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Studying the Behavioral Effects of Drugs in Group-Living Nonhuman Primates

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INTRODUCTION

Studies of the behavioral effects of drugs traditionally have emphasized isolated animal preparations. Such an approach has provided orderly, systematic data, and experiments with individual animals in isolation have been quite useful in characterizing drugs with respect to their behavioral effects and in predicting the effects of drugs on human behavior. In recent years, highly sophisticated techniques have also evolved for studying and quantitating the behavior of animals living together in groups normally characteristic of species in the wild. Through careful application of ethological techniques, one can now describe and quantitate drug-induced changes in behavior in group-living nonhuman primates. The availability of techniques for studying the behavior of nonhuman primates living in groups under seminatural conditions offers an alternative paradigm for studying the behavioral effects of drugs that can enhance our understanding of drug effects on human and animal behavior and permit an assessment of the generality of effects observed in experiments with individual animals. Moreover, the dynamic network of relationships characteristic of primate societies can be of substantial value in revealing the effects of drugs that may be less readily identifiable or measurable in isolated, individual subjects. Group-living nonhuman primates display a wide range of complex behaviors, many of which involve dynamic interactions with other members of the group. Studying the behavior of group-living nonhuman primates to determine the effects of drugs that act on the central nervous system is especially appropriate, therefore, because of parallels between human and nonhuman primates and some types of group or social behaviors (Raleigh and McGuire, 1980; Sassenrath and Chapman, 1976). Furthermore, the extent to which drug-induced behavioral changes may be influenced by group dynamics can be ascertained (see McGuire et al., 1982, for a complete discussion of some of the strengths and weaknesses of this approach). van Hooff (1972:4.10) has noted:

> An approach which compares the different effects of various pharmacological influences on a broad spectrum of natural responses appears to offer the best guarantee against premature and simplistic generalizations. . . . The benefits to interdisciplinary contacts will clearly be mutual, since pharmacological procedures may also be a valuable tool in unraveling the organization of behavior.

A number of investigators have undertaken research to determine the effects of drugs in groups of primates, and the results of several studies are summarized in Table I. The studies demonstrate that the behavior of group-living nonhuman primates can be of value in revealing experimentally induced alterations of behavior mediated via the central nervous system. Furthermore, the studies indicate that the type of response to a drug may vary with the context or social setting, and that specific drugs can differentially affect various behaviors exhibited in the social setting. These factors substantiate our view that it is desirable and advantageous to study drug effects in nonhuman primates living in relatively natural groups because of the more direct relevance to the use of drugs in human societies.

As can be seen, however, the studies summarized typically have not utilized groups that approximate those found in natural settings (cf. Burgess et al., 1980; Crowley et al., 1974) nor, with minor exceptions (Burgess et al., 1980; Raleigh and McGuire, 1980), with groups housed outdoors, although some chronic administrations have taken place in large social groups (Sassenrath and Chapman, 1976). The research paradigm that we have developed is based upon a study group that approximates the typical "macaque-like" pattern of social organization, with the group consisting of multiple adult males, adult females, and young of various ages, and with all members housed outdoors in a semi-free-ranging environment.

METHODOLOGICAL CONSIDERATIONS

Stumptail macaques (*Macaca arctoides*) (Fooden, 1967, 1976) were chosen as subjects for our studies for several reasons: 1) This species reproduces well in captivity and does not exhibit seasonal mating; i.e., there is little change in the reproductive behavior of the group during a 12-month period (Trollope, 1978; Trollope and Blurton Jones, 1970, 1975). Although some have suggested the presence of birth peaks (Estrada and Estrada, 1976, 1981), stumptail macaques maintain a relatively constant pattern of mating behavior

during the year and do not conform to the well-defined seasonal pattern characteristic of many macaques. 2) Stumptail macaques exhibit a well-organized dominance hierarchy that remains relatively stable over time (Bernstein, 1980; Bernstein and Guilloud, 1965; Boelkins, 1967; Gouzoules, 1975; Rhine, 1972, 1973; Rhine and Kronenwetter, 1972; Weisbard and Goy, 1976). 3) The behavioral repertoire of stumptail macaques living in heterogeneous groups has been studied extensively and is well documented (e.g., Bertrand, 1969; Blurton Jones and Trollope, 1968; Chevalier-Skolnikoff, 1974). The behavioral classifications that have been developed are quite appropriate to the study of drug effects. 4) Stumptail macaques have been used successfully in previous psychopharmacological research and a good foundation of basic information is available (e.g., Bellarosa et al., 1980; Evans, 1975; Lovell et al., 1980; Schlemmer, 1977; Wilson et al., 1977a,b).

Our study group consists of 39 animals, varying in age from newborn to old adult (Table II), and approximates what one would expect in a natural group in the wild (Bertrand, 1969). In the experiments to be described, adult males, weighing between 14.1 and 22.6 kg and ranging in age from 5 to 11.5 years, were selected as subjects to receive drug treatments. To avoid confounding influences due to age, only fully adult males (i.e., animals with fully developed canines, temporal musculature and body mass, and sexual maturity) were used. The males were distributed in rank throughout the dominance hierarchy of the group and included the highest-ranking and the lowest-ranking monkeys in the group.

The group of 39 animals is housed in a 28.4 × 32.7 m outdoor enclosure at the Yerkes Regional Primate Research Center Field Station near Lawrenceville, Georgia (Fig. 1). Positioned along one side of the chain link enclosure is (1) a 4.4 × 12.2 m animal housing unit and (2) an animal capture and isolation unit (Smith, 1981). Easy access to the animals is accomplished by previously entraining the daily movement of the subjects into the capture unit. Experimental animals now enter the capture/isolation unit whenever the door leading into the unit from the outdoor animal enclosure is opened (see Smith, 1981, for details). The capture/isolation unit was designed and fabricated so as to ensure that animals could be manipulated easily and a drug injection protocol could be instituted. Located adjacent to the animal enclosure, the unit consists of a series of tunnels linked together with sliding doors that terminate in a small animal cage with an opening through which the animal can extend an arm for an injection (Fig. 2). The unit is connected to the animal enclosure by two openings so that the animal's path is unidirectional. Target animals—i.e., those to receive drug treatment—receive training via operant conditioning techniques so they will present an arm without

coercion and voluntarily accept intramuscular injection in the manner described by Byrd (1973, 1977). Following training, target animals readily accept saline or drug injections on a regular basis without the use of force or aversive stimulation. The ability to ensure regular access to animals in a group without the use of physical force or stress is an important dimension of our research.

