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The Effects of "Psychotomimetic" Drugs on Animal Behavior[1]

JAMES B. APPEL, PH.D.

The University of Chicago, Chicago, Illinois

THE behavioral effects of drugs which have been called "psychotomimetic" or "hallucinogenic" in man have been extensively investigated in animals. The species studied range in size from ants and spiders to elephants and include fish, fowl, mice, rats, rabbits, guinea pigs, dogs, cats, goats, monkeys and, of course, men. The responses affected by these drugs are at least as numerous as the species studied. They range from synaptic inhibition, evoked cortical potentials, and EEG patterns to complex perceptual learning and social behavior. Moreover, even non-human animals have been blind, frightened, asleep and anesthetized when drug effects were measured. It is therefore not surprising that the objective as well as the subjective effects of "psychotomimetic" drugs are not always well understood. In this paper, I will review the literature and attempt to relate some of the effects which have been measured to variables which normally control behavior. I will concentrate on animal studies because it is important to know which of the many effects of these compounds have biological generality; other authors in this volume will discuss other aspects of the literature.

Unlearned or instinctual behavior

Lysergic acid diethylamide (LSD), chemically related compounds such as 2-brom-lysergic acid (BOL), psilocybin, mescaline, marijuana and tryptamine homologues affect naturally occurring, presumably unlearned or instinctual behavior in many species. Witt (1956), for example, has examined the effects of drugs on web building. A dose of 150 mg psilocybin/kg or 1 g mescaline/kg causes spiders to build webs with shorter and thicker threads (Christiansen et al., 1962)—an effect which can also be induced by increasing the insect's body weight. In fish such as carp, trout, goldfish, and Siamese fighting fish (Abramson et al., 1961; Gettner et al., 1964), LSD and its derivatives and congeners, but not 1800 other assorted compounds, increases surfacing behavior and general or spontaneous activity; they also darken the color of some of these animals' skins (Chessick et al., 1964). In fish (Evans et al., 1958; McDonald & Heimstra, 1964; Saxena et al., 1962), newts (Evans & Abramson, 1958), and ants (Kowtowski, 1966), LSD has also been found to increase "aggression" but in higher species, both increases and decreases in this complex, perhaps clinically relevant behavior may occur. In pigeons, which have proved to be useful experimental subjects in many laboratories (below), no effects of "hallucinogenic" drugs have been formally reported on "aggression" or on any other kind of complex social behavior but, in our laboratory, normally tame birds appear to be much more irritable and difficult to handle after being treated with LSD.

In the mouse, intracerebral injection of 0.2 mg LSD/kg has been found to increase "excitability" and "aggression" as defined by the occurrence of a direct attack upon any object placed in front of the subject (Haley, 1957), but when 0.1–1.6 mg/kg of LSD or of BOL is given parenterally, isolation-induced attack behavior is inhibited (Uyeno & Benson, 1965). Certain extracts of marijuana also inhibit fighting as well as spontaneous motor activity (Santos et al., 1966). In the rat, LSD has been said to increase "excitement" and "aggression" (Silverman, 1966; Taeschler et al., 1960) as well as to prolong "aggression" induced by painful electric shock (Brunaud & Siou, 1958) but in situations involving competition for food (Uyeno, 1966a) or an estrous female (Uyeno,

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1967) LSD inhibits "dominance" behavior and increases "submission."

Observation in at least two laboratories, in which the effects of other variables were being investigated, suggests that LSD increases both "excitement" and "aggression" in the cat (Elder & Dille, 1962; Gaddum & Vogt, 1956) but, in the monkey, both low, 0.1 mg/kg, (Chen & Weston, 1960) and high, 1.0 mg/kg, doses of LSD increase "docility" (Jonas & Downer, 1964).

The behavioral effects of "psychotomimetic" drugs on instinctual behavior are little clarified by the few additional studies thus far reported of such "unlearned" phenomena as level of activity, exploration or "emotionality." In the mouse, dimethyl tryptamine and its homologues suppress activity and exploratory behavior (Szara et al., 1962) but, in goats, LSD increases amount of walking (Koella et al., 1963). A decrease in activity and in "emotional" defecation was reported following eight out of ten "psychotomimetics" in rats in an open field (Brimblecombe, 1963).

It is difficult to reconcile these apparently contradictory findings concerning the effects of drugs on complex patterns of naturally occurring behavior. While differences in species, dose, route of administration and relative potencies of the drugs tested are no doubt important, behavior described in anthropomorphic terms such as "aggression," "docility," and "emotionality" can easily differ in different laboratories or can be readily misinterpreted. An apparently "docile" monkey or rat might be frozen in fear of some unknown stimulus and an "aggressive" dog or cat might be playful or hungry.

