On the Action Mechanisms of LSD 25

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Various approaches can be used to test the action mechanisms of LSD 25 and related drugs, each related to biochemistry, neurophysiology or psychopathology. We briefly abstract here types of research performed by us in recent years and compare them with the studies of other authors.

We started with studies on cross-tolerance in non-psychotic patients. The reaction was evaluated by the same observer rating effects from one to four in five classes (autonomic and kinesthetic, motor, emotional related to consciousness, psychosensorial). A statistical evaluation was based on the sum of points in each trial. Drugs examined were LSD 25, mescaline, BOL 148, JB 336, psilocybin (Balestrieri 1957, 1960, 1961[b]; Balestrieri and Fontanari 1959).

A tolerance to LSD 25 develops very rapidly after repeated administration of the drug for several days (Abramson *et al.*, 1956; Cholden *et al.*, and Isbell *et al.*, 1956). Our experiments in two subjects ruled out tachyphylaxis, since repeated administration of LSD 25 at six-hour intervals did not show any decrease of effect. We found that subjects who acquired a tolerance to LSD 25 are very resistant to mescaline. Tolerance to mescaline following administration of the drug itself was also observed in our subjects, but the phenomenon was less evident than with LSD 25. Subjects who became tolerant to mescaline were also resistant to LSD 25. Cross-tolerance between LSD 25 and mescaline has been confirmed in humans by Wolbach *et al.* (The phenomenon was observed in rats by Freedman *et al.*) Our research also showed a cross-tolerance between LSD 25 and psilocybin. This result agrees with data published by Isbell *et al.*, (1961).

We did not observe a statistically scientific tolerance to LSD 25 after repeated administration of BOL 148. With different dosages of BOL 148, some degree of a similar tolerance was, however, observed by Abramson *et al.*, (1958), and by Isbell *et al.*, (1959). We did not observe a cross-tolerance between LSD 25 and JB 336, a cholinergic blocking drug with hallucinogenic effect. A chemically related drug with a similar effect, JB 318, did not show cross-tolerance with LSD 25 in the experiments performed by Isbell *et al.*, (1964).

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In our subjects UML 491 (Methysergide; Sansert), a lysergic acid derivative having no hallucinogenic activity, greatly decreased the LSD 25 effects when administered for several days before LSD.

Abramson *et al.*, (1958) obtained a good resistance to LSD 25 by administering MLD 41, a lysergic acid derivative with a low hallucinogenic activity for several days. Rosenberg *et al.*, observed a very poor degree of tolerance to N, N-dimethyltryptamine (DMT) in subjects rendered tolerant to LSD 25.

The above mentioned results seem to indicate that cross-tolerance is not a constant phenomenon among hallucinogenic drugs, since JB 336, JB 318 and DMT do not appear in a similar relationship to LSD 25. On the other hand a non-hallucinogenic drug like UML 491 can provoke tolerance to LSD 25, chemically related to UML 49°. Cross-tolerance between LSD 25 and psilocybin can also be based on a chemical affinity. A similar affinity, however, is very difficult to conceive between LSD 25 and mescaline, since the hypothesis of the transformation of mescaline into an indole in the body is not supported by modern research on the metabolism of the drug. Isbell *et al.*, (1964) say that cross-tolerance studies appear useful in confirming the biological similarities and dissimilarities among psychotomimetic agents. The experiments performed by us and by other authors certainly prove the existence of different groups of drugs from the point of view of production of tolerance. A biochemical basis for classification is, however, still unknown.

Another approach to the action mechanisms of hallucinogenic drugs was attempted with the study of hallucinatory contents (Balestrieri 1961, 1964). Hallucinations are studied by a wide range of scientists, working in the fields of psychology, physiology, pharmacology, psychiatry and surgery who like to discuss them from very different points of view. Unfortunately, too many authors stress one set of factors to the exclusion of others. We have no general theory accounting for all hallucinatory phenomena.

According to Kluver's hypothesis, there are, however, some hallucinatory constants, probably related to various mechanisms at different levels in the nervous system. At present we know very little about these mechanisms, but can direct our research toward peripheral receptors, afferent paths, some cortical areas and particularly vestibular apparatus. Their activity might give us the reasons for certain characteristics (number, shape, size, spatio-temporal, situation, movement) that we find in the content of different sensations, of eidetic imagery, of synesthesias and hallucinations.

It seemed to us highly probable that hallucinogenic drugs have their effects at an "instrumental level" on sensory systems which belong to the above mentioned nervous mechanisms proposed by Kluver. Rough variations in all these structures can be further elaborated, at more psychic levels, in other brain areas having an integrative activity. In that way we could also attain images of a very complex nature.

° Editorial Note: See, however, paper in this volume by Abramson and Rolo.

