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Rehabilitating LSD history in postwar America: Dilworth Wayne Woolley and the serotonin hypothesis of mental illness

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Abstract
Revisiting the history of postwar LSD (lysergic acid diethylamide) research illuminates how the work of a chemist at the Rockefeller Institute contributed to the development of a biochemical paradigm for mental functioning. Dilworth Wayne Woolley proposed one of the first theories of the biochemistry of mental illness based on empirical evidence. His research with LSD and serotonin had wide-ranging repercussions for pharmacology and fit neatly into the emerging medicalization of mental illness. Reevaluating Woolley's ideas and the fruits of psychopharmacology leads to possible new approaches toward mental health and illness when considered alongside lessons learned from past research with psychedelic substances, and exemplifies a broader paradigm shift in cultural studies toward a biopsychosocial model that acknowledges the intersections between biology and culture.

Keywords
Biochemistry, biopsychosocial, LSD, mental illness, psychedelics, neuroscience, pharmacology, serotonin, Woolley

There is a small piece of the history of LSD (lysergic acid diethylamide) that has not been told in whole or framed within the larger context of the post-World War II history of psychiatry and psychopharmacology. In the 1950s and early 1960s, a chemist named Dilworth Wayne Woolley proposed a biochemical theory of mental illness based on

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analysis of the chemical structure of LSD and other psychedelic substances and their mind-altering properties. Retrieving this specific history can expand our knowledge of the role psychedelics played in the history of psychopharmacology, illuminate the current renewed interest in psychedelic research, and suggest some considerations for future research.

LSD, a mind-altering substance that has been illegal in the US since 1966, has a variegated history. It was first synthesized in 1938, and its psychoactive properties were discovered in 1943. Following the 1953 publication of Aldous Huxley's *Doors of Perception*, in which the public intellectual described his experience with mescaline and theorized various interpretations of it based on his extensive knowledge of philosophy and world religions, a handful of doctors and scientists began investigating psychedelic substances, including LSD. Psychedelics excited many researchers for the possible ways they might shed light on mental illness as well as mystical experiences. An initial wave of experimentation in the 1950s and early 1960s among intellectuals, the US military, artists, psychiatrists, and others interested in its mind-altering properties morphed into experimentation with LSD and other psychedelic substances as recreational drugs in the mid-1960s. The pharmaceutical company Sandoz, which had been supplying researchers with LSD, began to restrict the supply and California made LSD illegal. Shortly after this, in 1966, Congressional hearings concluded that LSD should be illegal on the federal level, and nearly all official research ended. A trickle of underground research continued (as did street use), and in the last few decades what has been called a psychedelic 'renaissance' or 'revival' of research has occurred.[1] Although the possible uses of psychedelic substances are still contested and research is tightly controlled, US regulatory agencies, including the Food and Drug Administration, began allowing limited studies in the 1990s. A growing body of research reveals promising results for specialized methods of psychedelic therapy treating anxiety in terminally ill patients and individuals suffering from post-traumatic stress disorder, and popular interest in these nontraditional healing methods has blossomed, as has exploration of psychedelic substances to explore spiritual growth. Also, advances in neuroscience and technology such as imaging technology have augmented our ability to understand the brain and consciousness in new ways and allow researchers to revisit the neurobiology of psychedelic substances.[2]

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1. In 2008, Erika Dyck called the renewed interest in therapeutic use of psychedelic substances a "revival" (Erika Dyck, *Psychiatric Psychiatry: LSD from Campus to Clinic* (Baltimore, MD: Johns Hopkins University Press, 2008), p.139). Her book was one of the first in a growing body of publications signaling renewed interest in psychedelics. See also Ben Sessa, "Shaping the Renaissance of Psychedelic Research," *The Lancet* 380 (2012): 200–1; Nicolas Langlitz, *Neuropsychedelia: The Revival of Hallucinogen Research since the Decade of the Brain* (Berkeley, CA: University of California Press, 2013).
2. An extensive article in the 9 February 2015 issue of *The New Yorker* offers an overview of contemporary psychedelic research within the medical field (Michael Pollan, "The Trip Treatment"). See also Tom Schroder, *Acid Test: LSD, Ecstasy and the Power to Heal* (New York: Penguin Group, 2014). Numerous books and popular culture references had appeared in the years previous to the publication of this article on the topic of using psychedelic substances or entheogens for spiritual and healing purposes.

As the psychedelic renaissance moves forward, a look back on previous research can rehabilitate the history of LSD and its cultural import and nudge us toward understanding how biology and culture intersect. Unearthing past research with LSD can illuminate a forgotten piece of medical and psychiatric history and suggest new directions for healthcare fields and cultural studies. Quite a bit has been written about the cultural history of psychedelics in the US, but its role in the development of psychopharmacology remains obscure. Historians of psychopharmacology David Healy and Elliot Valenstein, and neuropharmacologist Patricia Whitaker-Azmitia, are unique in their recognition of the role of LSD research in the development of psychopharmacology. More often, histories of psychology and psychiatry do not elaborate upon the role that psychedelic substances played in the development of biochemical theories of mental functioning. If LSD is mentioned at all, it is mentioned briefly. More often, the substance, which is odorless and colorless and can alter human consciousness profoundly, remains invisible. For example, a 2010 compendium of psychiatric history refers to the early work with psychedelic substances generically, without detail of any of the major figures or theories involved, as producing the 'toxic theory' of schizophrenia, which proposed that a metabolic error resulted in psychosis.[3]

However, in postwar America, when the fields of psychology and psychiatry were exploding, a handful of researchers were experimenting with LSD and other mind-altering substances to see what they could learn about mental illness. At the Rockefeller Institute, just north of New York City, a chemist named Dilworth Wayne Woolley conducted his investigation of LSD quietly, and proposed a theory of the biochemical basis of mental illness based on his findings. This theory was part of larger transitions taking place in mental healthcare that embraced pharmacological agents to arrest symptoms of severe mental illness and proposed new policies based on a belief in community care. A paradigm shift was taking place, and Woolley's research with LSD was part of the transition. Healy notes that "The identification of 5HT (serotonin) in the brain, recognition of its affinities with LSD, and the suggestion that LSD might act on 5HT receptors were the first hints of the revolution to come."[4] Although Healy and Valenstein have written exhaustive accounts of the history of psychopharmacology that include Woolley's work, and scholars like Edward Shorter, Gerald Grob, David Mechanic, E. Fuller Torrey, and others have illuminated the shifts in psychiatry of the post war era, little attention has been paid to the cultural repercussions of Woolley's research with LSD. In a 1999 paper about the history of serotonin, Whitaker-Azmitia provides the most complete published account of Woolley's research, and yet fails to flesh out its cultural significance.[5]

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3. Edwin R. Wallace and John Gach, *History of Psychiatry and Medical Psychology: With an Epilogue on Psychiatry and the Mind-Body Relation* (New York, NY: Springer Science and Business Media, 2010), p.403.
4. David Healy, *The Anti-Depressant Era* (Cambridge, MA: Harvard University Press, 1997), p.148.
5. Patricia Mack Whitaker-Azmitia, "The Discovery of Serotonin and its Role in Neuroscience," *Neuropsychopharmacology* 21 (1999): 2S–8S. Whitaker-Azmitia provides succinct biographies of the researchers involved in the discovery of serotonin and subsequent research with serotonin, including D. W. Woolley.

During World War II and the subsequent decades, many factors coalesced to heighten interest in mental health. The sheer number of potential soldiers who were turned away from US military service as psychologically unfit prompted a desire to understand mental illness, as did the psychological problems soldiers experienced when they returned from service. The number of people confined in psychiatric institutions in the 1950s skyrocketed, and they were being held for long periods of time with little hope of recovery.[6] Freudian ideas had galvanized the study of the psyche in the early 1900s, and these theories experienced a resurgence in popularity in the US in the 1950s. However, these theories existed alongside a long historical arc of trial and error in treating mental illness with somatic methods. The desperation of those suffering severe mental illness, their families, and their doctors is evidenced by the use of insulin treatment, electro-convulsive therapy (ECT), and even psychosurgery techniques (lobotomy) throughout the 1930s–1960s. Although each of these treatments resulted in improvement in some patients, each had drawbacks, and not one was based on a theory of the origin of mental illness founded on empirical evidence. The same is true of the psychotropic medications, also called neuroleptic drugs, developed in the 1950s. The postwar years ushered in what medical historian Edward Shorter calls "the second biological psychiatry"[7] when neuroleptic medications became increasingly popular, even though there was little understanding of how they worked. Nor, doctors acknowledged, were the medications able to cure mental illness. They arrested symptoms and made patients more functional and manageable. Given the bleak prospects for those suffering severe mental illness, this was welcome progress. Drugs that could curtail symptoms of mental illness lent credence to ideas of a biological basis for severe conditions like schizophrenia and bipolar disorder (formerly called manic depression).

