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A "Model Schizophrenia": Amphetamine Psychosis and the Transformation of American Psychiatry

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Introduction

During the early 1950s, dozens of individuals began to show up at London area hospitals with delusions of persecution. Some of them had auditory hallucinations that bolstered their delusional ideas. Clinicians promptly diagnosed them with paranoid schizophrenia and admitted them on an in-patient basis. Within days, their symptoms cleared up and they were discharged.

Further examination revealed that the ingestion of large amounts of amphetamines (or the habitual use of amphetamines over a prolonged period of time) precipitated these individual's psychotic episodes. In 1953, a medical student at the University of London, P. H. Connell, studied several patients and coined the term "amphetamine psychosis" for this rather infrequent but disturbing effect of amphetamine use. In 1958, he published a short, influential monograph by that title.[1] Connell was not primarily interested in the phenomenon from a biochemical perspective. Rather, he was interested in amphetamine psychosis from a clinical perspective, and also from the perspective of a public health advocate. In coining the term, he was not merely giving clinicians a valuable tool of differential diagnosis, but also framing recreational amphetamine use as a kind of silent epidemic or public health nuisance.

While Connell warned the medical profession about the dangers of amphetamine use, biochemical researchers extracted a very different lesson from his monograph. Could amphetamine psychosis be used as a biochemical model of schizophrenia? That is, by studying the mode of action of amphetamines on the brain, could one discover the biochemical basis of schizophrenia itself – and ultimately develop more exacting, pharmacological, treatments?[2] As Solomon Snyder, one of the American architects of the dopamine hypothesis of schizophrenia, later put it, "a drug which could elicit a "model schizophrenia" would be a boon to psychiatry."[3] To say that it would be a boon to psychiatry was an understatement. Amphetamine psychosis would give researchers a window into the mechanism of schizophrenia.

Biochemical researchers, however, were slow to adopt the theory that amphetamine psychosis constituted a "model schizophrenia." In fact, from 1959, when the American neuroscientist Seymour Kety suggested it, it took over a decade for the idea to catch on amongst researchers. On the contrary, by the mid-1960s, the handful of researchers who had investigated the question in any real depth were pessimistic about the ability of amphetamine psychosis to model schizophrenia.[4] Amphetamine psychosis only seemed to mimic some of the more florid symptoms of schizophrenia, such as delusions and, less commonly, hallucinations. It did not mimic Eugen Bleuler's core feature of schizophrenia, the "loosening of associations" or psychic disorganization later known as

[1] Connell 1958.
[2] Kety 1959, 1598; also Slater 1959.
[3] Snyder 1972, 169.
[4] Bell 1965; Gardner 1969.

"formal thought disorder."[5] Nor did amphetamine psychosis induce the bizarre "catatonic" states that define one subtype of schizophrenia, replete with its histrionic posturing or repetition of pointless actions.[6]

There was a second obstacle to the widespread acceptance of amphetamine psychosis as a "model schizophrenia." That title belonged to LSD. Before the dopamine hypothesis of schizophrenia, there was the serotonin hypothesis of schizophrenia, so called because many researchers, by the mid-1950s, believed that LSD could induce a state resembling schizophrenia, and that it did so by inhibiting serotonin. LSD would have to be displaced from that position before amphetamines could occupy it.

By the early 1970s, however, everything had changed. Schizophrenia researchers had converted to what I'll call the "mimicry thesis": that amphetamine psychosis is a faithful mirror of schizophrenia, and not just one small part of it, but the illness in its entirety.[7] By 1976, psychiatrists accepted, more or less unproblematically, that amphetamine psychosis is a precise clinical model of schizophrenia. This "mimicry thesis" was one of the two crucial pillars of the "dopamine hypothesis" of schizophrenia.[8] (The other pillar was the perceived effectiveness of dopamine-blocking drugs in relieving schizophrenia, though that is not part of my story here.) In the following, then, I will pose a simple question: what social, historical, and scientific changes took place that rendered the mimicry thesis so plausible, even *self-evident*, for psychiatric researchers by the mid-1970s?

There were at least three major changes that took place in the 1960s that led researchers to accept the mimicry thesis. First, Scandinavian researchers in the mid-1960s showed that amphetamines could induce stereotypy in laboratory animals.[9] The fact that amphetamines could induce stereotypy, and that stereotypy resembled some of the symptoms of catatonic-type schizophrenia, suggested that amphetamine use could model a broader range of schizophrenic symptoms than merely delusions and hallucinations.[10] The second shift came from the United States. In 1969, the New York clinicians Burton Angrist and Samuel Gershon observed a very small number of patients that showed evidence of thought disorder, as a result of their rambling and incoherent speech and writing.[11] Their research, like that on stereotypy, helped to close the perceived gap between amphetamine psychosis and schizophrenia.

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[5] Bleuler 1950.
[6] APA 2013, 88.
[7] Snyder 1972; Angrist and Gershon 1970.
[8] Snyder 1976; Meltzer and Stahl 1976.
[9] Randrup and Munkvad 1967. In humans, stereotypy has been associated with some types of autism spectrum disorders, such as rocking, tapping, spinning, hand flapping, and it is also associated with catatonic-type schizophrenia, which may involve holding bizarre postures for long periods of time (APA 2103, 88).
[10] Randrup and Munkvad 1972, 2-3.
[11] Angrist and Gershon 1970, 97.

A third factor in this transition emerged from an unexpected place. The American countercultural revolution of the late 1960s transformed, from outside of psychiatry, the meaning of "amphetamine psychosis." Some of the leading figures of the countercultural movement, such as Timothy Leary and Allen Ginsberg, worked tirelessly to invert public perceptions about LSD. They did so, in part, by contrasting the characteristics of the "acid head" and the "speed freak" (with the "acid head" coming out favorably in the comparison).[12] Journalists, sociologists, and musicians also adopted and broadcast these distinctions. According to these figures, the use of LSD, along with other psychedelic drugs such as mescaline and peyote, was a cornerstone of a philosophical and spiritual transformation that would reshape the foundations of American society.[13] There was just one hitch: speed. In Haight-Ashbury, Sunset Strip, and the East Village, artists, musicians, writers, and poets issued dire proclamations that speed was antithetical to the progressive values of the counterculture. The speed freak was antisocial, nihilistic, self-absorbed, hedonistic, nomadic, and unpredictable. But more than anything else, the speed freak was paranoid and violent. Speed, in fact, mimicked the paranoia and violence that characterized American society a whole. Speed was madness, because speed was America.