During the course of a study, all animals are restricted to the outdoor enclosure on a prescribed daily schedule, weather permitting. While in the outdoor compound, each member of the group can be observed from a tower located 4.27 m above one side of the enclosure (Fig. 3). Data characterizing the behavior of individual animals are collected and stored in a digital format using a commercially available, microprocessor-based data collection device, the Datamyte 900* (Smith and Begeman, 1980). Upon completion of each data collection period, the data are transferred to a PDP 11/23 computer for permanent storage and for data processing. The Datamyte and similar digital encoding devices have revolutionized observational studies by making it possible to record data almost as fast as the behavior occurs or is observed, to record data without having to interrupt direct observation of the experimental subject, and to record data in a format that is compatible with a wide variety of computers so that the observational data can be dumped or transferred directly without an intervening treatment or transformation.

In our studies, subjects are typically observed and data recorded during 15-minute test periods at preselected post-injection times using the focal-animal technique described by Altmann (1974). The focal-animal sampling technique is particularly appropriate for this type of study since it is designed to record all occurrences of behavioral actions and interactions of a specific monkey during each sampling period. A complete chronological record of the focal animal's actions is obtained as well as the actions directed toward him by others. For example, a focal-animal sample on animal A provides a record of interactions where A is either the initiator or recipient of the behavior. This means that during A's observation periods and B's observation periods, all interactions between A and B are recorded; data from either observation period or both may be used to estimate rates of interaction. An illustrative example of the data format and the information comprising each entry are shown in Fig. 4.

*The Datamyte Model 900 is manufactured by Electro/General Corporation, 14960 Minnetonka Industrial Road, Minnetonka, MN 55343.

TABLE I. Reports of Studies of Drug Effects in Groups of Nonhuman Primates

Drug	Species	Group size	Reference	Comments
Sedative-hypnotics				
Ethanol	*Macaca mulatta*	4 adult males	Peretti and Lewis (1969)	Dramatic changes in aggressive behavior in lowest-ranking animal. Lowest-ranking animal exhibited the highest mean daily ethanol consumption. Dominance hierarchy reorganized ($\bar{X}$ daily intake/animal = 19.41 cc).
Ethanol	*M. mulatta*		Cressman and Cadell (1971)	Produced significant increase in play behavior.
Ethanol	*M. mulatta*	2 groups: 3 infant males; 3 infant males and 1 infant female	Kraemer et al. (1981)	Peer separation paradigm; decreased separation-induced despair at low doses, but at high doses alcohol exacerbated the despair response as compared to placebo (1–3 g/kg/day) for three 4-week periods.
Ethanol	*M. nemestrina*	30 individuals	Crowley et al. (1974)	Five males as subjects–produced ataxia without motor slowing, regressive play-fighting typical of juveniles, and substantial increase in ratio of heterosexual-to-autosexual behaviors (0.5–2.0 ml/kg).
Pentobarbital sodium	*M. nemestrina*	30 individuals	Crowley et al. (1974)	Five males as subjects–reduced submissive behaviors and increased dominance-to-submission ratio (0.25–1.0 mg/kg).
Methaqualone	*M. mulatta*	2 males, 6 females	Claus et al. (1980)	Two males and one mid-ranking female drugged. Increase in affiliative acts. Males engaged in previously unrecorded sexual behavior. Female increased in aggressive behavior (10 mg/kg).
Methaqualone	*M. mulatta*	1 male, 2 females	Claus et al. (1981)	Simultaneous administration to all subjects. Five separate experiments. Increase in affiliative behavior from experiment to experiment (10 mg/kg).
Diazepam	*M. mulatta*	4 juveniles	Grove et al. (1977)	Increased proportion of food obtained by submissive animals in both tests between pairs of animals and when drugs were administered to all group members. Similar effects were noted when only the dominant animal of the pair was tested (2.5 mg/kg).
Diazepam	*M. mulatta*	2 males, 2 females	Lovell et al. (1980)	Similar to Lovell et al. (1980) with *d*-amphetamine (2.5 mg/kg).

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TABLE I. Reports of Studies of Drug Effects in Groups of Nonhuman Primates (continued)

Drug	Species	Group size	Reference	Comments
Stimulants				
Cocaine	*Saimiri sciureus*	4 groups: 6–9 animals per group	Miczek and Yoshimura (1982)	Increased rate, but not duration, of locomotion; increased frequency of stationary posture; reduced incidence of sitting; head-checking increased. Antagonist results similar to those for *d*-amphetamine (10 mg/kg).
Amphetamine	*M. mulatta*	6 juvenile males	Miller et al. (1973)	Increased frequency of social interactions (0.25 mg/kg).
d-Amphetamine	*Callithrix jacchus*	6 adolescents	Scraggs and Ridley (1978)	Dose-dependent increase in small head movements (checking), an almost total suppression of other activities including eating, grooming, playing, object manipulation and social interaction, but little change in amount of movement (2–8 mg/kg).
d-Amphetamine	*C. jacchus*	6 adolescents	Scraggs and Ridley (1979)	Results similar to Scraggs and Ridley (1978). Found head-checking is blocked in a dose-dependent manner by haloperidol, but not by propranolol, aceperone, or diazepam (*d*-amphetamine: 4.0 mg/kg; haloperidol: 0.03–0.18 mg/kg).
d-Amphetamine	*C. jacchus*	6 adolescents	Baker and Ridley (1979)	Chronic administration in increasing doses over 27 days. Head-checking increased, locomotion declined, social contact was reduced, and inactivity increased. Administration of haloperidol (0.01 mg/kg) was given in combination. Destructive self-grooming was eliminated (*d*-amphetamine: 4.0 mg/kg; haloperidol: 0.01 mg/kg).
d-Amphetamine	*Cercopithecus aethiops*	3 male-female pairs	Kjellberg and Randrup (1972)	Reduction in grooming, sexual behavior, and vocalization (0.05–0.37 mg/kg).
d-Amphetamine	*C. aethiops*	1 male, 2 females	Schiørring (1972)	Observed stereotyped self-grooming, "staring" into space, decrease in sexual behavior, and a change in the rank order of the females (0.1–0.15 mg/kg).
d-Amphetamine	*C. aethiops*	3 groups: 1 male and 2 females each	Schiørring (1977)	Disrupted total social interactions. Stereotyped mutual grooming. Rank order changes between females under treatment (0.2 mg/kg).

