Effects of Hallucinogenic and other Drugs on the Nest-building Behaviour of Mice

We have found that nest-building is ideally suited for the study of the effects of hallucinogenic drugs. Strains of laboratory mice differ in their nest-building activity. Males of the C57Bl/6j strain (Jackson Laboratory, Bar Harbor, Maine) are very reliable in daily testing and consequently well suited for experiment. Briefly, testing involves removal of the existing nest and provision of material for a new one. After a few days of adaptation to this procedure the mouse retrieves the material and builds the new nest within a few minutes after provision of the fresh material.

There are three primary components in nest-building: (*a*) retrieval of the nest material, (*b*) shredding behaviour (dismantling of the cotton dental balls), and (*c*) working the material together to form a single unit. We found that this sequence takes only 7 min, and the nest is in its final form within 45 min. Although nest-building may seem to be a cooperative endeavour in groups, our observations suggest that at least retrieval is competitive. In general, the pattern of behaviour is the same for isolated animals except for the occasional animal that may shred some of the cotton before retrieval. If animals are tested during their sleep period, they may only retrieve the material to make a mat, and the shredding and final shaping of the nest may not occur until the high activity period.

The drugs tested were chlorpromazine, chlordiazepoxide, desipramine, mescaline, 2,5-dimethoxy-4-methyl amphetamine (DOM), 2,5 - dimethoxy - 4 - ethyl amphetamine (DOET), 3,4,5-trimethoxy amphetamine (TMA), D-amphetamine and LSD_{25}. Animals were placed individually in 26×35 cm wooden boxes with a wire floor at least 3 days before receiving nesting material, to allow for exploration and choice of a sleeping corner, which usually became the nest site. Twenty animals, 60 days old at the beginning of treatment, received a wide range of doses of each drug. All injections were of 0·1 ml., administered intraperitoneally at intervals of at least 4 days. Each animal served as its own control, receiving saline injections at the beginning and the end of each set of drug treatments.

On a test day, an animal was injected with drug or saline, returned to its box, and the old nest was removed. Thirty minutes after injection, forty tightly packed fresh dental balls, 6 mm in diameter, were placed randomly on the floor of the box and we recorded the behavioural pattern, state of activity relating to retrieval, shredding, time required to complete retrieval, number of cotton balls retrieved and the quality of the completed nest. Twenty-four hours after administration of the drug, animals were tested without injection to determine whether recovery from the drug was complete.

There was no readily observable effect of chlorpromazine, chlordiazepoxide and desipramine on the primary components of nest-building except in doses which obviously impaired motor activity. In those cases there was only partial retrieval of the cotton balls, or the behaviour was completely inhibited, presumably until the effects of the drug had subsided.

Mescaline and the amphetamine compounds with known hallucinogenic properties, however, produced considerable changes in behaviour. Effects were most pronounced during the retrieval phase. All drugs induced a stereotyped behavioural pattern that competed with and disrupted the normal pattern. The duration of the competing behavioural pattern was dependent on the dose and type of drug and was typically followed by a period of inactivity before the onset of the normal retrieval pattern. Descriptions of the various induced behavioural characteristics observed during the time that retrieval of the material to the nest site would have occurred normally are presented in Table 1. A drug is not included in the matrix unless the behavioural characteristic was observed in at least 50 per cent of the animals.

Table 1. QUALITATIVE ANALYSIS OF THE DRUG EFFECTS AFTER INITIAL PRESENTATION OF NESTING MATERIAL

	Dose in mg/kg								
	0·25	0·50	1·0	2·0	4·0	8·0	10·0	20·0	25·0
Actively avoids cotton, runs between or jumps over			AMPH	AMPH	AMPH				
Shreds intensively						AMPH*			
Explores cotton with minimal handling		DOET	DOET	DOET					
Explores cotton vigorously, repeated stereotypic manipulation of dental balls	DOM	DOM	DOM	DOM*	DOET*	TMA	TMA* MESC	MESC	
Paroxysms of ear and neck scratching		DOET	DOET	DOET DOM*	DOET*		TMA*	MESC	MESC*
Mild tremors				DOM*	DOET*	AMPH*			MESC*
Inhibition of retrieval of nest material	DOET DOM	DOET DOM AMPH	DOET DOM AMPH	DOET DOM* AMPH	DOET* AMPH	TMA AMPH*	TMA* MESC	MESC	MESC*

* Maximum dose used.

