Discussion

Chairman—Edward B. Truitt, Jr.
Members of the Panel—Claudio Naranjo
Thornton Sargent
Alexander T. Shulgin
Andrer T. Weil

Chairman Dr. Truitt: We might begin with a comment. One of the guests found that there is a whole state in our fifty in the Union that has a reputation for nutmeg, and perhaps he would like to make his comment again, which was quite interesting: that of a psychotogenic substance identifying a state.

Dr. Phillips (from the floor): I am a psychiatrist. I understand that Connecticut is known as the Nutmeg State, and I remember when I was in college about twenty years ago there was some reference to the fact that people in Connecticut acted awfully crazy, because they ate so much nutmeg.

Mr. Weil: I am afraid the origin of Connecticut's nickname is somewhat less romatic. In colonial times, Connecticut traders often palmed off carved wooden nutmegs as the real thing. This practice was considered a fine example of Yankee shrewness in business; consequently, Connecticut acquired the name "Nutmeg State".

Chairman Dr. Truitt: I wonder if Dr. Naranjo would like to discuss the activity of the compound he is engaged in testing?

Dr. Naranjo: This amphetamine substituted with the methylenedioxy group is the first that was tested. The subjective reactions had been described by Gordon Alles from experimentation on himself. It was first used in a group of subjects under the assumption that this would be a hallucinogen, as suggested by Dr. Alles. This did not appear to be quite the case, for the drug produced only enhancement in feelings. In the face of this, it was suggested that it could be used as facilitating agent in psychotherapy. It is not something to be used as an antidepressant, but only to increase communication during a therapeutic session.

When we used this compound on patients with psychoneurotic symptoms, we saw that the effects were sometimes very dramatic in an unexpected way. I have tried several drugs to facilitate psychotherapy, including the more widely known hallucinogens, and never as with this compound has there been such a frequency of reminiscence of childhood events, in a very dramatic and spontaneous way, completely unexpected by the subjects.

This has been described in therapy with LSD and mescaline, but in my own experience has occurred spontaneously only once in approximately fifty experiences with LSD (though I understand that if a therapist searches for this, it could be precipitated). On the other hand, about half of the persons who in a therapeutic setting took this compound, (MDA), had this kind of experience an experience with almost no symbolic content, without

the aesthetic or mystical overtones that is so characteristic of most hallucinogens.

This was quite rare and, in turn, there was the experience of reminiscence. It is notable that in many of the subjects there was amnesia after it, and this was very much like the similar events that take place sometimes in the hypnotic trance. In two instances out of thirty, at least, the effects were those of a delirium, and in one of these there was erratic behavior, none of which was remembered afterwards.

Now with the trimethoxy substituted compound, which has been previously described as evoking hostile reactions when we used this in a therapeutic setting, this did not occur overtly; but the compound was remarkable in that the delusional content was more frequent that with any of the others that I know. This delusional content was very often paranoid.

CHAIRMAN DR. TRUITT: Could I ask if there were any color effects, which are characteristic of mescaline, seen with it?

DR. NARANJO: This produces the greatest incidence of color effects, whereas the previously mentioned one, (MDA), is notable for the absence of distortions and color effects.

The 3-methoxy-4,5 methylenedioxyamphetamine, (MMDA), has a methylenedioxy bridge in common with MDA, but has the oxygen substitution pattern of TMA. MMDA produces the qualities of both, and what is typical of this substance is that the experience, which has mostly a personal quality, enhancement of feeling, warmth, but very little symbolic content, makes it different from mescaline.

CHAIRMAN DR. TRUITT: There is one point, I think, that many people have possibly underestimated, and that is the theoretical importance of this aspect, which is pointed out by one question from Dr. Waser: "What is the evidence for direct amination of the olefinic side chain of myristicin in the body?"

