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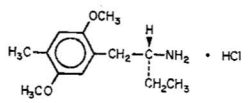
# *The "Social-Chemistry" of Pharmacological Discovery*



**Dimoxamine Hydrochloride**

## Interview with Dr. Alexander T. Shulgin.

January 26, 1986

**SE** *In what year did you first discover or synthesize Dimoxamine?*

**AS** I first synthesized it in 1968, and discovered its central nervous system activity in man the follow year.

**SE** *What led you to this discovery?*

**AS** It was really an outgrowth of my entire research approach directed to the discovery of new materials. Rather than starting with materials of a known class of activity and then modifying them, to vary primarily their potency and their toxicity, my approach has always been to produce a chemical that *should have* potent activity. My aim is to discover just what that activity is. I am not clever enough to have the whole structure-activity relationship in mind ahead of time. I'm still changing it every time I prepare a new compound and discover new activity.

**SE** *At the time that you discovered Dimoxamine, what did you foresee theoretically at least, as being its major contribution?*

**AS** At that time I thought that it would probably be psychedelic, and was rather surprised when it was not. It is extremely similar in chemical structure to *DOM (STP)*, the rather potent and dramatically

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active psychedelic which I had discovered five years earlier (Shulgin, 1970). *DOM* was introduced some four years later into the street scene of San Francisco by person or persons unknown, and had received some notoriety as a psychedelic drug. *Dimoxamine* turned out to have an entirely different action.

**SE** *If Dimoxamine had had similar properties to STP would you have anticipated that it could be used as a pharmaceutical?*

**AS** If it had been a psychedelic agent, it probably would not have been of interest to a commercial pharmaceutical house, as there was at that time hardly any awareness of the potential value of such agents in therapy. Sad to say, there is not much more awareness of this even today. So I presume, had *Dimoxamine* been another psychedelic, it would have been just one more tool to help the researcher who is trying to understand the structure-activity relationships amongst such drugs.

**SE** *Could you go into that a bit more?*

**AS** Every compound, every chemical that can be synthesized and that might have pharmacological action, is an absolutely unique individual. After it has been made and has been explored pharmacologically it can, retrospectively, be classified according to the discovered action. At that time it can be correctly pigeon-holed.

But when it is first synthesized there is no way to know, with any certainty, what one is going to find. It is like sitting down at the piano and improvising. You establish a kind of dialogue (you and the compound) but you have no idea where you're going to be in a while. Many of the compounds I have made, which have proven sufficiently free of risk from the toxicological point of view to allow further evaluation, have led to the discovery of some type of action which was often unexpected.

Most of the new compounds that I have come up with over the course of some three decades of research have fit into the so-called psychedelic classification. Some have been sensory amplifiers, such as *DIPT (N, N-diisopropyltryptamine)* which selectively distorts the auditory sensory input signals (Shulgin and Carter, 1981). Others such as *2C-B (2, 5-dimethoxy-4-bromophenethylamine)* appear to sensitize the sensory responses without distortion (Shulgin and Carter, 1975). *4-Thiomescaline* is close to being psychotomimetic (Braun et al, 1978; Jacob et al, 1981) and the drug *DOM,* mentioned above, is accepted by

many researchers as a prototypic hallucinogenic agent (Hollister et al, 1969; Snyder et al, 1967). Another compound in which I first published the human activity (Shulgin and Nichols, 1978) is *MDMA (3, 4-methylenedioxymethamphetamine)* which is finding value as an adjuvant to psychotherapy.

But in this small study that led from *DOM* to *Dimoxamine* (a compound that I had originally called *Ariadne*) I was surprised to see it evolve into an antidepressant. It went into clinical trials in about 1974.

**SE** *How was Dimoxamine responded to initially by the professional, medical, and scientific community?*

**AS** The first presentation in the medical scientific community was under the sponsorship of Bristol Laboratories, a well known and widely respected pharmaceutical house. At that time there was still some question as to the appropriate classification to give it; the final "pigeon hole" to put it in. I had initially called it an antidepressant, although it had stimulant properties without appreciable cardiovascular involvement. It was finally patented as a memory adjuvant (Stanridge, et al, 1976) for use in depressed and, especially, in older patients. It has been shown to be indeed without psychedelic properties in a patient population.

**SE** *Given that depression is a major ailment affecting many, many people, was this newly discovered "medicine" responded to by the media?*

**AS** Oh, no. The media never knew of it. The drug went through clinical studies up to Phase III of FDA approval. And then, for economic reasons, Bristol put it aside. It has been "shelved." Thus it has never achieved prescription status.

