I would like to describe in some details the circumstances 50 years ago that has lead to our discovery of the hallucinogenic properties of N,N-Dimethyl-tryptamine (DMT) and review the history of DMT research in those years.

PRELIMINARIES

Maybe I will have to go back to even earlier times in 1953, when I, somewhat reluctantly, accepted the assignment to organize a Laboratory of Biochemistry at “Lipótmező” in Budapest. I said “reluctantly” because I was previously an assistant professor at the Department of Biochemistry of the Medical School, working with proteins and polysaccharides, and I wasn’t sure if we could learn anything useful from molecules that would be relevant to mental illness. I was, however, persuaded by my new colleagues that very recently at least three events occurred in psychiatry that suggested some encouraging clues that chemistry may be indeed relevant. One was the introduction of a chemically well defined drug: chlorpromazine (Largactil) into the treatment of chronically ill schizophrenic patients with remarkable success (Delay & Deniker, 1955). The second was the discovery of LSD by Albert Hofmann ten years previously (Stoll & Hofmann 1943; Stoll 1947). The extreme potency of this drug (as little as 50 mcg) is producing symptoms in man that was held remarkably similar to naturally occurring psychoses. This suggested a very selective interaction with a specific receptor site somewhere in the brain. The third event was the appearance of an article in the Journal of Mental Science in 1954 (Hoffer, Osmond, and Smythies 1954) which pro-
posed a new theory of schizophrenia postulating a chemical agent, a “schizotoxin” with a chemical structure similar to serotonin. Perhaps a fourth event should be also mentioned that was not a scientific publication, nevertheless became very influential in psychiatric and psychological thinking about hallucinogenic drugs and mental illness: it was Aldous Huxley’s 1954 book: The Doors of Perception (Huxley 1954).

To get started in the laboratory in 1953, we set up with Dr Katalin Szilágyi some chemical assays for the determination of indole-based substances in the serum of patients with various diagnostic categories hoping to find some correlations between indole content and diagnosis. While this was going on, sometime in 1955 I have read Huxley’s new book “The Doors of Perception” and was quite intrigued by his description of the effects of mescaline. So much so, that I decided to get some mescaline to experience its effect myself and tried it at the end of 1955. I thought that it was absolutely essential to experience personally the effects of a known hallucinogen before I could consider doing research with this class of substances. I was glad that I tried it, as my experience was, in many ways, different from what I have read in the Doors of Perception. I became convinced that about 90 percent of the content of the book can be attributed to Aldous Huxley as a writer, and only 10 percent to the drug, mescaline.

While contemplating what could we do for research in this area, I have read somewhere, that the Sandoz Pharmaceutical Company in Basel, Switzerland was making LSD available to those who are interested doing scientific research with the substance. I have written an official letter requesting a few milligrams for research, but when the reply came, they simply said that they are sorry, but they cannot send me any LSD.

**THE INSPIRATION**

All this happened still in 1955. I was regularly scanning the scientific and clinical literature for any leads that might guide me to a new direction. In the hospital we had mostly clinically oriented journals, but I also frequently went back to the library of the Department of Organic Chemistry, where I did my doctoral thesis work, and found a fascinating article in the November issue of the Journal of the American Chemical Society (Fish, Johnson and Horning, 1955). The authors have found DMT and bufotenin (among others) in a snuff-powder, called “Cohoba”, which was used by native Indians in South-America, Haiti, and Puerto Rico in their religious ceremonies. This article suggested that bufotenin might be the psychoactive ingredient but they did not know whether DMT was active or not. Apparently nobody else did, so I decided to start a project for testing it. First I had to have the compound itself.

So I went back to my old lab, where I did my thesis work in organic chemistry and my colleague and friend, Miomir Mészáros allowed and helped me to synthesize about 20 grams of DMT and half a dozen homologues of it.

**CLINICAL STUDIES IN BUDAPEST**

Then I went to the director at my working place at the National Institute for Mental and Nervous Diseases in Budapest, Dr. Gimesné, Lili Hajdu who, after a review of the project by the Hospital’s Medical Review Board, gave me permission to do the required preclinical and clinical studies. In this I was joined by three other psychiatrists András Sai-Halász, Zoltán Böszörményi, and Györgyi Brunecker who helped me to recruit, and test about 30 volunteers. In agreement with my co-workers, I sent in a short, preliminary report to the Swiss journal Experientia in the summer of 1956 before the Hungarian Revolution happened (Szára, 1956). The full reports appeared only two years later (Sai-Halász, Brunecker and Szára, 1958; Bőszörményi and Szára, 1958). The effects of a medium effective dose (0.7 mg/kg) given intramuscularly, were similar to those of mescaline and LSD: visual illusions and hallucinations, distortion of body image, speech disturbances, and mood changes: euphoria or anxiety (depending on set and setting). The most remarkable aspect of the effects was the rapid onset (2-5 minutes) and short duration (30-60 minutes). These effects have been replicated by a number of independent groups of investigators (Turner and Merlis 1959; Rosenberg et al 1963; Gillin et al, 1976; Strassman et al 1994).