Basic biological functions such as eating, drinking, and mating, as well as life itself are also affected by "hallucinogens." Drugs such as LSD, in appropriate doses, suppress food intake in rats, birds, and no doubt other species. This seems to be true both when food intake is measured directly (Hamilton & Wilpizeski, 1961; Becker et al., 1967) or indirectly, by the amount

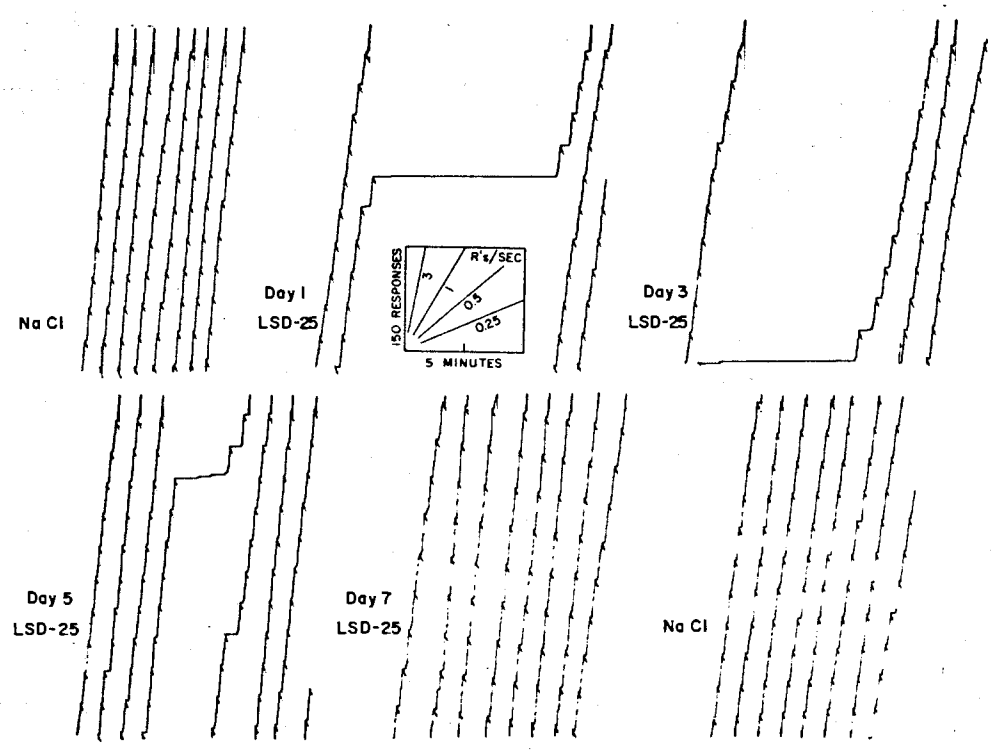

FIG. 1.—Cumulative records of bar-pressing on an FR 40 (fixed-ratio 40) schedule of reinforcement for a single rat. Control sessions before and after the tolerance run and the first, fifth and seventh days of treatment with 0.13 mg of LSD/kg are shown.

of suppression of behavior motivated by food deprivation and maintained by food reward (below). The mating behavior of the rat is affected in a dose-dependent fashion by LSD (Bignami, 1966). Low doses increase the number of ejaculations during a test period of standard duration (Soulairac & Soulairac, 1963) and high doses reduce the number of copulations preceding ejaculation (Gillett, 1960).

Sufficiently high doses of LSD often have very serious deletereous biological effects which are, however, not directly relevant to the present discussion. In one disturbing report, for example, an Asiatic elephant was killed by LSD (West & Pierce, 1962) and numerous articles have recently appeared in the scientific literature as well as the popular press implicating the ingestion of this compound during pregnancy in the induction of genetic abnormalities in mice (Auerbach & Rugowski, 1967), rats (Alexander et al., 1967), hamsters (Geber, 1967) and men (Cohen, 1967). These genetic effects, however, are probably not specific either to LSD or any similar agent.

"Simple" learned behavior

The effects of "psychotomimetic" drugs on relatively simple forms of instrumental learning have been extensively documented in both sub-human and human animals. Taken as a whole, these effects may seem as inconsistent as some of those I have been discussing; they are, however, more comprehensible because drug-induced changes in the behavior being measured can often be related to events in the animals' enviroment or history as well as to pharmacological and physiological variables.

Positive Reinforcement

"Psychotomimetic" drugs such as LSD, psilocybin, mescaline, and marijuana generally depress the rate of simple patterns of on-going behavior such as bar-pressing or rope-climbing when responding is maintained by food reinforcement (Freedman et al., 1964b; Gardner, 1965; Jarrard, 1964; Smythies & Levy, 1960) or by "rewarding" electrical stimulation of the lateral hypothalamus (Olds & Olds, 1964). The amount of depression is, as with most drugs, determined both by pharmacological factors such as dose and time since injection and by behavioral factors such as the schedule of reinforcement and level of deprivation. On a fixed-ratio (FR) schedule (in which food is presented if and only if an animal emits a fixed number of responses) 0.04–0.39 mg LSD/kg induce one or more periods of no-responding in the rat (Freedman et al., 1964b). The effects of 0.13 mg LSD/kg can, for example, be seen in the cumulative records of Fig. 1 (Day 1).[2] Less drastic changes in rate of responding, i.e. incomplete or partial suppres-

