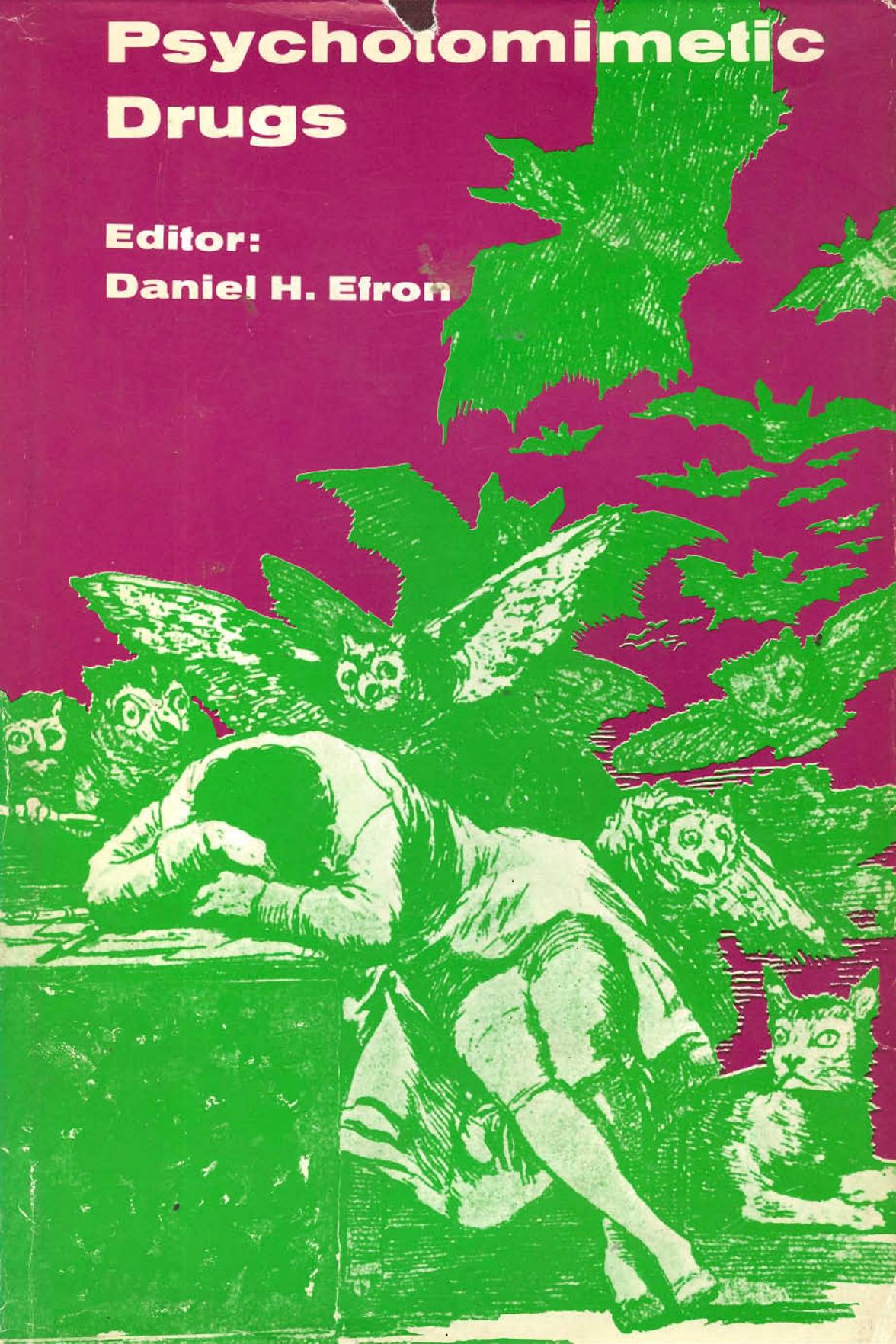


# Psychotomimetic Drugs

Editor:

Daniel H. Efron



# PSYCHOTOMIMETIC DRUGS

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Edited by

**Daniel H. Efron, M.D., Ph.D.**

*Chief, Pharmacology Section, Psychopharmacology Research Branch, National  
Institute of Mental Health, and Clinical Professor of Psychopharmacology,  
Department of Psychiatry, University of Maryland School of Medicine*

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# DMT (N,N-DIMETHYLTRYPTAMINE) AND HOMOLOGUES: CLINICAL AND PHARMACOLOGICAL CONSIDERATIONS

Stephen Szara, M.D.