**CLINICAL STUDIES IN WASHINGTON**

When I moved to the American National Institutes of Health (NIH) in 1957 I had the good fortune to spend some years working with Julius Axerlrod and others at the Clinical Center on the metabo-
lism of DMT and its homologues in normal volunteers and schizophrenic patients (Szára and Axelrod 1959; Szára 1961; Szára et al 1962; Szára 1964; Szára 1966; Szára et al 1966; Weil-Malherbe and Szára 1971). When in 1965 research with LSD and other hallucinogens were severely restricted in the U.S.A. I have expressed my dismay and concern in an article in the American Journal of Psychiatry that achieved some notoriety and the article recently became widely available on the internet (Szára 1967). In spite of the legal restrictions we managed to run a small (12 patients) study using N,N-diethyltryptamine (DET) as adjuncts to psychotherapy in chronic alcoholic patients in Washington (Faillace, Vourlekis and Szára 1967; Faillace, Vourlekis and Szára 1970) and we encouraged Stan Grof and his group in Baltimore to do a larger similar study on 50 patients using another homolog N,N-dipropyltryptamine (DPT) (Grof et al 1973; Soskin 1975).

CLINICAL STUDIES ELSEWHERE

For the last 30 years research with DMT (along with LSD and other hallucinogens) was slowed significantly by the Congressional Amendment of 1965 and by the Controlled Substances Act of 1970 by the United States Congress that classified the major hallucinogens as Schedule-I substances. In spite of these restrictions Rick Strassman at the University of New Mexico managed to obtain permission to conduct a clinical study of intravenously administered DMT in volunteers and studying the neuroendocrine, autonomic, and cardiovascular effects, in addition to recording their subjective reactions to the drug (Strassman and Qualls 1994; Strassman et al 1994). They also reported on tolerance developing to the physiological but not to the psychological effects to repeated doses of DMT (Strassman et al 1996). The only other clinical study using DMT in the last thirty years was reported only recently by Gouzoulis-Mayfrank and his colleagues from the University of Cologne, Germany (Gouzoulis-Mayfrank et al 2006). They have compared DMT with (S)-ketamine in a double-blind, cross-over study and claiming that both drugs produced global psychotic-like symptoms of the same intensity, but the phenomena, resembling positive symptoms of schizophrenia (thought-disorders or inappropriate affect) were stronger after DMT while those, resembling negative symptoms (attention deficits, motor phenomena) were stronger after (S)-ketamine. This study came to somewhat similar conclusions that Vollenweider (Psychiatric University Hospital, Zurich) has obtained in his comparison study with psilocybin and ketamine (Vollenweider 1994).

Since DMT is still a controlled substance and it is difficult to obtain permission to do clinical research on its effects, some researchers have turned to study the effects of Ayahuasca, a Brazilian native “tea” that contains DMT as its major psychoactive ingredient, and is used legally as a sacrament in religious ceremonies. Investigators, such as Dr. Ede Frecska and his collaborators are studying the effects on its users by measuring a high level perceptual function (binocular rivalry) (Frecska et al 2003 and 2004). There are a few other groups in the USA, Brazil, Spain and probably elsewhere that are also studying ayahuasca by some other means (Riba et al 2006; McKenna 2004; Stuckey et al 2005; Da Silveira et al 2005). Even more recently a study with psilocybin (a close relative of DMT) was published on the internet on July 11, 2006 (Griffiths et al, 2006). This article reported the results of a double blind, between-group, crossover study of psilocybin (30 mg/70 kg) vs. Ritalin (methyl-phenidate) (40 mg/70 kg) and the effects evaluated using established psychological scales. The results showed that 61% of the 36 subjects had a “full mystical experience” and 2/3rd of them rated their psilocybin experience as either the single most meaningful experience or among the top five most meaningful experiences of their lives.

PRECLINICAL STUDIES

I would like to add briefly that, in addition to the above mentioned clinical studies in the past 50 years, there was a large volume of pre-clinical research that has been conducted with DMT and its congeners. We ourselves have done some animal behavioral, and biochemical studies that focused on the interaction of these drugs with the serotonin system in the brain (Szára, Hearst, and Putney 1962; Szára 1962, 1964, 1968). Other, similar preclinical studies are reviewed by Domino (1974) and Aghajanian’s group (Aghajanian and Haigler 1975; Aghajanian and Marek 1999). In one of our studies (Szára 1968) we reported a surprising finding in mice, using tritium (3H) labeled 5HTP, that LSD and DET (but not of their non-hallucinogenic...
The methylated derivative of tryptamine, the de- 
only one that could also arise in the human body as 
pected natural hallucinogens DMT is probably the 
1954). Among the dozen or so proven or sus-
nonogenic” paradigm which is, in effect, proposing 
model psychosis (Hoffer, Osmond and Smythies, 
99). Today, however, the intimate 
ctions between cortex and brainstem nuclei, 
and the role of various subtypes of serotonin and 
other receptors in these interactions are more ap-
preciated (Lin and Glennon 1994; Nichols 2004), 
so a reexamination of my earlier findings may be 
in order. Perhaps the relatively recent identifica-
tion and cloning of the human indolethylamine 
N-methyltransferase enzyme could also help in 
this reexamination (Thompson et al 1999).