One of the first successful psychiatric medications was chlorpromazine (10-(3-dimethylaminopropyl)-2-chloro-phenothiazine) (CPZ), sold by Smith, Kline & French as Thorazine. It was hailed as a 'miracle drug' with the 'revolutionary' ability to control the symptoms of severe mental illness enough to allow patients to leave institutions.[8] The pharmaceutical industry surely noted that CPZ increased the sales volume of Smith, Kline & French by an astounding one-third.[9] Tranquilizers like meprobamate (marketed in 1955 as Miltown) and reserpine (a natural substance called *rauwolfia serpentina*, marketed as Serpasil by Ciba Pharmaceutical), and the first tricyclic antidepressant, imipramine (marketed as Tofranil by Geigy in 1957), quickly became staples of treatment for patients in mental institutions in the US.[10] Iproniazid, first synthesized in

6. E. Fuller Torrey, *American Psychosis: How the Federal Government Destroyed the Mental Illness Treatment System* (Oxford, UK: Oxford University Press, 2013), pp.22–3.
7. Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (New York, NY: John Wiley and Sons, 1997), p.238.
8. Judith P. Swazey, *Chlorpromazine in Psychiatry: A Study in Therapeutic Innovation* (Cambridge, MA: MIT Press, 1974), p.160.
9. Swazey, *Chlorpromazine in Psychiatry*, p.160 (note 8).
10. Meprobamate was synthesized in 1950. Nathan Kline developed reserpine for psychiatric use at Rockland State Hospital in New York. He later demonstrated that iproniazid was an MAOI. Swazey, *Chlorpromazine in Psychiatry*, pp.191–3 (note 8). See also Shorter, *A History of Psychiatry*, p.261 (note 7) for a narrative of the development of imipramine and Gerald Grob, *From Asylum to Community: Mental Health Policy in Modern America* (Princeton, NJ: Princeton University Press, 1991), p.149.

1951 and used to treat bone and joint lesions in tuberculosis, began a career as an antidepressant when doctors noted that it caused euphoria in patients.[11] Some doctors even hoped that these drugs could convince society that mental illness was a physiological disease, thus reducing the stigma of mental illness as a perceived character defect. A 1958 article in *Science* noted:

> the new drugs may aid in the production of a desirable change in our culture and remove mental disease from the field of mysticism and superstition. They may convince the public that mental disease is not a thing to be ashamed of and that it should be placed in the same category of any other disease which can be treated by medical means.[12]

If the symptoms of mental illness could be treated with medications, perhaps the illness fit a medical model of disease, postulating a biological origin, rather than Freudian paradigms theorizing an origin in childhood experiences, or the popular beliefs that mental illnesses were products of weak personalities, poor family environment, or character defects.

The flaw in this hope was that psychotropic drugs initially offered little insight into the origins of the mental illnesses that they were used to treat, because their physiological mechanisms were so difficult to pinpoint. The National Institutes of Mental Health did not even formally recognize the clinical efficacy of CPZ for psychosis until 1964.[13] Exactly how psychotropic drugs work to arrest symptoms of mental illness remained (and still remains) mysterious. For example, CPZ seemed to act on monoamines, but scientists could not agree on how it acted. Some studies showed that CPZ increased serotonin levels in the body; some studies showed that it had no effect on serotonin.[14] In 1955, researchers at Bernard Brodie's Laboratory of Chemical Pharmacology at the National Heart Institute linked the ability of reserpine to decrease serotonin levels in animal brains to a possible *biochemical* aspect of behavior. Although Shorter, Healy and other scholars call this research "the first hard-core link between biochemistry and behavior,"[15] and some histories mark the synthesis of CPZ as the origin of modern psychopharmacology,[16] these assertions overlook psychedelic research occurring at the same time as research with CPZ and reserpine and the role of LSD research in facilitating Brodie's research. Specifically, the importance of serotonin to mental functioning, first proposed by Woolley and Shaw in a 1954 article, arose from Woolley's recognition of LSD as an analog of serotonin.

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11. Iproniazid was marketed as Marsilid by Hoffmann La Roche. David M. Bosworth, "Iproniazid: A Brief Review of its Introduction and Clinical Use," *Annuals of the New York Academy of Sciences* 80(3) (1959): 809–19.
12. Harold E. Himwich, "Psychopharmologic Drugs," *Science* 127(3284) (1958): 59–72, 59.
13. Swazey, *Chlorpromazine in Psychiatry*, p.191 (note 8).
14. K. F. Gey and A. Pletscher, "Influence of Chlorpromazine and Chlorprothisxene on the Cerebral Metabolism of 5-hydroxytryptamine," *Journal of Pharmacological and Experimental Therapeutics* 133(1) (1961): 18–24.
15. Shorter, *A History of Psychiatry*, p.66 (note 7). Healy credits Brodie's research with establishing biochemical psychopharmacology (Healy, *The Anti-Depressant Era*, p.64 (note 4)), although he also acknowledges that Brodie's research built upon Woolley's serotonin thesis (Healy, *The Anti-Depressant Era*, p.148 (note 4)).
16. Wallace and Gach, *History of Psychiatry and Medical Psychology*, p.401 (note 3).

Humphrey Osmond, a British psychiatrist working in Canada, and Dilworth Wayne Woolley both proposed theories based on research with psychedelic substances that advanced biochemical theories of mental illness. A 1952 publication by Osmond had wide-ranging repercussions for research with psychedelic substances, both within and beyond the psychiatric fields. Osmond was the first to publish a theory of mental illness based on his subjective observations of the effects of mescaline, a mind-altering substance. He considered mescaline a useful tool to investigate the nature of schizophrenia, and many in the field of psychiatry agreed. Woolley's examination of the molecular structure of LSD, which prompted him to publish a theory that serotonin played a crucial role in mental illness (first published in 1954, subsequently published in book form in 1962), also took place in the early 1950s. Although neither man was a neuroscientist, their interest occurred during years in which the expanding fields of both psychiatry and neurochemistry were posing broad questions about the nature of human consciousness.

Neurochemistry, psychopharmacology, and psychedelics

In the first half of the twentieth century, the popular model for neural functioning was electrical rather than neurochemical. The origins of neurochemistry date as far back as J. L. W. Thudichum's 1884 book *Chemical Constitution of the Brain*, but the field did not enjoy much attention for quite some time.[17] Even when evidence for biochemical mechanisms in the human body was extant, most scientists were skeptical that biochemicals like epinephrine (isolated in 1898) and acetylcholine (isolated in 1904) were crucial to neural functioning. Many scientists believed that biochemical mechanisms affected only peripheral nervous systems, not the central nervous system or brain. Advances in biochemistry such as the theory that cells had receptors that responded to biochemicals according to the presence of excitatory or inhibitory substances (proposed by John N. Langley in 1905), and even the specific theory developed in the 1930s that norepinephrine inhibited epinephrine, didn't result in overarching theories of biochemical action in the central nervous system or brain.[18] Nor did researchers link biochemistry to mental states or behavior.[19] It was only in the 1950s, when a confluence of factors allowed researchers to slowly begin understanding the importance of biochemistry, that the fields of neurochemistry and psychopharmacology began to develop.

Irving Page, who helped create the Department of Brain Chemistry at the Kaiser Wilhelm Institute for Psychiatry in 1928, noted in 1957 that neurochemistry was a recent interest for biochemists and psychiatrists, and even for neurologists. According to Page, several factors in the postwar era augmented interest, including the discovery of new drugs: anti-convulsants, tranquilizers, and LSD, and the discovery of new neurotransmitters, including serotonin. The development of psychopharmacology in the 1950s as an

17. Irvine H. Page, "Certain Aspects of the Chemistry and Metabolism of the Brain," in Madison Bentley and E. V. Cowdry (eds) *The Problem of Mental Disorder* (New York, NY: McGraw Hill Book Co., 1934), pp.162–77.
18. Wallace and Gach, *History of Psychiatry and Medical Psychology*, p.401 (note 3).
19. Healy, *The Anti-Depressant Era*, pp.143–7 (note 4).

applied branch of neurochemistry that investigated manipulating mental functioning with chemical substances arose from this research. Healy credits the term "psychopharmacology" to several different origins, but traces the development of the field in part to research with LSD. He recounts the history of trying to tease out aspects of the psyche with mind-altering drugs and explains that with the discovery of LSD researchers felt they had a new tool to create a "model psychosis," which, in tandem with the new medications that seemed able to arrest symptoms of mental illness, offered new promise for doctors who wished to understand the psyche.[20]

Intellectuals in the western world had long been experimenting with psychoactive compounds like mescaline, nitrous oxide, and peyote, and writing accounts of their adventures. Founding figures of the burgeoning discipline of modern psychology, including William James and Sigmund Freud, contributed their observations and reflections of altered states of consciousness and initiated a scientific approach to the study of the mind.[21] Post-World War II interest in using science to reengineer the self mated with the postwar growth of the U.S. pharmaceutical industry, and birthed a new interest in manipulating mental states with chemical substances. Healy describes a modern era of psychiatry running parallel to the modernization of medicine, in which ideology shifted to a belief that elements of mental functioning, similar to physical functioning, could be compartmentalized, targeted, and treated separately from broader contexts of health, society, or even the holistic functioning of the human body or mind.[22] This parceling out of elements of the psyche is a crucial forerunner to the biochemical model of mental functioning, and served as a catalyst to the desire to mechanistically tweak and tune up many aspects of the self in postwar America. Science conveniently provided substances that could arrest symptoms of psychosis, calm frayed nerves, or seemingly produce symptoms of psychosis on demand.