DOM, TMA and mescaline produced the same behavioural profile with a potency relationship similar to that reported for humans[1]. DOET and D-amphetamine induced behavioural patterns unique to each drug and easily differentiated from the effects produced by the other drugs. Four mg/kg of DOET had an effect similar to that of DOM, however. Likewise, the behaviour induced by 8 mg/kg of D-amphetamine changed from apparent avoidance of the cotton to intensive fine shredding.

We found that the animals were shredding the tightly packed dental balls a single strand at a time. Avoidance of the dental cotton balls after injection with D-amphetamine is not merely the result of increased activity. All drugs used increase activity, without the same end result. Furthermore, other experiments with morphine, resulting in high activity, did not induce active avoidance of the

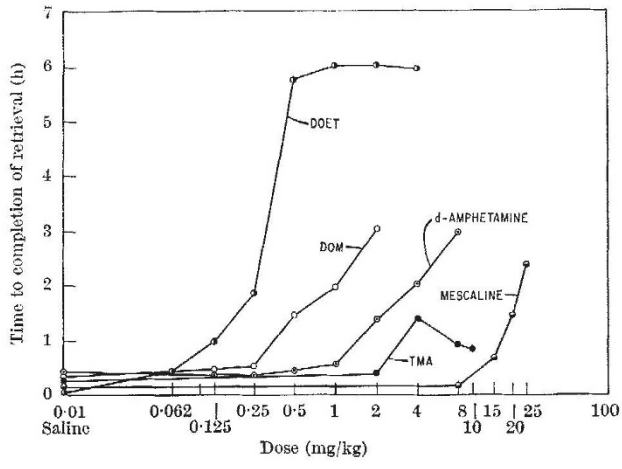

Fig. 1. Curves showing the time passed before retrieval of cotton to the nest site. Each curve is based on the mean of twenty animals.

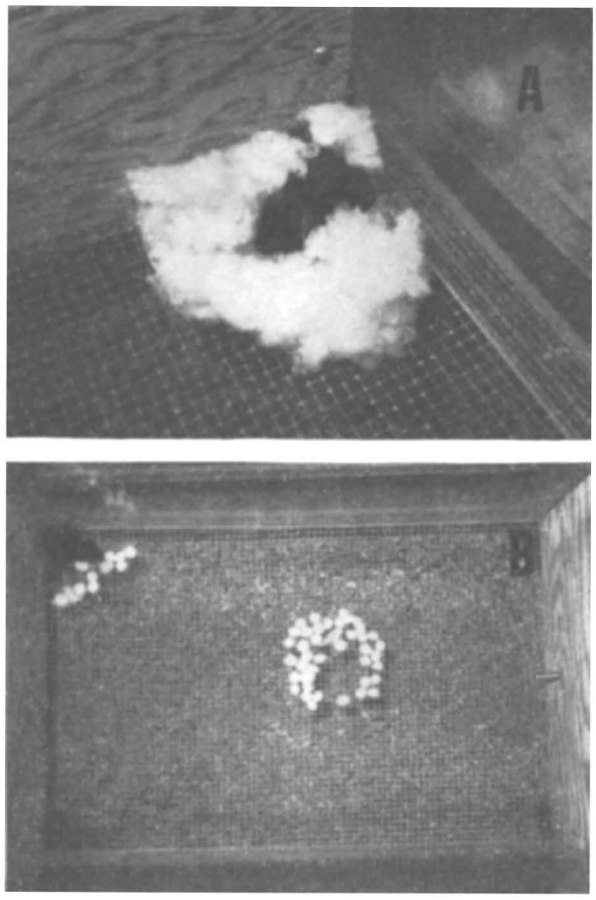

Fig. 2. *A*, Picture of a saline control taken 2 h after injection. *B*, Same animal 5 h after an injection of 100 μg/kg of LSD. The animal surrounded itself with cotton, sat in the centre for 1 h, moved to the nest site, placed the remaining cotton across the front of the area and remained in the same position for 6 h before completing the nest.

cotton balls. All drugs except D-amphetamine produced paroxysms of ear and neck scratching that were concurrent with the other competing responses, although they did not seem to interfere with the behaviour.