**SE** *When it was being used as an experimental drug, early on in the clinical trials, what was it used for?*

**AS** Initially, it was used primarily to reverse chronic depression. However, additional clinical studies were conducted on a sizeable population that was composed of both psychotic and normal senile geriatric patients. The psychotics that demonstrated schizophrenia and manic depression showed a general improvement of behavior at doses of about 100 mg per day. The catatonic patients were more relaxed and sociable. In the non-psychotic elderly patients, doses of half this amount had the effect of making them more alert and interested in life.

**SE** *And the emphasis was on chronic depression, as distinct from acute depression?*

**AS** I believe that was the area in which it was found to be most effective, but I have never dissected the clinical reports that came to Bristol. My interest has always been in the exploring and discovering, and not in the exploiting.

**SE** *When you began the research which led to Dimoxamine, did you have a sense or an aspiration about what potential impact such medication might have on the quality of care in this area of medicine?*

**AS** Not particularly. As I have said, the uncovering is more exciting to me than the utilization.

**SE** *This particaular drug that you discovered went the "normal route" with the pharmaceutical firm and then became shelved. For what reason?*

**AS** It is important to note that it was not abandoned, it was shelved. Clinical trials are always carried out with a continuing concern for the maintainance of a necessary balance between what's being invested and what return can be obtained from that investment. This is known as "the bottom line." As I was given to understand, it was felt at the executive level in Bristol that there were other avenues to pursue that would be more profitable to the company than synthetic psychopharmacological agents. The material was not faulty; it simply did not have the economic potential to warrant the investment.

**SE** *As you look back at what has happened with your discovery of Ariadne, this particular antidepressant, and if you had the chance to do it all again, how would you do it differently?*

**AS** I do not own a pharmaceutical house and so I do not have the means of exploiting a discovery. If I feel that a material has a valuable potential I will either patent it or publish it. I see no reason to do anything differently with one possible exception — today I might consider some kind of agreement which would allow me to take back a drug such as this after a period of time, should the drug company fail to develop a final product.

**SE** *Where do you feel research into these kind of antidepressants should be going at this time?*

**AS** You should remember that the "pigeon-hole" of antidepressant was used mainly to fit a familiar name to a new drug. The patent that was issued for the drug used the term memory enhancement, as this classification is often used in the medical and scientific literature. As was mentioned above, it could also be considered as an anti-Parkinson drug and as an effective antipsychotic drug. In all these publications there has been a continuing emphasis on the fact there are no so-called psychedelic properties either expressed or experienced by this drug in man. This brings up an interesting question. Why can we not bring ourselves to acknowledge the possible value of giving drugs to a normal population for the enhancement of sensory or intellectual capacities?

Very simply, we cannot bring ourselves in our society to acknowledge the giving of drugs to a normal population for enhancement of any sensory or intellectual modality. If a drug produces a sensory "sparkle" in the so-called normal person, we feel compelled to find an abnormal population as the only acceptable group that can be allowed it. Let us give it to the geriatric patients — we all know they lack sparkle. If a drug produces insight or creative motivation in a healthy individual, let us see it only in terms of some pathology — perhaps autism or amotivation — as a target for its use. We all know that "normal people' don't want for motivation. Our present society insists that drugs are for the unhealthy. Their use with anyone else is simply labeled and responded to as *abuse.* And the medical community confirms this stance with inescapably logical advice — the risks of a drug must be weighed against its benefits; there are no benefits accepted for "sensory-sparkle drugs" or "insight-givers." Therefore no risks can be tolerated.

A sad corollary of this attitude is that it is in a sense self-confirming. Without medical research in areas that might confirm such potential values for drugs, these very values are difficult to discover and acknowledge.

And so many of these effects are seeable only in the human animal. How does one measure sadness, repressed anger, or empathy in a rat colony? Drugs which have effects associated with these psychological states can be discovered *only in man,* since their effects can be expressed only in man. The search for these has to be a continuing search, and both mistakes and discoveries will be made.

There is another point that pertains to the discovery of new drugs, especially drugs active in man. Most of them were actually discovered first in man, with man as the test animal, sometimes by accident and

sometimes by design. And once the activity is known, then the research direction returns to animal models, for verification and for the development of screening tools. As an example, *chlorpromazine* was an antihistamine that was explored clinically without preconception of qualitative action, and it unexpectedly proved to be a sedative (Swazey, 1984). From its discovery has come a major class of tranquillizers. Private exploration by physicians, by scientists, by naturalists, has been the major origin of many drug classes.

In this area there is legislation currently being proposed in the United States that disturbs me very deeply. This has been prompted by the irresponsible manufacture and sale of subtle structural varients of illegal drugs by sociopaths who are attempting to circumvent existing law. But because of the proposed wording of certain parts of this bill, there is a threat to make illegal any scientific research in man that might uncover new drugs, unless that research has been explicitly approved by the government. And if a researcher is put into a position of requiring approval, he is in the position of having this approval denied him.