*Section on Psychopharmacology, Division of Special Mental Health Research,  
National Institute of Mental Health, St. Elizabeths Hospital,  
Washington, D.C. 20032*

During the past 13 years we have been working on the biochemistry and pharmacology of the various N-alkylated tryptamine derivatives, both in man and in animals.

Interest in the possible hallucinogenic activity of N,N-dimethyltryptamine (DMT) stems from the report by Fish, Horning and Johnson (1955) who found DMT, together with bufotenin, in snuff powder prepared by Haitian natives from *Piptadenia peregrina* seeds which the natives used in their religious ceremonies to produce mystical states of consciousness.

In 1956 the hallucinogenic action of bufotenin was reported by Fabing, but no information as to whether DMT had similar psychotropic activity was available. We prepared DMT by chemical synthesis and tested its activity on animals and humans. It was found that it produced symptoms similar to those caused by mescaline and LSD and which lasted for a surprisingly short period of time (45 min-1 hr) after intramuscular injection of about 1 mg/kg of the drug (Szara, 1956).

The hallucinogenic activity of N,N-diethyltryptamine (DET) was first reported in 1957 (Szara, 1957), and a more systematic study was reported later by us (Szara, *et al.*, 1966) and independently by Boszormenyi *et al.* (1959).

Speeter and Anthony (1954) reported that N,N-dipropyltryptamine (DPT), another tryptamine derivative, produced observable effects in dogs. The similarity in chemical structure between DPT (Fig. 1) and other hal-

Compound						Psychotropic dose
1	Tryptamine (T)	-H	-H	-H	-H	500mg $\varnothing$
2	DMT	-H	-H	-CH <sub>3</sub>	-CH <sub>3</sub>	60 mg i.m.
3	DET	-H	-H	-C <sub>2</sub> H <sub>5</sub>	-C <sub>2</sub> H <sub>5</sub>	60 mg i.m. or p.o.
4	Dipropyl-T	-H	-H	-C <sub>3</sub> H <sub>7</sub>	-C <sub>3</sub> H <sub>7</sub>	60 " " "
5	Di allyl-T	-H	-H	-C <sub>3</sub> H <sub>5</sub>	-C <sub>3</sub> H <sub>5</sub>	60 " " "
6	$\alpha$ -methyl-T	-H	-CH <sub>3</sub>	-H	-H	20 mg p.o.
7	$\alpha$ -ethyl-T	-H	-C <sub>2</sub> H <sub>5</sub>	-H	-H	20 mg p.o.
8	Psilocybin	4-OPO <sub>3</sub> H <sub>2</sub>	-H	-CH <sub>3</sub>	-CH <sub>3</sub>	15 mg p.o.
9	Bufotenin	5-HO-	-H	-CH <sub>3</sub>	-CH <sub>3</sub>	16 mg i.v.

FIG. 1. Simple derivatives of tryptamine with psychotropic activity.

lucinogenic tryptamine derivatives and its reported effects in animals suggested that this compound might be capable of producing hallucinogenic effects in humans.

One of the major problems in evaluating hallucinogenic compounds is the absence of an effective placebo which could mimic some of the effects of these drugs, such as physical symptoms and mood changes, without producing the psychedelic effects.

On the basis of animal experiments and some human metabolic data we came to the conclusion that the 6-hydroxylation of the indole ring of the hallucinogenic tryptamine derivatives might be an important pathway for the metabolism of these compounds (Kalir and Szara, 1963). We prepared a series of compounds substituted at the 6-position. One of these synthesized compounds, 6-fluorodiethyltryptamine (6-FDET), was observed to produce autonomic symptoms and mood changes in humans without producing the characteristic perceptual and thinking disturbances usually seen with psychotomimetic drugs. From this initial data, we postulated that 6-FDET might be useful as an active placebo in clinical studies.