These discoveries posed profound questions about human consciousness, as well as the nature of mental illness. Specifically, what was the relationship between mind and body? The idea that human consciousness, or "psyche" or "mind," had a biological substrate was controversial, even into the 1950s. Page, who directed research at the Cleveland Clinic Foundation and was a professor at the Frank E. Bunts Educational Institute in Cleveland in the 1950s, addressed the threat inherent in a materialistic model of human functioning that he termed "switchboard theory." This theory, which predated the biochemical paradigm of mental functioning, conceived of human instinct and awareness as arising solely from electrical impulses in the brain. The biochemical model, like the electrical model, was also potentially materialistic. Although Page claimed, "I personally see nothing to persuade me that the functions of the brain are not the functions of protoplasm and that these functions encompass both the material and the transcendent," he admitted that discoveries in neurochemistry might "cast doubt on the religious nature of

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20. Healy, *The Anti-Depressant Era*, pp.112–14 (note 4).
21. S. L. Goulart, B. C. LaBate and H. Carneiro, "Introduction," in B. C. LaBate and S. L. Goulart (eds) *O Uso Ritual das Plantas de Poder* (Mercado de Letras: 2005), 22 October 2013; Mercado de Letras: Campinas/SP, Brazil 2004.
22. Healy, *The Anti-Depressant Era* (note 4).

man." Page proposed a reconciliation of the mind–body dilemma via study of both neurochemistry of the brain and the nature of thought. "The brain is no more than a physical mechanism, which, without the mind, is not unlike the so-called 'electric brains' of industry. But without the guiding mind, the brain comes to little. This is not a problem to be taken lightly, for the worlds of belief, of faith, of beauty, of happiness are at stake." Although Page urged investigators not to be overly enthusiastic in their investigation of psychedelic drugs to learn about the chemical causes of schizophrenia, he clearly saw value in this approach. He considered both LSD and serotonin to be key chemicals for learning about mental illness.

> The problem of the function […] of serotonin in the brain is far from solved. Its importance currently has been to provide, along with LSD, a nidus around which thinking about chemical reactions and the psyche revolve. It is such approaches as these that will […] provide many of the keys to the solution of the problem of mental disease.[23]

A small handful of researchers in the 1950s used psychedelic substances to probe these connections between mind and body. Prior to Woolley's serotonin theory, which will be discussed in the section "Dilworth Wayne Woolley's serotonin theory," was Humphry Osmond's substance M theory, prompted by his experimentation with mescaline.

Humphry Osmond's substance M theory

During his psychiatric training at the Royal Naval Hospital in Britain in the 1940s, one of the overriding problems confronting Humphry Osmond was his inability to empathize with the schizophrenic patients he treated. According to Osmond, doctors at the time had no concept of the profound visceral changes in perception that schizophrenic patients experienced. The common paradigm of mental illness as a stubborn inability to adapt to social norms inhibited serious investigation of the mental and sensory processes of the ill. Osmond noted that patients were usually reluctant to describe their experiences for fear of the repercussions. Discussing symptoms might lead to institutionalization and traumatizing somatic treatments (like ECT), further prolong his or her treatment, and subject the patient to judgmental attitudes from others. As Osmond noted, "doctors, nurses and friends often combine to make the patient so ashamed of his illness that he dare not talk about it." Few textbooks described the inner world of a person suffering a mental illness in depth, and practitioners were not especially interested in the subjective experience of their patients. For example, Osmond claims that few doctors would have considered asking a patient about synesthetic sensory experiences. "It is something which one would have never dreamt of asking a patient, unless one knew that such things can and do happen in this strange illness."[24] In an effort to learn more, Osmond read an autobiographical account of severe mental illness entitled *The Witnesses* by Thomas

23. Irvine H. Page, "Chemistry of the Brain: Past Imperfect, Present Indicative, and Future Perfect?" *Science* 125 (1957): 721–7.
24. Humphry Osmond, "On Being Mad," *Saskatchewan Psychiatric Services Journal* 1(2) (1952): 63–70, 63.

Hennell. This vivid narrative of Hennell's schizophrenic hallucinations, delusions, and other experiences served as a guide for Osmond as his career progressed. When Osmond ingested mescaline in 1950 he noted an important connection between his mescaline-induced state and the world of schizophrenia that Hennell described. The altered sensory perceptions, distortions of time and space, and intense sensitivity to his surroundings experienced under the influence of mescaline echoed many of the experiences Hennell recorded in *The Witnesses*.[25]

When Osmond claimed that mescaline "reproduced every single major symptom of acute schizophrenia"[26] in 1952, he created a theory of psychedelic experience that sparked further psychiatric research, and influenced mainstream interpretations of psychedelic experiences when it was restated in Huxley's book *The Doors of Perception*. Huxley, who read widely in both the arts and sciences, read Osmond's ideas with fascination and contacted Osmond to obtain some mescaline. Huxley's brief meditation on his mescaline experience, published in 1953, introduced the US public to the effects of mind-altering substances and the idea that these substances could illuminate vast expanses of the psyche, including wondrous emotional landscapes and hellish glimpses of madness.[27]

Not only did his mescaline experience help Osmond empathize with his patients, it led him to investigate a possible link between the biochemistries of mescaline and mental illness. He and his coworker, psychiatrist John Smythies, realized that the molecular structure of mescaline resembled the molecular structure of a chemical produced by the human body.

In their 1952 article entitled "Schizophrenia: A New Approach," Osmond and Smythies addressed the present state of knowledge about schizophrenia and proposed a new theory of its origin based on their experiences with mescaline. In the early 1900s Eugene Bleuler had theorized that schizophrenia was a metabolic disorder, and yet no definitive evidence had appeared to persuade mental healthcare professionals that mental illness originated in physical dysfunction. In the 1950s many Freudian psychoanalysts believed severe mental illness to be psychogenic in origin, even though it seemed to be very different from neurosis, which Freudian theory claimed was rooted in the interaction between childhood experiences and psychic mechanisms. Various non-Freudian professionals considered mental health problems to be a complex combination of factors, but a common characterization of emotional and mental problems was that they were

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25. Humphry Osmond, "Introduction," in Thomas Hennell, *The Witnesses* (New Hyde Park, NY: University Books, 1967), pp. VII–LVI, pp. XXII.
26. Osmond, "On Being Mad," p.64 (note 24). This is not accurate, and one of the criticisms of the adrenochrome theory rests on disputing the claim that perceptual distortions are the core of schizophrenia. John A. Mills, "Hallucinogens as Hard Science: The Adrenochrome Hypothesis of the Biogenesis of Schizophrenia," *History of Psychology* 13 (2010): 178–95, 190.
27. Elements of Osmond's description of his mescaline experience presage Huxley's description to an uncanny degree. Osmond described a fresh perception of a faded carnation and the "chairness" of a chair, as well as his reactions during a walk (Osmond, "On Being Mad," p.65, 66, 67 (note 24)). Huxley describes similar elements of his trip in *The Doors of Perception* (New York, NY: Harper & Row, 1954).

rooted in psychodynamics. A range of theories and treatments existed, but little evidence could move the mental healthcare field, or the public, to any definite conclusions.

After a brief review of extant literature about mescaline, Osmond and Smythies noted similarities between symptoms of mescaline intoxication and schizophrenia. They remarked upon the similar chemical structures of mescaline and adrenaline, and described the process by which adrenaline, also known as epinephrine, transforms into noradrenaline in the human body, also known as norepinephrine. The natural process entails the elimination of one methylene group from the original molecule. Osmond and Smythies theorized that if this process malfunctioned, a mescaline-like substance would be produced, thereby causing perceptual and sensory changes like those present in schizophrenia.[28] They called this substance 'the M substance'.[29] According to their theory, the presence of M in the human body would produce schizophrenic symptoms. Osmond used this theory to refute the idea that a mentally ill individual was caught up in a psychogenic drama or not trying hard enough to conform to society's rules. Osmond's theory attributed the origin of severe mental illness to a physical cause, and specifically to an internal biochemical malfunction. After his mescaline experience, Osmond determined that: "We can recognize that the schizophrenic person is not imagining or fantasying when he says that the world has changed and looks different: it is different for him […]. We must accept what he says as true." As a result, "we should listen seriously to mad people" when they attempt to describe their experiences.[30] Osmond was suggesting that rather than arising from – or signifying – a Freudian psychic drama, the delusions and hallucinations of schizophrenia or psychosis were caused by faulty biochemistry and experienced as absolutely real by the patient.