It is my belief that no scientist with integrity can pursue a quest for knowledge and still accept such censorship.

In our earlier conversations you had mentioned Dr. Schultes and his discovery of *Virola* (Schultes, 1954). Here is an exquisite example of discovery and of potential. There is no clinical use for *Virola.* It is not in the pharmacopoeia of the prescription market. But the teasing apart of the several compounds found in this snuff and their evaluation in man have revealed two hallucinogens. One of them might be a natural component of the human brain, and the other a *monoamine oxidase inhibitor* that closely resembles a hormone associated with the human pineal gland. This is raw research stuff of immense potential, discovered in man without the permission of any governmental agency.

**SE** *Using this interview as an opportunity to communicate with people who may consider picking a profession of pharmacological innovation...of discovery..., to novices, to students, to fellow colleagues..., what responsibilities, if any, do you think a discoverer in the field of medications has?*

**AS** I think that one of his major responsibilities is to be honest with himself and honest with others. If he finds something that is of interest, something that is an unknown, my personal philosophy is that he should publish it, making it available to others. A person who works under a certain amount of professional obligation, such as for an

industry or in response to a financial grant, may have some restrictions on that freedom... to talk or to give away. One must live with the quid pro quo of that situation. In my own case I happen to be sufficiently enthusiastic about the way I conduct my research, to have assiduously avoided these types of restrictions by not taking funding from any industry or any government agencies. This leaves me totally free to publish what I find, making it available in the medical and scientific literature. Thus, I may search at my own pace, and answer only to myself.

**SE** *You've suggested that your independent role has facilitated your style of work. What kinds or roles do you think are more likely or most likely to facilitate pharmacological discovery and innovation?*

**AS** I don't think that you can say one role is preferable to the others. All possible roles should be, and will be pursued.

There are some researchers who will systematically vary some minor aspect of a known material to see what that variation does in a given pharmacological screen. This diligence is very necessary. And there are people who walk into the unknown and taste the red flower, and then taste the blue flower, and from that discover that red causes the blood pressure to go up and blue causes the blood pressure to go down. This type of serendipitous research is also absolutely necessary.

And all these explorers must communicate with one another so that each may build upon the other's findings. I don't think that any one role is preferred. All of them have proven to be needed.

**SE** *What rewards do you think discoverers and innovators have, or should have, from their work?*

**AS** I think that the person has to decide for himself what reward would justify his labors. If it is prestige and recognition, then he must emphasize the presentation of his work. If it's for early retirement so that he can tend his rose gardens, then he must emphasize the financial return from his work.

In my own case, my satisfaction is totally personal, in that my reward is the pleasure of understanding one thing today that I didn't yesterday. This is completely adequate, and I have trimmed my recognition needs and financial needs down to where I can continue to support my own home and my own laboratory.

**SE** *What obligations, if any, do you think discoverers have? To themselves? To the community at large? And for those working in laboratories or corporations, to the funding agencies?*

**AS** A scientist's obligations to the funding agencies represent restrictions. These are often implicit in the phrasing of the question being researched: "Find out if thus and so is really so," or "What is the risk in this?" or "Is that safe?" These are restrictions that are imposed upon a research person and he accepts these restrictions at one level or another by the very act of accepting the assignment from that authority. I think the most important obligation of a person in research is that of being honest with himself. A researcher must feel free to report what he sees and what he finds without any concern as to who might be offended by the findings. He must be free of being imposed upon by moral or ethical standards that are not his own. His sole responsibility is for the factualness of his findings. If you work with integrity and you work with honesty, you cannot be faulted by a person of similar honesty.

**SE** *You have raised the issue of integrity. Are there ethical aspects of pharmacological discovery which indeed must be considered?*

**AS** That is a difficult, difficult question to approach because your ethical structure is not my ethical structure. Each man's personal set of standards is unique. As an illustration, by experimenting directly in man, let us say that I find that a new drug is a hallucinatory drug. And further, that it is active in man at such and such a level, and provides such and such a change in his sensorium. Someone else who happens to believe that all drugs should be tested in animals until they have been proven safe might think that my work is not ethical. I believe that it is. So with regard to the ethics of pharmaceutical research, there is no absolute standard. Integrity, however, I define not so much as honesty to others — or agreeing with your, or other people's standards — as it is honesty with yourself. If you conduct yourself with integrity within this definition, you are incontestably ethical.

**SE** *If you were put in the position of having to define or describe the process of discovery to a person who did not understand the concept, how would you define discovery?*

**AS** I would define discovery as the act of searching for an unknown — asking a question and searching for the answer. And preparing yourself to be excited in finding that answer, rather than being

frightened or disturbed. The concept is that of answering a question with an attitude of the excitement of the search. I think this is a philosophy that could motivate a new young scientist.