In order to test the hypothesis that DPT is another effective hallucino-

genic drug, and to confirm the previous work that 6-FDET is an active placebo, a double-blind pilot study was undertaken at Saint Elizabeths Hospital. This research project set out to measure psychological, biochemical and physiological effects produced by DPT and 6-FDET as compared to the related chemical compound, DET, a potent, known hallucinogenic compound, in the same experimental subjects (Faillace, Vourlekis and Szara, 1967).

Twelve chronic, non-psychotic, alcoholic, hospitalized patients volunteered to participate in the program. They all were in good physical condition without evidence of organic deterioration, schizophrenia or manic depressive illness. They ranged from 29 to 48 years of age, with a mean age of 38.2. The length of hospitalization prior to treatment varied from one month to five years. All had been drinking heavily for over ten years. All had had multiple arrests for alcoholism. Prior to treatment, all the subjects had an extensive medical work up which included CBC, BUN, glucose, thymol turbidity, alkaline phosphatase, cephaline flocculation, SGOT, SGPT, EKG and EEG. Thus, they were considered to be in excellent physical health. The subjects were informed about the nature of the drug experience; however, they were not informed of the possibility of receiving an active placebo in one or more of the sessions.

Several questionnaires have been devised to measure the subjective effects of LSD-25 in humans. However, the 74 item questionnaire by Linton and Langs (1962; 1964) was selected because it contained a wide range of perceptual, cognitive, affective and somatic items. The main focus of the questionnaire is on the subject's altered state of consciousness. Linton and Langs also classified the major dimensions of the subjective effects of LSD-25 into four empirical scales: Subscale "A" contains items related to impaired attention and loss of inhibition; subscale "B" deals with feelings of unreality, of having lost control and with paranoid ideation; subscale "C" deals mainly with body image changes and certain somatic symptoms; finally, subscale "D" contains questions dealing with overt anxiety and related somatic symptoms.

The Rockland-Pollin (RP) scale (Rockland and Pollin, 1965) consisting of 16 items, was used to record observable psychotic behavior by assessing mental status data. Two psychiatrists scored the patients independently on this scale before the drug session and at the termination, but before the subjective questionnaire was answered. The RP scale is grouped in three main categories: (1) general appearance and manner (6 items); (2) affect and mood (4 items); and (3) content of thought and thought processes (6 items). This instrument was chosen because it was originally derived partly from observing the effects of DET on normal individuals.

The double-blind design allowed each patient to receive DET, DPT and 6-FDET at least once, with one of these drugs given in two different dosages (0.7 and 1.0 mg/kg) intramuscularly. In our patient population, seven subjects received each drug at the 1 mg/kg dose in a random design.

The evaluation of the results is based on data obtained from testing the seven patients of our series who each received 1 mg/kg of DPT, DET and 6-FDET during their second or subsequent drug session. The data from the first session were not used because the results from these sessions would be highly influenced by the patient's initial anxiety. Since this kind of experience is unique for most individuals, data obtained from the first session would be most biased and could not be reliably compared to subsequent sessions.

We shall examine this problem a little later, but first let me show you some of the results of these comparisons (Fig. 2).