Dr. SHULGIN: Dr. Sargent mentioned one experiment where the formation of amphetamine in rats was actually observed. Administration of allylbenzene led to chromatographically distinct spots, with the strong implication that these spots were amphetamine. Although allylbenzene may be converted to propenylbenzene first, the simple addition of ammonia to the allyl double bond would be the most direct route. I don't know if it has any validity.

CHAIRMAN DR. TRUITT: We have a related question: "Could the transformation of a non-saturated aromatic side chain to a carbonyl group be possible?"

DR. SHULGIN: I don't know of this specific transformation having occurred. Certainly the double bond can participate in oxidation reactions, and substitution isomers have been converted to their corresponding acids in the body. Therefore the double bond is capable of being oxidized, or at least partially oxidized.

CHAIRMAN DR. TRUITT: We have two questions apparently directed to Mr. Weil, and I wonder if he would like to read them and comment.

Mr. Weil: The first one is, "What are the comparative psychoactivating potencies of nutmeg and mace?"

They are the same, but mystiques about the uses of the two spices have sprung up. It is interesting, for example, that at Haverford College students believed they could only get "high" with mace, even though they knew nutmeg to be very similar in taste. Other groups use nutmeg only, and are unaware of mace as an intoxicant.

The second question is, "Do other kitchen spices have any psychoactive properties?"

Who knows? Perhaps in five years we will have a symposium just on spices. I have received scattered reports on the use of cinnamon for these effects: One bit of information is that cinnamon sticks are smoked by certain Indian tribes of Mexico. I have no documentation for this report.

People who are avid for experimenting with possibly active substances often try spices. In fact, a distant friend writes that anything in the spice cabinet except monosodium glutamate will get you "high". Ginger, paprika, cinnamon and pepper have all been said to have effects on the mind, but we have no reliable evidence on them.

Chairman Dr. Truitt: We really must resolve the action of somatic input on the gastrointestinal tract, and other sources on the psychic effects before we accept them, too.

I am a little chary of the next two questions. I have an antagonistic question from Dr. Efron, and a protagonistic question from Dr. Kline.

Dr. Efron (from the floor): Being a pharmacologist, I would like to comment on the pharmacology of the tested compounds. Dr. Truitt has really done an excellent pharmacological job but I have some small objections.

First, in my opinion the psychopharmacology testing is such a difficult one that we never can use one or two tests. One has to use a battery of tests, and even then, often we are not sure what they mean.

In this case, you have put all your chips on the monoamine oxidase inhibition. If this would be really the only action of these drugs, then we should forget about them, because we have much more potent reversible and irreversible monoamine oxidase inhibitors that we can use.

Further about the test that you used: the antagonism to reserpine, we all now agree that it is not valid as an antidepressant activity measurement. It was used for tricyclic types of drugs, and even then there was a question as to its validity. Is there a correlation between this test and the activity of nutmeg?

The other problem I would like to comment on is that I really don't know why everybody is working with myristicin, the compound represented mostly in this large mixture of compounds found in nutmeg extracts. There might be a possibility that one of the other compounds present in a very small amount may be much more potent.

The next thing that would be very interesting would be to elucidate for structural-activity relationship, and to see the activity of all the compounds in some battery of tests. Then we really could see how the location of one

methyl group, adding another methyl group or taking one off, affects the activity of the compounds.

CHAIRMAN DR. TRUITT: Thank you very much, Dr. Efron. I fully agree with your comments.

DR. KLINE: Dr. Efron's remarks are as a pharmacologist; mine are as a psychiatrist.

The anti-reserpine part of the story is the one I am protagonizing for you. A very curious cycle is involved, because every drug which has been useful in the treatment of schizophrenia or the major psychoses has produced Parkinsonism as one of its side effects. Another part of the curious business is that the monoamine oxidase inhibitors or other antidepressants, if given in large enough doses, will produce hallucinations, delusions and uncontrolled euphoria.