d-Amphetamine	*C. aethiops*	3 groups of 3 individuals: 1 adult male; 2 adult females	Schiørring (1979)	Disruption of normal social patterns; grooming relations significantly altered. Rank reversal between two females in one of the three groups. Increased stereotyped behavior, social isolation, and long periods of visual fixation noted in all groups. Normal social interaction disrupted at even low doses (0.1–0.7 mg/kg).
d-Amphetamine	*C. aethiops*	2 mother-infant pairs	Schiørring and Hecht (1979)	Individual variability noted but general disruption of normal social contact. Mothers did not engage in ventro-ventral contact with infants nor respond to infant distress calls. Administration to the infants resulted in general disruption of interactions with mother and abolition of distress calling (0.1–0.2 mg/kg).
d-Amphetamine	*S. sciureus*	2 groups: 8 adult males; 4 adult males	Poignant and Avril (1978)	Administered to one or two animals in two groups. Reduced levels of social interaction, increase in number of solitary behaviors (locomotion, self-grooming, feeding, drinking) (0.6 mg/kg p.o.).
d-Amphetamine	*S. sciureus*	4 groups: 6–9 animals per group	Miczek et al. (1981)	Experiment I: Nine adult males used; decreased affiliative responses to familiar group members; decreased attack and threat toward intruding conspecifics; increased frequency of stereotyped movements (3 × 0.5 mg/kg over 24 hr). Experiment II: Six juvenile animals used; increased time spent away from mother when no unfamiliar male was present (0.3–1.0 mg/kg).
d-Amphetamine	*S. sciureus*	4 groups: 6–9 animals per group	Miczek and Yoshimura (1982)	Amphetamine administered three times in 24-hr period, then chlorpromazine, haloperidol, physostigmine, or vehicle. Increased rate, but not duration, of locomotion; increased frequency of stationary posture; reduced sitting posture; increased head-checking movements. Increase in locomotor frequency antagonized by chlorpromazine, haloperidol, and physostigmine. Chlorpromazine and physostigmine increased duration of locomotion. All antipsychotics increased duration of stationary posture (amphetamine: 1.0 mg/kg; chlorpromazine:0.25–1.0 mg/kg; haloperidol: 0.25–0.50 mg/kg; physostigmine: 0.04–0.08 mg/kg).
d-Amphetamine	*M. mulatta*	3 males, 3 females	Bellarosa et al. (1980)	Increased vocalization, self-grooming, play, social grooming, and aggression (low doses). Higher doses decreased most forms of social interaction. Increased food-getting behavior in subordinate animals when entire group was drugged (0.125–2.0 mg/kg).
d-Amphetamine	*M. mulatta*	2 groups: 3 males, 6 females	Haber (1979)	Increase in submission from low-ranking animals; increase in aggression from high-ranking animals. Increase in percent time spent in proximity to close associates (1.5–2.0 mg).

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TABLE I. Reports of Studies of Drug Effects in Groups of Nonhuman Primates (continued)

Drug	Species	Group size	Reference	Comments
d-Amphetamine	*M. mulatta*	2 groups: 3 males, 6 females	Haber et al. (1977)	Similar results to Haber (1979).
d-Amphetamine	*M. mulatta*	2 groups: 3 males, 6 females	Haber et al. (1979)	Similar results to Haber (1979).
d-Amphetamine	*M. mulatta*	2 males, 2 females	Lovell et al. (1980)	Low-ranking animals were able to obtain preferred food items when higher-ranking subjects were drugged (0.125–2.0 mg/kg).
d-Amphetamine	*M. mulatta*	2 groups: 22–24 individuals	Burgess et al. (1980)	Significant decrease was observed in nearest neighbor distance and increase in percent touching. Drugged three males (2.0 mg/kg).
d-Amphetamine	*M. mulatta*	4 juveniles	Grove et al. (1977)	Effects on food competition in paired animals. Extensive food capture by least dominant animal when either both subjects were drugged or when only the dominant animal was drugged. When administered to the entire group, submissive animals obtained all food. Dominance status of subjects influenced drug effect (0.5 mg/kg).
d-Amphetamine	*M. mulatta*	14 animals: 3 male-male pairs; 3 female-female pairs; 1 male-female pair	Thierry et al. (1981)	Simultaneous injection to both members of each pair. Significant reduction in social interaction (0.2 mg/kg).
d-Amphetamine	*M. mulatta*	8 juvenile males	Miller (1976)	Acute administration to one individual at a time. Affiliative behavior abolished under treatment; agonistic behavior increased 2.5 times (1.0 mg/kg).
d-Amphetamine	*M. arctoides*	3 males, 3 females	Nail et al. (1980)	Similar results to Lovell et al. (1980) (0.07–1.0 mg/kg).
d-Amphetamine	*M. arctoides*	2 males, 1 female	Miller and Geiger (1976)	Produced decreased social interaction in all subjects. Social grooming was decreased in all subjects; self-grooming and stereotypic behavior increased. Haloperidol blocked stereotypic effects (*d*-amphetamine: 1.0–4.0 mg/kg; haloperidol: 0.7–0.14 mg/kg).

d-Amphetamine	*M. arctoides*		Schlemmer et al. (1980a)	Produced decreases in social grooming, although increased overall activity.
d-Amphetamine	*M. arctoides*	3 males, 3 females	Wilson et al. (1977a)	Administered individually; produced significant decreases in social grooming, playing, and feeding. Increased frequency of sexual presentation in both males and females; frequency of mounting not affected (0.125–2.0 mg/kg).
d-Amphetamine	*M. arctoides*	3 males, 3 females	Wilson et al. (1977b)	Administered to all group members; decreases in frequency of play and feeding, while frequency of sexual presentation and vocalization increased; mounting did not increase. Dominance hierarchy affected (0.125–2.0 mg/kg).
d-Amphetamine	*M. arctoides*	3 males, 3 females	Wilson et al. (1981)	Concurrent administration to all group members for 12 days. Reduction in investigatory and fleeing behaviors and in social proximity, and elimination of social grooming. Agonistic interactions increased as duration of the study increased (1.0 mg/kg).
d-Amphetamine	*M. arctoides*	6 groups: 4–6 animals per group	Schlemmer and Davis (1981a)	Two females treated for 12 days. Treatment increased stereotyped behavior, social withdrawal, scratching, hyperactivity, checking, and initiation of submissive behaviors. Rank differences may have influenced expression. Haloperidol and pimozide antagonized increase in submissive gestures (*d*-amphetamine: 3.2 mg/kg/day; haloperidol:0.57 mg/kg; pimozide: 0.50 mg/kg).
d-Amphetamine	*M. arctoides*	1 male, 4 females	Schlemmer and Davis (1981b)	See Schlemmer and Davis (1981a).
l-Amphetamine	*C. jacchus*	6 adolescents	Scraggs and Ridley (1978)	Similar results to *d*-amphetamine (Scraggs and Ridley, 1978) (4–12 mg/kg).
Meth-amphetamine	*M. nemestrina*	30 individuals	Crowley et al. (1974)	Five males as subjects—decreased dominance-to-submission ratio; produced hyperactivity, stereotypies, and social unresponsiveness (0.0625–0.5 mg/kg).
Meth-amphetamine	*M. fuscata*	7–9 4-year-old males	Machiyama et al. (1970)	Administered to pairs of subjects. Increased behavioral activity of highest-ranking animal; decreased activity of lowest-ranking animal (1 mg/kg).
Diethyl-propion	*M. arctoides*	3 males, 3 females	Bedford et al. (1977)	See Bellarosa et al. (1980) for *d*-amphetamine.