The American architects of the dopamine hypothesis freely borrowed, and modulated, the new meanings that the counterculture attached to speed. This helped to displace LSD intoxication as an appropriate biochemical model of schizophrenia, and instill amphetamines in its place. As Angrist and Gershon summarized their results on Bellevue admissions, "Because of…their sociopathy and their frankly hedonistic reasons for drug use, [the amphetamine users] resemble heroin addicts as a group far more than the philosophically and religiously preoccupied and less sociopathic hallucinogen users."[14] As the American psychiatrist and researcher Solomon Snyder argued, taking a page from the novelist Aldous Huxley, LSD usage does not mimic schizophrenia; *it merely enhances normal perception*: "The mental state elicited by psychedelic drugs is one of greatly enhanced perception of oneself and one's environment. Similar states occur during mystical and religious introspection and when an individual is profoundly moved by emotions or external events."[15] Snyder was clearly adopting some of the characterizations of LSD use that had become platitudes in the wake of the countercultural revolution. Snyder was eventually able to weave these and other strands of evidence together into support for the "dopamine hypothesis" of schizophrenia.[16]

To begin to tell this story, I first describe the construction of "amphetamine psychosis." By the mid-1960s, researchers and clinicians concluded that amphetamine psychosis was not an appropriate model of schizophrenia, Next, I describe the scientific and social changes that took place in the late 1960s that helped to close the gap between amphetamine psychosis and schizophrenia, including the Scandinavian work on

[12] Rosenfeld 1967; Davis and Munoz 1968; Smith, D. 1969; Smith, R. 1969.
[13] Dyck 2008; Conners 2010.
[14] Angrist and Gershon 1969a, 205.
[15] Snyder et al. 1974, 1252.
[16] Snyder 1976; Meltzer and Stahl 1976.

stereotypy, and research in the United States that attempted to identify evidence of thought disorder amongst amphetamine users. The American countercultural revolution waged a kind of war on speed by emphasizing the violent and paranoid qualities of amphetamine users. In doing so, it helped to displace LSD as a "model schizophrenia" in psychiatric research circles. Finally, I'll describe how the American architects of the dopamine hypothesis exploited these new meanings to support the mimicry thesis, and ultimately, the dopamine hypothesis itself. The dopamine hypothesis, in turn, transformed American psychiatry in the 1970s by putatively demonstrating that a major mental disorder could be successfully reduced to neurotransmitter abnormalities. In conclusion, I will suggest some ways that historians and philosophers of science might use this episode to reconstruct the history of biomedical research into other major mental disorders.

Others have recounted parts of this story. Erika Dyck provided an overview of the way that researchers such as Abram Hoffer and Humphry Osmond in Canada converted LSD into a "model psychosis" in the 1950s, and the way that public figures such as Timothy Leary helped to make LSD a symbol of an emerging youth counterculture in the 1960s.[17] I aim to extend her narrative by showing how speed came to replace LSD as a "model schizophrenia" for researchers, and how this came about, in part, as a result of widespread shifts in cultural attitudes regarding speed and LSD in the late 1960s. Nicolas Rasmussen detailed the transformation of amphetamines from the wonder drug of the 1940s to the public menace of the 1960s.[18] He noted, as I do, how early researchers used the threat of amphetamine psychosis to alert a complacent medical profession to the dangers of speed. He also touched upon the tensions in the American counterculture between the speed and acid subcultures. My story homes in much more specifically than his does on the vicissitudes of the concept of amphetamine psychosis, and how researchers came to use it as a stand-in for schizophrenia itself.

The Constitution of Amphetamine Psychosis

The British psychiatrist P. H. Connell constituted "amphetamine psychosis" as a distinct diagnostic entity in 1958, in a monograph bearing the same title.[19] He based the book on research he had conducted from 1953 to 1956 as an MD thesis for the University of London. He observed 48 subjects who had been admitted to four different hospitals with symptoms resembling paranoid schizophrenia, but which, on closer examination, were precipitated by the ingestion of large amounts of amphetamines (or the habitual use of amphetamines over a prolonged period of time). Almost half of those individuals had broken open amphetamine or methamphetamine inhalers and consumed their contents,[20] since, although amphetamines had been placed on Schedule IV of the Poison Rules in 1955 (which ensured that amphetamine tablets were not distributed without a prescription), the inhalers were still available without prescription. The Benzedrine

[17] Dyck 2008.
[18] Rasmussen 2008.
[19] Connell 1958.
[20] Ibid., 65.

inhaler, an amphetamine-based inhaler manufactured by Smith, Kline, and French Laboratories, was the prototype for this product and had been on the market as a decongestant from 1934. By the early 1950s, copycat products, including the methamphetamine inhaler, had flooded the market.[21]

For Connell, "amphetamine psychosis" performed two different roles: diagnostic and normative-legal. First and foremost, it served to facilitate differential diagnosis. Connell believed that amphetamine abuse, and its psychotic sequelae, was much more widespread than assumed, but that its prevalence was masked because it was easily confused with schizophrenia by unwary clinicians. The clinician's role was particularly vexing as there were "no physical signs diagnostic of amphetamine intoxication."[22] "Amphetamine psychosis," however, did much more than to describe a syndrome somehow precipitated by amphetamines. The label asserted a direct causal relationship between the consumption of amphetamines and the subsequent symptoms. In so doing, it tied the phenomenon to the normative-legal realm and provoked the question of responsibility and blame. As Connell put the point, "The medical profession as a whole…must bear responsibility for the development of a number of cases of amphetamine addiction and amphetamine psychosis."[23] Or, as Burton Angrist, one of the architects of the dopamine hypothesis, was later to put the point, "It seems difficult to say…whether the medical profession needs protection from amphetamine users or vice versa…"[24]

Prior to Connell's monograph, few clinicians or biomedical researchers had frankly asserted that amphetamines cause psychosis. After all, Connell never claimed to have made a new discovery, but simply reinterpreted the significance of established facts. The first recorded instance of a psychotic episode precipitated by amphetamines occurred in 1938, and several episodes had been reported since that time.[25] Researchers had dismissed such cases in the past by claiming that amphetamine use merely *unmasked* preexisting psychotic tendencies in a handful of disturbed individuals.[26] This was the "latent psychosis" theory. In fact, Smith, Kline, and French aggressively promoted this line of defense when the first reports of psychotic episodes associated with the drug became public.[27] One must keep in mind that, during the 1940s, the governments of Germany, Japan, Britain, and the United States, amongst others, freely dispensed amphetamine tablets to their combat soldiers in an effort to boost morale and vigor.[28] Nobody was eager to think of amphetamines as psychotomimetic agents.

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[21] Rasmussen 2008.
[22] Connell 1958, 75.
[23] Ibid., 58.
[24] Angrist and Gershon 1969a, 200.
[25] Young and Scoville 1938.
[26] See Connell's (1958) literature review which comprises Chapter 1; also p. 60 on the 'latent trait' hypothesis.
[27] Rasmussen 2008, 48.
[28] Rasmussen 2008.

Connell attacked the "latent psychosis" theory with a fervor unusual for the otherwise dry monograph. The concept of "latent personality traits," he argued, is "specious and dangerous," and it promotes "a complacency which stifles further inquiry and shifts attention from the possible disrupting influence of the drug."[29] He attempted to refute the "latent psychosis" theory by demonstrating amphetamine psychosis in a small number of patients, "whose backgrounds and personalities were normal, so far as could be ascertained."[30] Contrary to received medical opinion, amphetamines could induce psychosis in otherwise healthy people.

