have been possible with LSD. Rather than focus on the disappointing long-term results of treatment, a developer could have analysed clinical trial results for what effects treatment reliably did have on patients. The Spring Grove researchers found significant results in favour of high-dose psychedelic therapy at the six-month follow-up point, and even Leo Hollister found his chemotherapeutic form of LSD therapy effective at the two-month follow-up point. Additionally, patients in many of the studies reported that their drug experience was beneficial and had motivated them to stop drinking, but then returned to drinking when faced with life’s difficulties after discharge. Therefore, as with Antabuse, a developer’s claim of effect for LSD could have focused on it being a tool of treatment, rather than a treatment in itself: an aid in motivating patients to stop drinking, rather than a treatment that causes them to stop drinking. For LSD, this would still have been a more difficult path to approval than it had been for Antabuse, as that drug’s potential usefulness was based on an objective physiological response—it was a magic bullet drug. Using LSD as a tool to promote patient motivation still required crafting a subjective drug experience in order to inspire a change in the patient’s personality. This would be a highly unorthodox use for a drug in medicine, and proving that it could reliably be achieved through controlled trials would still be very difficult. Nevertheless, it could potentially have been less difficult than proving that LSD therapy cured alcoholism.
Without a developer, LSD research moved sideways instead of forwards. Each research team used a different treatment method and clinical trial design, so results were not directly comparable. Furthermore, each research team set out to test a hypothesis that was needlessly ambitious, at least for the sake of FDA approval. Even had the researchers established the efficacy of some form of LSD therapy for some indication, that still would not have resulted in FDA approval unless someone used the results to support an NDA. Establishing LSD as an approved therapeutic tool clearly required the skills of a developer as well as those of researchers. However, did this developer have to be a pharmaceutical company? As discussed in chapter four, the Spring Grove researchers did at least briefly consider submitting an NDA for LSD when Sandoz withdrew its sponsorship of research. Charles Savage mentioned the significant costs involved as a major obstacle to this idea. As commercial distributors, pharmaceutical companies were in the best position to act as a drug’s developer, as they were both motivated and equipped to make the necessary investment in the interests of turning it into profit. However, in the case of a drug with limited profit potential but great medical significance, there was nothing theoretically stopping a non-profit government or private organization from acting as a developer and sponsoring an NDA.

In practice, however, the case of lithium’s development as a mood stabiliser for manic-depressive patients suggests that the cooperation of a pharmaceutical company was necessary to develop a drug through to FDA approval. Lithium had been in limited use in medicine in the United States since the mid-nineteenth century, however the FDA banned it in 1949 due to dangers that appeared when
it was used as a salt-substitute in diets for cardiac patients. Unfortunately, this happened just as its usefulness in treating mania was discovered in Australia. Over the next two decades evidence of its efficacy mounted, despite vigorous debate over how to evaluate it as a prophylactic for recurrent bouts of mania and depression. Rowell Laboratories, a small pharmaceutical firm in Minnesota, had been manufacturing supplies for American investigators. However, as the drug was unpatentable, there was little incentive for firms to push it through the NDA process. The drug was finally licensed in 1970, after several prominent psychopharmacologists, including Jonathan Cole, Nathan Kline, and Frank Ayd, publicly promoted the drug and pressured the FDA to approve it. Kline even attempted to convince the American College of Neuropsychopharmacology to sponsor the drug. Responding to the pressure, the FDA finally persuaded major pharmaceutical firms Smith, Kline, and French, and Pfizer, to submit NDAs, which they did along with Rowell.\textsuperscript{47}

Lithium therefore came to market through the combined effort of independent researchers, FDA officials, and pharmaceutical companies. For LSD, had the results of the controlled trials of the 1960s clearly demonstrated the efficacy of treatment, such a development path could have been possible. Sandoz or another pharmaceutical firm may have been convinced to sponsor the drug if they had the support of the government and the scientific community. However, FDA and NIMH officials were unconvinced of its efficacy, psychiatry was increasingly focused towards magic bullet drug treatments, and the public controversy over