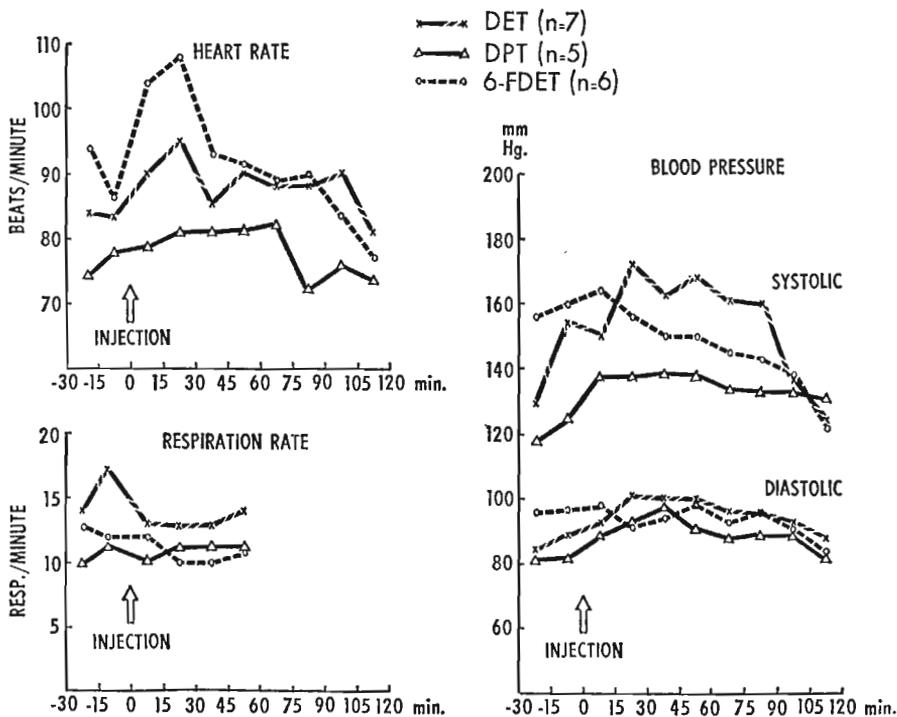


FIG. 2. Time course of autonomic changes produced by three psychotropic tryptamine derivatives in man.

The time course of autonomic changes produced by these three compounds shows that all three produce a slight increase in heart rate and blood pressure, returning to normal within two hours (Szara *et al.*, 1967).

The psychological effects, which were evaluated by the two scales already mentioned, are summarized in Tables I and II.

TABLE I  
*Significance of difference between pre-drug and drug scores—  
Wilcoxon Matched Pairs Signed Rank Test;  
P Values<sup>a</sup>*

	Subscales				Rockland-Pollin Scale
	A	B	C	D	
DET	< 0.05	< 0.05	< 0.02	< 0.02	< 0.05
DPT	< 0.02	< 0.02	< 0.02	< 0.02	< 0.05
6-FDET	N.S.	N.S.	< 0.02	< 0.02	N.S.

<sup>a</sup> For drug schedules and other experimental details, see text.

Table I summarizes the significance of the difference between the pre-drug and drug scores as measured by the Wilcoxon Matched Pairs Signed Rank Test. Both DET and DPT show a significant difference between pre-drug and drug scores on all the subscales of the Linton and Langs questionnaire. However, with 6-FDET, subscales A and B show no significant difference.

TABLE II  
*Summary of Friedman's Two-Way Analysis of Variance By Ranks  
for subjective and objective scales.<sup>a</sup>*

Scale	P value
Linton and Langs	subscale A < 0.001
	" B < 0.005
	" C < 0.02
	" D N.S.
Rockland-Pollin	N.S.

<sup>a</sup> For experimental details see text.

Table II shows Friedman's Two-Way Analysis of Variance comparing the difference between pre-drug and drug scores of the three compounds for each patient. Only subscale D, concerned primarily with somatic symptoms, shows no significant difference when comparing the three drugs.

The Wilcoxon Signed Rank Test for measuring the significance of difference between pre-drug and drug scores of the RP Scale showed a significant difference ( $p < 0.05$ ) for DET and DPT. However, there was no significant difference for 6-FDET. Friedman's Two-Way Analysis of Variance comparing the scores on the RP Scale for the three drugs showed a difference ( $p < 0.1$ ) between the drugs which was not considered to be statistically significant.

The data presented here tend to affirm the assumption that 6-FDET produces some of the same physical and mood changes as the known hallucinogen, DET, and the new hallucinogen, DPT. These changes produced by 6-FDET are indistinguishable from the changes produced by the two hallucinogenic compounds in the same patients. From the results presented, which must be viewed cautiously because of the small sample, 6-FDET appears to be an effective placebo and warrants further study.

I would like to direct attention to a point mentioned earlier, namely that the psychological data from the first session were not used because of the possibility of distorting the evaluation with the effects of anxiety generated by the novelty of the first experience.

There is no question in anybody's mind who has ever taken an effective dose of a hallucinogen that the experience is new in many ways at the perceptual, emotional and cognitive levels, and at subsequent occasions, if the drug is taken repeatedly, this novelty value of the experience is diminished. Since novelty is an important aspect of the experience, it is expected that the first and subsequent experiences will differ from each other.