Biochemist Abram Hoffer joined Osmond and Smythies, both then working at the Saskatchewan Hospital in Weyburn, Canada, and together they sought substance M. Investigation revealed that adrenochrome, a substance that occurs when adrenaline degrades, could produce altered states of consciousness. The chemical structure of adrenochrome, also called "pink adrenaline" because of its characteristic color, resembled the chemical structure of mescaline. The authors theorized that certain individuals might produce adrenochrome when under stress.[31] "What was particularly elegant about this theory," historian Jay Stevens notes, "was the way it combined both a neurological and a psychological dynamic, thus marrying what were usually two mutually exclusive bodies of research."[32] The theory proposed biochemical action within a social context as an origin of schizophrenia. However, Hoffer, Osmond, and Smythies' theory proved difficult to verify. Although the theory enjoyed attention and some success for several years, the adrenochrome hypothesis could

28. The natural process is called the transmethylation of nor-adrenaline, meaning a methyl group moves from one compound to another.
29. Humphry Osmond and John Smythies, "Schizophrenia: A New Approach," *Journal of Mental Science* 98 (1952): 309–15.
30. Osmond, "On Being Mad," p.70 (note 24).
31. Abram Hoffer, Humphry Osmond and John Smythies, "Schizophrenia: A New Approach. II. Result of a Year's Research," *Journal of Mental Science* 100 (1954): 29–45.
32. Jay Stevens, *Storming Heaven: LSD and the American Dream* (New York, NY: Harper & Row Publishers, 1988), p.27.

not be proven, and in the late 1950s met with some stringent criticism.[33] Still, Osmond collaborated with Hoffer to pursue investigation into biochemical origins of mental disorders and their ideas continued to challenge psychodynamic theories and prompt interest in biochemical etiology, while still touting the need to listen to the subjective experiences of patients and locate those experiences within a cultural milieu.[34] They felt that understanding the ways different cultures used psychoactive substances might illuminate cultural interpretations of altered states of consciousness, including madness.

In the meantime, however, Aldous Huxley had footnoted Osmond and Smythies' theory in *The Doors of Perception* and pondered the origins of schizophrenia. He asked: "Is the mental disorder due to a chemical disorder? And is the chemical disorder due, in its turn, to psychological distresses affecting the adrenals?"[35] At the Rockefeller Institute, Woolley developed a different theory that advanced another biochemical theory of mental illness. Parallel to the substance M theory in its search for a biochemical in the human body that could alter consciousness, Woolley's serotonin hypothesis was more sophisticated and more fruitful.

Dilworth Wayne Woolley's serotonin theory

In 1948, Woolley, a chemist who has been virtually forgotten, won the Eli Lilly award for promising young American scientists. It was not the first time he had achieved such distinction. Although Woolley died in 1966, his career at the Rockefeller Institute was consistently stellar. Not only did he make significant contributions to the field of nutrition, but his investigation into the properties of LSD helped shift paradigms of the etiology of mental illness, particularly schizophrenia. Woolley's serotonin theory of mental disorder helped direct psychiatry away from psychogenic models, to models that considered a biochemical origin for mental illness. The interdisciplinarity of his knowledge, entwining chemistry, psychiatry, and pharmacology, is indicative of the cross-fertility of these fields in the postwar United States and foreshadows the development of neuroscience as an interdisciplinary field in the 1970s.

Woolley's early career as a chemist portended his later successes. Woolley accrued first-class honors when he graduated from the University of Alberta in 1935. He left

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33. Mark D. Altschule and Zoltan L. Hegedus, "The Adrenochrome Hypothesis of Schizophrenia—1972. The Role of Rheomelin Formation in Some Toxic Effects of Catecholamine Derivatives," in David Hawkins and Linus Pauling (eds) *Orthomolecular Psychiatry: Treatment of Schizophrenia* (San Francisco, CA: W.H. Freeman & Co., 1973), pp.93–119. See Mills, "Hallucinogens as Hard Science," (note 26) for a history of the rise and fall of the adrenochrome hypothesis and a critique of its flaws. Some of the methodological flaws, for example, include misdiagnosis of schizophrenia in the patients used in the experiments and lack of accounting for spontaneous recovery from schizophrenia. Even Smythies later critiqued his research methods. In: John Smythies, "The Adrenochrome Hypothesis Revisited," *Neurotoxicity Research* 4 (2002): 147–50.
34. Dyck, *Psychiatric Psychiatry*, pp.45–7 (note 1). Dyck provides an extensive history of the research with psychedelics in Canada.
35. Huxley, *The Doors of Perception*, pp.11–12 (note 27).

Canada to attend the University of Wisconsin, where he studied agricultural chemistry in C. A. Elvehjem's nutrition laboratory and met and collaborated with his future wife, Janet McCarter, a bacteriologist.[36] Woolley made "brilliant" contributions to the isolation and identification of the B3 vitamin (nicotinic acid, also called niacin) and the discovery of its role in preventing pellagra. Shortly after, he synthesized and purified pantothenic acid, another important B vitamin.[37]

At the time of his graduation, a letter of recommendation described Woolley as "an unusual youngster" and one of the most outstanding graduate students of the past ten to fifteen years, who "devote(d) himself indefatigably and enthusiastically to his research." His professor, Harry Steenbock, described Woolley as a "modest," "fine chap," and an omnivorous reader who kept abreast of many lines of research and published ten articles during his graduate school career. In spite of Woolley's modesty, he was confident; the kind of person who "translates his knowledge into action with little if any hesitancy."[38] A second letter of recommendation praised Woolley highly and described him as equal to the older faculty in his maturity and grasp of knowledge. "[He is] one of the most outstanding research students I have had contact with in 25 years. I would not rate him second to any."[39]

Woolley's career fulfilled the early promise revealed when he was a student. His early expertise focused on the molecular mechanisms of vitamins and the factors that inhibited vitamins, and he pioneered work in understanding antimetabolite action. Woolley's work had far-reaching implications for treating vitamin deficiencies, developing new drugs, and understanding metabolic mechanisms,[40] and garnered many awards in relevant fields. In December 1940, at age 26, Woolley won his first Eli Lilly award, bestowed by the Society of American Bacteriologists for exceptional contributions in bacteriology.[41] The American Institute of Nutrition awarded Woolley a Mead Johnson Prize in 1945 for his work on vitamins,[42] and his research on vitamins and antivitamins garnered a second Lilly Prize and $1,000, a tidy sum in 1948, awarded at the annual American Chemical Society meeting. *The New York Times* highlighted the importance of Woolley's award with a photograph of him. The previous year, Woolley had accepted a research award from the American Pharmaceutical Manufacturers Association.[43] In 1949, The University of Amsterdam

36. Thomas H. Jukes, "Dilworth Wayne Woolley (1914–1966)," *Journal of Nutrition* 104(5) (1974): 509–11.
37. George W. Corner, *A History of the Rockefeller Institute: 1901-1953: Origins and Growth* (New York, NY: The Rockefeller Institute Press, 1964), pp.374–5.
38. Harry Steenbock to Dr. H. A. Matthill, 3 June 1938. Rockefeller Institute Archives, Woolley file 450 W885, folder 1.
39. W. H. Peterson to H. A. Mattill, no date, Rockafeller Institute Archives, Woolley file 450 W885, folder 1.
40. Daphne A. Roe, "Impact of the Pioneer Work of Dilworth Wayne Woolley on Antimetabolite Research," *The Journal of Nutrition* 117 (1987) 10: 1324.
41. "Scientific News and Notes," *Science* 93 (1941): 57–8.
42. "Scientific News and Notes," *Science* 101 (1945): 402.
43. "Award Scheduled for Blind Chemist: Rockefeller Institute Associate will get $1,000 Lilly Prize at Session Sept 1," *The New York Times*, 10 August 1948, p.19. "$1,000 Lilly Prize Goes to Rockefeller Chemist," *The New York Times*, 31 August 1948, p.25.

bestowed an honorary medical degree upon Woolley, and the University of Alberta awarded him an honorary degree in 1958.[44] Woolley served as president of the Institute of Nutrition in 1959.[45] He established himself at the elite Rockefeller Institute for Medical Research (which later became Rockefeller University) during the span of his career.