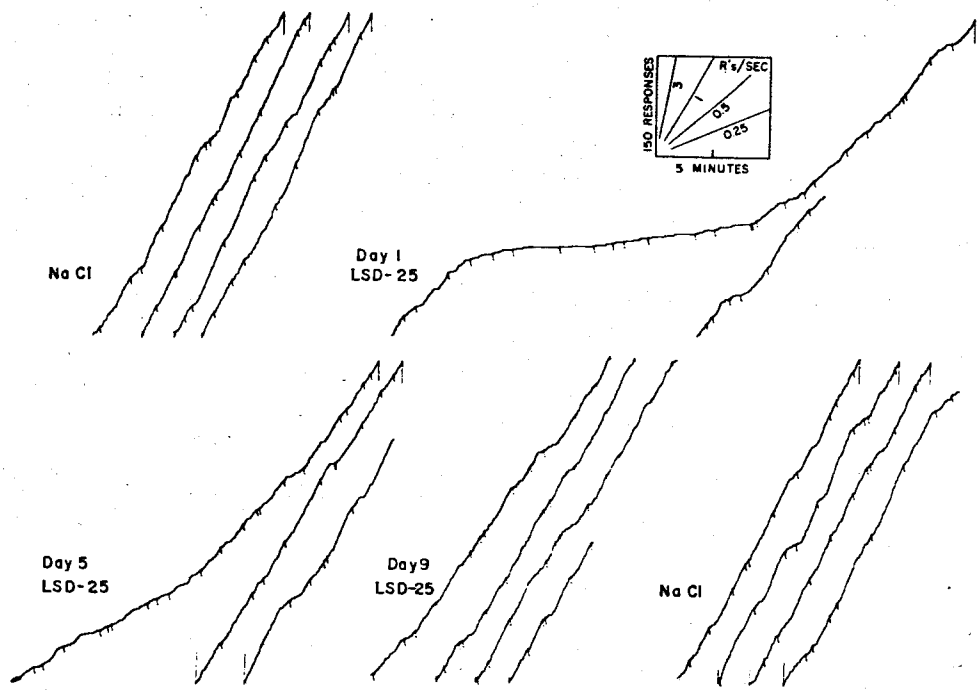

FIG. 2.—Cumulative records of bar-pressing on a VI 1.5 schedule of reinforcement for a single rat. Control sessions and the first, fifth, and ninth days of treatment with 0.195 mg of LSD/kg are shown.

sion, can occur following low doses of LSD or higher doses of less potent compounds (Appel & Freedman, 1965; Becker et al., 1967) but these changes are more frequent when food-motivated behavior is maintained by a variable-interval (VI) schedule (Freedman et al., 1964b; Jarrard, 1964). (On VI, food is presented on the basis of elapsed time rather than on number of responses emitted by the animal.) Figure 2 shows the effects of 0.195 mg LSD/kg on VI 1.5.

On VI, but never on FR, relatively low doses of LSD can sometimes *increase* the rate of responding for either food (Jarrard, 1964) or lateral hypothalamic stimulation (Horvitz et al., 1965). Tetrahydrocannabinol (the presumed active ingredient of marijuana), like LSD, depresses ratio more than interval responding (Boyd et al., 1963).

It is probable that effects of drugs on food-motivated behavior are related to a drug-induced reduction in an animal's disposition to eat (Hamilton & Wilpizeski, 1961; Becker et al., 1967), but LSD and other "hallucinogens" also increase level of physiological arousal and behavioral distractibility or generalization which might interfere with the sustained performance of goal-directed behavior (below). The depressing effects of "psychotomimetics" cannot, however, be attributed to motor inhibition because behavior maintained by different contingencies is often remarkably resistent even to high doses of the most potent psychotomimetic known, LSD (Appel et al., 1967).

A bar-pressing situation involving a fixed-ratio schedule of food reinforcement proved to be a reliable means of comparing or scaling the relative potencies of various chemically or functionally related drugs (Appel & Freedman, 1965). In the rat, the order of potencies parallels that seen with "psychotomimetics" in mice (Uyeno, 1966b) and men (Abramson & Rolo, 1965; Isbell, 1959; Wolbach et al., 1962 a,b) i.e. LSD is far more potent than psilocybin and psilocybin is much more potent than mescaline (Fig. 3).

We have also found that measuring effects on FR is useful because changes in rate are generally abrupt and can therefore be readily detected and quantified (Fig. 1). Pausing or no-responding begins 4–8 minutes after i.p. injection of LSD and the duration of these effects is contingent on dose (Freedman et al., 1964b).

If behavior is measured on FR over long periods of time (6–8 hours) and LSD is given orally, rate of bar-pressing partially returns to base line levels after an initial period of no-responding and a second period of no-responding occurs in the monkey (Peterson, 1966). During this second period, perceptual changes such as persisting visual images and increases in perceived brightness apparently occur (below). This result confirms previous findings that different periods involving different kinds of responses to LSD occur in animals as well as in man (Freedman et al., 1958; Salvatore & Hyde, 1956); similar results have also been obtained with mescaline (Smythies, 1963).