What exactly *was* amphetamine psychosis? Besides the fact that amphetamine psychosis could provoke symptoms not unlike paranoid schizophrenia, its clinical symptomatology was extremely diverse. Over the next fifteen years, psychiatrists and researchers reconfigured substantially this clinical symptomatology. The malleability of amphetamine psychosis explained both its allure, as well as its weakness, as a research prototype for schizophrenia.

The *clinical profile* of the patient with amphetamine psychosis was stable enough: paranoid delusions accompanied by auditory hallucinations. But Connell noted dozens of additional symptoms that may or may not co-occur with paranoid delusions or auditory hallucinations. These included: visual hallucinations; grandiose delusions; delusions with homosexual content; homosexual conduct itself; depression; suicidal ideation; anxiety; confusion; mania; catatonia; hyperkinesis; hypertension; insomnia; violent outbursts; thought disorder and logorrhea; increased libido; decreased libido; twitching and spasms; olfactory hallucinations; transvestitism; and a very distinctive tactile hallucination of worms or bugs crawling under one's skin. During the 1960s, clinicians added, removed, or corroborated various symptoms on Connell's list.[31] In the early 1970s, researchers such as Solomon Snyder attempted to organize these into a cohesive narrative, that is, to show them to be diverse moments of a complex and multilayered pathological process.

Almost immediately, biochemical researchers such as Seymour Kety recognized that amphetamine psychosis could potentially function as a powerful biochemical model of schizophrenia.[32] That is, by tracing the biochemical mechanisms that are disrupted in amphetamine psychosis, one could perhaps understand the biochemical basis of schizophrenia, too. In fact, an early review of Connell's *Amphetamine Psychosis*, published in 1959, criticized Connell for failing to note the broader theoretical implications of his work.[33]

Yet it would take another decade for Kety's suggestion to grip the imagination of the psychiatric community. One obstacle, as Kety indicated, was that at the time of his writing, researchers widely considered LSD to be the "model of choice" for investigating

[29] Connell 1958, 64.
[30] Ibid., 63.
[31] Marley 1960; Bell 1965.
[32] Kety 1959; Slater 1959.
[33] Slater 1959.

both the subjective experience and the biochemical mechanisms of schizophrenia. Researchers would have to strip LSD of that title before amphetamines could occupy that role. Another obstacle was that closer examination of the symptomatology of amphetamine psychosis revealed crucial differences between it and schizophrenia.

Breaking the Link between Amphetamine Psychosis and Schizophrenia

Shortly after the publication of *Amphetamine Psychosis*, researchers published a handful of reports that seemed to confirm the clinical similarity of amphetamine psychosis with schizophrenia.[34] A key issue turned on the question of thought disorder. In 1960, the British psychiatrist Edward Marley claimed to have diagnosed the presence of "disconnection of thought" in one of his patients.[35] The fact that amphetamine psychosis could mimic thought disorder *in addition to* delusions and hallucinations suggested that amphetamine psychosis was closely analogous to schizophrenia itself and hence that it shared the same mechanisms. Three years later, another British psychiatrist, W. B. McConnell, also reported thought disorder in several patients with amphetamine psychosis:

> "The conversation of all patients, except the patient who had been ill for 10 years, was at times disjointed, incoherent, and irrelevant. Various forms of schizophrenic thought disorder occurred. Thought blocking was common in all the acute illnesses and was associated with marked perplexity. One patient described it thus: 'I just can't think of the word to say…it is light a light switch going on, it breaks my train of thought…maybe it is because I'm not thinking of what I'm saying.' Abstract and concrete meanings were confused by two of the patients."[36]

By the mid-1960s, however, further clinical work threw this emerging consensus into question. In 1965, the Australian psychiatrist D. S. Bell published a paper that systematically explored the connection between the two conditions. Bell gathered reports of 14 patients who had been admitted to different hospitals for amphetamine psychosis. His conclusion was that, contrary to Connell, amphetamine psychosis *could* readily be distinguished on clinical grounds from schizophrenia. First, amphetamine psychosis is associated with both visual and auditory hallucinations, while schizophrenia is typically characterized by only auditory hallucinations.[37] But secondly, and more importantly, amphetamine psychosis rarely produces the kind of disorganization of thought characteristic of some forms of schizophrenia. The delusions and hallucinations typically take place in an otherwise lucid frame of mind. This alone, he thought, threw into

[34] Marley 1960; McConnell 1963.
[35] Marley 1960, 82.
[36] McConnell 1963, 219.
[37] Bell 1965, 705.

question the "goodness of fit" of amphetamine psychosis as a biochemical model for schizophrenia.[38]

But what about the supposed thought disorder that had been observed by psychiatrists such as McConnell and Marley? Bell conceded that some patients gave outward indications of disordered thought. Patients often spoke quickly, flitting from topic to topic in an apparently disorganized way. But Bell argued that such instances were hardly demonstrative of *actual* thought disorder. This was because such verbal evidence could not discriminate between formal thought disorder, on the one hand, and the mere "flight of ideas in euphoric patients" that could be mistaken for it. In other words, one must distinguish between actual incongruence of thought, on the one hand, and the *acceleration* of thought, on the other. As the amphetamine user's thought speeds up, an outside observer may fail to note the logical connections that are nonetheless present in it, and hence *mistakenly* make a diagnosis of thought disorder. As Bell put it, the "schizophrenic thought disorder described by McConnell was not convincingly distinguished from the disturbance that may be secondary to elation or paranoid delusions."[39]

This is not to say that genuine thought disorder could not be clinically distinguished from the flight of ideas due to "elation." The two could be easily distinguished *simply by asking the patient what he or she meant* by a certain utterance. If the patient could adequately reconstruct the inner logic that was incompletely expressed by his or her utterances, then it was not genuine incongruence of thought. In order to confirm or disconfirm thought disorder, one must question the patient: "As an accompaniment of their heightened mood, the thought process of two patients were accelerated leading to rapidity of associations with flight of ideas…However, when persuaded to make the effort these patients were able to explain the logical associations involved in their flight of ideas."[40]

Despite Connell's bold proclamation that amphetamine psychosis and schizophrenia were "indistinguishable," then, by 1965, medical psychiatry had discovered an important gap between them. Medical opinion quickly followed Bell's assessment. For example, the British physician R. Gardner of Maudsley Hospital also concurred with Bell's judgement,[41] as did American psychiatrist John D. Griffith of the Vanderbilt University School of Medicine.[42] The Swedish psychiatric researchers L. E. Jönsson and L. M. Gunne of the Psychiatric Research Center of the University of Uppsala remarked on what they call "disorganization of thought" in their patients, but also noted that the patient was able to adequately clarify his or her meaning on questioning.[43] Solomon Snyder, one of

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[38] Ibid.
[39] Ibid.
[40] Ibid., 704.
[41] Gardner 1969, 113.
[42] See Griffith et al. 1970, 202, which also describes earlier research involving the first experimental administration of amphetamines to human subjects.
[43] Jönsson and Gunne 1970.

the founders of the dopamine hypothesis, conceded that the absence of thought disorder marked a crucial difference between amphetamine psychosis and schizophrenia.[44] One of the projects of American psychiatry of the late 1960s would be to close this gap.