Woolley had emerged from his doctoral program at the University of Wisconsin at an auspicious time, poised to succeed in a field that was entering an upswing. Biological chemistry had coalesced into a field in the first decade of the 1900s as the American Society of Biological Chemists formed, and *The Journal of Biological Chemistry* and *Biochemistry Journal* began publication. The Food and Drug Act of 1906, which required food labels to list all ingredients, had inspired chemists to concentrate on chemical analysis, and the majority of research in the early twentieth century focused on amino acids, nucleic acids, and protein metabolism. This rudimentary research acknowledged the importance of some vitamins during the second decade of the century, and biochemists and organic chemists developed a deeper interest in nutrition during the 1920s. Shortly after Woolley completed his doctoral degree in 1938, the field of nutritional biological chemistry began to blossom. World War II prompted research into food composition, which resulted in important progress in the isolation, characterization, and synthesis of vitamins during the 1940s,[46] as well as new theories of chemical interactions. Woolley was part of that progress.

As a scientist during World War II and the decades following, Woolley exemplified what *Fortune* magazine called "the most characteristic figure of the age," and yet his position in research rather than applied science made him a rare figure. During the war years, U.S. government funding for science and industrial enterprises increased and funding continued to grow after the war. (note 47) By 1947, the government budget for scientific research had risen to $1.2 billion, triple the 1940 budget, and continued to increase during the 1950s. However, although more college students than previously were majoring in science, and scientists were earning more than ever, the popular fields of nuclear physics and electronics attracted the most attention, while other areas suffered. Few scientists embarked upon careers in research and a shortage of scientists especially affected basic research fields such as physics and math. In 1947, The Steelman Report on science and public policy reported that scientific workers comprised less than 1% of the population, and that a mere one-sixth of scientists held doctoral degrees. According to *Fortune* magazine, the individuals who entered scientific professions were poised to enjoy freedom of thought in spite of scrutiny imposed by Cold War fears of espionage. "Science is probably the only profession that not only encourages radical thought, in the sense of an experimental search for new principles below the surface of the accepted, but reserves its highest honors for radical ideas."[47]

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44. "Wayne Woolley, Researcher, Dies: Blind Rockefeller Professor an Authority on Vitamins," *The New York Times*, 26 July 1966, p.35.
45. Jukes, "Dilworth Wayne Woolley (1914–1966)," p.509 (note 36).
46. C. A. Elvehjem, "Seven Decades of Nutrition Research," *Science* 109 (1949): 354–8.
47. Henry Luce, "The Scientists: A Sympathetic Portrait," *Fortune* (October 1948): 106–12, 166–76.

Deltev Bronk, who was chairman of the National Research Council in 1949, pointed out that "society will gain the most from scientists if they are given the freedom to observe, to experiment and think."[48] The Rockefeller Institute, which Bronk directed between 1953 and 1968, offered its scientists a tremendous degree of freedom to conduct the research of their choice.[49]

In the first decades of the twentieth century, The Rockefeller Institute, which had been founded in 1903 by John D. Rockefeller, had established itself as the nation's premier research institute,[50] in part due to its policy of scientific freedom. While Bronk directed the Rockefeller Institute, he encouraged Woolley and the other researchers at the institute to pursue their interests in accordance with Rockefeller Institute "traditions of exacting devotion to excellence, freedom for self-directed research as a means of teaching and learning, [and] a truly international staff of eminent scientists, and courage to adventure."[51]

Woolley achieved much at the Rockefeller Institute, where he began working the year after he received his doctorate and remained until his death in 1966. In 1938, Woolley spoke with the director of the institute, Herbert S. Gassner, about the possibility of setting up a nutrition unit. Although Gassner at first said the lab was not immediately possible, he offered Woolley a position[52] and within a few months agreed to provide facilities for research in bacterial nutrition.[53] Within three years, Woolley discovered three new vitamins.

Woolley's discovery of the vitamins applied cutting edge methods in the forefront of scientific thought during World War II and the postwar era. Although Woolley began his vitamin research a decade before Norbert Weiner coined the term "cybernetics,"[54] he used fundamental cybernetic principles of positive and negative feedback. Cybernetics is a systematic method based on communication theory in which a system relies on information produced by the system to alter itself according to that same information. Positive feedback increases what the system is doing, while negative feedback decreases the system's operation, changes the direction of the system, or otherwise opposes the system functions. In 1949, expert in cybernetics Churchill Eisenhart claimed that cybernetics was "of vital importance to psychologists, physiologists, electrical engineers, radio engineers, sociologists, philosophers, mathematicians, anthropologists, psychiatrists, and

48. Detlev W. Bronk, "Science and Humanity," *Science* 109 (1949): 477–82.
49. Gaynor C. Wild and John G. Hildebrand, "Dilworth Wayne Woolley 1914–1966: A Biographical Memoir," National Academy of Science 2014, Washington DC: National Academy of Sciences, 2014.
50. James H. Cassedy, *Medicine in America: A Short History* (Baltimore: Johns Hopkins University Press, 1991), p.84.
51. Detlev W. Bronk, "Foreword," in Corner, *A History of the Rockefeller Institute*, pp.v–vii (note 37).
52. Herbert S. Gassner to Dilworth Wayne Woolley, 14 February 1939, Rockefeller Institute Archive, Woolley file, 450 W885, folder 1.
53. Herbert S. Gassner to Dilworth Wayne Woolley, 2 May 1939, Rockefeller Institute Archive, Woolley file, 450 W885, folder 1.
54. Norbert Weiner, *Cybernetics: Or Control and Communication in the Mind and the Machine* (New York, NY: John Wiley, 1948).

physicists" as well as "astronomers, geologists, meteorologists, geneticists and others."[55] As Woolley applied the idea of feedback to nutritional studies, cybernetics became important to the field of chemistry.[56]

For example, Woolley found that guinea pigs fed a diet precisely manipulated to provide only all their known necessary dietary items[57] died within weeks. When Woolley added linseed oil to the diet, the pigs lived for a few more weeks. When Woolley added dried grass to the diet, the pigs thrived. Chemical analysis of these items discovered three previously unknown vitamins: two in linseed oil, and one in grass. Further tests showed that guinea pigs deprived of any one of these three vitamins would quickly die. Woolley's method of adding to a strictly minimized animal diet was based on a feedback loop in which the interaction of diet and lifespan informed Woolley of the value of the dietary substance.

Woolley's powers of observation and inductive reasoning led him to research methods based on the principle of antimetabolite action. An antimetabolite is a specific kind of analog, which blocks the action of another molecule. Analogs are so similar in molecular structure to another chemical that the two can act almost interchangeably at the receptor site for the molecule. The antimetabolite is an analog which "competes with, replaces, or antagonizes a particular metabolite."[58] Chemists often explain the action by using the metaphor of a key and a lock to parallel the interaction between a molecule, its antimetabolite, and the biological receptor site that will accept both. Although both the molecule and its antimetabolite, acting like keys, fit the receptor (lock), only the "original" molecule activates the receptor, unlocking the door that prompts a specific physiological reaction. The antimetabolite fits the receptor but does not have the same effect as the other molecule. Instead of "unlocking" the receptor, it stymies it and jams the lock, rendering it inactive or replacing the interaction with a new interaction. The chemical metabolite that fits the lock cannot usurp the antimetabolite in order to activate the receptor or return to the original course of action. By replacing it, the antimetabolite antagonizes the metabolite.

Researchers had noticed similar chemical interactions in the early decades of the twentieth century, even before proof of receptors on human cells was confirmed. In the 1940s, chemists and biologists were just beginning to recognize and employ the principles of antimetabolite action as they searched for the causes of different diseases. For example, researchers began to search for an antimetabolite that might be the cause of pellagra. Pellagra had been linked to a diet high in corn consumption. Exploring the idea that a naturally occurring antimetabolite might play a role in the etiology of the disease led researchers to search for an antagonist that would act as a toxic agent in corn.[59] Studies concluded that because corn is low in tryptophan, which is needed to produce

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55. Churchill Eisenhart, "Cybernetics: A New Discipline," *Science* 109 (1949): 397–9.
56. Years later, during the early 1960s, Nathan Kline would use similar principles to investigate psychotropic drugs in his research at Rockland State Hospital in New York.
57. The diet consisted of all known vitamins, sucrose, casein, and corn oil.
58. *Stedman's Medical Dictionary, 24th Edition* (Baltimore, MD: Williams & Wilkins, 1982), p.90.
59. Dilworth W. Woolley, *A Study of Antimetabolites* (New York, NY: John Wiley & Sons, 1952), p.15.

niacin, pellagra is the consequence of a deficiency in niacin. Based on this theory, pellagra was successfully treated with niacin or dietary tryptophan. Woolley aided in this discovery and also found a substance in corn that acts as an antimetabolite for niacin,[60] advancing understanding of pellagra and its treatment.