the drug’s non-medical use continued. Considering LSD’s unfavourable status in both medicine and the public, and the lack of a clear financial incentive, there was little chance that a firm could be convinced to aid in the drug’s development. Therefore, by the time psychedelic research came to a halt at the MPRC in 1976, there had long been little prospect of LSD becoming an approved tool of psychiatry in the United States.
This thesis has closely followed LSD psychotherapy research in the United States from the 1950s through to its end in the 1970s, and contextualised that activity within the period’s changing regulatory frameworks and scientific standards for pharmaceutical research and development. This has resulted in an analysis and narrative that in many ways challenges previous accounts of LSD’s medical history. Whereas regulation and the FDA have typically been portrayed as forces that increasingly hampered or prohibited LSD research, in reaction to the increasing controversy over the drug’s non-medical use, closely examining the provisions and implementation of the regulations in the 1960s and 1970s reveals that they played a much more complex and impartial role in LSD psychotherapy’s demise. None of the regulations prohibited legitimate clinical research with LSD, and indeed research continued as the public and political controversy over the drug raged. While the number of researchers using LSD decreased over the 1960s, this was a symptom of the formalization of pharmaceutical research and development engendered by the Drug Amendments of 1962, rather than a deliberate restriction of research. Prior to 1962 research had progressed in a disorganised fashion, with numerous independent researchers conducting mostly small-scale and uncontrolled studies, in a variety of settings. This reflected the limited government oversight of pre-market clinical drug testing prior to 1962. The LSD research programs that remained after 1962 were hospital based, large-scale, systematic, and well-
controlled clinical trials assessing treatment outcome—the form of research that not only complied with FDA requirements, but also which had the best chance of resulting in convincing proof of efficacy. Additionally, the FDA not only objectively regulated LSD research according to the law, but also actively and voluntarily worked with the National Institute of Mental Health and Veterans Administration to save it from extinction after Sandoz withdrew its sponsorship of the drug in 1966.

While the regulations of the 1960s and 1970s did not prohibit LSD psychotherapy research, the Drug Amendments of 1962 did frustrate the progress of research by requiring researchers to use a method of efficacy testing that was poorly suited for the treatment. The randomized double-blind controlled trial methodology was designed to isolate a treatment’s “true” effects from any placebo effects, through blindly comparing the experimental treatment with a comparison treatment that incorporated all the nonspecific variables of the experimental treatment, but not the theoretically effective specific variables. This was a simple and effective strategy when a treatment’s only specific variables were the drug and how it was administered. However, LSD psychotherapy incorporated extensive psychotherapy, therefore not only was finding an adequate control condition to allow blinding near impossible, but the lines between specific and nonspecific variables were blurred—the very concept of the placebo effect was complicated when factors such as suggestion, expectation, and empathic support were integral parts of treatment.
As psychiatric and psychological researchers attempted to follow-up the claims of effectiveness for psychedelic therapy in the treatment of alcoholism in the years after 1962, they faced the difficulty of incorporating its unique treatment methods into the randomized controlled trial framework. In doing so, many of the researchers expressed their bias for chemotherapeutic treatments by stripping psychedelic therapy of its psychotherapeutic framework. The debased treatments produced negative results. The researchers at Spring Grove State Hospital, later the Maryland Psychiatric Research Center, maintained and developed the original treatment method of psychedelic therapy. They attempted to balance the clinical requirements of their treatment with the methodological requirements of randomized controlled trials. Yet their need to find an active placebo treatment to blindly compare with psychedelic therapy left them using a control treatment that was too similar in effect to that experimental treatment. This influenced underwhelming results. Scientific authorities judged the trials on their design and results, rather than their treatments, leading them to conclude that LSD therapy was ineffective. Research subsequently dwindled, before coming to a halt in the mid-1970s.

While this argument accounts for the demise of LSD research in the 1970s, answering why LSD failed to become an accepted tool of medicine also involves further considerations. After 1962, without proof of efficacy through controlled clinical trials, the FDA could not approve a New Drug Application (NDA) for LSD. In this way, the research difficulties of the post 1962 period frustrated the prospects of anyone submitting an NDA. Yet this does not explain why Sandoz did not submit an NDA prior to 1962, did little to direct research towards NDA
development, and withdrew its sponsorship of LSD before the conclusion of the post 1962 controlled trials. In these regards, consideration needs to be given to how the limited financial incentives that LSD provided, and the increasing controversy over its non-medical use, could have influenced Sandoz to take a backseat role in LSD’s development, and to prematurely withdraw its sponsorship. While research continued after Sandoz’s withdrawal, without a pharmaceutical company to strategize and finance LSD’s development, the prospects of research resulting in an NDA were poor.

As well as providing a new analysis of the history of LSD psychotherapy research in the United States, this thesis has broad implications for the history of psychiatry and pharmaceutical research and development, as it charts the complex relationships between clinical science, regulation, and therapeutics. LSD psychotherapy’s emergence in the 1950s reflected the eclectic nature of psychiatry in the post-war period. Although the discipline has often been characterized as divided between the conflicting paradigms of psychodynamic and biological psychiatry, more recent research has emphasised how in practice psychiatrists were not constrained by their theoretical frameworks. Psychiatrists frequently took an eclectic and pragmatic approach to treatment, utilizing a mixture of psychological, physical, and pharmacological methods. This is perhaps nowhere better demonstrated than in the case of LSD psychotherapy, where psychiatrists from a variety of backgrounds wove together drug effects and psychotherapy to create therapeutic experiences greater than the sum of their parts. Psychodynamic psychiatrists such as Harold Abramson used the drug to deepen and quicken the process of psychotherapy, while the biologically
orientated psychiatrists Humphry Osmond and Abram Hoffer developed psychedelic therapy on the basis of observations made during attempts to simulate delirium tremens in alcoholic patients.