A second reason that researchers could not generally accept amphetamine psychosis as a model of schizophrenia is that LSD had already earned that place of pride. By the early 1950s, psychiatrists and medical researchers had begun to appreciate the power of LSD to serve as a "model psychosis."[45] At that time, the idea of a "model psychosis" had two crucially different meanings. According to one meaning, LSD served as a model psychosis in a *phenomenological* sense, rather than (or in addition to) a biochemical sense. Its importance lay in the fact that psychiatrists could ingest LSD in order to better appreciate and understand their psychotic patients. Whether or not LSD shared a biochemical mechanism with schizophrenia was not the point. It was enough that it could induce an "artificial psychosis" in non-schizophrenics that could advance clinical understanding through eliciting a direct, though fleeting, glimpse of the psychotic patient's experiences.

Even before LSD, the idea of using hallucinogens to induce schizophrenia-like experiences was on the table. This phenomenological sense of the term "artificial psychosis" goes back at least to the 1930s, when the German psychiatrist Erich Guttmann, at the Maudsley Hospital in London, encouraged his colleagues to ingest mescaline for the purpose of inducing an "artificial psychosis," which would assist in "understanding the mental life of schizophrenics," and ultimately, perhaps, in deriving "hints for the solution of the great problem of psychiatry, that of schizophrenia."[46] Guttmann's long-time colleague William Mayer-Gross – who had fled Germany with him and Alfred Mayer to take up a post at Maudsley – made the same recommendation about mescaline.[47] Mayer-Gross later oversaw LSD studies as well.[48] The psychiatrists Humphrey Osmond and Abram Hoffer developed this line of research systematically with LSD in the 1950s at the University of Saskatchewan, though they were also aware of the importance of understanding the biochemical mechanisms involved.[49]

In 1954, however, the concept of a "model psychosis" would come to assume a second meaning: namely, LSD could elicit a model psychosis in a *biochemical* sense. In that year, two research teams, one in the US and one in Britain, independently concluded that LSD primarily acted on the serotonin system and appeared to inhibit its production or availability. These researchers immediately drew the tentative conclusion that, since LSD intoxication mimics schizophrenia, then schizophrenia, too, probably results from the

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[44] Snyder 1972, 170.
[45] Dyck 2008.
[46] Guttmann 1936, 220.
[47] Mayer-Gross 1951, 321.
[48] Greenland 2002, 469. Both Guttmann and Mayer-Gross note that the ingestion of drugs such as hashish, peyote, or opium, specifically for the purpose of gaining theoretical insight about the nature of the mind, goes back at least to Emil Kraepelin.
[49] Dyck 2008.

inhibition of serotonin. This became known, in Kety's words, as the "serotonin hypothesis" of schizophrenia.[50] As the chemists D. W. Woolley and E. Shaw, co-discoverers of the "serotonin hypothesis" at the Rockefeller Institute for Medical Research, put it:

> The demonstrated ability of [LSD and similar ergot-based agents] to antagonize the action of serotonin in smooth muscle and the finding of serotonin in the brain suggest that the mental changes caused by the drugs are the result of a serotonin-deficiency which they induce in the brain. If this be true, then the naturally occurring mental disorders – for example, schizophrenia – which are mimicked by these drugs, may be pictured as being the result of a cerebral serotonin deficiency... Possibly, therefore, these natural mental disorders could be treated with serotonin.[51]

Independently, a chemist at the University of Edinburgh, J. H. Gaddum, arrived at substantially the same conclusion: "It is possible that the HT [5-HT or serotonin] in our brains plays an essential part in keeping us sane and that the effect of LSD is *due* to its inhibitory action on the HT in the brain."[52] Even in the mid-1950s, the dream of mastering schizophrenia was very much alive; LSD would be the key to mastering it.

Stereotypy, Amphetamine Psychosis, and Schizophrenia

The first phase in the transformation of amphetamine psychosis into a "model schizophrenia" came with the work of Axel Randrup and Ib Munkvad at St. Hans Hospital in Denmark in 1967. They found that stereotypy could easily be induced in laboratory animals through intravenous injection of amphetamines. Somewhat more circuitously, they reasoned that stereotypy resembled certain outward features of amphetamine intoxication in humans, as well as certain features of schizophrenia, namely, the pointless and repetitive actions sometimes associated with catatonic-type schizophrenia. As a consequence, they claimed, amphetamine psychosis could model a much greater range of schizophrenic symptoms than researchers like Bell appreciated.[53]

To perfect the analogy to schizophrenia, however, they had to argue that stereotypy was not just a somewhat uncommon side effect of long-term amphetamine use (e.g., back and forth jaw movements), but was at the very heart of amphetamine intoxication itself. To this end, they greatly expanded the accepted meaning of "stereotypy" in humans to encompass a much broader range of symptoms and behaviors. For example, they noted that amphetamine users often get "hung up" on the actions they performed. One of the effects of amphetamines, they noted, was a kind of hyper-attentive fascination with certain minutiae, such as, "sorting objects in a handbag, manipulating the interiors of a

[50] Kety 1959, 1593.
[51] Woolley and Shaw 1954, 587-588.
[52] Gaddum 1954, 77; emphasis in original.
[53] Randrup and Munkvad 1967, 307.

watch, polishing fingernails to the point that sores are produced, etc."[54] The Swedish researcher Gösta Rylander coined the term *punding* to describe this particular effect. Randrup and Munkvad cited Rylander approvingly and described *punding* as a kind of stereotypy.[55] In the eyes of Randrup and Munkvad, this *punding* was no different, in principle, from a repetitive mechanical twitch: they are but "more *complicated* forms of stereotypy."[56]

What was the connection between stereotypy, amphetamine psychosis, and schizophrenia? In their 1967 paper, Randrup and Munkvad tantalizingly suggested that this stereotyped behavior was also found in some schizophrenic patients. Thus, stereotypy might even provide an animal model for schizophrenia as well: "it may be that studies of amphetamine effects will lead to results of interest for basic research into the psychoses."[57] In short, the authors associated amphetamine psychosis with stereotypy, schizophrenia was also associated with stereotypy, and therefore, perhaps, the two conditions shared the same biochemical mechanisms. By the early 1970s, Randrup and Munkvad had entirely abandoned their earlier modesty about the theoretical significance of their work for psychiatry. Their research on stereotypy had blossomed into a firm conviction that amphetamine psychosis was the ideal biochemical model of schizophrenia. As they announced to the American Schizophrenia Association in 1971: "all schizophrenic symptoms have apparently been observed in the amphetamine psychosis", including "thought blocking" and "stereotyped behavior."[58] The use of stereotypy as an animal model for amphetamine psychosis not only helped to close the gap between madness and speed, but provided a crucial clue that amphetamine psychosis was mediated specifically by its effects on dopamine, rather than norepinephrine – a stepping stone in the evolving dopamine hypothesis of schizophrenia.