Woolley tested various derivatives of niacin for relieving the symptoms of black tongue, which is the canine version of pellagra. Woolley observed that two derivatives did not relieve the symptoms of black tongue as niacin did. In fact, the two derivatives seemed to intensify the condition, which seemed odd as they were so similar in structure to niacin. As Woolley pondered this dilemma, he learned that an English biochemist had confronted a similar situation with two structurally similar substances, one of which seemed to inhibit the action of the other. Woolley concluded that the substances were competing due to antimetabolite action.[61] As he continued his research he discovered that not only did niacin treat black tongue and pellagra, it arrested the symptoms of psychosis caused by pellagra. In Canada, Osmond and Hoffer had also noticed that niacin (B3) could relieve pellagra-induced dementia, and were experimenting with high doses of niacin to treat schizophrenia.[62] These links between nutritional biochemistry and altered states of consciousness spurred Woolley's interest in the biochemistry of mental states.[63]

Woolley applied his knowledge of antimetabolite action to search for the origins of mental illness. Although the concept of one substance antagonizing another because of its similar structure was not new, Woolley was the first American chemist to apply this principle to psychopharmacology and psychiatry. Woolley developed his serotonin theory of the origin of mental illness by noting the chemical structure and consciousness-altering properties of LSD and conducting experiments with LSD-altered mice.[64] He published his work with the help of coworker Ellicott N. Shaw, a chemist who enjoyed an appointment at the Rockefeller Institute until 1957. Shaw had arrived at the Rockefeller Institute in 1948, when Woolley arranged to hire him as a visiting investigator appointed for one year.[65]

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60. Corner, *A History of the Rockefeller Institute*, p.377 (note 37).
61. Corner, *A History of the Rockefeller Institute*, p.376 (note 37).
62. Mills, "Hallucinogens as Hard Science," pp.183–4 (note 26).
63. Dilworth Wayne Woolley, *The Biochemical Bases of Psychoses or the Serotonin Hypothesis about Mental Disease* (New York, NY: John Wiley and Sons, 1962), pp.2–3.
64. D. W. Woolley, "Production of Abnormal (Psychotic?) Behavior in Mice with Lysergic Acid Diethylamide, and Its Partial Prevention with Cholinergic Drugs and Serotonin," *Proceedings of the National Academy of Sciences of the USA* 41 (1955): 338–44. Woolley observed behavior which he interpreted as evidence of hallucinations in mice who had been given LSD, and was able to arrest the observed behaviors in some of the mice by injecting them with serotonin.
65. Shaw had studied chemistry at the Massachusetts Institute of Technology, where he received his doctorate in 1943. He worked in the Division of Medical Chemistry at the Squibb Institute for Medical Research in New Brunswick, New Jersey, until his appointment at the Rockefeller Institute. In 1949, Shaw secured reappointment to the Institute as a Fellow under a National Institutes of Health fellowship, and again as an Assistant of the Institute in 1951 (Rockefeller Institute Archive, Shaw folder 450.1 (28) 11), the position he kept until he resigned in 1957, complaining that he was unable to pursue his ideas fully at the Rockefeller Institute (Philip R. White to Detlev W. Bronk, 2 January 1958, Rockefeller Institute Archive, Woolley file 450 W885, folder 1).

The implications of Woolley and Shaw's ideas were not immediately apparent, both because biochemical ideas of mental functioning were not well accepted at the time and because Woolley was seen as a bit of an outlier. In spite of the vast respect colleagues accorded Woolley, his wide-ranging interdisciplinary thinking apparently astounded some at the institute, who regarded him with some distrust and perhaps never fully understood the implications of his work. A graduate student told Woolley's wife, Janet, for example, that when he (the student) first entered the institute, "Dr. Woolley was regarded as some sort of nut."[66] In 1958, Philip R. White wrote to the director of the Rockefeller Institute, Detlev W. Bronk, expressing his admiration of Woolley and acknowledging that few of Woolley's colleagues seemed to understand his work. "Although Dr. Woolley's work has been widely commended, I think few people fully grasp the fundamental importance of his ideas. That man has an imagination and a breadth in his thinking that is rare indeed! He needs all the help and encouragement he can get, and he will well repay your attention."[67] Luckily, Bronk accorded Woolley the freedom, and what resources he could, to pursue his research.

Another factor must be considered when evaluating the creativity and importance of Woolley's work. Perhaps Woolley's keen insight was so highly developed because of his inability to rely on the sensory vision that others took for granted. In the late 1930s Woolley began to experience retinal hemorrhages due to diabetes and subsequently lost his sight.[68] Like another figure in psychedelic history, Aldous Huxley, Woolley was visually impaired. Although Huxley regained some vision after his corneal infection rendered him blind, Woolley's sight was permanently lost. In 1945, the Superintendent of Maintenance at the Rockefeller Institute petitioned the New York Telephone Company to install a phone in Woolley's apartment on East 68th Street in New York City. Woolley's blindness, explained the Superintendent, necessitated that he be able to be contacted by phone.[69] By the time he published his definitive study of antimetabolites, Woolley was relying heavily on his memory, which he had honed to an amazing extent.[70] Although his blindness necessitated help from his wife, friends, and fellow workers to keep up with the scientific literature, prepare scientific reports, manipulate laboratory apparatus, measure substances, and observe visible chemical reactions, he executed many ordinary laboratory procedures in spite of his lack of sight. His persistence surely matched the creativity of his research made possible by "keen chemical insight, vivid imagination, and a powerful memory."[71]

Bruce Merrifield, who began his tenure at the Rockefeller Institute in 1949 as Woolley's assistant and went on to earn a Nobel Prize in 1984 for his work on the

66. Janet Woolley, letter to Frederick Seitz, 8 January 1970, Rockefeller Institute Archive, Woolley file 450 W885, folder 1. Janet Woolley wrote to Seitz expressing the wish to write a biography of her husband, who had died of a heart attack at age 52 on 23 July 1966.
67. Philip R. White to Detlev W. Bronk, 2 January 1958, Rockefeller Institute Archive, Woolley file 450 W885, folder 1.
68. Jukes, "Dilworth Wayne Woolley (1914–1966)," p.509 (note 36).
69. Bernard Lupinek to Mr. Howrigin of New York Telephone Co., 8 October 1945, Rockefeller Institute Archive, Woolley file W885, folder 1.
70. Wild and Hildebrand, "Dilworth Wayne Woolley 1914–1966."
71. Corner, *A History of the Rockefeller Institute: 1901–1953*, p.378.

chemical synthesis of proteins, acknowledged his debt to Woolley as his mentor and friend. According to Merrifield, although Woolley was assisted with his work in the lab, he often worked alone through the night. When the morning cleaning staff would come, they were often surprised by the presence of Woolley working in the dark. When Woolley lectured, he possessed such "sensitivity, intelligence and gifts of innocent showmanship" that audience members often didn't realize he was blind. He was even able to write easily on the blackboard as he spoke.[72]

Paralleling a theme that has persisted throughout the history of psychedelic research, Woolley's theory seems in part based on intuitive insight and an ability to hold a gestalt view of a problem to be solved, rather than solely to rely on visual, "objective" rationalism. Woolley's ability, and his *need* to rely on senses other than the visual, led him to investigate several psychedelic substances as analogs of serotonin. There is no evidence that Woolley experimented with LSD by taking it, but it is an interesting coincidence that both he and Aldous Huxley were visually limited and able to make wide-ranging connections between aspects of psychedelic experiences and mental functioning.

In 1952, Shaw and Woolley published an important paper about antagonists of serotonin. Scientists had isolated serotonin only a few years prior to this paper. An Italian scientist had first theorized in the late 1930s that an amine substance which he had isolated in gut tissue (which he named enteramine) was responsible for muscle contraction. When this substance was isolated from blood at the Cleveland Clinic by Maurice M. Rapport, Irvine H. Page, Arda Alden Green, and Betty Mack Twarog in 1948, they demonstrated its ability to contract the smooth muscles of blood vessels in rabbit ear tissue. This vasoconstriction narrowed the blood vessels, raising blood pressure. The American pharmaceutical company Upjohn first synthesized and marketed the substance for research under the name serotonin in 1951.[73] As Rapport and his fellow researchers tested the newly isolated vasoconstrictor, they noted that its chemical and biological activity resembled that of epinephrine (also known as adrenaline), although its vasoconstrictor action was twice as powerful.[74] In 1949, Rapport, then working alone at Columbia University, confirmed the chemical structure of serotonin and called it 5-hydroxytryptamine (5HT).[75] A few years later, in 1953, Twarog and Page discovered that serotonin is present in the brain, a landmark discovery for the fledgling field of neuroscience.[76]

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72. Richard Perham, "Bruce Merrifield: Winner of 1984 Nobel Prize in Chemistry for his Elegant Work in the Chemical Synthesis of Proteins," *The Independent (London)*, 31 July 2006, p.32.
73. Whitaker-Azmitia, "The Discovery of Serotonin and its Role in Neuroscience," 2S–8S (note 5). Whitaker-Azmitia provides succinct biographies of the researchers involved in the discovery of serotonin and a vivid description of how Rapport would collect blood from the slaughterhouse and bring it to the lab to coagulate, thus isolating a serum which was named serotonin.
74. Maurice M. Rapport, Arda Alden Green and Irvine H. Page, "Serum Vasoconstrictor (serotonin) IV. Isolation and Characterization," *Journal of Biological Chemistry* 176 (1948): 1243–51.
75. Maurice M. Rapport, "Serum Vasoconstrictor (serotonin) V. The Presence of Creatinine in the Complex. A Proposed Structure of the Vasoconstrictor Principle," *Journal of Biological Chemistry* 180 (1949): 961–9.
76. Whitaker-Azmitia, "The Discovery of Serotonin and its Role in Neuroscience," pp.2S–8S (note 5).