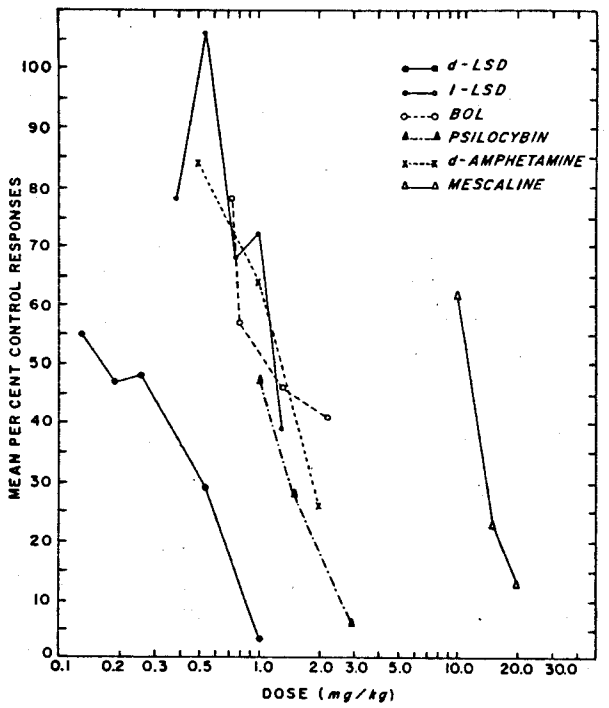

FIG. 3.—Dose-response curves of six psychoactive compounds. The mean per cent of bar-pressing responses normally occurring on an FR 30 schedule of food reinforcement is on the ordinate and dose, on a log scale, is on the abscissa.

That a sequence of effects rather than a single effect may occur following drugs such as LSD or mescaline is of crucial importance for at least three reasons. The most obvious of these is that the particular "effect" an investigator reports depends upon how soon after drug administration he happens to test his subjects. Second, more than one "effect" may imply that a metabolite or derivative of LSD or mescaline is also active. Finally, a description of both the duration and sequence of the behavioral effect(s) of drugs is needed if we wish to relate such effects to endogenous biochemical mechanisms. While the half-life of LSD, for example, in rat plasma is of roughly the same duration as acute, i.e. immediate, behavioral effects (Freedman et al., 1964a), Rosecrans et al. (1967) describe a sequence of biochemical effects in which three "periods" of change in serotonin (5-HT) metabolism occur after LSD. Precisely how these periods of metabolic change correlate with behavioral change has not yet been established.

Aversive Contingencies

The effects of "psychotomimetic" drugs on positive Pavlovian or classical conditioning are essentially unknown in the West. Three studies involving a shock unconditioned stimulus (US) and auditory

conditioned stimulus (CS) suggest that mescaline interferes with classical aversive or "defense" conditioning. Rats (Bridger & Mandel, 1967; Courvoisier & Joulou, 1956; Sivadjian, 1934) and dogs (Bridger & Gantt, 1956) exhibit autonomic disturbances and increased "excitability" following i.p. injection of this compound and generally react to the CS as if it were the US. In addition, 3,4-dimethoxyphenylethylamine (DMPEA), a compound found in the urine of schizophrenics (Friedhoff & Van Winkle, 1962), has an excitatory effect on a potentiated startle response mediated by Pavlovian conditioning (Bridger & Mandel, 1967), no effect on positively motivated instrumental behavior (Appel & Freedman, 1965), and an inhibitory effect of the CAR (below).

It is possible to analyze operant or instrumental behavior motivated by painful or aversive stimulation into two classes according to whether the particular contingency involves conditioning or suppressing the response an experimenter chooses to measure. Aversive contingencies commonly used to condition behavior include escape, in which the animal must terminate a noxious conditioned or unconditioned stimulus, and avoidance (the CAR), in which the animal delays, postpones, or avoids a similarly aversive stimulus. In experiments involving punishment or conditioned suppression (the CER), a painful or conditioned aversive stimulus is used to suppress or eliminate a response which is, or once was, maintained by some other means, usually an intermittent schedule of food reinforcement, and two concurrent motivational systems are thus involved. (An approach-avoidance conflict is a special case of punishment in which the same response is always followed by both reinforcing and aversive stimuli.)

Escape behavior has proven remarkably resistant to the effects of psychoactive drugs with the exception of CNS depressants such as barbiturates and motor inhibitors such as curare. In a straight alley, 0.13–1.0 mg LSD/kg was found to act like amphetamine, i.e., to increase the running speed of rats trained to escape from shock (Hamilton, 1960); a similar effect may occur with marijuana (Carlini & Kramer, 1965). In a water-filled T-maze, 0.5 mg LSD/kg increased the number of errors when rats were required to reverse the direction of a previously learned escape response (Wilpizeski & Hamilton, 1964). In our laboratory, doses up to 1.0 mg LSD/kg had little or no effect on the rate of turning a wheel to escape either from shock or from a CS (buzzer) paired with random presentation of brief intermittent shock (Appel et al., 1967). Figure 4 contrasts the effects of LSD on two FR schedules of escape-from-shock with those obtained on a ratio schedule of food reinforcement.