A similar hypothesis for the hallucinogenic activity of drugs is very attractive. Before accepting it we must discuss, however, another possible mechanism for the activity itself. Studying hallucinatory phenomena in general, especially in mental patients, some psychopathologists put forward opinions based on the utilization of sensorial contents in some way previously stored in the central nervous system. We may remind you of the well known hypotheses of Tanzi, Pero, Buscaino and Goldstein. In more recent times, the experimental studies of Penfield with electrical stimulation of the temporal lobe also raised the question of possible evocation of images recorded and stored in some brain structures.

We analyzed the hallucinatory content of 86 experiments performed on 50 of our subjects who were either psychoneurotics or affected by neurological diseases. In half the experiments we used LSD 25, in the remaining half mescaline, psilocybin, JB 336, LSM 775 and BOL 148.

Our aim was to differentiate between simple hallucinations and the more complex ones. We considered as simple phenomena geometries, colors and sounds without significance, "stars," "lights," changes in shape, in number, in localization and so on; as complex hallucinations we considered images of persons and things, autoscopies, landscapes, etc.

Actually, we believe that a rough variance in the sensory systems or an interference with the nervous mechanisms supposed by Kluver are more apt to cause elementary or simple hallucinations, at least at first. More complex phenomena could derive from the activation of images already recorded and retained in the brain. We must also consider the gradual transition from simple to complex hallucinations reported by some of our subjects and also beautifully described by Baudelaire and A. Huxley. The further integration of elementary abnormal stimuli, mentioned above, could account for this phenomenon. On the other hand, it cannot be excluded that complex hallucinations reported alone are preceded or accompanied by simple ones, at least in some cases. A subject will probably pay more attention to the more significant images and may refer to them only.

Coming to our results, simple hallucinations appeared in a very large majority of trials (about 90 percent). In 80 percent of cases they were alone or preceded the appearance of complex hallucinations. The latter appeared in 20 percent of trials, but were reported alone in only 10 percent and never preceded the simple hallucinatory phenomena. It can be inferred from our data, and from the above mentioned considerations, that the pharmacological activity which is the origin of hallucinations is very probably related to some variances in the sensory systems, including nervous mechanisms connected with the perception of number, shape, localization and movement of images. The reactivation of complete images as recorded in the CNS seems unlikely, even if it cannot be positively excluded.

In the clinical field, our results give further support to the opinion that mental patients, too, may find a basis for their complex hallucinatory activities in some rather simple phenomena occurring in the nervous structures connected with the sensorial functions. As a matter of fact, the

gradual transition from simple to complex psychosensorial phenomena appeared to us a rather common occurrence.

Hallucinogens may be termed chemical agents having the ability to induce hallucinatory phenomena without any necessary occurrence of mental confusion. Nevertheless, there are peculiar conditions of consciousness due to the drugs which sometime lead to disorders of confusional type. We attempted to investigate the problem of giving LSD 25 to patients suffering from psychomotor epilepsy (Balestrieri and Fontanari, 1957). LSD 25 was administered (100 to 200 mcg orally) to eight subjects. In five of them we observed a clear tendency to reproduce, under the effect of the drug, psychopathological phenomena which had already appeared during the spontaneous seizures (visual hallucinations, sensation of blocking of thoughts, olfactory, taste and visceral sensations, preaccessual anxiety, and a peculiar head paresthesia). Our patients had the feeling that their usual ictal episode was repeated.

Further investigation was performed with 30 mg of amphetamine rapidly injected intravenously. This technique does not induce disturbance of consciousness in normal subjects. However, in four out of seven psychomotor epileptics it produced transient outbursts with confusional and hallucinatory manifestations, which also tended to imitate the usual seizures although less evidently than with LSD 25 (Balestrieri, 1959). EEG controls performed during all trials with amphetamine and during three of the five positive cases of LSD 25 experiments never gave signs of an epileptic activation. Patients during psychomotor epileptic attacks seem to have a low threshold for drug induced mental disturbances of the confusional type. This observation raises the difficult question of the role played by a similar disposition in the epileptic symptomatology. M. Dell, stressing that every episode of epilepsy is a dialogue between the paroxysmal phenomenon and the psychophysiological background, asks herself whether some psychomotor attacks have a psychic character just because of the peculiar background existing in the subject. H. Ey affirms that a low threshold for a consciousness destructuration, due to different etiologies, can be associated to a slow progressing outcome of the symptomatology. This could be the case of psychomotor epileptics, showing what the author calls the *"crise graduo-comitiale."*

In our opinion, the subject, owing to an affinity for the dream-like hallucinatory state due to the drug, or an epileptic dreamy state, tends to relive with greater ease those psychic experiences, often related to his previous life, which appear repeatedly during the seizures and which are therefore impressed on his mind through facilitation or conditioning processes.