Serotonin is present in several areas of the body, including the gastrointestinal tract, and present in large quantities in the brain.[77]

These findings led Woolley and Shaw to investigate LSD as an antagonist of serotonin to treat high blood pressure. Woolley and Shaw investigated several substances that were structurally similar enough to serotonin to take its place in living tissues, thus ameliorating its hypotensive effects. Among these substances were the ergot alkaloids, including LSD.[78]Although another chemist in the United Kingdom, John Gaddum, was simultaneously proving that LSD antagonized serotonin, his results were published somewhat later than Woolley and Shaw's.[79] The fact that several serotonin antagonists also had mind-altering properties intrigued Woolley, and he began to develop an idea that serotonin played an important role in mental health. As early as 1953, Woolley proposed a treatment to suppress schizophrenia based on his serotonin theory. Two chemicals were involved: a precursor to serotonin (5-hydroxytryptophane), and an analog of serotonin (1-benzyl-2-methyl-5-methoxytryptamine, also known as BAS), which protects the body from the undesirable effects of too much serotonin by blocking its action. Woolley proposed investigating these two chemicals for the treatment of schizophrenia based on their ability to regulate serotonin in the body. He compared his

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77. Irvine H. Page, "Neurochemistry and Serotonin: A Chemical Fugue," *The Pharmacology of Psychotomimetic and Psychotherapeutic Drugs: Annuals New York Academy of Sciences* 66(3) (1957): 592–601. Serotonin is made in the gastrointenstinal tract and is found there as well as in the spleen, blood platelets, the cortex, the brain stem, and the pineal gland, where it is highly concentrated (Woolley, *The Biochemical Bases of Psychoses*, p.63 (note 64)). Psychedelic research by Rick Strassman investigated the connection between the pineal gland and the hallucinogenic effects of N,N-Dimethyltryptamine (DMT). (Rick Strassman, *DMT: The Spirit Molecule: A Doctor's Revolutionary Research into the Biology of Near Death and Mystical Experiences* (VT: Park Street Press, 2001).

78. Dilworth W. Woolley and Ellicott Shaw, "Some Anti-metabolites of Serotonin and Their Possible Application to the Treatment of Hypertension," *American Chemical Society Journal* 74 (June 5, 1952): 2948–9. Ellicott Shaw and Dilworth W. Woolley, "Yohimbine and Ergot Alkaloids as Naturally Occurring Metabolites of Serotonin," *Journal of Biological Chemistry* 203 (1953): 979–89.

79. J. H. Gaddum, "Antagonism between Lysergic Acid Diethylamide and 5-Hydroxytryptamine," *Journal of Physiology (London)* 121 (1953): 15. In *The War of the Soups and Sparks: The Discovery of Neurotransmitters and the Dispute over How Nerves Communicate* (New York, NY: Columbia University Press, 2005), p.161, Elliot S. Valenstein offers a thorough history of the paradigm shift from belief that the brain was essentially electrical to acknowledgment that neurotransmitters played a crucial role in the brain. In his 1988 book, Valenstein credits Woolley with the "first explicit statement of biochemical theory," although he also recognized Gaddum's work (Elliot S. Valenstein, *Blaming the Brain: The Truth about Drugs and Mental Health* (New York, NY: The Free Press, 1988), p.80). A thorough history of simultaneous research with LSD and 5HT in the United Kingdom is offered by A.R. Green, who asserts that Gaddum gave LSD to cats and took LSD four times to develop his ideas that LSD antagonized serotonin and was extant in the brain. A. R. Green, "Gaddum and LSD: The Birth and Growth of Experimental and Clinical Neuropharmacology Research on 5-HT in the UK," *British Journal of Pharmacology* 154 (2008): 1583–99, 1591.

proposed treatment to the use of reserpine and CPZ, which were used to diminish psychotic symptoms. "The advantage of this (new) method," said Woolley, "is that it gives an insight into what the disease is caused by, whereas reserpine and chlorpromazine do not."[80] Woolley theorized that the two chemicals would normalize the level of serotonin in the body. If psychotic symptoms diminished, his serotonin theory of mental illness would advance.

After determining that several psychedelic substances were serotonin antagonists, Woolley and Shaw published a theory of the biochemical etiology of mental disorders. Published as an article in *Science* in 1954, and greatly expanded into a book in 1962, Woolley and Shaw's theory proposed that serotonin mediated mental processes, and that psychosis was caused by a disturbance of serotonin in the brain.[81] Woolley and Shaw had been unable to pinpoint whether mental illness was caused by an excess or deficiency of serotonin, in part due to experiments with LSD that showed that it sometimes antagonized serotonin and at other times acted like serotonin.[82] However, in 1962 Woolley presented evidence to support the idea that an excess of serotonin caused psychotic excitement, while a deficit caused depression. In support of his theory, Woolley recapped much of the current research with psychedelic substances (which he termed psychotomimetic, which was a popular term at the time) and more recent insights into the mechanisms of psychotropic medications that supported his theory. Psychotropic drugs (like reserpine and CPZ) seemed to work by decreasing serotonin, which Woolley proposed as their important mechanism of action, as these medications were used to arrest symptoms of schizophrenia. Monoamine oxidase inhibitor (MAOI) drugs, which seemed to help relieve depression, seemed to decrease serotonin levels (as well as epinephrine levels). Finally, elevated levels of serotonin seemed to exacerbate symptoms of schizophrenia.[83] Woolley emphasized that his theory resulted from the recognition that several psychotomimetic substances were antimetabolites of serotonin, including LSD, yohimbine, harmala alkaloids, ibogaine, bufotenine, and psilocybin. However, he also acknowledged the possible importance of many neurotransmitters to mental functioning, including histamine, adrenaline (epinephrine), noradrenaline (norepinephrine), and acetylcholine, as well as a possible genetic predisposition to neurochemical malfunction. Woolley also readily admitted that the states induced by LSD only mimicked certain aspects of schizophrenia, a complex and multidimensional experience. Although many of these theories of neurochemistry and the actions of psychotropic medications have been disproven, or

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80. Washington AP story dated 24 April 1953. Rockefeller Institute Archive, Woolley file 450 W885, folder 1. Woolley entitled his proposed project, "Chemotherapy of Manic Depressive Psychosis w/Serotonin Derivatives."
81. Dilworth W. Woolley and E. Shaw, "A Biochemical and Pharmacological Suggestion about Certain Mental Disorders," *Science* 119 (1954): 587–8. See also Woolley, *The Biochemical Bases of Psychoses*, (note 64) and Dilworth W. Woolley and Ellicott Shaw, "A Biochemical and Pharmacological Suggestion about Certain Mental Disorders," *Proceedings of the National Academy of Sciences US* 40 (1954): 228–31.
82. Dilworth W. Woolley and E. Shaw, "Some Serotonin-like Activities of Lysergic Acid Diethylamide," *Science* 124 (1956): 121–2.
83. Woolley, *The Biochemical Bases of Psychoses*, pp.131–2 (note 64).

remain unproven, Woolley's theory was one of the first broad theories of biochemical origins of mental disturbances based on empirical evidence.[84]

Theories that neurons secreted neurotransmitters and that biochemical action was crucial to brain function were met with skepticism in the early 1950s. However, Woolley's serotonin theory prompted several researchers, including Joel Elkes and Avrid Carlsson, to consider the idea that neurotransmitters played a central role in the brain, mental states, and behavior.[85] Eventually this led to heightened interest in designing neuroleptic drugs to manipulate neurotransmitters.[86] The link to modern psychopharmacology came from Bernard Brodie's lab at the National Institutes of Health in 1955. Based on the link between LSD and serotonin, and the idea that reserpine (which was being used as an antipsychotic medication similar to CPZ) ameliorated the effects of LSD, Brodie decided to investigate the interaction between reserpine and serotonin. When he and his coworkers developed a way to measure levels of serotonin in rabbits' brains, and proved that reserpine temporarily lowered serotonin levels, a new era of drug development was born.[87] Pharmacologists focused on controlling levels of serotonin and norepinephrine, which led to the development of the tricyclic antidepressants. Although pharmacologists went through a long period in which they turned away from interest in serotonin and toward examining the roles of catecholamines and dopamine, they eventually returned to serotonin. Pharmaceutical manipulation of serotonin reached new levels of precision with the development of fluoxetine hydrochloride by David Wong and Bryan Molloy in 1974. When Eli Lilly marketed this compound as Prozac in 1987 it became a highly successful, and highly profitable, antidepressant in part due to its reputation as a 'clean' drug that supposedly targeted only serotonin and induced few side effects. Development of a new class of antidepressants called selective serotonin reuptake inhibitors (SSRIs) followed.[88]