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TABLE I. Reports of Studies of Drug Effects in Groups of Nonhuman Primates (continued)

Drug	Species	Group size	Reference	Comments
Fenfluramine	*M. arctoides*	3 males, 3 females	Bedford et al. (1977)	Produced anorexia and increase in sexual presentation; presentations were homosexual rather than heterosexual. Masturbation increased in frequency among males. Drug effects may depend on subject's status in dominance hierarchy (1–10 mg/kg).
Methyl-phenidate	*M. arctoides*	3 males, 3 females	Bedford et al. (1977)	Similar effects to that reported for *d*-amphetamine (Wilson et al., 1977a). Produced decrease in grooming and feeding, increase in frequency of sexual presentation (1.0–5.0 mg/kg).
Opiates and antagonists				
Morphine	*S. sciureus*	4 groups: 6–9 animals per group	Miczek et al. (1981)	See results for *d*-amphetamine for details. Juveniles treated with morphine increased time near mother both in and out of presence of unfamiliar male in test situation (0.5–2.0 mg/kg).
Morphine	*M. nemestrina*	30 individuals	Crowley et al. (1974)	Five males as subjects; blocked sexual behavior without impairing motor activity (0.05–0.4 mg/kg).
Morphine	*M. mulatta*		Ternes and Colon (1976)	Alpha male addicted while living in social group. Under treatment, aggression toward group members reduced; affiliative relations increased.
Naltrexone	*Miopithecus talapoin*	2 groups: 8 males, 10 females	Meller et al. (1980)	Treatment significantly reduced sexual behavior in two highest-ranking males. Grooming invitations increased for all males.
Naltrexone	*M. talapoin*	16 individuals: 8 pairs	Fabre-Nys et al. (1982)	Half of each pair drugged twice daily for seven days, the procedure reversed. Significant increase in grooming and grooming invitations (0.25–1.0 mg/kg).
Nalaxone	*M. talapoin*	16 individuals: 8 pairs	Fabre-Nys et al. (1982)	Similar to results for naltrexone (Fabre-Nys et al., 1982).
Antipsychotic agents				
Chlor-promazine	*M. mulatta*	6 juvenile males	Miller et al. (1973)	Decreased frequency of social interactions (0.25 mg/kg).
Chlor-promazine	*M. mulatta*	4 3½-year-old males	McKinney et al. (1980)	Daily administration for 113 weeks. Incidence of huddling increased; locomotory behavior, proximity, and social exploration decreased; aggression increased in initial phases (8–40 mg/kg).
Chlor-promazine	*M. cyclopis*	4 individuals	Hsi-Lin and Shih-Chie (1977)	Treatment reduced overall behavioral output, especially grooming and play (0.25 mg/kg/day).

Hallucinogens				
Δ^9-Tetrahydrocannabinol	*S. sciureus*	2 groups: 2–3 adult males, 3 adult females, 1 infant per group	Miczek (1978)	Introduced intruder animals into resident groups. Drug administration to intruder animals did not alter their reaction to defense, submission, and flight when confronted with nontreated attacking residents. Administration to resident animals reduced frequency of attacks in a dose-dependent manner (0.25–2.0 mg).
Δ^9-Tetrahydrocannabinol	*S. sciureus*	12 dyads	Jones (1976)	Observed drinking, social and competitive behaviors—found total competitive behaviors decreased in frequency when both members received 1.0 mg/kg, but increased when either the lesser member or both members of low competition dyads were treated with 0.25 mg/kg. Noncompetitive social behaviors increased when both animals were drugged (0.25–1.0 mg/kg).
Δ^9-Tetrahydrocannabinol	*S. sciureus*	14 dyads	Kaplan (1979)	Treated mothers from 2 weeks to 6 months after birth. Treated animals showed no differentiation in response to their infants from other infants (5.0 mg/kg).
Δ^9-Tetrahydrocannabinol	*M. mulatta*	2 groups: 22–24 individuals	Burgess et al. (1980)	Used two groups; 3–4 individuals administered simultaneously. Produced decreases in distance between all animals, decreases in nearest neighbor distance, and an index of clumping increased significantly (4 mg/kg).
Δ^9-Tetrahydrocannabinol	*M. mulatta*		Hooley et al. (1979)	Effects different for high- vs. low-ranking subgroups.
Δ^9-Tetrahydrocannabinol	*M. mulatta, M. fascicularis*	8 groups: 3–6 individuals per group	Sassenrath and Chapman (1975)	One subject in each group drugged. Subjects displayed less aggression toward cagemates; however, they were threatened and attacked more frequently by cagemates. Decreased frequency of grooming and play (2.4 mg/kg p.o.).
Δ^9-Tetrahydrocannabinol	*M. mulatta, M. fascicularis*	8 groups: 3–6 individuals per group	Sassenrath and Chapman (1976).	See Sassenrath and Chapman (1975).
Δ^9-Tetrahydrocannabinol	*M. mulatta, M. fascicularis*	6 groups: 3–4 individuals per group	Chapman et al. (1979)	In a long-term chronic study, relative effects predominated for the first 2–3 months. Acute effects diminished, aggressiveness increased, and low-ranking animals began to rise in dominance hierarchy (2.4 mg/kg).

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TABLE I. Reports of Studies of Drug Effects in Groups of Nonhuman Primates (continued)

Drug	Species	Group size	Reference	Comments
Δ^9-Tetrahydro-cannabinol	*M. mulatta*	5 mother-infant dyads	Golub et al. (1981)	Treated mothers chronically through gestation and nursing. Maternal rejection behaviors in treated mothers were initiated earlier than in controls, while infant-initiated maternal approach increased in treated subjects (2.4 mg/kg).
5-Methoxy N,N-di-methyl-tryptamine	*M. arctoides*	4 individuals	Schlemmer et al. (1977)	Administered to 2 of 4 group members. Found dose-dependent induction of abnormal behaviors and attenuation of normal affiliative behavior. Induced doglike "wet shakes," involuntary limb jerks, stereotyped behavior, and hypervigilance. Dose-dependent decreases in social grooming, submissive behavior, and initiated social activity were noted (5–250 μg/kg).
5-Methoxy-N,N-di-methyl-tryptamine	*M. arctoides*	3 groups: 4–5 individuals per group	Schlemmer and Davis (1981a)	Administered once per day for 5 consecutive days. Observed increase in submissive behavior without increase in aggressive behavior received. Methiothepin, haloperidol, and trifluoperazine antagonized increase in submissive behavior (5-MeODMT: 0.25 mg/kg; methiothepin: 0.15 mg/kg; haloperidol: 0.2 mg/kg; trifluoperazine: 0.04 mg/kg).
5-Methoxy N,N-di-methyl-tryptamine and 3 serotonin antagonists (cinanserin, methiothepin, and metergoline)	*M. arctoides*	2 groups: 4–5 individuals	Schlemmer et al. (1979)	All decreased drug-induced limb jerks and body shakes to baseline level. None antagonized the decreased social grooming, and only methiothepin antagonized the increased submissive behavior (0.003–5.0 mg/kg).
N,N-dimethyl-tryptamine	*Pan troglodytes*	2 groups: 4 individuals per group	Brower and Siegel (1977)	Found dose-dependent increase in locomotion and decrease in social interactions. Subjects did not exhibit the high levels of bizarre behavior sometimes associated with hallucinogens (0.5–4.0 mg/kg).