While some of these apparent differences in results might reflect procedural differences in different laboratories, most investigators agree that normally potent drugs such as LSD have relatively small effects on aversively conditioned behavior or, turning this statement around, sufficient or appropriate motivation can overcome the disruptive effects of otherwise potent drugs. This is not unlike the behavior of humans asked to perform under LSD.

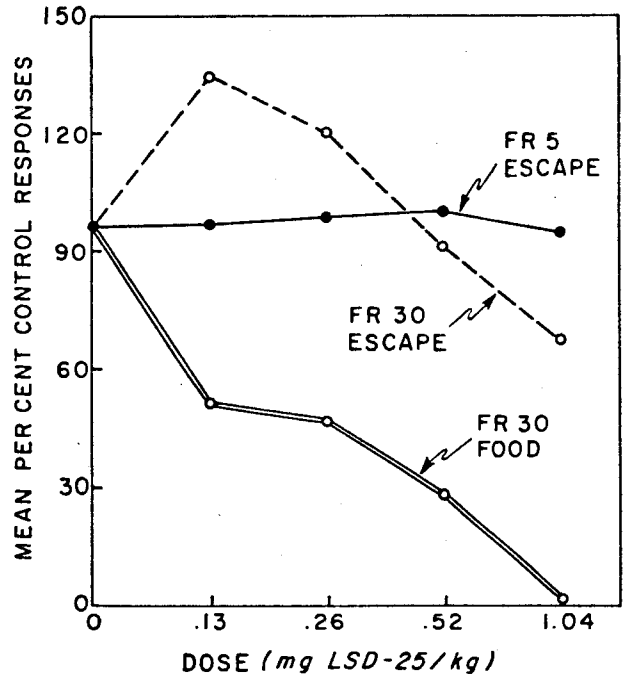

FIG. 4.—Dose-response curves of the effects of LSD on two fixed-ratios of escape-from-shock (FR 5 and FR 30 Escape) and one FR schedule of food reinforcement.

"Hallucinogenic" drugs, unlike other psychoactive compounds, have surprisingly few consistent effects on avoidance behavior. Only exceedingly high doses of LSD (1.5 mg/kg) or mescaline block a well-learned pole-climbing avoidance response (CAR) in the rat (Cook & Weidley, 1957; Pfeiffer & Jenney, 1957). If, however, 0.025–0.1 mg LSD/kg is given during avoidance *training*, the same response is apparently depressed (Domino et al., 1965). Mescaline causes previously acquired avoidance behavior in a shuttle-box to extinguish more rapidly in rats (Chorover, 1961) and less rapidly in cats (Key, 1961). In a shuttle-box, LSD, substituted tryptamines (Gessner & Page, 1962) as well as harmalan and 10-methoxyharmalan (McIsaac et al., 1961) increase the numbers of errors (jumping in the absence of the CS) in the rat. In a Skinner box, low doses of LSD increase the rate of non-discriminated (Sidman) avoidance behavior, and higher doses depress it (Jarrard, 1964; Smythies et al., 1967).

Some of the most interesting work on the effects of mescaline and its derivatives on the CAR has been

reported by Smythies and his colleagues (Smythies & Sykes, 1954, 1966; Smythies et al., 1967). In a shuttle-box, mescaline (25 mg/kg) initially depresses or inhibits the number of barrier crossings in the presence of an auditory CS but later induces a prolonged "excitatory" phase during which reaction time is decreased (Smythies & Sykes, 1964). Smaller doses cause only excitation. Thus, sequential effects may occur after psychotomimetics when behavior is motivated by shock-avoidance as well as by hunger (above).

While Smythies interprets his excitatory phase as being caused by the effects of a metabolic degredation product of mescaline, "excitement" could also be a function of Pavlovian defense conditioning. Since the animal has been shocked, it may react to the avoidance situation (CS) in the same way as it does to the shock itself (US). In any event, dimethoxy derivatives of mescaline such as DMPA have no bi-phasic effect and merely depress the CAR: the N:N-dimethyl derivative abolishes the inhibitory effect of mescaline and augments its excitatory action (Smythies & Sykes, 1966). More recent studies indicate that methoxy groups in the 3,4, and 5 positions on the mescaline molecule are necessary to induce "hallucinogenic-like" effects and an extra methoxy group in the 6th position increases activity (Smythies et al., 1967).