There are also a number of observations which suggest that even after a single drug experience, in many subjects there is a more or less long lasting aftereffect which might have physiological and/or biochemical as well as psychological origin.

The Spring Grove group refers to this aftereffect as the "psychedelic afterglow" which seems to appear quite regularly in patients after the LSD session, lasts sometimes for weeks, is characterized by a greatly reduced anxiety level and, psychologically, by a "shifting of the emotional center towards loving and harmonious affections" and "a seemingly enhanced capacity and disposition to enter into close interpersonal relationships and a sort of generalized benignity of outlook" (Kurland and Unger, 1969).

W. H. McGlothlin, S. Cohen and M. S. McGlothlin (1967) have found a significant increase in a passivity test at 2 weeks after a single LSD ex-

perience, indicating increased preference for "quiet receptivity, contemplation and humble obedience" as opposed to "group action, progress through realism and physical interaction." There were some less spectacular changes in other psychological measures at 6 month follow-up time (Marlow-Crowne Social Desirability Scale, and in Rosenzweig's Picture Frustration test, this last measuring the manner in which aggression is expressed). These same authors have also found a significant drop in galvanic skin response to a stress situation, which seems to confirm the clinical observation of the Spring Grove group about the reduced anxiety level during the period of the "after-glow."

In our own study the repeated administration of the hallucinogenic tryptamine derivatives at weekly intervals for 5 weeks allowed us to make a comparison between the first and the subsequent reactions at the psychological and at the biochemical levels. (Only two later sessions were followed by electrophysiological recordings, so we cannot make comparisons at this level.)

Various items at the Linton and Langs Scale were clearly different between the first and all the subsequent sessions. No statistical evaluation is feasible, since only 5 subjects received hallucinogenic drugs as the first dose, but the clinical impression was that the bodily symptoms were different when the drug was first taken from all subsequent sessions.

At the psychological level, however, it was fairly general that items referring to sense of time, passage or stopping of time, were answered negatively at the first session, while at all the subsequent sessions there was a marked change in these subjective time sensations. On the other hand, positive answers to some other items (feeling silly, awareness of changed judging ability, etc.) seemed to be more pronounced at the first session than in the subsequent sessions.

At the biochemical level, none of the routine medical laboratory tests showed pathological changes when the before and after specimens of blood and urine were examined. However, in the more specific area of metabolizing hallucinogenic drugs, we did find a subtle but significant change after the first exposure to a particular drug.

Before presenting these results, let us review briefly the pathways involved in the metabolism of the alkylated tryptamine derivatives (Fig. 3).

Table III shows the average 24 hr excretion values for the unchanged drug, for the apparent 6-hydroxy bases and for the apparent 3-indoleacetic acid (3-IAA) after the administration of each of the three drugs.

Please note the differences between the DET and DPT line in the unchanged and 6-hydroxy-base column. The 3-IAA values were essentially

