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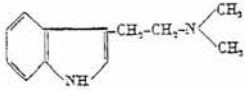
THE SOCIAL CHEMISTRY OF DISCOVERY: THE DMT STORY



N-N-Dimethyltryptamin

An Interview
with Dr. Stephen Szara
January 27, 1986

SE *Dr. Szara, in 1955 you began work to discover the drug activity of DMT. What led you to this work?*

SZ In 1953 I was working at the University of Budapest in the medical school's Biochemistry Department. I had an offer to organize a biochemistry lab in a mental hospital to work on a problem of the biochemistry of mental disease. That was the major goal. After I moved to the lab I started looking for some clues or some leads which I could follow. The area was not only new, but in many, many ways it was an untreaded one. Nobody really knew what was happening in the brain. Not in "normals" and even less so in the brains of patients with schizophrenia or other mental diseases.

Early in 1955 I found what I thought was a clue in an article which I read in the Journal of the American Chemical Association which was published by Fish, Johnson and Horning (1955). The article was about the chemical content of *cohoba*, which was a snuff powder used by Native American Indians, in South America, to induce religious ecstasy. That particular chemical analysis revealed that the substance contained *bufotenine* and *dimethyl-tryptamine*. The article noted that bufotenine was probably the active ingredient. Fabing (1956) had found a year or two before, that bufotenine helped produce some strange phenomena in man.

So in order to get started with my own work I was trying to get some LSD from Sandoz. But at that time I was behind the Iron Curtain

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and obviously they were suspicious of sending any LSD to Hungary. Indeed they said that they couldn't send me any. I began looking around for alternatives. And that was when I found the Fish, Johnson and Horning article which was my clue that maybe dimethyltryptamine was involved in the effect of that particular drug. Since there were no other data about dimethyltryptamine I decided that I would synthesize it myself using an already known synthesis which had been developed by the Upjohn people. Speeter and Anthony (1954) had published a relatively simple synthesis of dimethyltryptamine a few years earlier. So I synthesized some. I should mention that I have a Ph.D. in Organic Chemistry as well as being an MD. I went back to my old lab and asked my colleagues: "let me synthesize a few grams of this substance and let us work on it." In a few days I got some ten grams of a crystalline substance and started to inject some animals in order to carry out some preliminary evaluation. The substance indeed seemed to be active. Obviously you can not ask the animals — a cat or a rat — to know what he's feeling or what he's seeing...or whether he's hallucinating. Although you have some clues that a cat, for example, behaved very strangely when we gave it a 1 mg/kilo dose. The cat, which was a young animal, appeared to be very afraid at first. But when I injected the drug it became quiet and very friendly. This behavior lasted maybe for half an hour or so and then he started to be afraid again and ran away. So it was a strange little experiment and nothing really systematic at that point. But then I finally got into using systematic doses in rats and mice in order to see what is the dosage range. Then I decided that somebody would have to try it because that's the only way, in humans, that we can find out whether it is or isn't psychoactive. I volunteered to be the first person to try it. When I first tried it I took it by mouth... a quarter of a milligram of the substance. I remember, having read Hoffman's story (Stoll,1947), that he took what he thought was a small dose like a quarter of a milligram of LSD and he really was "bombed out". So I decided to start at a very small level. And after taking a quarter of a milligram nothing happened. Two day afterwards I took a higher dose, and so on. I went up to about ten milligrams per kilogram dose. And still nothing happened. I got discouraged for a moment. Somebody suggested that maybe taking it that way was the wrong way to do it...maybe you have to take it parenterally, either intra-muscularly or intraveneously or subcutaneously, or whatever.

I went down to my friend in the Pharmacy Department, at the hospital, and asked him to prepare a sterile injectable solution of

dimethyl- tryptamine for me. The first small dose, which I injected intramuscularly, was at the level of half a milligram per kilo.

In three or four minutes I started to experience some visual sensations which were very similar to what I had read in the descriptions by both Hoffman (Stoll, 1947) and Huxley (1954).