With the possible exception of the results from Smythies laboratory, the studies I have discussed thus far indicate that drugs which are psychotomimetic in man have generally greater, more reliable effects at lower doses on relatively simple kinds of positively reinforced behavior than they do on aversively conditioned behavior. This conclusion is supported by the results of two experiments in which the effects of various drugs were compared directly in situations involving the suppression of food-rewarded responding by means of aversive stimulation. In one study (Barry et al., 1963) rats were trained to press a bar for food. From time to time a tone (CS) of gradually increasing loudness was introduced in the presence of which, bar-presses were punished by shock. Drugs such as LSD and alcohol selectively decreased performance in the *safe* period, when the CS was not present, whereas tranquilizers such as chlorpromazine had more effect during CS periods. In a similar situation, LSD, mescaline, serotonin (5–HT), amphetamine, and iproniazid had more effect in inhibiting bar-pressing for milk in the presence of a tone than on responding on a second lever to avoid shock—again in contrast to tranquilizers (Ray, 1965).

Perception: Generalization and Discrimination

That "hallucinogenic" or "psychotomimetic" drugs alter the nature of perceptual experience in man is, of course, well-known. Indeed, this fact is probably responsible for the various names given to the class of compounds I have been discussing. What may be less well-known is that numerous perceptual phenomena are also affected by drugs such as LSD in unique ways in sub-human animals.

Generalization

While the absolute visual threshold is increased in both pigeons (Blough, 1957) and man (Carlson, 1958) by LSD in the absence of any corresponding impairment in motor function, there is considerable evidence that the same and related compounds, increase both physiological "arousal" and the extent to which animals (Bradley & Key, 1958) and men (Cohen, 1964; Hartman & Hollister, 1963; Hollister & Hartman, 1962; Oster, 1966) respond to external, often irrelevant, visual and auditory stimuli, i.e., stimulus generalization. A series of studies on cats indicates that relatively low doses of LSD (0.015–0.025 mg/kg) causes both behavioral "excitement" (Bradley & Key, 1958) and an alerting EEG pattern (Bradley & Elkes, 1957). In a later experiment, 0.005 mg LSD/kg was found to lower the threshold of responsivity to stimuli to which cats had never been conditioned and 0.01 mg LSD/kg increased overall "alertness" (Key & Bradley, 1960). That is, in the absence of the drug, normally sleeping animals were awakened only by a tone of a given frequency paired with shock. Under the drug, however, many tones produced the same conditioned pattern of wakefulness. Cats were also found to respond to tones under LSD to which they had previously been habituated.

Similar increases in the number of auditory (Key, 1961) and visual (Key, 1964a) stimuli which evoke a conditioned response under LSD when avoidance behavior is measured in a shuttle-box have also been reported (Key, 1961; 1964a). In our laboratory, Peterson (1966) found that increased generalization based on brightness occurs after LSD in a situation in which monkeys were trained to work for food. Finally, the distracting influence of auditory environmental stimuli on the LSD response was analyzed by comparing the reaction times of cats trained to avoid shock in the presence of a visual CS (Key, 1964b). When tones of three different intensities were presented in the presence of the visual CS, the reaction time increased but, in the absence of these distracting stimuli, LSD decreased reaction time.

Discrimination

Increased levels of generalization, distractibility, and arousal accompanied by decreased ability to habituate can lead to "disorganized" behavior. This

has been reported following LSD in species as low (phylogenetically) as rabbits, rats, and guinea pigs (Liberson et al., 1962; McGaugh et al., 1965). Spatial disorientation in species as high as monkeys also occurs (Cohen, 1965). Increased distractibility or disorganization might account for the disruptive effects of "psychotomimetics" on the sustained, goal-directed behavior required by fixed-ratio schedules of food reinforcement (above). But, if by "disorganization" we are referring to some aspect of an animal's ability to discriminate stimuli in its environment, it must be pointed out that the effects of drugs like LSD on *accuracy* of perception, (as opposed to effects on rate of discriminated responding) are sometimes quite the opposite of what we might predict. While the drug, in doses as low as 0.005 mg/kg, may impair monkeys' performance of a delayed alternation task (Jarvik & Chorover, 1960) or tachistoscopic recognition (Fuster, 1957, 1959) and high doses can even cause blindness (Evarts, 1956), no change in accuracy of discrimination was noted in an auditory discrimination in cats (Key, 1961b). In the pigeon, 0.05 mgLSD/kg has been found to have no effect on accuracy of matching colored lights (Berryman et al., 1962), but 0.1–0.3 mg/kg had an *enhancing* effect on a complex visual discrimination based on brightness (Blough 1957a).