Other				
Alpha-methyl-para-tyrosine	*M. arctoides*	1 adult male, 4 adult females	Redmond et al. (1971a)	Two females treated for 6 and 7 weeks, respectively. Treated animals initiated fewer social interactions, social and self-grooming decreased, and one female decreased in rank under treatment (160–250 mg/kg).
Alpha-methyl-para-tyrosine	*M. arctoides*	1 adult male, 4 adult females	Redmond et al. (1971b)	See results in Redmond et al. (1971a) above.
Phencyclidine	*M. mulatta*	6 juvenile males	Miller et al. (1973)	Decreased frequency of social interactions. Increased aggression by untreated subjects toward treated subjects (0.25 mg/kg).
Phencyclidine	*M. arctoides*	1 adult male, 4 adult females	Schlemmer et al. (1978)	Four adult females treated. Two different doses (0.025 and 0.5 mg/kg) were studied for 21 days, while a dose of 1.0 mg/kg was studied for 14 consecutive days. Stereotyped behavior was induced in all animals at all doses. Pimozide (0.1 mg/kg) was found to completely antagonize the induced stereotyped behavior.
6-Hydroxydopamine	*M. mulatta*	2 groups: 35 individuals per group	Redmond et al. (1973)	Six adult females and two adult males were used (four were treated). Subjects were treated with 30 mg/kg over 4 days and released. One treated female was found in another social group. Treated animals were attacked when they returned to their group; treated animals initiated fewer threats and attacks, and engaged in less social and self-grooming than controls. Treated male eventually became peripheral to his social group.
Parachlorophenylalanine	*C. aethiops*		Raleigh and McGuire (1980)	Social group. Chronic treatment (14 days) produced irritable, aggressive, and hypermobile animals. Treatment of alpha males resulted in significant reduction in grooming among nontreated subjects. Low-ranking males did not exhibit similar changes (80 mg/kg/day).
Tryptophan	*C. aethiops*		Raleigh and McGuire (1980)	Daily administration for 14 days in males resulted in increased approaching, grooming, resting, and eating, and decreased locomotory, solitary, vigilance, and avoidance behaviors (20 mg/kg/day).
Apomorphine	*M. arctoides*	1 male, 3 females	Schlemmer et al. (1980b)	Significant dose-dependent increases in vigilance behavior, submissive behavior, and vocalizations were found. Grooming was eliminated at all dose levels (0.05–3.0 mg/kg).

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TABLE I. Reports of Studies of Drug Effects in Groups of Nonhuman Primates (continued)

Drug	Species	Group size	Reference	Comments
Apomorphine	*M. arctoides*	1 male, 4 females	Schlemmer and Davis (1981a,b)	Results similar to *d*-amphetamine (see 1981a), except apomorphine significantly increased locomotion and significantly reduced self-grooming levels.
Piribedil	*S. sciureus*	2 groups: 8 adult males, 4 adult females	Poignant and Avril (1978)	Decreased social and solitary behaviors (5 mg/kg).
Amineptine	*S. sciureus*	2 groups: 8 adult males, 4 adult females	Poignant and Avril (1978)	Significantly increased solitary and social interactions (20 mg/kg p.o.).
Reserpine	*M. mulatta*	2 males, 4 females	McKinney et al. (1971)	One male and two females treated daily for 81 days. Frequency of abnormal posturing increased under drug treatment. Visual exploration decreased, huddling increased, locomotion decreased, and self-mouthing decreased. Dosage increased from 1 mg/kg to 4 mg/kg by 10th day and remained at 4 mg/kg/day for 10 weeks.
Imipramine	*M. mulatta*	2 males, 6 females	Suomi et al. (1978)	One male and two females treated in separation experiment. Treated subjects seemed less severely affected by separation than controls. Chronic treatment reduced passive self-directed behavior and increased exploration (10 mg/kg/day).
Amitriptyline	*S. sciureus*	2 groups: 8 adult males; 4 adult females	Poignant and Avril (1978)	Decreased social and solitary behaviors (5 mg/kg).

A group-scoring observational technique can also be used. This technique involves recording the number of individuals engaged in each of several molar classes of behavior (e.g., aggression, submission, affiliation, general social activity, play, sexual, and self-directed or solitary behavior) at 1-minute time intervals. Table III presents a detailed definition of these classes and their major constituent behaviors. This procedure does not allow the precision or detail of the focal-animal technique, but does allow the collection of group interaction profiles. The number of group members engaged in the molar classes of behavior gives an indication of the overall group interaction

TABLE II. Birthdates of Group Members

Males		Females	
Code	Birthdate	Code	Birthdate
06	1970	01	1961
10	2/04/70	02	4/29/66
13	9/16/72	03	1965
18	2/15/74	04	1965
24	8/11/75	05	1970
26	11/12/76	07	1970
28	12/24/76	08	1970
30	7/04/77	09	1970
33	3/04/78	11	6/06/72
35	8/05/78	12	8/28/72
37	1/22/79	15	1/01/73
38	6/12/80	16	1/22/73
39	7/09/80	17	6/18/73
41	9/05/80	19	9/19/74
42	12/13/80	20	2/20/75
45	4/17/82	21	3/06/75
46	6/01/82	22	3/18/75
49	11/22/82	23	7/13/75
		25	7/05/76
		27	12/16/76
		29	12/31/76
		31	9/09/77
		32	9/20/77
		34	3/22/78
		36	8/10/78
		40	8/11/80
		43	7/31/81
		44	1/20/82
		48	7/05/82

patterns. Hence, we can determine the effect of a drugged individual on other members of the group.

DRUG EFFECTS IN A GROUP

The availability of refined techniques for quantitating behavior, for administering drugs without disrupting ongoing behavior in a group, and for computer processing of data characterizing activities of members of a group has made it possible to study and describe relations between the behavioral effects of drugs and group dynamics. Using the methods described above, we have studied changes in behavior in a group as a consequence of drug administration. Typically, the drug is dissolved in sterile normal saline (0.9%) and injected intramuscularly in a volume of less than 1.0 ml; saline (0.9%) alone serves as a control (placebo) injection. On a given day, each of several adult male subjects will receive either a drug injection, a saline (placebo) injection, or no injection. However, only the experimental animal for that day will receive the drug. Those personnel responsible for data collection do not know whether saline or drug is administered. A drug may be administered 2 days per week, but a given animal is the experimental or drug subject no more frequently than once per week. In general, each dose (0.01–0.30 mg/kg) is studied two or three times in each subject. Immediately after injection in the capture unit, the subjects return to the compound and observations begin. The initial observation period encompasses the first hour post-injection (i.e., four periods of 15 minutes each), and one 15-minute period of observation is scheduled during each hour thereafter for several hours.