Capturing Thought Disorder

There was still a major barrier to the acceptance of amphetamine psychosis as a model of schizophrenia: the problem of thought disorder. To all appearances, amphetamine psychosis, like LSD intoxication, took place in a lucid frame of mind. One of the defining symptoms of schizophrenia, disorganization or incongruence of thought, was absent. To remedy this difficulty, researchers had to demonstrate that amphetamine psychosis could induce thought disorder – precisely the claim that Bell famously denied in his 1965 report. Recall that in Bell's view, amphetamine psychosis did not induce thought disorder, but was sometimes mistakenly believed to do so because it led to the acceleration of thought. This endowed the amphetamine user's speech with a fragmentary quality that made it appear very similar to thought disorder.

[54] Randrup and Munkvad 1967, 307.
[55] Rylander 1966; 1969
[56] Randrup and Munkvad 1970, 707; emphasis added.
[57] Ibid.
[58] Randrup and Munkvad 1972, 2-3.

The second phase of the transition of amphetamine psychosis into a model schizophrenia stemmed from the work of Burton Angrist and Samuel Gershon of the NYU Medical Center, both of whom conducted clinical research at Bellevue Psychiatric Hospital in New York. In particular, they wanted to find evidence of thought disorder. Angrist and Gershon were extremely well-positioned to be able to study, in depth, the symptomatology of amphetamine psychosis, because they had plenty of material for observation. In 1969, they reported a spike in amphetamine-related admissions to Bellevue Psychiatric Hospital that began in 1966, and that "rapidly surpassed in frequency the admissions for LSD, marijuana, and all other drugs with the exception of the opiates."[59] In addition to amphetamine admissions, they also administered amphetamines directly to four experienced research volunteers and monitored their behavior closely.[60]

In 1969, Angrist and Gershon also published a description of their observations of 60 amphetamine-related admissions.[61] Of those 60, they reported on one patient, a young man, who seemed to show first-rate evidence of thought disorder: "a formal thought disorder was noted during the acute phase."[62] In particular, the patient gave rambling or incoherent responses to various promptings:

> "He showed a formal thought disorder some examples of which are as follows: On the day of his transfer, speaking of his brother's drug use, he said, "My brother has been playing with the fires of hell." On the same day, when asked what 'a stitch in time saves nine' meant, he said, 'Hurry up with that date and don't be late' (laughs) 'make that first stitch right and the rest will follow.'"[63]

The following year, they reported a similar episode, which was to be the crucial bit of evidence for thought disorder in amphetamine users. These observations stemmed from research involving the experimental administration of amphetamines to volunteer subjects. One of the four seemed to exhibit signs of thought disorder and at one point launched into an:

> "agitated philosophical diatribe with riddles that made little sense. For example, 'one man goes to school, the other can't. Then the other "cuts out" say, "fuck you, buddy."' This he explained meant that there is no brotherhood in the world. Questions the meaning of gold and source of its value.""[64]

Later, the same subject began referring to himself as a kind of prophet, "writing and talking excitedly".[65] The latter could have been classed as a delusion of grandeur; this

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[59] Angrist and Gershon 1969a, 196.
[60] Angrist and Gershon 1970.
[61] Angrist and Gershon 1969b.
[62] Angrist and Gershon 1969b, 515.
[63] Ibid.
[64] Angrist and Gershon 1970, 102.
[65] Ibid.

would have represented a somewhat novel clinical insight about the symptomatology of amphetamine psychosis, but it would not have broken from the basic clinical portrait. More importantly, in the absence of a verbal questioning – that is, in the absence of engaging the patient in something like a *conversation* – the evidential value of such texts were, as Bell observed, dubious. Observation alone would not reveal the difference between formal thought disorder *proper* and the mere "flight of ideas" due to elation. However, without any further argumentation, Angrist and Gershon interpreted the patient's text as an indication of thought disorder, and drew the conclusion that amphetamine psychosis is the ideal model of schizophrenia:

> "These phenomenologic features [auditory hallucinations and thought disorder] give amphetamine psychosis a greater resemblance to naturally occurring schizophrenia than the states induced by other psychotomimetics….This clinical resemblance of amphetamine psychosis to schizophrenia justifies study of its mechanisms of pathogenesis." [66]

Randrup and Munkvad had expanded the symptomatology of amphetamine psychosis to include stereotyped behavior. Angrist and Gershon expanded it further to include formal thought disorder as well. Amphetamine psychosis was starting to look just like schizophrenia again.

"Drugs that Even Scare Hippies": Acid Heads and Speed Freaks

The completion of the transformation of amphetamine psychosis from a disturbing, but uncommon, sequela of amphetamine use, to a biochemical model of schizophrenia, awaited one last step. LSD had to be displaced decisively as the reigning model of schizophrenia in the biochemical researcher's arsenal. This final transformation would come from an unlikely source. The ideological architects of the American countercultural revolution, such as Timothy Leary, Allen Ginsberg, Gary Snyder, Richard Alpert (Ram Dass), and Michael McClure, worked tirelessly to engineer the public perception of LSD, the kind of experience it induced, and the kind of person who used it.

They did so, at least in part, by contrasting the kind of person who used LSD with the kind of person who used speed: the "acid head" versus the "speed freak." The use of LSD became, in their teaching, synonymous with a philosophical or even spiritual quest for wholeness, and an escape from the alienation produced by a militaristic and competitive society. Speed, in contrast, exacerbated the values of competition and militarism. The speed freak was unpredictable, paranoid, and violent. Speed was madness, because speed was America. The ideological clash of the twentieth century, it turned out, was not only between capitalism and communism, or between pacifism and militarism, but between acid and speed.[67] Allen Ginsburg summarized a theme that ran throughout the countercultural literature: "Speed is anti-social, paranoid making. All the nice gentle dope

[66] Ibid., 106.
[67] E.g., Rosenfeld 1967; Davis and Munoz 1968; Smith, D. 1969; Smith, R. 1969.

fiends are getting screwed up by the real horror monster Frankenstein Speedfreaks who are going around stealing and bad mouthing everybody."[68]

What prompted the need for these fine discriminations amongst recreational drug users? The problem was that speed users were beginning to subvert, from within, the countercultural revolution that LSD was poised to bring about. In the eyes of its leaders, speed was undermining the values they sought to promote. As the historian Philip Jenkins put it, "At the end of the 60s, methamphetamine already had the distinction of being one of the very few drugs stigmatized within a drug culture of seemingly limitless tolerance."[69] To exemplify the campaign being waged on behalf of LSD and against speed, I will focus on the events leading up to, and following, the 1967 "Summer of Love," in the Haight-Ashbury district of San Francisco. I will also focus on the perspective of the leader and founder of the Haight-Ashbury Free Clinic, David Smith. The clinic not only provided free medical assistance for young people affected by drug-related illnesses, but also gathered information about patterns of drug use in the area.