I got very, very excited. It was obvious that this is the secret...that you would have to give it parenterally, intramuscularly. As I remember it now, I think that I repeated it once again on myself, at a slightly higher dose, before two of my friends and colleagues volunteered. We were trying to find out whether these effects were indeed reproducible and what were the parameters which were involved. Based upon these experiments on ourselves we developed an evaluation protocol and we decided to test the drug on a number of other subjects.

SE *At the time that you were able to begin to pinpoint the drug's action and under what conditions the drug's action would appear, did you foresee this active chemical substance as being a new and accepted medicinal contribution? Did you see it being a new chemical research tool or a therapeutic tool?*

SZ What we were looking for was a tool for research.

SE *What kind of research?*

SZ Psychomimetic drugs, by definition, were supposed to mimic the symptoms of psychoses. We were hoping to develop a psychomimetic substance which would be very close to a natural relative like *serotonin*. We were hoping that, by having a substance like that, we would be able to test a reasonable hypothesis as to whether or not such a substance can be formed in schizophrenia? We also wanted to investigate whether or not this might be a "*schizo- toxin*" which could be responsible for symptoms in schizophrenia. These were our original foci...and hypotheses. That was the major goal which we were trying to get into.

SE *How was your work, at that time, more than thirty years ago, responded to by the professional, medical, scientific community?*

SZ We had a committee in the hospital to whom I had to present my plans and my proposed work...along with the background material that could be found in the literature. They had to approve my plans before I could go on...evaluating the potential danger, or potential benefits, of this particular research.

This was at the hospital in Budapest, Hungary and the work began

about the end of 1955. As a matter of fact it was during the summer of 1956. When we had finally completed some twenty-six or twenty-seven experiments with human subjects, all of them were taking the same dose...about 0.8 mg/ kg i.m.

We had collected, from our clinical observation, the data on the time course of action, the types of symptoms which were produced and so on. We were, at that time, about ready to send in a publication or to present it somewhere. My decision was that we should send it in, then, as a preliminary publication to the Swiss journal *Experientia.* (Szara, 1956) We sent it during the summer of 1956. The more detailed description of what we had done was sent to the journal... *Psychiatria et Neurologia.* It was in a German translation. The shorter paper, sent to *Experientia* was published in English. We didn't present the paper anywhere in Hungary at that time. As you may well remember there were some political difficulties during October 1956 in Hungary which were not resolved to my satisfaction. So I decided to leave the country and temporarily settled in West Berlin. While working at the Neurological and Psychiatric Clinic there, I was invited by Silvio Garattini, who organized a meeting on psychotropic drugs which was to be held in Milan Italy in May 1957. He invited me to present the earliest data because he had seen the preliminary data in *Experientia.* That was the first large scientific community to which I presented my findings.

SE *And how did your colleagues respond to you and your data?*

SZ I think that my paper was very well received. They thought of it as being a novel finding. And because of the then current interest in serotonin I was trying to measure serotonin metabolites in the urine. We had some preliminary data on increased excretion of 5-hydroxyindole-acetic acid. But they were not very clear cut. Everyone was trying to get into the hot area...and serotonin was the hot area at this time. As a matter of fact it was because of some of the results in my paper, which I gave in Milan, that Joel Elkes offered me a job at NIMH. And that's how I got to be in Washington eventually.

SE *What was DMT used for in its early history?*

SZ There is no recorded use for DMT as a substance. I don't remember seeing any applications or use for it besides the analytical findings that it is contained in cohoba as a snuff.

SE *When you had begun your research, you had hoped to add an important research tool to our armamentarium of tools.*

SZ That's right.