Woolley's ability to combine broad ideas with exacting observations about chemical structure, and to apply theories of antimetabolite action, led to an original theory of the role of serotonin in mental functioning. He incorporated knowledge of the mind-altering properties of LSD and other psychedelic substances with his knowledge as a chemist, and thus psychedelic substances played a small role in the shift toward the

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84. In 2009, Abram Hoffer published a paper reviewing and updating the adrenochrome theory. He claimed the theory might still be viable and called for new research. Interestingly, he also linked the theory with Woolley's serotonin hypothesis by suggesting that low levels of serotonin might produce adrenochrome, thus inducing psychotic symptoms. Abram Hoffer, "The Adrenochrome Hypothesis of Schizophrenia Revisited," *Journal of Orthomolecular Medicine* 24 (2009): 160–82.
85. David Healy, *The Creation of Psychopharmacology* (Cambridge, MA: Harvard University Press, 2002), p.205. Carlsson is best known for his work discovering the importance of dopamine in Parkinson's disease. He won a Nobel Prize for this work in 2000.
86. Healy, *The Creation of Psychopharmacology*, p.289 (note 86).
87. Woolley, *The Biochemical Bases of Psychoses*, p.192 (note 64); Healy, *The Anti-Depressant Era*, p.148 (note 4); Healy, *The Creation of Psychopharmacology*, pp.205–6 (note 86); Valenstein, *Blaming the Brain*, p.70 (note 80).
88. Peter Kramer, *Listening to Prozac: A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self* (New York, NY: Penguin Books, 1993), pp.57–66.

biochemical paradigm of mental illness, the inchoate field of psychopharmacology, and to the development of neuroscience as an interdisciplinary field. In the United Kingdom, John Gaddum was conducting parallel research and, although there is still little evidence that levels of serotonin are definitively linked to depression, the biochemical theories proved key to subsequent research and the pharmaceutical industry.[89] Although Woolley's research indirectly led to huge profits for the pharmaceutical industry, the larger implications of a biochemical paradigm for the study of human consciousness are perhaps less enriching.

A critical appraisal of psychiatric history from medical writer Robert Whitaker encourages us to develop a broad view of the history of psychopharmacology and reevaluate its successes and failures. While early experiments with psychedelics were often dismissed as being unable to conform to the medical model, Whitaker and others point out that psychotropic medications have not been the miracle solution first thought. Although neuroscience continues to amass more knowledge about how the brain functions, research has failed to ascertain exactly how the medications work, or even if they really work long-term. Whitaker sees the use of psychotropic medications as cloaking the need for sustainable recovery, and circumventing the need to assimilate individuals diagnosed with mental illness into society. Like Healy, he clarifies how the medical model favors a unidimensional, mechanistic model of targeting a specific disease with a specific medication, which benefits patients in the short term and the pharmaceutical industry financially, while paying little attention to side effects, long-term consequences, relapse rates, or social issues.[90]

Woolley's 1954 theory that serotonin was a crucial substance for understanding "mental disturbance" was part of a larger shift toward a biochemical paradigm of mental functioning and led to a great deal of research which in turn produced many medications, but few answers and no cures. The origins and characteristics of severe mental illnesses still elude us. There has still been no definitive explanation of how, why, or even if psychotropic medications can benefit those suffering from mental illnesses. In part, this is because evolving research incessantly confounds our knowledge of mental health and illness, psychopharmacology, diagnoses, treatments, and how the mind and body are entwined. The trajectory of past research suggests that the triumph of biological psychiatry has had limited success in answering broad questions, in part because it augmented the compartmentalization of the human psyche into increasingly smaller units of neurotransmitters that could seemingly be manipulated with precise medications. Revisiting early research with psychedelic substances forces a reevaluation of this paradigm. The biochemical paradigm considers altered states of consciousness as products of physiology without considering the multitude of environmental, psychological, and cultural factors that may be influencing biological processes. Instead of parceling human health

89. Green, "Gaddum and LSD," p.1596 (note 80).

90. Robert Whitaker, *Mad in America: Bad Science, Bad Medicine and the Enduring Mistreatment of the Mentally Ill* (Cambridge, MA: Perseus Publishing, 2002). In *Blaming the Brain* (note 80), Valenstein offers a detailed critique of how the pharmaceutical industry influences the popularity of psychiatric medications without regard for evidence that questions their effectiveness.

and illness out to psychiatrists and consumers in ways that are amenable to the medical marketplace, perhaps we need to search for ways to approach human health, illness, and consciousness holistically, acknowledging both individual mind–body ecosystems and the idea that individuals cannot be separated from larger narratives of the social and cultural context and history within which they function. In *Of Two Minds: The Growing Disorder in American Psychiatry*, anthropologist Tanya Luhrmann discusses the morality of the medical model of mental illness in ways that reveal its pitfalls and offer a more complex view. Although paradigms of biochemical psychiatry diminished some of the stigma of mental illness, and medications have helped many people, to rely only on a biochemical interpretation of mental functioning and human consciousness impoverishes us. Luhrmann argues that not only has research shown that psychodynamic therapy combined with pharmacology is more fruitful for treating mental illness, but a medical model alone channels our empathy for the diagnosed patient in a particular way that robs him of full agency and humanity. It also removes the need to analyze the patient's interaction with her environment. A model in which the biochemistry of a 'brain disorder' is only one aspect of a patient shifts diagnosis and treatment away from being the province only of medicine and psychiatry and into the cultural realm. It allows for a different moral model of the diagnosed person that necessitates considering interactions with the surrounding society.[91] This more complex view forces us to consider policy issues as well as cultural values and moves us toward a biopsychosocial model and biopolicy.

A renewed interest in psychedelic research points to a richness of psychedelic experience that necessitates this more complex, holistic approach to mental health and mental illness. Woolley and Shaw's 1954 article noted that several psychedelic substances are serotonin antimetabolites, and that several of them occur in nature and are used to alter consciousness for various purposes in various cultures. For decades it has been known that the altered states of consciousness induced by psychedelic substances are strongly influenced by the cultural context, the immediate environment, and the mind-set of the person, or what anthropologist Nicholas Langlitz calls the "historical and cultural contingency of hallucinogen experiences."[92] What might have happened if, instead of spurring a paradigm shift to a biochemical model of mental illness (and consciousness), Woolley and Shaw's observation had provoked an interest in where these substances occur in nature and led to an effort to understand the cultural contexts for their use? Postwar glorification of science and the desire to reengineer oneself using the tools of empiricism led to experimentation with psychedelic substances. However, when confronted with the need to conform to medical models of illness, and stymied by the cultural turmoil and moral drug panics of the 1960s, psychedelic experimentation faltered. Perhaps now it is time to reevaluate the foundations and uses of the biochemical paradigm and see what other models might be useful and what other lessons might be learned from psychedelic research. Out of necessity, contemporary research with psychedelic substances has to consider complex questions about the influence of the "physical, atmospheric, social and cultural

91. T. M. Luhrmann, *Of Two Minds: The Growing Disorder in American Psychiatry* (New York, NY: Alfred A. Knopf, 2001), pp.266–93.

92. Langlitz, *Neuropsychedelia*, p.256 (note 1).

qualities of the setting" that influence how an organism responds to a drug.[93] Some psychedelic researchers are even exploring the idea that the actions of antipsychotic medications may also be influenced by physical and psychological factors in the environment, even in animal studies, which subverts the mechanistic pharmacological model by inserting the idea that social context may be important.[94] This "contextualist conception of pharmacological activity"[95] is gradually gaining traction in the study of mental health as biopsychosocial models are applied to the study of mental health and illness. Psychedelic research, it seems, can help us integrate not just the study of mind and body to understand individuals, but also help us integrate biology and cultural studies to find a more sophisticated model for understanding the relationship between individuals and culture.

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93. Langlitz, *Neuropsychedelia*, p.126 (note 1).
94. Nicolas Langlitz, "Lullaby for a Mouse: Anthropological Observations of an Animal Model of Psychosis," Horizons conference, 15 October 2011, New York, NY, <https://vimeo.com/33803995> (12 February 2015).
95. Langlitz, *Neuropsychedelia*, pp.119–22 (note 1).