As regards the hypothesis of Penfield on memory mechanisms, we prefer not to consider the temporal lobes as storehouses of memories, but rather as neurological structures primarily involved in the regulation of consciousness. We believe that a peculiar disposition leads some subjects to react with dream-like manifestations when their temporal lobes are altered by an epileptic discharge, a stimulating electrode or involvement in a drug action. The hallucinatory content does not depend, in our

opinion, on the direct stimulation of a ganglionic pattern being the substrate of an engram, but on the psychological organization of the subject, as in normal dreams or in hallucinatory psychoses. As said before, some contents may be especially facilitated.

In conclusion, we must remember that an analogy between psychical conditions under the effect of hallucinogenic drugs and psychomotor attack has been stressed by many authors (Weber and Jung; H. Ey; Schwarz *et al.*, Bercel *et al.*). Our experimental results give further support to this analogy and we believe that it is quite probable that consciousness modifications due to LSD 25 depend on a pharmacological action at least partly directed to the structures of temporal lobes.

DISCUSSION

Dr. Fremont-Smith: Did the patients, the neurological patients, know what they were getting?

Dr. Balestrieri: No.

Dr. Fremont-Smith: Did they know they were going to get LSD?

Dr. Balestrieri: No.

Dr. Fremont-Smith: What did they expect? What did they think they were getting?

Dr. Balestrieri: They thought they were getting their usual treatment.

Dr. Fremont-Smith: You don't think they knew what the others anticipated?

Dr. Balestrieri: No. These experiments were made at a certain time, and the patients had no opportunity to compare treatments.

Dr. Pahnke: I would like to comment on your results of the tolerance studies and refer back to the work done on goats at the Worcester Foundation. Giving LSD to goats every day for two weeks produced psychical tolerance. In other words, giving the same dose every day, on the fifth day the initial response was the same. The LSD response came back again even though LSD had been given previously five days in a row. In your work with man, how many days did you give LSD?

Dr. Balestrieri: In order to obtain complete tolerance, from five to seven days.

Dr. Pahnke: Did you keep giving the drug every day?

Dr. Balestrieri: We used it in increasing doses. We started with low doses and increased them every day. In some subjects we obtained a good tolerance to 200 mcg.

Dr. Pahnke: In Isbell's work he gave it for three days to establish tolerance and then quit. I wondered if you kept on going for, say, a week or fourteen days, giving it every day?

Dr. Balestrieri: Not for more than eight days.

Dr. Fremont-Smith: Dr. Abramson can answer this last question.

Dr. Abramson: I can't answer it in great detail, but I can present some data obtained using the Cold Spring Harbor Questionnaire.

Subject A received 100 mcg of the drug on six successive days and once again five days later. Table 1 indicates the psychic areas in which changes were reported and the total number of times psychic changes were reported during the day. The subject was questioned

TABLE 1

Number of Times Subject *A* Had Certain Psychic Changes
(Subject was questioned six times during each of seven experiments with 100 mcg of LSD 25.)

Area	Number of times changes were reported — Day 1*	2	3	4	5	6	11
1. Motor behavior	4	0	0	0	0	0	0
2. Control	0	0	0	0	0	0	0
3. Consciousness	0	0	0	0	0	0	0
4. Concentration	0	0	0	0	0	0	0
5. Mood	0	0	0	0	0	0	0
6. Attitude toward environment	0	0	0	0	0	0	0
7. Orientation	0	0	0	0	0	0	0
8. Memory	0	0	0	0	0	0	0
9. Hallucinations	3	1	0	0	0	0	0
Total	7	1	0	0	0	0	0