SE *What impact, do you think, did the synthesis and the spelling out of the drug action of DMT have on research in mental health, for example?*

SZ I think that the best way to approach this question is to describe what happened after I came to NIMH and continued to work in this area for about fourteen years. We ourselves contributed quite a bit to the working out of the metabolic processes which are involved (Szara, 1961; Weil-Malherbe and Szara, 1971). I was active in Julius Axelrod's lab for about two years, from 1959 to 1961. We had worked out the metabolism of DMT and published together with him (Szara and Axelrod, 1959). Dr. Axelrod also got interested in DMT and he later found an enzyme, in the brain, that actually can use tryptamine to make N.N.-dimethyl tryptamine (Axelrod, 1961). This was a very, very exciting comcomitant of our original finding. There are a number of well known research laboratories which are using dimethyl-tryptamine now as a routine tool in neuro-physiology (Aghajanian, 1972). George Aghajanian of Yale University, for example, has published numerous papers in which he uses dimethyl-tryptamine and LSD side-by-side in his studies of serotonergic neurons found in the brain.

SE *From your unusal perspective and vantage point at the National Institute on Drug Abuse, for many, many years now, what problems, if any, do you think DMT has created...contributed to or reinforced...and for whom?*

SZ I was obviously interested in knowing whether or not this was going to get out of hand...getting out to the streets and into the hands of street pharmacologists. In 1967 there was a major drug outbreak, as you may recall, with a major focus in the Haight Ashbury district of San Francisco. I was in California for ten days at that time. I was looking around for clues to see whether dimethyl- tryptamine had "escaped" and whether or not it was part of the "scenery". I found very few references to the use of this substance in my discussions with people in the University. It was clearly on the street at that time and it can still be found occasionally. But it is a very, very minor part of the whole drug scene. It never became a major drug of misuse.

SE *Given the work which you began more than thirty years ago, where do you think that we have gotten to in our knowledge about DMT, and what are the implications of that knowledge that people such as yourself have brought to us?*

SZ The major impact would obviously be a finding, at a clinical level, whether or not in some cases of mental illness, dimethyl-tryptamine can be found to be actually produced. If it can be found, the main question is to establish if it is related to the disease. This is not an easy question to answer as many factors will come into play...such as: the availability of precursors, differential metabolism in the schizophrenic state, development of tolerance and correlation with treatment or spontaneous recovery. These questions have been critically examined by Gillin and his associates and their conclusions were published in 1976. They felt that although, theoretically, dimethyl-tryptamine can be formed in the brain and occasionally they find it in the blood and urine of schizophrenics, that its levels can not be related *directly* to the intensity of the disease. They were not convinced that endogenous formation of DMT can be regarded as a unique or a major factor in schizophrenia. So, although the clinical conclusion is inconclusive at this point, I understand that there still are a number of laboratories working on the question using a variety of chemical, physiological and behavioral methodologies (Trulson and Schlemmer Jr., 1986).

Although DMT may not turn out to be the sought-after "*schizotoxin*", nevertheless, it has become an important research tool in identifying sorotonin-sensitive neurons (along with LSD) in the brain. Eventually this research may help to formulate sharper hypotheses about the role of neuro-transmitters in brain functions. In very general terms new ideas are usually created at the intersection or border of established disciplines. Take for example chemistry and biology. They had been established in the 18th and the 19th centuries as well defined scientific disciplines, each with its specific methodologies and philosophical assumptions. At the border between these two lies what is known today as biochemistry..."born", as it were, as a series of discoveries of enzymes, vitamins, hormones etc., mostly during the first half of this century. Psychiatry was developed essentially as a specialized medical practice with no conceivable relationship to biochemistry. It was there — in 1952 or '53, that I thought that there was an interesting opportunity for exploration. Since I had a background in both areas I felt reasonably qualified to go on and to try to do something.

SE *What kinds of responsibilities do you think discoverers should have in the field of medicinal research?*

SZ First of all we have to keep in mind the Hippocratic Oath. We are expected to do no harm! This is the most important thing in any medical intervention...and this includes research on and with human beings. If you proceed with this in your mind, then our next responsibility is to set up some reasonable hypothesis that can be scientifically tested to expand our knowledge. If you do no harm but we do learn something which is scientifically valid, eventually it might be for the benefit of everybody.

SE *Are there particular rights which are more likely to facilitate the process of discovery.?*

SZ I don't think that we have any special rights. We have the right of following whatever our background...whatever our schooling and whatever our experience provides. Scientists have only as much right to do something in a certain area as they are qualified by their training and experience.