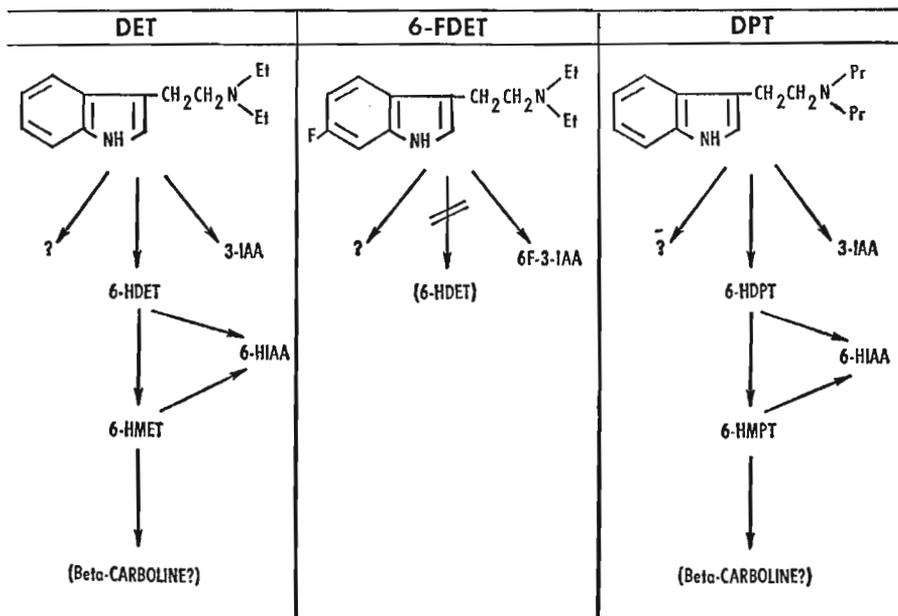


FIG. 3. Metabolic pathways for three psychotropic tryptamine derivatives.

the same for both drugs, but for 6-FDET the apparent 3-IAA (actually 6F-3-IAA, but indistinguishable by the method used) was significantly higher.

Breaking up the data in a different manner would enable us to see whether the metabolism at the second exposure to a drug was significantly affected by the first exposure one or two weeks earlier (Table IV).

TABLE III

*Metabolism of tryptamine derivatives in man;  
24 hour excretion values expressed as  
percent of administered drug*

Drug	n	Drug excreted as		
		Unchanged	6-hydroxy base (apparent)	3-IAA (apparent)
DET	15	3.68 ± 2.24	4.04 ± 2.05	14.5 ± 5.9
DPT	20	1.04 ± 1.05	.76 ± .33	13.1 ± 8.6
6-FDET	12	2.86 ± 1.94	(.33 ± .23)	33.8 ± 13.1

Data are expressed as the mean percentage of the administered dose ±S.D.

TABLE IV<sup>a</sup>

Drug Exposure	DPT (n = 8)		DET (n = 5)	
	1st	second	1st	second
unchanged	.92 ± .19	.96 ± .34	4.48 ± .94	3.80 ± .82
as 3-IAA	12.2 ± 2.0	14.8 ± 3.2	12.3 ± 1.2	17.1 ± 2.7
as 6-hydroxy base	.81 ± .14	.73 ± .10	3.64 ± .75	4.53 ± .94

<sup>a</sup> Data are expressed as the mean percentage of the administered dose found ±S.E.M.

In this last table the DPT values were not significantly different when the values for the first day or for a larger exposure to the drug were compared.

In case of DET however (in 5 subjects) the unchanged drug excreted after a later exposure was significantly lower, while the excretion of the metabolites which were measured in this case were higher than at the first exposure to DET ( $p < .05$ , Wilcoxon test).

Since we could account for only a fraction of the administered drug in the 24 hr urine of the patients, these data have to be interpreted with extreme caution. We don't know what happens to the rest of the administered compounds. In animals these metabolites account for more than 90% of the administered drugs, and we did not have the opportunity yet to study the fate of the radioactive labeled hallucinogenic drugs in man.

It seems to be safe to conclude from the presented data that a first exposure to some hallucinogenic drugs does affect the metabolic machinery of the human organism in the direction of increased metabolism. Enzyme induction comes immediately to our mind as a possibility, but the data do not allow us to propose this as the only possible explanation.

Whether or not this biochemical change is related to some long term psychological and physiological effects cannot be ascertained. We can only suggest that the clinical significance of the "psychedelic afterglow" (Kurland and Unger, 1968), the increased reactivity of chronic "acid heads" to low intensity light stimuli (Blacker *et al.*, 1968) and the increased psychological responses to marihuana after the first exposure (Weil, 1968) seem to be strong enough impetus for a continued search for biochemical and physiological correlates of long lasting effects of hallucinogenic drugs.

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## DISCUSSION

DR. WEST: This interesting paper is now open for discussion.

DR. SHULGIN: I believe some years ago in a book by Garattini mention was made of the N,N-dibutyltryptamine. Do you know of any subsequent work that has been done?

DR. SZARA: I have tried it. It's psychopharmacologically inactive, at least in doses of one mg/kg, although the other three compounds which were discussed here were active.

There are several more compounds which belong to this tryptamine series which have been synthesized and tested in animals, and they probably are active in humans. One of these is the pyrrolidine derivative of tryptamine, which is probably active; I had a personal communication from Dr. Smythies in San Juan before Christmas who said that this is an extremely active compound. He must have tested it in humans. We have only animal data on it.