By the early 1960s, the recreational use of amphetamines was in full swing in both the UK and the US.[70] These were primarily ingested orally, in tablet form or by consuming the contents of amphetamine-based inhalers. However, by the early 1960s there was also a segment of amphetamine users that began administering it intravenously (a form sometimes known as "splash.") According to one sociologist at the time, heroin users began this form of ingestion in the US in the late 1950s "at a time when the heroin market was precarious," and it had become common by the mid 1960s.[71] But speed came to take on a new set of meanings during the Summer of Love.

The first Human Be-In, a gathering of about 30,000 "hippies" from the San Francisco Bay area, took place at Golden Gate Park's Polo Field on January 14, 1967. It defined not only the counterculture of the late 1960s but enshrined LSD as a kind of sacrament of the movement: this was the occasion on which Timothy Leary, high on LSD, coined the phrase, "tune in, turn on, drop out," shortly before spending the afternoon playing paddy-cake with a little girl.[72] Within weeks, rumors began to circulate that the summer of 1967 would see about 100,000 teenagers from around the country descend onto the Haight-Ashbury district.

In response to the impending invasion, pharmacologist David Smith and concerned colleagues at the University of California Medical School began organizing a free clinic that would provide much needed medical assistance, both for drug overdoses as well as problems associated with unhygienic living conditions.[73] In the vision of its founder, the clinic would emphasize, "medical treatment free from red tape, free from value

[68] Cited in Rasmussen 2008, 183.
[69] Cited in Owen 2007, 104.
[70] Rasmussen 2008, 171-181.
[71] Rawlin 1968, 58.
[72] Connors 2010, 204.
[73] Sturges 1993, 39.

judgements, free from eligibility requirements, emotional hassles, frozen medical protocol, moralizing, and mystification."[74] The clinic also provided a crucial alternative to the public hospitals, which likely would have treated drug-related admissions as a criminal problem and thereby deterred young people from seeking help.

The Haight-Ashbury Free Clinic also played a pivotal role in collecting information about drug use in the area. In 1968, David Smith and Dr. Frederick Meyers of the University of California Medical School received a large grant from the National Institutes of Mental Health to study amphetamine use in Haight-Ashbury. This led to the formation of the Amphetamine Research Project, housed in the clinic and led by criminologist Roger Smith, who became known to locals as the "Friendly Fed." The clinic documented the transitions that were taking place within the drug culture of the Haight-Ashbury district.

From 1967 to 1969, the clinic produced several reports on patterns of drug use in the district. The most noticeable trend consisted of a sharp transition, from 1967 to 1969, from the use of LSD and marijuana to the use of amphetamines. According to one of David Smith's reports, the intravenous use of amphetamines was "practically unknown in the Haight" prior to the Summer of 1967; the Fall brought "an increasing number of adverse reactions to intravenous amphetamine" at the clinic, and "more moderate users of marijuana and LSD began to dwindle in number as they left the Haight when the two groups began to conflict."[75]

The transition from LSD to speed was not an isolated event, but occurred in other countercultural "hubs" in the US. A similar pattern emerged in New York's East Village around the same time period. As noted above, from 1966 to 1968, Burton Angrist and Samuel Gershon documented a sharp increase in amphetamine-related admissions to Bellevue Psychiatric Hospital, one that "rapidly surpassed in frequency the admissions for LSD, marijuana, and all other drugs with the exception of the opiates."[76] The popular press also picked up and broadcast the growing use of amphetamines, and labeled it as a "drug that even scares hippies."[77]

Clearly, it was time for some fine ideological discriminations to be made amongst those who self-identified as recreational drug users. By 1967, a number of artists, musicians, journalists, sociologists, and criminologists began to distinguish the characteristics of amphetamine users and LSD users – the "speed freaks" and the "acid heads." Ideologues such as Leary and Ginsberg attempted to convey a simple message: the use of LSD (and other psychedelics such as mescaline and peyote) could become incorporated into a coherent philosophical worldview that emphasized the values of communal living and pacifism over the "mainstream" cultural values of competition and militarism. The speed freaks were another story entirely. The transient and volatile "communities" formed by speed freaks had none of these qualities – no guiding philosophy, no social mandate, and

[74] Ibid., ix.
[75] Shick, Smith, and Myers 1970, 43-44; also see Smith and Fischer 1970.
[76] Angrist and Gershon 1969a, 196.
[77] E.g., Rosenfeld 1967.

no template for communal organization. Any such "speed freak" communities would rapidly degenerate in a cycle of paranoia-fueled violence culminating in a hospitalization or criminal investigation.[78]

Like Leary and Ginsberg, David Smith, the founder of the clinic, articulated what he understood to be the chief differences between LSD and speed. Smith (who occasionally used LSD himself) framed the contrast, tellingly, in terms of a clash of two different worldviews, or philosophies. He described the exodus of the LSD user from Haight-Ashbury in the following terms:

> "Because of the violent characteristics of the [speed freak], the hippies have moved to the country where they can establish small rural communes which tolerate and reinforce their belief systems. Urban areas such as the Haight-Ashbury can never be a permanent haven for the acid subculture, because in the conflict of *speed freaks* vs. *acid heads*, *speed* always drives out *acid* – as in the broader society the philosophy of violence dominates the higher aspirations of nonviolence, peace and love."[79]

One particular metaphor that seemed to summarize the differences was that the madness of amphetamines reflected, and mimicked, the madness of American culture itself. A lucid statement of this mimicry between speed and America was due to the New York sociologist Seymour Fiddle:

> "…the amphetamine abuser is a burlesque of certain elements of contemporary civilization. First, his hyperactivity is a caricature of urban hustle and bustle…The amphetamine user is an overreacher. One of the models of our day is that of man breaking through boundaries…This underlying purpose of the drug dependent gives us a mock image of the American as a passive consumer searching for stimulation."[80]

As one young user put it, amphetamines mimic the manic velocity of American culture itself.[81] The same theme was summarized by Frank Zappa, in one of many public service announcements promoted by the Do It Now Foundation, an anti-speed organization formed in 1968 that solicited the participation of a large number of artists:

> "I would like to suggest that you do not use speed. And here's why: It's going to mess up your heart, mess up your liver, your kidneys, rot out your mind. In general, this drug will make you just like your mother and father."[82]

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[78] E.g., Rosenfeld 1967; Davis and Munoz 1968; Smith, D. 1969; Smith, R. 1969.
[79] Smith 1969, 188.
[80] Fiddle 1968, 81-85.
[81] Quoted in Grinspoon and Hedblom 1975, 3.
[82] http://www.doitnow.org/psasounds/zappamomdad11.aiff, accessed April 18, 2012.