A general objective of our research is a detailed characterization of the way in which specific drugs can affect various naturally occurring behaviors exhibited by members of a group. Toward this objective, we have conducted studies to determine the behavioral effects of acutely administered *d*-amphetamine. In order to determine the time course of the behavioral effects of *d*-amphetamine in a group under the conditions of our research laboratory, doses of the drug were administered to two monkeys and changes in self-directed aggressive behavior (e.g., self-biting and hair pulling) were quantitated. Over a range of doses encompassing 1½ log units (0.01–0.30 mg/kg), *d*-amphetamine had dose-dependent effects on self-directed aggression and the resulting dose-effect curves were of an inverted U-shape; i.e., self-directed aggressive behavior increased at intermediate doses and then decreased at higher doses (Fig. 5). The time course of the enhancing effect of *d*-amphetamine was then determined using the dose that produced the maxi-

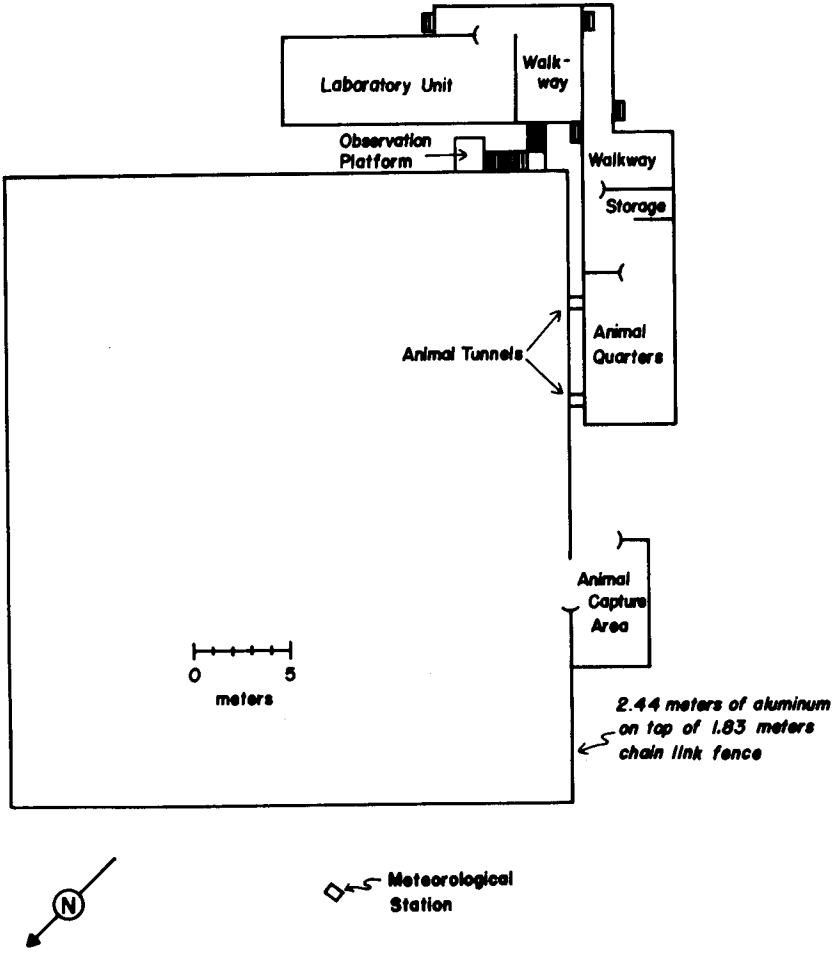

Fig. 1. Line drawing representing an aerial view of the outdoor enclosure, animal quarters, and capture/isolation unit in a group of stumptail macaques.

mum increase in self-directed aggressive behavior. After 0.1 mg/kg, self-directed aggressive behavior increased in frequency to a maximum during a period 45–105 minutes post-injection and then gradually returned to baseline levels as time since injection increased (Fig. 6). The time course of this effect was consistent with time-course data reported by others for *d*-amphetamine.

In addition to the striking effect of *d*-amphetamine in enhancing self-directed aggressive behavior, we have also obtained interesting results in experiments to study changes in affiliative and aggressive behavior as a

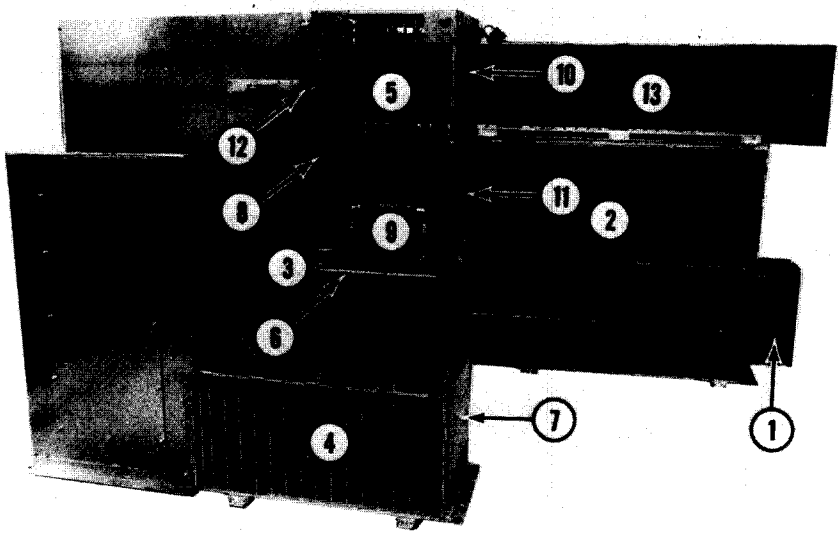

Fig. 2. Close-up view of the animal capture/isolation unit used for effecting drug administration. Specific features include (1) an entrance from the outdoor area, (2) initial holding area, (3) secondary holding area, (4) tertiary holding area, (5) isolation or restraint area, (6) removable bottom panel, (7) lower exit door, (8) restraining or squeeze accessory, (9) removable door to facilitate separation of infant from mother, (10) removable door for accessing sedated subject, (11) small opening for arm extension and drug injection, (12) sliding panel for separating the isolation/restraint area, and (13) exit tunnel to outdoor area. Reprinted by permission from Laboratory Animal Science.

consequence of *d*-amphetamine. Following the administration of a range of doses of *d*-amphetamine (0.003–0.56 mg/kg), four of five adult male subjects showed a dose-related decrease in the rate of affiliative behavior that they initiated. Doses of 0.003–0.03 mg/kg produced little effect, and higher doses (0.30–0.56 mg/kg) decreased rates in a dose-dependent manner (Fig. 7). Moreover, the initiation of affiliative behavior was affected similarly in the high-ranking and low-ranking subjects with no discernible evidence of differ-

