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**Gross Behavioural Changes in Monkeys
Following Administration of LSD-25,
and Development of Tolerance to LSD-25**

By

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LSD-25 has dramatic and reversible effects on behaviour in monkeys. It was thought necessary to study development to tolerance to the drug in this species before proceeding to a study of its effects on memory and learning.

The effects of large doses of d-lysergic acid diethylamide (LSD-25) injected intravenously into monkeys (*Macaca mulatta*) have been described (EVARTS 1956). Several observations have been made on development of tolerance to LSD-25 in different species (ABRAMSON et al. 1956; CHOLDEN et al. 1955; FRASER et al. 1955; FREEDMAN et al. 1958; JARVIK and CHOROVER 1960; ISBELL et al. 1955).

These studies have shown that:

1. In normal humans, using gross behavioural changes as a measure of drug effectiveness tolerance develops in four to seven days of daily administration and lasts for approximately three days (ABRAMSON et al. 1956).
2. In schizophrenic humans, tolerance develops in two to three days (CHOLDEN et al. 1955).
3. In rats, using rope-climbing ability as a measure of drug effectiveness tolerance develops in four days and lasts for approximately three days (FREEDMAN et al. 1958).
4. In *Macaca mulatta*, using performance on delayed alternation problems tolerance "develops quickly." No details of dose schedules were given. Tolerance was found to persist for two weeks (JARVIK and CHOROVER 1960).

Since it is proposed to study further the effects of LSD-25 on learning and memory in *Macaca mulatta*, it was felt necessary to obtain further information about the development of tolerance to LSD-25.

Materials

The subjects were three immature female monkeys, weighing approximately 3 kg each. LSD-25, 1 mg/kg, was administered by intraperitoneal injection. The drug was freshly weighed out from light-proof vial in which it was supplied and was dissolved in sterile physiological saline just prior to each injection.

Methods

The measure of effectiveness of the drug were gross changes in the animals' behaviour. After the first injection, the drug was administered to each animal at intervals of six days, four days, three days, two days, (one injection for each interval,) and finally for four consecutive days. (For the third animal the six day and four day intervals were omitted and observations were made directly from the three day interval.) In all a total of twenty-five injections were made in the three animals.

Results

Behavioural changes were observed in each instance. The onset of action was noted within one to eight minutes of injection. In eighteen of the twenty five observational periods the onset of action was noted within four minutes. The changes were drooping of the eyelids, salivation, pupillary

Table

Characteristic	10 min	30 min	60 min
Eyelid drooping	++	+	—
Salivation	++	+	—
Pupillary dilatation	++	++	+
Visual and non-visual placing reactions	—	—	Normal
Hopping reactions	—	—	Normal
Spontaneous movement	—	±	±
Tameness	++	++	±
Vestibular righting reflex	++	++	—
Grasp and sucking reflexes	++	+	—
Visual perception	Normal	—	Normal

++ = marked, + = moderate, — = absent.

dilatation, loss of visual and non-visual placing reactions and hopping reactions, and marked and sudden decrease in spontaneous movement and aggressive behaviour (i.e. monkey did not bite observer's finger when placed in monkey's mouth). The animal assumed a prone position with all four limbs spread out laterally when placed on a flat metal grid cage top.

This prone position in all observations. In most trials the eyelids closed of the cage, only to change continued, then tained for a injection. In made during on its back, panying lack and forcibly immediately

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This prone position, which is atypical for a *Macaca mulatta*, was seen in all observational periods within ten minutes of the injection, and in most trials within five minutes. Each animal would lie quietly with eyelids closed, but could be roused at any time by a loud noise, shaking of the cage, or by being touched. It seemed that the animal reacted only to changing background levels of activity, for if the loud noise was continued, the eyelids would again close. The prone position was maintained for a period of from twenty to thirty minutes following each injection. In addition to the above changes, the following observations made during this period: a strong righting reflex if the animal was placed on its back, a moderate to strong grasp reflex, a sucking reflex accompanying lack of biting and a loss of vision. When one took the animal and forcibly turned it from the prone position onto its back, it would immediately and violently flip over onto its abdomen again.

The loss of vision appeared to last for a brief period of time, in most cases from about ten minutes to about thirty-five minutes following injection. The animals visual perception was determined by its ability to pick up a raisin with the hand when the raisin was held near the monkey. The movement of the hand towards the raisin was always smooth and precise, as was the movement of hand to mouth, although once the animal grasped the raisin it was not always able to hold onto it.

Twenty-five to forty minutes after each injection, the animals began to lift their heads, raise their eyelids, look about, and rise up on all fours to a sitting position. They then would sit quietly on their haunches but required the use of their forearms for support to prevent themselves from toppling over. If they began to topple over, they would grab hold of the grid strongly and jerk themselves back to a sitting position. This sometimes became a rhythmic pattern, occurring every two-three seconds, and lasting for several minutes. They were still quite tame, allowing themselves to be petted. They would occasionally crawl, in a circular manner. On any one day the movement was to the same side. More often than not, this was to the left. Visual and non-visual placing reactions and hopping reactions were still absent. At approximately one hour following the injection, the animals were usually capable of sitting up without using their arms for support and they became more active and sometimes climbed down from the cage top. They would climb into the cage through the open doorway, in contrast to the normal animal, which would leap off the cage top, and vigorously run around the room. However, once inside the cage the animal sat quietly, usually in a corner, unlike a normal animal which would be occupied with jumping about the cage, chattering, screeching and cooing when someone approached the cage. After one hour, the animals would again be resistant to being handled and would often attempt to bite the observer who tried to

do so. The vocal and physical passivity, which seemed to be the last effect of LSD-25 to disappear, lasted for two to two and one half hours, at which time animals appeared to be normal again.

Discussion and Summary

Massive doses of LSD-25 produced marked behavioural changes in *Macacca mulatta*. The animals became quite tame and passive, visual and non-visual placing reactions and hopping reactions were lost, grasp and sucking reactions appeared, and the vestibular righting reflex was greatly augmented. Salivation and pupillary dilatation were pronounced. The effects lasted from the onset of action until about one hour after injection. Visual perception disappeared after approximately ten minutes following the injection and then returned approximately twenty-five minutes later. This is in contradiction of EVARTS (1956) who found animals to be blind for about seventy-five minutes following injection. It is difficult to conclude whether or not the apparent inability to see was due to a real interference with visual processes, or whether it was due to the general decrease in motor activity which was seen during this time.

The gross behavioural changes described above were noted after every injection. It may therefore be concluded from this study, that a dose of LSD-25 of 1 mg/kg, does not produce tolerance, as measured by changes in gross behaviour, over a four-day course of daily injections.

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