SE *Do you think that scientists — discoverers — working in this area as researchers or innovators, have any obligations?*

SZ We have obligations for society, obviously, as well as for our fellow human beings.

SE *What kinds of obligations?*

SZ General obligations such as trying to help others who are less fortunate and are in distress.

SE *We have been discussing the process of discovery. How would you define discovery?*

SZ I would probably go back to Thomas Kuhn's idea of the paradigm...within the context of what Kuhn called "normal science" (Kuhn, 1970). In normal science, the work of scientists involves primarily "puzzle solving", i.e. fitting new data and new experimental findings into the current paradigm. Paradigms are seen by Kuhn as frameworks of basic assumptions, beliefs, values and techniques which are shared by scientists working in particular fields. *Discovery* involves finding anomalies which *can not be related* to these basic assumptions. As

these anomalies accumulate it becomes increasingly difficult to hold onto the old paradigm. When a major discovery occurs — one that I might call a *breakthrough* — it can not be fitted into the old paradigm(s) anymore. You have to break it up and establish a new paradigm. This is the process which Kuhn refers to as a "scientific revolution". Now this is a different kind of discovery. Examples of this are the discovery that Watson and Crick made in 1953 when they discovered the double helix structure of DNA which revolutionized the old-fashioned genetic paradigm (Baltimore, 1979), and what Albert Einstein had done earlier in this century that overturned the plausibility of Newton's physics (Lakatos and Musgrave, 1970). What they did, obviously at that point in research, represented major paradigm shifts; scientific revolutions. These are just two examples of major breakthroughs. Obviously not everybody can be Albert Einstein, or James Watson or Francis Crick. "Normal science" involves a lot of drudgery which occasionally leads to exciting discoveries which are not that major. Nevertheless they are still important since they increase and broaden our knowledge base on which all scientific progress depends.

SE *What types of economic resources are needed which are more likely...most likely... to facilitate medicinal discoveries?*

SZ This is a complicated question. It really involves social and political factors as well as a nation's cultural background. All of these play an important role in understanding how "they" have gotten to where they have gotten...to where they currently are.

Research...basic research or scientific research could be done by any kind of economic support. It could be funded by the government intramurally...such as the NIH. The government also supports extramural research done mostly in University laboratories. Research support is also provided by foundations as well as by various industries.

SE *What kinds of barriers have you found, or do you know of, which by and large have interfered with the discovery process?*

SZ The very process of institutionalized research support which involves peer-review to assure that the money goes to the "productive" laboratory and the "proven" research people, may, to a certain degree interfere with the development of novel ideas which may eventually lead to a major discovery. If, for example, somebody would propose that they would solve the problem of schizophrenia by a unique magnetic

theory...or whatever...that sounds so out of place and out of line from the current paradigm(s) that nobody would approve it and nobody would fund it. And if this somebody is going to discover something on his own, it may be a breakthrough...but his breakthrough would probably not be supported by the powers that be. I am not alone in claiming this. Many have said that the institutionalization of "normal science" is really hindering explorations and discoveries. Peer review, by its very nature, is very conservative. I am seeing this, everyday, in my own work at the National Institute on Drug Abuse.

SE *Considering the various implications of your discovery, what do you think, or suggest, as being the single most critical issue necessitating further exploration...research?*

SZ Probably it is the identification of the subset of mental patients in whom the endogenous formation of DMT plays an etiological role. This could lead to the eventual development of a new drug specifically targeted to block the formation or action of DMT and would represent a major advance, if not a breakthrough in psychopharmacology.

SE *What do you consider to be some of the ethical considerations which should be an integral part of the process of medicinal discovery? What ethical issues should we be paying attention to?*

SZ I can only repeat what I said previously: to make sure that we are not doing harm to people. And I might add not doing unnecessary things which cause suffering in animals while doing animal studies.

SE *What kind(s) of support system(s) are needed, in your view, in order to facilitate innovative pharmacological discoveries? (institutional — non-institutional; private — public; individual — team, etc.)*

SZ Continuation of general (and generous) research support to explore and establish a better understanding of brain-behavior relationship would facilitate the emergence of innovative approaches to new drugs and treatments.