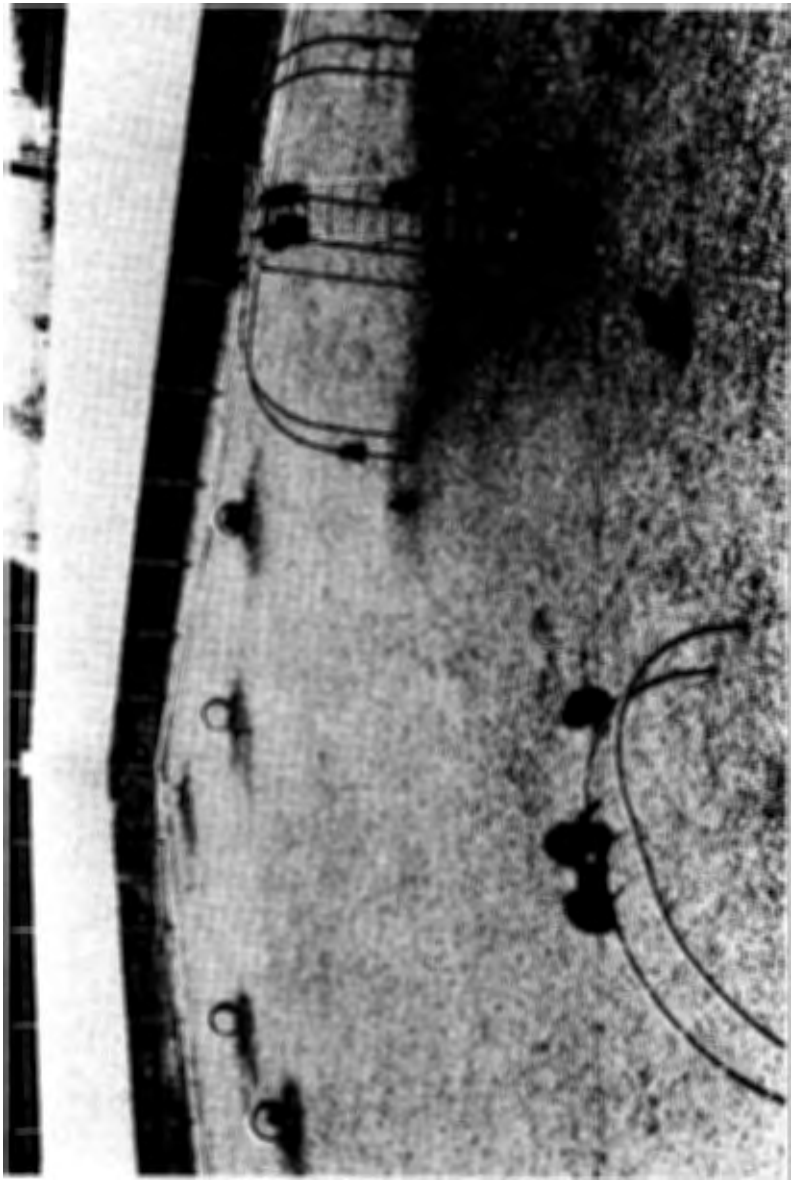

Fig. 3. View of outdoor enclosure from observation tower.