All this would seem to tie somewhere into the extrapyramidal system. We reviewed this problem a few years ago with Mettler, and although there is a lot of presumptive evidence, one cannot yet draw a comprehensive picture. At a meeting which Dr. Efron chaired last year, it was pointed out that tricyclic antidepressants reduce the frequency of extrapyramidal side effects from phenothiazines and reserpine. The rats and mice who developed reserpine depression were given much higher doses per kilogram than we use on humans. When asked how one judges if depression is present in rats and mice, the answer was that this is judged upon the basis of reduced activity and reduced "sociability"; i.e. they didn't go poking around at each other. Then I asked: "What about Parkinsonism in the rats and mice?"—and I discovered to my amazement that the animals were barely able to move because they were so Parkinsonized. What was called depression might simply be the fact that the animals couldn't get to sniff their neighbors. The monoamine inhibitors, and perhaps the tricycle antidepressants, act as anti-Parkinsonian agents. Professor Holmstedt mentioned yesterday that Lewin has found harmine, a monoamine oxidase inhibitor, useful in the treatment of Parkinsonism.

CHAIRMAN DR. TRUITT: I heartily agree with you, Dr. Kline, because you recognize our problems in the laboratory. We have a great deal of difficulty in defining these parameters, isolating them, and analyzing them. Certainly I would be the first to disclaim that we can extrapolate easily this way from a test to the whole animal. When we speak of the appearance of tremor and absence of tremor or antagonism of tremor, we are dealing with a fairly precise parameter. When we are speaking of emotional effects rising and falling, we are speaking of a complex set of behavior changes that we have a healthy respect for.

A couple of other related questions that might follow Dr. Kline's. This is from Dr. Buckley: "Does myristicin have anticholinergic activity?"

Only in the respect that generally anticholinergic activity in the CNS is in some ways similar to potentiation of adrenergic activity. We have not specifically tested this in any respect.

"Does myristicin inhibit adrenergic reuptake of norepinephrine by the nerve endings?"

This is postulated as the mechanism of action for the tricyclic antidepressants. This hypothesis is too new for our consideration. If it is, perhaps a combination of a weak monoamine oxidase inhibitor, such as nutmeg, and the trycyclic agents, might be of interest.

Going to the more physical aspects, we have a question from Dr. Beavers, concerning the effects of nutmeg on blood pressure in human subjects, and asking whether we have any evidence of monoamine oxidase inhibitors either increasing or decreasing effects of nutmeg in humans. We certainly need to know more about this. Dr. Naranjo, have you done blood pressure examinations with the compound?

DR. NARANJO: There is slight variation in blood pressure. There is occasionally an increase but this is not consistent, and it is hard to evaluate to what extent the observed changes are secondary to the emotional states, for sometimes anxiety is a prominent component of the induced reaction.

No lowering of blood pressure has been observed. This is in contradiction to the observations on some persons who experienced intoxication with nutmeg.

CHAIRMAN DR. TRUITT: Dr. Leake has a question.

DR. LEAKE: I want to amplify a point made by Dr. Efron. This concerns the systematic investigation of all of the phenyl amines. This actually was Dr. Gordon Alles' undertaking, as you know. One extremely important feature of it I would recommend to all workers in the field. It bears on some of the reports that were made today. Even though chemical compounds in a series are very close, insofar as their molecular weights are concerned, Gordon Alles insisted on using equal molecular concentrations so as to compare each drug with the other on a molecular basis. This is important, particular when there is any significant difference in molecular weight.

Alles had an enormous amount of material that has never been published, and I don't know whether it will be. He made a methylenedioxy derivative of an amphetamine, in which he found extraordinary enhancement of auditory sensation. This he did describe informally at one of the Macy Conferences. This compound produced another remarkable effect: if he were to strike his finger, he could see the strike, and feel it afterwards by a definitive period of time.

DR. SHULGIN: That was the methylenedioxyamphetamine compound that we called MDA earlier.