Table 2. PROPORTION OF ANIMALS IN WHICH VARIOUS DOSE LEVELS OF DRUGS INDUCED COMPETING RESPONSES INHIBITING RETRIEVAL OF NESTING MATERIAL

Dose level	DOM	DOET	D-Amphetamine	TMA	Mescaline
0·062	0·00	0·10	0·00	—	—
0·125	0·40	0·30	0·20	—	—
0·250	0·85	0·70	0·40	—	—
0·500	1·00	1·00	0·65	—	—
1·000	1·00	1·00	0·85	—	—
2·000	1·00	1·00	1·00	0·00	—
4·000	—	1·00	1·00	0·40	—
8·000	—	—	1·00	0·55	0·00
10·000	—	—	—	0·75	0·60
20·000	—	—	—	—	0·75
25·000	—	—	—	—	1·00

Table 2 shows the proportion of animals displaying competing responses at each dose. DOET and DOM are clearly the most potent of the drugs used. DOET is also much longer lasting, as indicated by the length of time before completion of the nest (Fig. 1). The curve for TMA (Fig. 1) suggests that the animals were developing a tolerance to the drug. But this did not seem to alter the quality of the competing response, although it shortened the duration. Tolerance was not observed with any of the other drugs.

Because our supply of LSD_{25} was limited, the results, while compelling, must remain tentative. Six animals were tested with 25, 75 and 100 μg/kg and the behavioural effects observed contained none of the characteristics of the stereotyped response induced by mescaline and the amphetamine compounds. Retrieval of the cotton may begin normally but is interrupted by frequent periods of inactivity. Some animals retrieved cotton to corners other than the nest site. Animals were observed carrying the same cotton ball from one corner to another continuously. Marked alterations in the topography and location of the nest (Fig. 2) were common. Behaviour was always altered by 100 μg/kg, and only two animals revealed any effect at smaller doses.

We thank Rose Eng and Sally Evans for technical assistance and Paul Pietsch for critical comments.

C. W. SCHNEIDER
M. B. CHENOWETH

Biochemical Research Laboratory,
The Dow Chemical Company,
Midland,
Michigan 48640.

Received September 9, 1969.

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Antennae: Another Wind-sensitive Receptor in Locusts

FIVE pairs of wind-sensitive hair beds at the upper part of the head control flight posture and wing movement of locusts[1–7]. But the antennae of flies and bees are airflow receptors which regulate the insect's flight speed relative to the surrounding air and stabilize the flight course in the horizontal plane[8–12]. During tethered flight these insects hold their antennae in a characteristic flight position. Exposed to the air current of a wind tunnel, they will move their antennae actively against the direction of the air current. This movement is considered as an antennal positioning reaction, which adapts the operating range of the receptor to different air speeds[10–12].

A similar forward movement of the antennae can be seen in locusts during tethered flight in the air current from a wind tunnel. It is of interest whether this antennal movement is induced passively by aerodynamic forces or actively by the animal itself, and whether this movement is connected with flight control.

The antenna of *Locusta migratoria* consists of the basal scape, the pedicel and a number of smaller segments forming the flagellum. The joint between head capsule and scape and the joint between scape and pedicel may be moved actively by muscles[13,14], whereas the morphological arrangement of the joint between pedicel and flagellum makes possible only slight passive movements caused by exterior forces acting on the flagellum. These passive movements are perceived by mechanoreceptors of the pedicel: the organ of Johnston, another chordotonal organ and campaniform sensillae[14–16].

In locust at rest the antennae may be held in different directions. Uvarov[17] has noted that "the antennae during flight are kept in a very rigid state at an angle to the body and may serve to record changes in the direction of air currents". For the exact evaluation of antennal movements I photographed the head region of locusts in tethered flight from above, some seconds after removal of the support (subdued red light; exposure time 1 s). The "antennal angle" (γ = angle between antenna, projected in horizontal plane, and longitudinal axis of the wind tunnel) was measured on the films. The antennal position of locusts in tethered flight depends on the speed of the