Just like your mother and father: a generic stand-in for the "old America," everything that the counterculture wished to escape.

Yet madness always wins. In the contest between speed and acid, speed emerged victorious. Though speed won, the acid heads left their distinctive imprint on the state of discourse about LSD and amphetamines in the popular imagination. The madness of speed, and the (relative) sanity of LSD, had been amply demonstrated by a massive social experiment the likes of which seem now unprecedented in psychiatric history. By the 1970s, key schizophrenia researchers freely borrowed these new meanings in their attempt to demonstrate that amphetamine psychosis, rather than LSD intoxication, was the correct model of schizophrenia itself.

The Dopamine Hypothesis: Closing the Gap Between Speed and Madness

The American architects of the dopamine hypothesis freely borrowed and modulated the new meanings that LSD and amphetamines assumed in the wake of the Summer of Love. They used those meanings successfully to argue that speed, not LSD, is the real model of madness.[83] Since speed was known to produce its effects by amplifying the dopamine system, then schizophrenia, too, must arise from an overproduction of dopamine as well. This was one of the crucial pieces of evidence for the dopamine hypothesis of schizophrenia. The other crucial piece of evidence was the apparent effectiveness of dopamine-blocking agents, such as chlorpromazine, in alleviating schizophrenic symptoms.

The dopamine hypothesis, in turn, was to become the leading biochemical theory of schizophrenia during the 1970s and 1980s, as well as a kind of "poster child" for the idea that mental disorders, generally, could be successfully "reduced" to neurotransmitter abnormalities. In particular, I will focus on the work of Solomon Snyder of Johns Hopkins Medicine in Baltimore, as he was the author of one of the two canonical papers on the dopamine hypothesis, though I will also describe the way that Burton Angrist and Samuel Gershon borrowed and modified these meanings.

Snyder's own interest in schizophrenia seems to have been prompted by the work of Angrist and Gershon. His primary preoccupation had been, like the Scandinavians Randrup and Munkvad, with amphetamine-induced stereotypy in animals. Prior to 1971, it did not seem to have occurred to Snyder that animal stereotypy would have any special relation with schizophrenia – reasonably enough, as the relation had always represented a somewhat stretched analogy. Instead, Snyder utilized amphetamine-induced stereotypy as a model for Tourette's syndrome.[84] At some point after coming into contact with the work of Angrist and Gershon, however, he submitted an article to *Archives of General Psychiatry*, the first line of which announces that, "amphetamine psychosis appears to be

[83] Snyder 1972; Angrist and Gershon 1970.
[84] Snyder et al. 1970, 122.

a fruitful experimental model of paranoid schizophrenia or paranoid state."[85] Angrist and Gershon's work rescued Snyder's humble research from oblivion, and endowed his work on stereotypy with major research significance.

Before he could defend the dopamine hypothesis, he had to get around two obstacles: the fact that LSD was still considered a model schizophrenia, and the fact that amphetamine psychosis did not seem to elicit thought disorder, a defining feature of schizophrenia. Regarding LSD, Snyder articulated a set of important disanalogies between LSD and schizophrenia. The most important of these was that LSD usage did not induce madness, *but merely enhanced normal perception*: "The mental state elicited by psychedelic drugs is one of greatly enhanced perception of oneself and one's environment. Similar states occur during mystical and religious introspection and when an individual is profoundly moved by emotions or external events."[86] Solomon was clearly adopting some of the characterizations of LSD use that had become platitudes in the wake of the counterculture.

Like Snyder, Angrist and Gershon also borrowed the contrasts between LSD and speed developed by the counterculture during the late 1960s. They used those contrasts to justify their view that amphetamine psychosis is a better "model" of schizophrenia than LSD intoxication. As Angrist and Gershon summarized their results on Bellevue admissions, "Because of…their sociopathy and their frankly hedonistic reasons for drug use, [the amphetamine users] resemble heroin addicts as a group far more than the philosophically and religiously preoccupied and less sociopathic hallucinogen users."[87]

It is crucial to emphasize the importance of these passages: two of the most important schizophrenia researchers of the early 1970s, and two of the strongest advocates for the idea that amphetamine psychosis mimics schizophrenia, clearly adopted the language of the American counterculture in sketching the differences between *the kinds of people who take acid and the kinds of people who take speed*. LSD users (and the users of other hallucinogens) are "religious," "mystical," "introspective," and "philosophical," and have a "heightened" sense of awareness of self and other. Amphetamine users are "sociopathic" and "hedonistic," mere thrill seekers incapable of authentic relationships.

One final problem remained. This was the problem of thought disorder. To all appearances, amphetamine psychosis, like LSD intoxication, took place in a lucid frame of mind. One of the defining symptoms of schizophrenia, disorganization or incongruence of thought, was absent. To remedy this difficulty, as described above, Angrist and Gershon attempted to demonstrate that amphetamine psychosis does, in fact, possess the power to induce thought disorder, even if it is extremely uncommon. Snyder, however, took a different route to explaining away this disanalogy. Snyder never attempted to demonstrate a relation between amphetamine psychosis and thought

[85] Snyder 1972, 169. This paper, unlike Snyder 1970, cites an article by Angrist and Gershon to the same effect.
[86] Snyder 1974, 1252.
[87] Angrist and Gershon 1969a, 205.

disorder. As he put it, "a key aspect of amphetamine psychosis is that it occurs in a setting of clear consciousness and correct orientation."[88]

How, then, did Snyder avoid the apparent implication that amphetamine psychosis was a bad model of schizophrenia? He reasoned that *amphetamines do elicit a "pure" schizophrenia, but some of their incidental chemical properties bar the expression of certain symptoms*. They produce a true, but *hidden*, schizophrenia: "It is conceivable that amphetamines possess a "pure" schizophrenia-mimicking action, but that some other effect of the drug transforms the clinical picture into a predominantly paranoid one."[89]

Snyder bolstered this possibility with imaginative deliberations on the inner unity of schizophrenia itself. Paranoid-type schizophrenia, in *essence*, is no different from disorganized-type schizophrenia (that is, the type associated with thought disorder). The only difference is that paranoid schizophrenics have found a means to consolidate the bizarre and incoherent medley of thoughts, perceptions, and emotions into a rigid system of delusions that endows them with order and significance.[90] Presumably, the disorganized-type schizophrenic is one who has not figured out how to accomplish this feat; all that remains is pure psychic chaos.

Snyder suggested that the dual psychiatric properties of amphetamines – the thought disorder-making component and the paranoid-making component – may be related to its actions on two separate transmitter systems, the dopamine system and the norepinephrine system, respectively. In other words, if amphetamines *merely* agonized the dopamine system, they *would* produce "pure" madness in the form of thought disorder. However, amphetamines had the incidental property that they also worked on the norepinephrine system, *which elicited the intellectual infrastructure that transforms the incoherence of madness into a meaningful system of delusions*. In other words, the norepinephrine agonism, "forces the patient to strive for an intellectual framework in which to focus all the strange feelings that are coming over him as the psychosis develops."[91] Amphetamines, then, generated *both* madness and reason; delusions represent a compromise, or a perverse victory, of reason *over* madness.