Another compound has an oxygen in the ring and it may be called morpholinotryptamine. This compound in animals shows some activity, but we don't have any human data on it.

DR. SHULGIN: Did you mean the 5-membered pyrrolidine or the 6-membered piperidine?

DR. SZARA: 5-Membered pyrrolidine. A series of them was synthesized by Nogradi, by the way.

DR. FREEDMAN: What effects have they in animals?

DR. SZARA: They cause hyperactivity in mice.

DR. FREEDMAN: I think Dr Smythies studied it only in rats. He has a very nice test.

DR. USDIN: Do you have any intention of trying to go on and get a third and fourth experience with people who had used DET, to find out if there has been any enzyme induction?

DR. SZARA: If it is long-lasting, you mean? Some of these people are still around in the hospital and could be tested.

By the way, these subjects were alcoholics for years, and they were really skid row alcoholics; we had followed them for two years. In one year, we had four or five who showed improvement in terms of drinking behavior or getting a job and finding their way outside the hospital. But after a two-year follow up we had only three of these subjects who actually improved. So, we still have some of them in the hospital, and we could actually study them.

DR. USDIN: You suggest that the differences in the amount of 3-indoleacetic acid formed from DET may depend on enzyme induction. Are these differences significant? I feel that it might be useful to repeat this experiment at even a later time, when the enzyme induction would be more obvious and the changes in metabolite level more pronounced.

DR. SZARA: We had only two or three occasions when we gave the same drug to the same subjects, so we didn't have much opportunity to find out what happens to these measures on repeated administration.

DR. LEHRER: In how many patients was there a decrease in excretion of, say, indoleacetic acid when the average showed an increase?

DR. SZARA: I would have to go back to the data. I think two of them showed reduced amounts, and all the ten others showed increases.

DR. HOLMSTEDT: I have a comment and also a couple of questions.

The isolation of bufotenine and dimethyltryptamine by Fish, Johnson, Horning and Stromberg from the seeds of *Piptadenia peregrina* was made, I think, 15 years ago. They had a sample of seeds grown in Puerto Rico, and it so happens that the amounts of these well known tryptamines vary with location, soil, and season. This sample, which is still available (I have analyzed it myself since), happened to contain bufotenine and dimethyltryptamine, whereas other samples of *Piptadenia* that I have analyzed so far contain as the main component 5-methoxy-N,N-dimethyltryptamine and small amounts of dimethyltryptamine.

Now, my questions are the following: Some years ago you attached particular importance to 6-hydroxylation, and you were of the opinion that the 6-hydroxylated product was essential for the psychotomimetic effect. Do you still have this opinion?

DR. SZARA: Well, I'm not attaching as much significance to this. Let's put it this way. I maintain that 6-hydroxylation may still be rather relevant, a view based mainly on the clinical finding that there is a compound, 6-fluorodiethyltryptamine, which cannot be hydroxylated and does not produce hallucinations.

DR. HOLMSTEDT: Neither does 6-hydroxydimethyltryptamine.

DR. SZARA: No, it doesn't. It may be involved in a way which is unexplained. It might be in intermediate for a carboline derivative. So, it is really still an open question.

DR. HOLMSTEDT: Did the 6-hydroxylation have any bearing on the data that you presented in Table 4?

DR. SZARA: No. At least in these particular subjects, the rate of 6-hydroxylation did not change significantly. The rate went up a little on the second exposure to DET, but it was not significant (Table 4).

DR. HOLMSTEDT: The third question is, how do you determine these metabolites?

DR. SZARA: For the indoleacetic acids we used the Weissbach method (H. Weissbach *et al.*, *J. Biol. Chem.*, 234: 81-86, 1959). It's a colorimetric method.

DR. HOLMSTEDT: Then you have to separate them by some kind of extraction or chromatography?

DR. SZARA: Correct. The extraction precedes the colorimetric determination.

DR. HOLMSTEDT: That is, the colorimetric method may not give you the right answer unless you are very sure about your separation.

DR. SZARA: Certainly, we have to find the best solvent system and pH to extract these compounds in their proper solvents.