**DMT: MODEL OF SCHIZOPHRENIA**

The first half of the history of DMT may be char-
acterized as the period, when the focus of research 
was guided by the “psychotomimetic” or “halluci-
nogenic” paradigm which is, in effect, proposing 
that these drugs are producing an experimental or 
model psychosis (Hoffer, Osmond and Smythies, 
1954). Among the dozen or so proven or sus-
pected natural hallucinogens DMT is probably the 
only one that could also arise in the human body as 
the methylated derivative of tryptamine, the de-
caroylated product from tryptophan. Trypta-
mine itself is normally present in the brain (Martin 
et al 1972). An enzyme that can methylate trypt-
amine was first found in the lung of rabbits (Axel-
rod, 1962) and later also in the brain of both ani-
imals and humans (Saavedra and Axelrod 1972; 
Saavedra, Coyle and Axelrod 1973; Mandell and 
Morgan 1971). Numerous laboratories reported 
finding DMT in the blood and urine of some but 
not all schizophrenic patients and also in some 
other patients and even in normal subjects (Re-
viewed in Gillin et al 1976). This review comes to 
the conclusion, that “synthesis of DMT in man has 
yet to be demonstrated” and that the evidence for 
the role of DMT in schizophrenia is “currently in-
complete”. This pessimistic view, however, is not 
shared by everybody in the field and further re-
search needed to clarify this issue. Further clinical 
work may also substantiate DMT’s potential use-
fulness as an adjunct to psychotherapy, perhaps 
not by itself, but in a modified form, or in combi-
nation with other substances.

The Author is Retired Chief of Biomedical Branch 
at the National Institute on Drug Abuse. He is 
Emeritus Fellow of ACNP and CINP, member of 
AAAS, American Society of Pharmacology and 
Experimental Therapeutics, and member of the 
Scientific Advisory Board of the Heffter Research 
Institute. He was elected Honorary Member of the 
Hungarian Association of Psychopharmacology 
(2007). He is also recipient of ADAMHA Admin-
istrator’s Meritorious Achievement Award (1984) 
and the Kováts Medal of Freedom from the Amer-
ican Hungarian Federation (2005).

**Current address:** 
Stephen Szára 
10901 Jolly Way, Kensington, MD, U.S.A. 
E-mail: siszara@earthlink.net

IRODALOM

Aghajanian, G.K., Haigler, H.J. (1975): 
Hallucinogenic indoleamines: Prefer-
ential action upon presynaptic seroto-
in receptors. Psychopharmacol 

Aghajanian, G.K., Marek, G.J. (1999): 
Serotonin and hallucinogens. Neuro-
psychopharmacology. 21 (2 Suppl): 
16S-23S. Review.

Barbosa, P.C, Giglio, J.S, Dalgalarron-
do, P. (2005): Altered states of con-
sciousness and short-term psychologi-
cal after-effects induced by the first 
time ritual use of ayahuasca in an ur-
bam context in Brazil. J Psychoactive 
Drugs. 37(2):193-201.

Dimethyltryptamine experiments with 
psychotics. J. Ment. Sci. 104: 445-
453.

Da Silveira, D.X, Grob C.S, de Rios, 
M.D, Lopez, E, Alonso, LK, Tacla, C, 
Doering-Silveira, E. (2005): Aya-
huasca in adolescence: a preliminary 
psychiatric assessment. J Psychoactive 
Drugs. 37(2):129-33.

Delay, J., and Deniker, P. (1955):
Neuroptic effects of chlorpromazine in 
therapeutics of neuropsychiatry. J 

Faillace, L., Vourlekis, A., and Szára, 
S. (1967): Clinical evaluation of some 
hallucinogenic tryptamine derivatives. 

Faillace, L., Vourlekis, A., and Szára, 
S. (1970): Two-year follow-up of 
chronic alcoholics treated with hallu-
cinogenic drugs. Comprehensive Psy-
chiatry, 11, 51-56.

Fish, M.S., Johnson. N.M., Horning, 
Indole bases of P. Peregrina (L.) 
Benth. and Related Species. J. Am. 

Effects of ayahuasca on binocular ri-
valry with dichoptic stimulus alterna-
tion. Psychopharmacology (Berl). 

Frecska E, White K.D, Luna LE. 
(2003): Effects of the Amazonian psy-
choactive beverage Ayahuasca on bi-
ocular rivalry: interhemispheric switch-
ing or interhemispheric fusion? J 
Psychoactive Drugs. 35(3):367-74.


Rockville, MD, National Institute on Drug Abuse.


Rockville, MD, National Institute on Drug Abuse.