SE *What generic and/or specific characteristics, abilities, traits, attitudes, interests, behaviors, values, energy levels, etc. would you look for in a person whom you would want to hire to work in a program involved in medicinal discoveries? What is necessary, from your perspective, for a person selecting a career as a medicinal/pharmacological discoverer/innovator?*

SZ I think that in addition to professional competence you also need personal commitment and enthusiasm as primary characteristics to stay with the everyday drudgery of research, as behind every discovery and invention, there lies 1 percent of inspiration and 99 percent perspiration, to pharaphrase Thomas Edison.

SE *What criteria would you suggest, as being reasonable ones, for assessing the outcomes of pharmacological/pharmaceutical discoveries...both* with regard to success as well as failure?

SZ By far the best criterion is the adoption of a new drug by the medical community as an effective treatment of patients. Next best, I would say, is the adoption of a discovery by the research community as a tool, or building block, in their work towards the first goal. To my mind, DMT has reached the second goal, but not the first one...as yet.

SE *What has your involvement and committment to the process of discovery taught you?*

SZ I think my previous comments pretty much cover the answer to this question.

SE *What personal "price", if any, have you had to pay, having chosen to be involved in the process of discovery generally, and specifically as a consequence of your work with DMT?*

SZ As I think back to the past 35 years or so of my life, I would say that leaving my country and the comfort of my mother-tongue may be considered to be a personal "price" I had to pay to follow my commitment to psychopharmacological research with DMT. The opportunity that my adopted country gave me, however, more than amply compensated for this sacrifice.

SE *We have covered many factors, issues and processes. What do you think facilitates discovery? What makes "discovery" work when it indeed does work?*

SZ Discovery "works" when it fits into the prevailing paradigm of the field and if the scientific community adopts it as a standard tool of the trade.

SE *Are there any other parameters of medicinal/pharmacological discovery — innovation, which we have not touched upon, with regard to your discovery*

of DMT or the process of discovery in general, which you would want the reader to consider?

SZ I just hope that some young, budding molecular biologist reading this story gets interested enough in the tryptamine-N-methyl transferase enzyme to clone it, and investigate the conditions that regulate its expression. That should really unravel the etiology of at least some form of mental illness and provide further clues to its treatment and prevention. It would also represent the first direct connection between psychiatry and molecular biology, where 30 years ago we had only speculations and dreams.

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BIOGRAPHY

Stephen Istvan Szara, M.D., D.Sc., currently Chief, Biomedical Branch, Division of Preclinical Research, National Institute on Drug Abuse (N.I.D.A.), has taught at the Medical University of Budapest and George Washington University; carried out research in Hungary, Austria, Germany and the U.S.A., written more than 70 publications (articles and chapters) and co-edited 2 books: *The Pharmacology of Marihuana.* New York City: Raven Press, 1976; *Benzodiazepines: A Review of Research Results, 1980.* NIDA Research Monograph, 33, 1981; is an editorial consultant to: *International Review of Neurobiology; Research Communications in Substance Abuse; Progress in Neuropsychopharmacology and Biological Psychiatry.* Member of numerous American and international scientific societies his research interests include: polysaccharides in fibrinogen and fibrin; dimethyltryptamine and other hallucinogens; opiate receptors and endogeous opiates; marijuana and its health effects, and brain structure and function.

الكيمياء - الاجتماعية للاكتشاف : قصة

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مقابلة مع الدكتور ستفن سزارا

發現的「社會化學」：訪問 Dr. Stephen Szara

"СОЦИАЛЬНАЯ ХИМИЯ" ОТКРЫТИЯ: ИСТОРИЯ DMT. ИНТЕРВЬЮ С Д-РОМ СТЕФАНОМ СЦАЗА

LA "QUIMICA SOCIAL" DE DESCUBRIMIENTO: LA HISTORIA DEL DMT. UNA ENTREVISTA CON EL DR. STEPHEN SZARA