In this way, the mimicry thesis – the view that amphetamine psychosis replicates schizophrenia without flaw and thus should be used as a biochemical model of schizophrenia – rested almost entirely upon Snyder's creative imagination and a handful of feverish notes scribbled by speed freaks. In 1976, largely on the basis of this mimicry thesis, the "dopamine hypothesis" of schizophrenia was unveiled to the world.

Beyond the Dopamine Hypothesis

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[88] Ibid., 170.
[89] Snyder et al. 1974, 1245.
[90] Ibid.
[91] Snyder 1973, 66.

Angrist and Gershon's team and Synder's team developed a kind of positive feedback loop, supporting each other's research on the relation between schizophrenia and dopamine.[92] By 1976, with the publication of two influential reviews, the dopamine hypothesis entered the mainstream of American psychiatry.[93] The fact that Snyder labeled the view a "hypothesis," rather than a "theory," only made the view more seductive, even irresistible, in the eyes of psychiatric researchers. "By definition," announced Snyder, "the dopamine hypothesis is supported by no direct evidence."[94] Though there was ample *indirect* evidence for the hypothesis, American psychiatrists responded to this provocative claim as a kind of taunt.

By the late 1970s, researchers were engaged in a wholesale scramble to find direct biochemical evidence of dopamine abnormalities in schizophrenic patients.[95] Researchers carried out a host of sophisticated research studies involving collection and analysis of urine, cerebrospinal fluid, and blood, in order to find heightened metabolites of dopamine.[96] They also carried out post-mortem brain studies of schizophrenic patients in search of elevated dopamine receptor concentrations. Although some laboratories were successful in finding elevated dopamine receptor concentrations, these early studies were plagued by the problem of contaminated evidence, as many of the patients had also been taking antipsychotic medications for years.[97] The possibility that elevated dopamine receptor concentrations represented a compensatory response to antipsychotic dopamine blockade could not be ruled out. In the 1980s, and afterwards, these studies were supplanted by brain imaging studies of schizophrenic patients. Though the biochemical "smoking gun" was never discovered, after a while, nobody seemed to care too much. The dopamine hypothesis had become entrenched in the culture of American psychiatry.[98]

The apparent success of the dopamine hypothesis not only triggered a scramble for direct biochemical evidence, but it also emboldened biologically- and behaviorally-oriented psychiatrists in the American Psychiatric Association (APA) in their aggressive campaign to wrest control of American psychiatry from the hands of psychodynamic psychiatrists. Thus, the dopamine hypothesis played a particularly strategic role in the years leading up to the 1980 publication of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), which was the first of the DSMs to practically eliminate the old-fashioned psychodynamic terminology. They did so by using theories such as the dopamine hypothesis as leverage for promoting the so-called "medical model" of psychiatry, according to which mental disorders result from inner or biological "dysfunctions," and thus are analogous to non-psychiatric medical disorders.[99]

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[92] Snyder 1972; Angrist and Gershon 1972; Snyder et al. 1974; Angrist et al. 1974.
[93] Snyder 1976; Meltzer and Stahl 1976.
[94] Snyder 1976.
[95] Heinrichs 2001.
[96] See, e.g., van Kammen et al. (1986) and references therein.
[97] E.g., Farde et al. 1990.
[98] Kendler and Schaffner 2011.
[99] See Spitzer and Endicott 1978 for a particularly clear articulation of this position.

Today, support for the dopamine hypothesis has waned significantly, for two reasons.[100] First, a host of "atypical" antipsychotic drugs developed in the 1990s appeared to achieve their therapeutic efficiency by engaging a wider profile of neurotransmitters than dopamine. Thus, while dopamine abnormalities were likely implicated in schizophrenia, researchers began to think that they characterized only one small part of a vast puzzle. Secondly, some evidence suggested that dopamine abnormalities in schizophrenia actually constituted a secondary by-product of other, more "primary," dysfunctions. In particular, some researchers actively promoted the view that *glutamate* transmitter abnormalities occupied the privileged role of "primary dysfunction" of schizophrenia. A small number of researchers even advanced the thesis that dopamine abnormalities in schizophrenia have the function of *compensating* for hypothesized glutamate abnormalities.[101] If so, this would undermine the foundations of the dopamine hypothesis entirely because it would suggest that, far from being "dysfunctional," dopamine abnormalities have some kind of functional or adaptive significance, much like getting a fever after a bacterial infection.

Apart from the dopamine hypothesis, the analysis undertaken here could be used as a potential "model" or template for writing the history of research into schizophrenia, and perhaps other major mental disorders. The above analysis supports the following generalization. Any theory of schizophrenia (e.g., the biochemical or psychological mechanisms at issue) starts with a conception of what the "essence" of the thing is. That is, any attempt to discover a single mechanism underlying the diverse symptomatology of schizophrenia seems nearly hopeless. Therefore, the schizophrenia researcher, in order to make progress, *must* conceptualize certain symptoms of schizophrenia as "constitutive," "primary," or "essential." Other symptoms must be conceptualized as "derivative," "contingent," or "secondary." Are the so-called positive symptoms of hallucinations and delusions somehow primary, and thought disorder a secondary effect? Is thought disorder the primary effect, and delusions a way of coping with the psychological chaos it brings? And how do the avolition and apathy associated with catatonic-type schizophrenia fit in?

The philosopher of science William Bechtel called this sort of work – that is, characterizing the phenomenon at hand as a prelude to biochemical investigation – "reconstituting the phenomenon."[102] That is, once the researcher or research community has "constituted" or "reconstituted" the phenomenon, then that researcher or research team can set about the "proper" scientific task of building a model to explain these "primary" or "essential" phenomena, or describing a mechanism that would generate them. The "secondary" or "contingent" symptoms can be, at least at the outset, ignored. Focusing on certain symptoms and ignoring others forms a strategic handle for "getting a grip" on schizophrenia itself.

[100] See Grace 2000; Pliszka 2003.
[101] E.g., Grace 2000, 332.
[102] Bechtel 2008.

But this first task, this "reconstituting the phenomenon," is itself, while guided by scientific results, largely driven by imagination and guesswork. It is a "pre-scientific" or, if one prefers, an "extra-scientific" task (assuming that one can distinguish sharply between those aspects of scientific work that are "properly" scientific, such as building and testing models, and those that are not, such as reconceptualizing the phenomenon or publicizing the results). It represents an exercise of the scientific imagination, such as Snyder's deliberations on the nature of schizophrenia. Hence, looking at schizophrenia research at a given moment in time – the models and mechanisms that are considered the most promising avenues of research – is going to reveal what we take schizophrenia to *be*, at that time. This, in part, will be determined by what we *need* schizophrenia to be at that time: it gives us a window on the way that madness is being collectively imagined.

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