In our laboratory, discrimination behavior has been studied in pigeons over a critical range of LSD doses (Becker et al., 1967). Six birds were trained to discriminate between a flickering and a steady light. Responses on the left key in a two key array were reinforced with food on FR 35 if a light, flashing behind both translucent keys, was steady; responses on the right key were reinforced on FR 35 if the light flickered. Incorrect responses were never rewarded. The doses of LSD were 0.02, 0.04, and 0.08 mg/kg, administered by intramuscular (i.m.) injection. Figure 5 shows that 0.02 mg LSD/kg produced a significant

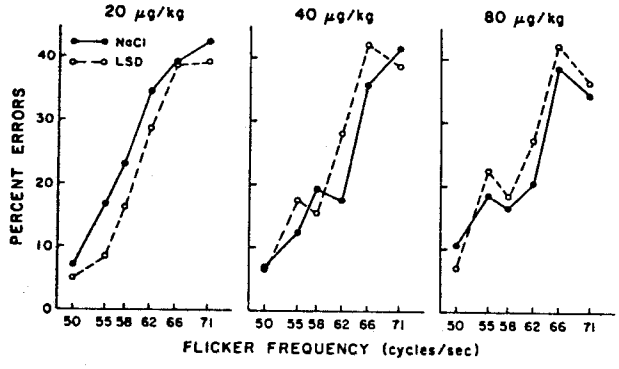

FIG. 5.—Average per cent errors in the performance of a flicker vs. steady discrimination task as a function of flicker frequency after saline and three doses of LSD.

increase in accuracy of performance and the results with 0.08 mg/kg suggest a decrement in accuracy.

The occurrence of persisting or positive after-images is related to both generalization and discrimination. Since Freedman (personal communication) has argued that such images, involving a coexistence of what was just seen and what is currently being seen, often occurs as the basis for hallucinations and illusions in human subjects, Peterson (1966) investigated a similar phenomenon in monkeys in our laboratory. The problem was to discriminate between 1) a white dot on a red background and 2) either a white dot or red background alone. Oral administration of LSD increased the occurrence of apparent after-images during a second period of decreased rate of bar-pressing (above), i.e., the monkey often responded as if the complex stimulus was present (dot plus red background) when actually the stimulus elements were presented successively. It is interesting to note that Keeler (1965) obtained increased after-images with psilocybin in man.

While the physiological effects of compounds like LSD are not the proper subject of this review, our present knowledge of these effects is not sufficient to explain drug-induced changes in visual or auditory perception. In general, LSD *inhibits* synaptic transmission in the lateral geniculate (Evarts, 1957; Bishop et al., 1958) as well as other cortical loci (Marrazzi, 1962) but this effect only occurs at exceedingly high doses (Evarts, 1967). Purpura (1967) reports that transmission across axosomatic, but not axodendritic synapses is *facilitated* by LSD. The drug has been said to specifically act upon diffuse neural mechanisms concerned with the "filtering" and "integration" of sensory information (Bradley & Key, 1963) but exactly how this action is manifested in specific behavioral changes remains to be established.

While the effects of "hallucinogenic" drugs on the perception of auditory and visual stimuli are perhaps the most interesting and clinically relevant of all of those studied, drug-induced perceptual changes are by no means limited to these modalities. Indeed, in rats trained to run a Hebb-Williams maze, 0.03–0.25 mg LSD/kg has more severe effects on blinded animals than it does on normal rats so that non-visual cues might be even more severely affected by LSD than visual ones (Ansfield & Johnson, 1961).

Time perception is altered in both humans (Fischer et al., 1966; Fischer & Mead, 1966) and rats (Maffii & Constantini, 1961) by psilocybin and LSD; spatial (Butters, 1966; Powlowski, 1962; Wilpizeski & Hamilton, 1964) as well as stimulus perseverative tendencies are sometimes enhanced by LSD (Butters, 1966). In squirrel monkeys, a difficult tactile discrimination based on size was disrupted by 0.01–0.04 mg LSD/kg and 0.1 mg BOL/kg while an easy discrimination was relatively unaffected (Sharpe et al., 1967).

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Thus, "psychotomimetic" drugs have numerous effects on discrimination behavior probably depending on dose, time since injection, and nature of the problem as well as other variables not yet explored; they do not necessarily impair accuracy of perception.

Drug-Induced Alterations in Drug Effects

Tolerance and Cross-Tolerance

Many of the behavorial effects of "psychotomimetics" can be altered by pre-treatment with other drugs. A special case of pre-treatment, called tolerance, occurs when the "pre-treating" agent is the test drug itself.

Figures 1 and 2 show that the amount of disruption of food-rewarded bar-pressing on FR and VI schedules diminishes with repeated, daily injection of LSD (chronic tolerance) (Freedman et al., 1964b). Similar effects have been observed with psychoactive congeners of LSD and with mescaline on tasks such as rope or pole climbing (Freedman et al., 1958; Freedman & Aghajanian, 1959; Mahler & Humoller, 1959) but the effects of LSD on mating (Gillett, 1960) and escape behavior (Hamilton, 1960) do not show tolerance at comparable doses. In goats, cyclicity in the pattern of tolerance to high and sustained doses of LSD has been reported (Koella et al., 1964).

Acute tolerance occurs when three injections of 0.13 mg LSD/kg are given to rats in a single day (Freedman et al., 1964b) and long-term tolerance, a decrement in amount of LSD-induced disruption of key-pecking over a 10 month period has recently been demonstrated in birds (Becker et al., 1967).