**SE** *What kinds of barriers, if any, have you yourself experienced or witnessed, which indeed have slowed up and perhaps inhibited necessary medicinal research form being carried out?*

**AS** No one should expect to encounter any barriers to exploration — to discovery — that are serious unless they are taken seriously by the researcher himself. If one relishes confrontation, one will encounter barriers. At the simplest level, the asking of a question in private, and the finding of an answer to this question in private, cannot offend anyone or provoke anything, and no barriers exist. It is the emergence from this privacy to some degree, be it by announcing, or publishing, or sharing your findings in some way, that brings one into contact with the public area. This exposure can be seen as an attempt to influence or convince someone, and it can be a source of potential confrontation. It's the motives and the goals that are important. If the goal is to "prove Professor Jones wrong," or to "convince Dr. Smith that I am right," you will find yourself interacting with people who may not choose to change their opinions. Thence confrontation, followed by attack, followed by defence. All of which robs you of valuable time and energy.

**SE** *In the process of discovery, what institutionalized or non-institutionalized support systems would you feel are necessary or perhaps just useful to have, in order to facilitate discovery?*

**AS** Research is expensive, and costs are increasing daily. One must have some form of funding to support it. And the source of funds is also the source of assignment of responsibilities and certain aspects of approval and authority. I believe that a scientist should attempt to remain curious with a minimum amount of external funding, thus keeping his responsibilities to the funder at a minimum. The drive for ever increasing funds and size of operation suggests motives for research other than simply those of curiosity. In my own case, I have managed, through a limited amount of consulting in areas outside of my research, to get sufficient funds to run my own laboratory research. And I have been doing this for some twenty years now, quite satisfactorily. A person who does not have the experience to be a

consultant and thus bring in this form of unfettered funds, must invest the time and study needed to become acknowledged as an authority in an area which will provide him payment for his ideas. Otherwise he must accept funds that have strings attached. And one can always find some acceptable compromise between the extremes of total independence (and freedom from both censorship and security) and total dependence (with the luxury of state-of-the-art equipment, warm facilities, and continuous unsolicited advice).

**SE** *Given what you have just said, what types and sources of economic support are necessary in order to facilitate pharmaceutical discovery?*

**AS** There is plenty of industrial funding available in commercial labs, and there are governmental grants and contracts that are the mainstay of academic research. However there is no *unrestricted funding* to be had in the private area.

**SE** *What personal price, if any, have you paid for your involvement in a lifetime of pharmacological and pharmaceutical innovation and discovery?*

**AS** In order to pursue the research that has led to my discoveries, and the research which I still pursue, I must pay the price of not having access to any governmental or academic financial support. I pay for my own research completely.

**SE** *In what way(s) could the public-at-large facilitate pharmaceutical discovery and innovation?*

**AS** They should be aware of, as well as help to reverse, the ever-increasing body of legal and regulatory restrictions and controls that are being imposed on fundamental science at all levels.

**SE** *In the best of all worlds, if you were developing a model discovery process, what parameters, in your experience, have been those which have facilitated the discovery process? What makes "it" work when it works? "It" may not work all the time, but when it does, what seems to make it work?*

**AS** There are a number of points that come to mind. One is to have a completely open mind about what one is going to see. Pre-judging, the casting of a hypothesis to be confirmed, the goal-directed search in areas that are totally unknown — all of these lay traps that can get in the way. There is a thesis of inductive inference first formalized by

Francis Bacon, long known but often ignored. It consists of the following steps:

- Devise alternate hypotheses;
- Devise an experiment (or several experiments with alternate possible outcomes) which will exclude one or more of the hypotheses;
- Carry out the experiment to get a clean result;
- Recycle this procedure with sequential hypotheses that refine the possibilities that still remain.

The principle is that nothing can be proved, only that one can fail to disprove. A hypothesis can never be verified by an experiment. Its merit can be measured only by the diligence and skill that you can bring to challenge it, for it will take only *one inconsistency* to bring down the house of cards! All one can do is try to disprove and fail in this try. If you make an observation that flies in the face of what you think is so, you will devise a better hypothesis.

**SE** *As you reviewed the issues we've been discussing, what parameters which you haven't touched upon, would you want the reader to consider as he looks at the discovery process?*

**AS** Simply follow the excitement of learning. Never assume that something you don't understand has no value for you. Uncover what it is you didn't understand and try to move a slight step towards better understanding, and it doesn't matter if this is or is not in your field of expertise. Remain continuously curious. Remain continuously critical. A person who evolves from the student to the teacher role is very often a person who has stopped learning. And so he has stopped being a true discoverer. Remain always the student — remain always curious.

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## BIOGRAPHY

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