The Drug Amendments of 1962 changed this scenario, as they required psychiatry’s drug treatments to conform to efficacy standards that the unregulated psychotherapies did not. The conceptual and practical difficulties in evaluating LSD psychotherapy through randomized double-blind controlled trials reveals how the supposedly objective testing methodology carried with it an assumption that a drug’s therapeutic activity was based on a direct biological action. This assumption reflected the magic bullet antibiotics that were pharmacology’s greatest success story, and which randomized controlled trials had been developed and popularized alongside. The breakthrough psychiatric drugs of the 1950s—the tranquilizers, antidepressants, and anxiolytics—conformed to the magic bullet form of drug therapy, and their efficacy was easily established through double-blind trials. By contrast, LSD psychotherapy faded from psychiatry as researchers struggled to demonstrate the efficacy of their neither purely pharmacological nor psychological treatments. Increasingly psychopharmacology became solely orientated towards magic bullet treatments, while psychiatrists focusing on psychological forms of treatment abandoned their use of drugs as facilitators. Even without the passage of the Drug Amendments of 1962, the success of the magic bullet psychoactive drugs would have led to a tightening of the relationship between psychopharmacology and biological concepts of drug efficacy in mainstream psychiatry. Nevertheless, without the regulation researchers interested in drug-assisted psychotherapy
would have faced less insurmountable obstacles in establishing their niche in psychiatry.

The case of LSD psychotherapy under the Drug Amendments of 1962 therefore highlights the complex interplay between clinical science, regulation, and therapeutics in post-war American medicine. Clinical scientists’ rising concern for objectivity in research, and their experience with the wildly successful magic bullet drugs, led them to develop and promote the randomized controlled trial as the gold standard form of efficacy testing. Legislators and regulators, concerned that drugs available to the public were effective, therefore incorporated the methodology into the required development path for drugs. In doing so, however, they did not simply ensure that efficacy testing would be objective, but shaped future drug research to conform to the magic bullet concept of drug efficacy. For psychiatry, this drove a wedge between pharmacology and psychology in research and treatment: psychoactive drugs were regulated in a way that presumed they acted objectively on the brain, while psychotherapy remained unregulated as it acted subjectively on the mind. The hitherto purely theoretical rift between biological and psychological treatments in psychiatry therefore became formalized. Drug-assisted psychotherapy subsequently faded from psychiatry. Clinical science therefore influenced regulation, which in turn influenced clinical science and therapeutics in profound and unintentional ways.

Although this thesis has explored the complexity of the concept of drug efficacy, and many of the theoretical and practical limitations of randomized controlled trials, in intent, the efficacy requirements of 1962 amendments were clearly in
the best interests of American society. Ineffective treatments had the potential not only to waste the time and money of patients and health care providers, but also to cause harm by replacing other more effective treatments. The randomized controlled trial was an ideal methodology for evaluating most conventional drug treatments. Yet, while the long and rigorous process of efficacy evaluation can protect patients from ineffective treatments, it can also harm them by excessively delaying their access to new effective treatments. Regulating efficacy in the best interest of patients therefore involves balancing complex risk versus benefit equations.

This thesis has shown that the negative reports of efficacy for psychedelic therapy in alcoholism were based on flawed research, and that the FDA and scientific community’s insistence on randomized controlled trials frustrated LSD psychotherapy research. However, it is ultimately not clear whether the end result was the public being spared from an ineffective treatment, or being denied an effective one. Prior to 1962, careful uncontrolled empirical research, performed by responsible scientists, led to the discovery of many effective drug treatments. Ultimately how useful a drug was came clear over time through its widespread routine clinical use. As historian Edward Shorter has emphasized, requiring proof of efficacy through comparison to an inert placebo does not ensure that drugs approved for sale are useful, as they may be effective but less so than other drugs already on the market.¹ Therefore, the market will often remain the ultimate site of efficacy evaluation. This thesis therefore highlights

the importance of sensitively weighing the need for definitive research against
the potential significance of treatments, when standard research techniques are
problematic. Alcoholism was, and remains, a severely debilitating illness, to both
the individual and society, associated with considerable mortality, and with
limited treatment options. With such an illness, it would seem necessary to ask
whether the risk to patients in leaving them untreated outweighs the risk that
the apparent benefits from treatment may be due to nonspecific factors.