In the rat, cross-tolerance among various hallucinogens can be observed on tasks which show tolerance (Freedman & Aghajanian, 1959; Appel & Freedman, 1965) with results which are almost identical to those seen in man (Abramson et al., 1958; Balestrieri, 1959; Isbell et al., 1955, 1956, 1959, 1961; Rosenberg et al., 1963, 1964). That is, when a subject is made tolerant to a drug like LSD it is also tolerant to appropriate doses of chemically or pharmacologically related compounds (e.g. psilocybin and mescaline), but not to stimulants such as amphetamine (Isbell et al., 1962).

Many drugs have been said to diminish the action of LSD in man including monoamine oxidase (MAO) inhibitors such as isocarboxazide and nialamide (Grof & Dytrych, 1965; Resnick et al., 1964) and serotonin (Pare & LaBrosse, 1962). In the rat, however, the only compounds that seem to block or diminish the action of LSD other than psychoactive congeners of LSD (above) are a minute (0.03 mg/kg) dose of chlorpromazine (Appel & Freedman, 1964; Ray & Marrazzi, 1961) and certain steroids (Bergen et al., 1960). Pre-treatment with agents like reserpine and tetrabenazine, which deplete the endogenous amines nor-epinephrine (NE) and serotonin (5–HT), enhance sensitivity to LSD in both man (Freedman, 1961, 1963; Resnick et al., 1965) and rat (Appel & Freedman, 1964). Parachlorophenylalanine (PCPA), a specific 5–HT depleting agent, has similar effects (Appel, Lovell & Freedman, unpublished data).

Summary and Conclusions

While there are still many questions about the nature and extent of behavioral effects in animals of drugs which are "psychotomimetic" in man, it is nevertheless possible to delineate a number of reasonably well-established facts:

1) These compounds affect a wide variety of unlearned (instinctual) as well as learned behaviors in just about every species to which they have been given. Thus, the drugs have some general biological significance; certainly their effects are not limited to animals capable of (verbally) reporting subjective experiences.

2) Learned behavior maintained by simple schedules of food reward (such as FR and VI) or by other kinds of positive reinforcement (such as electrical stimulation of the lateral hypothalamus) is generally depressed by low doses of LSD and related compounds (about 0.04 mg/kg in the rat); the nature and extent of this depression is determined both by pharmacological and behavioral variables.

3) The relative potencies of "psychotomimetic" drugs is the same in animals such as the rat and man; LSD is by far the most potent compound followed by such drugs as psilocybin and psilocin; mescaline is the least potent well-known "hallucinogen" thus far tested. Among mescaline derivatives, relative potency seems to be related to occupation of the 3,4,5 and 6 carbon atoms.

4) There may well be more than one "effect" of a single injection of a "psychotomimetic" drug in animals as well as in man and the particular changes in behavior an experimenter obtains will therefore depend upon how long after drug administration he happens to measure them.

5) The effects of "psychotomimetic" drugs on appetitive classical (Pavlovian) conditioning are unknown; but Pavlovian defense conditioning is affected in such a manner that the animal reacts to the CS while under the influence of mescaline and some of its derivatives as if it were the US—usually with increased "excitement" and other forms of autonomic activity. Since these compounds usually, but not always, inhibit instrumental behavior, drug effects may be dependent on the kind of learning being measured (Pavlovian or operant).

6) While instrumental avoidance (CAR) and, to a lesser extent, escape behavior is sometimes disrupted by "psychotomimetic" drugs, particularly during ac-

quisition and extinction, the doses necessary to induce *reliable* effects on well-learned patterns of aversively conditioned behavior are exceedingly high (at least 1.0 mg LSD/kg in the rat). This distinguishes the compounds we have been discussing from (1) stimulants like d-amphetamine which generally increase the amount of activity in avoidance situations (2), general "depressants" such as pentobarbital which normally depress both escape and avoidance behavior and (3), "tranquilizers" such as chlorpromazine which selectively depresses the CAR. In punishment or approach-avoidance situations, "psychotomimetics" have more effect on approach or positively motivated elements of the situation while tranquilizers have more effect on the avoidance or "fear" motivated elements.

Finally 7), low doses of drugs such as LSD (0.005 mg/kg in the cat) increase level of physiological arousal or alertness and decrease the ability of an animal to habituate to environmental stimuli which once were, but no longer are, relevant. Behaviorally, increases in amount of generalization to auditory, visual and other kinds of environmental stimuli and what may be described as "enhanced sensory impact" occur. Increased arousal and generalization may induce changes in an animal's ability to discriminate events in its environment but whether such changes take the form of increased or diminished accuracy of perception is multi-determined (e.g. dose, time since the drug is given, and the nature of the task are extremely important).

At the end of the last decade, J. M. Fuster wrote: "The experimental effects of psychotomimetic substances on animal behavior, other than human, are usually either disregarded or unsatisfactorily disclosed, particularly because of the lack of sensitive objective and quantitative methods to carry out their observation (Fuster, 1959)." I do not think this is still true.

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