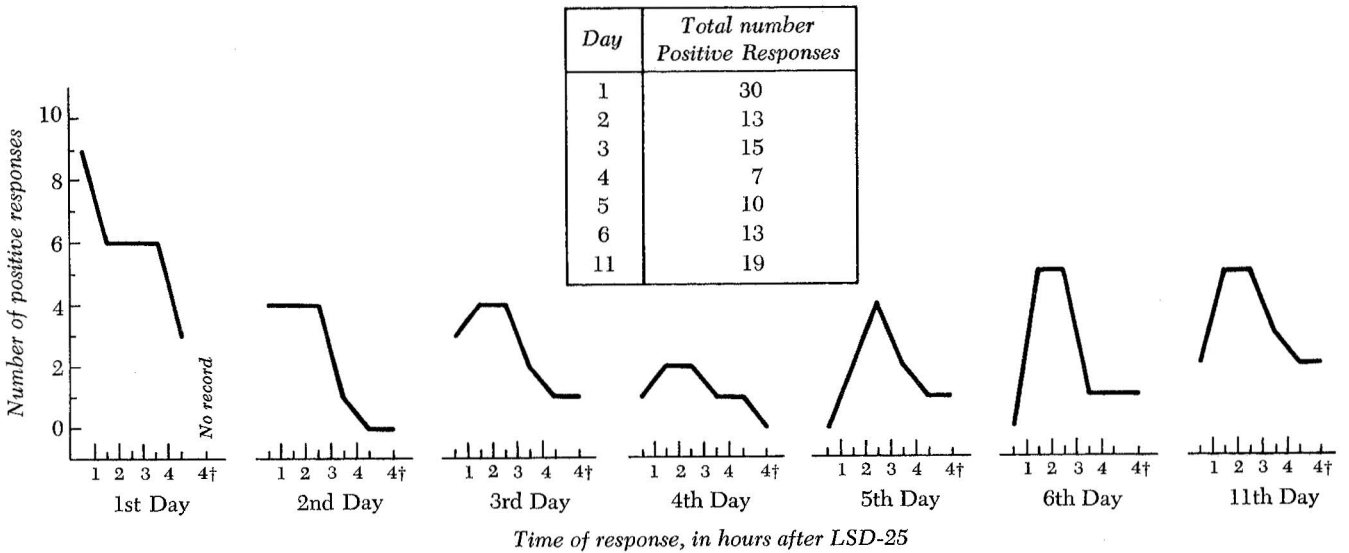
*Subject was questioned only five times on this day.

six times. There were hallucinations on the first two days and changes in motor behavior on the first day. On subsequent days the subject was normal in all areas.

Figure 1 shows the total number of questions receiving positive responses during each question period on each experimental day and the total number of responses made each day.

The subject responded at ½, 1½, 2½, 3½, 4½, and more than 4½ hours after receiving the drug, except on the first day when there was no response during the last interval. The boxed insert on the figure shows that the total number of responses went from 30 to 13, to 15, and to 7 on the first four days, and then up to 10 on the fifth, and 13 on the sixth. Five days later, when the subject again received 100 mcg of LSD 25 she gave a total of 19 responses. On the fifth day a decreased response occurred only during the first ½ hour. The maximum number of responses given during the last three intervals was two on all but the first day. On the eleventh day the number of responses given was greater than on the second day (except for the first ½ hour) but not as great as on the first day.

Dr. Van Rhijn: I should like to comment on the tolerance between LSD and psilocybin. When you give first LSD, let us say 200 mcg, and after two hours in the same patient 6 mg of psilocybin intravenously, you get a typical reaction; no tolerance is observed. But the reverse is not true. When you give first 6 mg of psilocybin intravenously and



Day	Total number Positive Responses
1	30
2	13
3	15
4	7
5	10
6	13
11	19

Fig. 1. Total number of positive questionnaire responses given by Subject *A* on Section I during each of seven experiments. The subject received 100 micrograms of LSD-25 on six successive days and again after five days. (*Journal of Psychology*, 1956, **41**, 81-105)

two hours later 200 mcg of LSD, there is a great tolerance for LSD. I would like to know if you have an explanation for this.

Dr. Balestrieri: It could be that this phenomenon has to do with a cross-tolerant effect of LSD. That's the only explanation I can think of.

Dr. Freedman: I would like to comment. There are no simple ways of explaining tolerance. It is simply an operational definition. When we speak of tolerance, it is simply an estimate of effect contingent on our dosage schedule. Dr. Balestrieri's work has always been very interesting in segregating various phenomena, but we don't know the mechanisms. When you are studying tolerance you have to study the dose, the interval, etc. You may get different phenomena if these are varied. In rats, for example, you can give a low dose and get no tolerance; at 200 mcg, however, you get some tolerance. What is interesting about tolerance in rats is that not all signs or effects of the drug show tolerance. If you could ever systematically observe in humans which effects do show tolerance, and which don't, we could begin to look at the brain for underlying mechanisms.

Dr. Ketchum: Dr. Balestrieri referred to cholinergic blocking agents as hallucinogenic drugs. It's true that this class of compounds produces hallucinations, as do atropine, scopolamine, bromides, alcohol, barbiturates, lead, etc. Would you be inclined to extend the term hallucinogenic to all these possible causes of toxic deliria?

Dr. Balestrieri: Do you mean definition of hallucinating drug?

Dr. Fremont-Smith: Remember what I said about definitions? They are good only for specific purposes. Give a definition for this morning, but don't try to give a general definition.

Dr. Balestrieri: I call a hallucinogenic drug a drug which gives hallucinogenic phenomena without the necessity of confusion phenomena.

Dr. Osmond: Just a point: this question on the elaboration from very simple distortions to extremely complex ones is extremely important. Much of the psychotic phenomena can far better be understood in these terms. The question of time, which is so extremely important in these studies, doesn't receive as much attention as it deserves. So much depends on time.