DR. LEAKE: He made similar observations of this sort on other compounds. Since he had them all on an equal molecular basis, and since he did most of the experimentation on himself as one subject, at least his findings had that comparative validity.

DR. MARRAZZI (from the floor): In line with what is being said, and the comparison with mescaline, I thought you might be interested in the comparison that we have been making of methoxyphenylethyl amines, using cortical synaptic inhibition. At the moment it looks like mescaline (a trimethoxy compound), would have a potency of 1, the dimethoxyphenylethylamine of 1.8, while the demethylated or dihydroxyphenylethylamine, dopamine, would have a potency of 10.

This is reminiscent of the old work of Gunn, which showed that the methoxylation has a muzzeling action, decreasing activity. Apparently in preliminary data it seems to decrease cortical inhibitory activity.

CHAIRMAN DR. TRUITT: How much do you think this variation in activity is due to rate of transfer across the blood-brain-barrier, and how much to the differences in actual potency?

DR. MARRAZZI: I am not able to answer that. These are closearterial injections, and the latency of beginning action is approximately the same. It should be measured more carefully than I have done so far, but there is no remarkable difference, which would suggest that it is not a difference in passing through the blood-brain-barrier.

CHAIRMAN DR. TRUITT: We have a question directed to Dr. Shulgin and Dr. Sargent: "Could you describe your human bioassay methods further?"

DR. SHULGIN: The human bioassay follows a preliminary pharmacological and pharmacodynamic analysis of the investigated material on animals. Generally, three species, the mouse, the rat and the dog, are used. Most of the cardiovascular work is done on the dog. The compounds were then assayed within our experimental group. The human threshhold level was established by successively increasing the dose in small increments until this level was reached. This testing and the subsequent psychopharmacologic comparisons of the several compounds were done essentially by the "double conscious" method of Alles. (see our reference *10*).

DR. SARGENT: I would like to comment on the remarks of Dr. Efron and Dr. Leake, as far as the structure-activity relationship studies go.

Actually this was originally Dr. Shulgin's and my interest in investigating these compounds, and we could perhaps elaborate a little bit on one of the slides in which two other substituted phenylisopropylamines are mentioned, the precursors of which are not present in nutmeg. They were tested specifically to measure the effect of the orientation of these methoxy groups.

Our scale in mescaline units is the same as Dr. Leake's. However, we assign some of the numbers a little differently from his. We grade LSD as 3000 in mescaline units, the effect dose being a tenth of a milligram.

DR. LEAKE: You understand that my grading was off the cuff.

DR. SARGENT: I might mention in regard to the previous discussion of Parkinson effects of harmine and harmaline, these compounds are also hallucinogenic. To get back to the structure-activity relationships of these methoxy-substituted amphetamines, which are summarized in our figure 7, note that when the structure of TMA with the 3,4,5-methoxy substitutions is changed to 2,4,5-, or TMA-2, the activity in humans of the compounds is increased tenfold. Again, when the structure of the 3-methoxy-4,5-methylenedioxy compound, MMDA, is changed to 2-methoxy-3,4-methylenedioxy or MMDA–3a, the activity is again increased, this time by a factor of 6. In both cases, the change of a methoxy group from a meta- to an ortho-position markedly increased the potency of the compound. The more active compounds are derived from croweacin and asarone, which occur in natural oils but not oil of nutmeg.

CHAIRMAN DR. TRUITT: We have one last question that I would like to direct to Mr. Weil: "What significance would you give to hypothermia observed after nutmeg intake?"

MR. WEIL: In the acute intoxications that have come to clinical attention—and there have been few—a number of symptoms suggestive of vasomotor instability has been noted. I suspect that many of the constituents of nutmeg might have effects on the autonomic nervous system and on general homeostasis that we have not spelled out very well: possibly, this fall in temperature is one of them.

CHAIRMAN DR. TRUITT: This is the end of our time for this afternoon. I thank you again for your indulgence.