Since the 1990s a modest but significant resurgence in psychedelic research has
been underway in the United States. Since the mid 2000s, Charles Grob at the
University of California, Los Angeles, Roland Griffiths at Johns Hopkins
University, and Stephen Ross at New York University have led renewed research
into psychedelic therapy for the treatment of anxiety associated with terminal
cancer, using psilocybin, however, rather than LSD.2 The researchers’
understandings of the history of psychedelic research will likely play a major
role in shaping their studies. While it is still early days for the research led by
Griffiths and Ross, Grob has completed a small pilot study, and results appear
promising.3 Even so, it is significant that Grob frames his research in relation to

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2 These studies are supported by the Heffter Research Institute, a non-profit organization
founded in 1993 to promote research with classical hallucinogens. For an overview of the
studies, see <www.heffter.org> viewed 10 December 2013. The Multidisciplinary Association for
Psychedelic Studies (MAPS), a non-profit organisation founded in 1986, also supports research
with psychedelics as well as marijuana. Its primary focus has been developing
methylenedioxymethamphetamine (MDMA) for the treatment of post-traumatic stress disorder.

3 Charles S. Grob et al. "Pilot Study of Psilocybin Treatment for Anxiety in Patients with
Advanced-Stage Cancer," Archives of General Psychiatry 68, no. 1 (2011), pp. 71-78. While the
Johns Hopkins psilocybin trial with cancer patients is still underway, the research team has
published research exploring the drug’s effect on healthy volunteers. In a double-blind
randomized study they confirmed that the drug could produce mystical types of experiences that
were of great meaning to subjects, and to which subjects attributed lasting positive changes in
their attitudes and behaviour. Significantly, this research team includes Spring Grove researcher
William Richards. See R. R. Griffiths et al., "Psilocybin Can Occasion Mystical-Type Experiences
the standard narrative of psychedelic research's earlier demise, seeing it as cut short by controversy and prohibitive regulation before it reached scientific maturity. He therefore argues that closely adhering to rigorous scientific standards is the best way of avoiding the fate of the previous era. Indeed, in an article on the lessons learnt from past research, Grob wrote “In the future, the putative value of hallucinogens in psychiatry can no longer rest on claims deriving from anecdotal case studies, as inspiring as they may be, but rather must evolve out of the findings of well-structured, controlled, scientific investigation.”

Missing from his discussion is recognition that this statement almost exactly mirrors many made by researchers in the early 1960s. Further missing is recognition that those researchers did in fact attempt such rigorous research, but that the problematic practical and theoretical relationship between psychedelic therapy and the randomized controlled trial prevented a clear picture of treatment efficacy from emerging.

While these trials utilized LSD in the treatment of alcoholism, rather than psilocybin for anxiety associated with terminal cancer, the treatment method is essentially the same, therefore the same research difficulties can be expected.


5 Grob does recognize that reports of LSD’s efficacy were criticised on the grounds of poor research methodology in the 1960s, and that some researchers (including Ludwig, Levine, and Stark) conducted controlled trials that reported negative results. However he portrays these trials as deliberately "designed to refute" the efficacy of LSD therapy, and does not discuss the difficulties researchers who had a positive outlook on psychedelic therapy (such as those at Spring Grove) had proving the efficacy of their treatments though controlled research. See Ibid., pp 16-17.
Grob, considering that utilizing the prevailing scientific method would bring rationality to the tempestuous topic of psychedelics, designed his study as randomized and double-blind: patients received treatment sessions with both psilocybin and a niacin placebo, in random order. Unsurprisingly, however, investigators and subjects alike could differentiate between the two drugs. Grob’s report, published in 2011, describes a treatment setting and guidance similar to that of the psychedelic therapy sessions of the Spring Grove studies, and discusses the importance of building rapport and trust with patients prior to the sessions. This was done through discussions reviewing past and present life issues, the goals of treatment, and issues to be examined during drug sessions, as well as preparatory discussions on drug effects. Follow-up discussions after the drug sessions are also mentioned.6 Yet the term “psychotherapy” is never used, and average durations for the pre and post-treatment discussions are not given. Why this is the case is not clear, however researchers need to be careful to emphasize that the drug is merely a component of a psychotherapeutic treatment, rather than a treatment in itself, lest treatment methods again become overshadowed by research methodology. Furthermore, while Grob argues that “To maintain an iconoclastic insistence that the very nature of these substances transcends standard research designs would be to prolong their marginalization,” equally, ignoring the problematic relationship between psychedelics and controlled trials could again lead to cycles of inconclusive research.7 For psychedelic research to progress, a nuanced and accurate understanding of the frustrations of the previous era of research is needed.

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7 Grob, “Research with Hallucinogens,” p. 15.
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