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H1092479
H202
H31170
H4001
H50800,00000,
001*19,00021,19*030,00024,045*19,00027,040*05,00033,041*05,00036
05*052,00039,128*05,00045,05*043,00047,31*086,00051,31*137,00054
045*31,00058,101*06,00066,
H1092479
H202
H31170
H4001
H50815,00000,
001*19,00007,19*030,00012,045*19,00015,040*05,00018,041*05,00021
05*052,00023,128*05,00026,05*043,00029,31*086,00032,31*137,00036
045*31,00040,101*06,00045,
```

INITIATOR	BEHAVIOR	RECEIPIENT	TIME	DATE	OBSERVER	ENVIRONMENTAL DATA	EXPERIMENTAL CONDITIONS	FOCAL ANIMAL	START TIME	BEHAVIOR CLASS	COUNTER
01	001	19	80021	092479	02	1170	0	01	0800	1	1
19	030	01	80024	092479	02	1170	0	01	0800	3	2
01	045	19	80027	092479	02	1170	0	01	0800	3	3
01	040	05	80033	092479	02	1170	0	01	0800	3	4
01	041	05	80036	092479	02	1170	0	01	0800	3	5
05	052	01	80039	092479	02	1170	0	01	0800	4	6
01	128	05	80045	092479	02	1170	0	01	0800	3	7
05	043	01	80047	092479	02	1170	0	01	0800	4	8
31	086	01	80051	092479	02	1170	0	01	0800	5	9
31	137	01	80054	092479	02	1170	0	01	0800	3	10
01	045	31	80058	092479	02	1170	0	01	0800	3	11
01	101	06	80066	092479	02	1170	0	01	0800	4	12
01	001	19	815 7	092479	02	1170	0	01	0815	1	1
19	030	01	81512	092479	02	1170	0	01	0815	3	2
01	045	19	81515	092479	02	1170	0	01	0815	3	3
01	040	05	81518	092479	02	1170	0	01	0815	3	4
01	041	05	81521	092479	02	1170	0	01	0815	3	5
05	052	01	81523	092479	02	1170	0	01	0815	4	6
01	128	05	81526	092479	02	1170	0	01	0815	3	7
05	043	01	81529	092479	02	1170	0	01	0815	4	8
31	086	01	81532	092479	02	1170	0	01	0815	5	9
31	137	01	81536	092479	02	1170	0	01	0815	3	10
01	045	31	81540	092479	02	1170	0	01	0815	3	11
01	101	06	81545	092479	02	1170	0	01	0815	4	12

Fig. 4. Format of raw data derived during focal-animal observation (top). Data from two periods of observation are preceded by the date (line 1), observer I.D. (line 2), environmental conditions (line 3), focal-animal I.D. (line 4), and time (line 5). Lines 6–8 for each set of data are digitally encoded records of behavioral actions. The edited and formatted forms of the data as they are stored in the PDP 11/23 computer are shown in the bottom half of the figure. Reprinted by permission from Behavior Research Methods and Instrumentation.

ential effect among those monkeys. The only subject in which *d*-amphetamine did not produce a pronounced decrease in rate of affiliative behavior was monkey M-06, a mid-ranking animal. In retrospect, his data suggest that doses even moderately higher than those studied would have produced a decrease in this subject.

In contrast to the monotonically depressive effect of *d*-amphetamine on affiliative behavior initiated by the adult male subjects, the drug markedly increased the rate of aggressive behavior initiated by the same monkeys. *d*-Amphetamine increased the rate of aggressive behavior initiated by the highest- and lowest-ranking monkeys and had little or no effect in the two mid-ranking subjects (Fig. 8). The largest increase in rate was observed in monkey M-13, the highest-ranking animal in the group. Rate of aggression in that monkey increased in direct relation to increases in dose, and at the

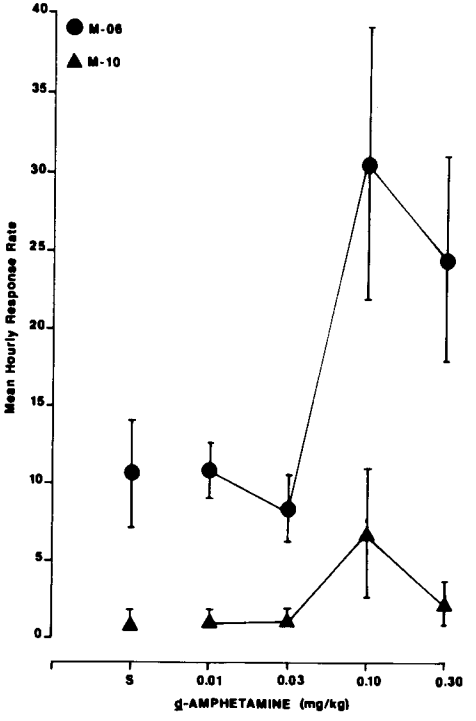

Fig. 5. Effect of *d*-amphetamine on rate of self-directed aggression in two adult male stumptail macaques. Each data point is the mean + SEM based on three administrations. Data points to the left of the dose-effect curves were obtained when saline was administered as a control.

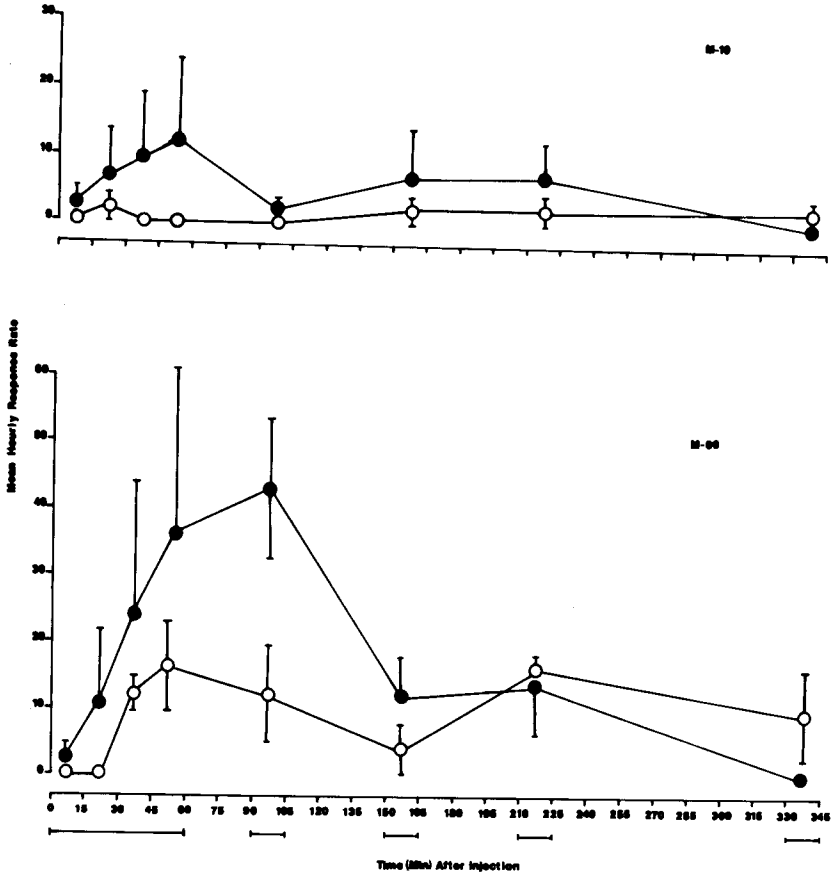

Fig. 6. Time-course effects of *d*-amphetamine (0.1 mg/kg) on self-directed aggressive behavior in monkeys M-10 (top) and M-06 (bottom). Each data point is the mean + SEM based on three administrations of the drug (solid circles) or saline (open circles).

highest dose studied (0.56 mg/kg), rate increased sixfold over the next lowest dose (0.30 mg/kg). *d*-Amphetamine also increased the rate of aggressive behavior initiated by monkeys M-18 and M-24, the two lowest-ranking adult males in the social group, with a dose of 0.003 mg/kg having no effect and a dose of 0.30 mg/kg producing decreases in rate. Intermediate doses increased rate of aggressive behavior two- to eight-fold over saline rates, and the dose-effect curves conformed to inverted U-shaped functions. There was no change in the rate of aggressive behavior over a range of doses of *d*-amphetamine (0.01–0.30 mg/kg) in monkeys M-10 and M-06, the two mid-

TABLE III. Molar Class of Behavior for Group Scan and Focal Animal Data

Molar class	Description
Aggression	Behaviors which cause actual physical injury or signal the potential for harm; also, behaviors which result in priority access to incentives.
Submission	Behaviors which are a reaction to a real or perceived possibility of bodily injury.
General social behavior	Behaviors, such as looking at another animal or moving toward or away from another, which convey no apparent specific social message and which, as a class, indicate general activity.
Affiliation	Positive association with or attempt to safeguard another.
Play	Vigorous, exaggerated but relaxed movements; structurally similar behavior seen in aggressive and submissive classes, but contact is less forceful and silent, and the roles of the interactants are frequently reversed.
Sexual behavior	Behaviors that are regularly a component of heterosexual mating; however, may be scored regardless of the reproductive potential of the participants.
Self-directed behavior	Self-maintenance behaviors, or any behavior directed to the self.

ranking subjects in the group. Their behavioral rates remained in the range of rates observed in the absence of the drug and suggested differential effects of the drug as a function of dominance position in the group.

CONCLUSIONS

The data presented here show that *d*-amphetamine can have qualitatively contrasting effects on two types of naturally occurring behavior in individual monkeys comprising part of a large, heterogeneous social group. *d*-Amphetamine decreased affiliative behavior to as little as one-third of saline control values, and the effect was dose-dependent. In contrast, comparable doses of *d*-amphetamine increased aggression in three of the subjects that exhibited marked decreases in affiliative behavior. Given the relatively uniform decrease in affiliative behavior by the subjects treated with *d*-amphetamine in the present study, it was surprising that the drug had a qualitatively dissimilar effect on aggression in the same subjects. The high- and low-ranking subjects exhibited pronounced, dose-related increases in aggressive behavior at doses that either decreased affiliation or had no effect.

These data also show that *d*-amphetamine can increase the rate of occurrence of self-directed aggressive behavior in individual monkeys living in a

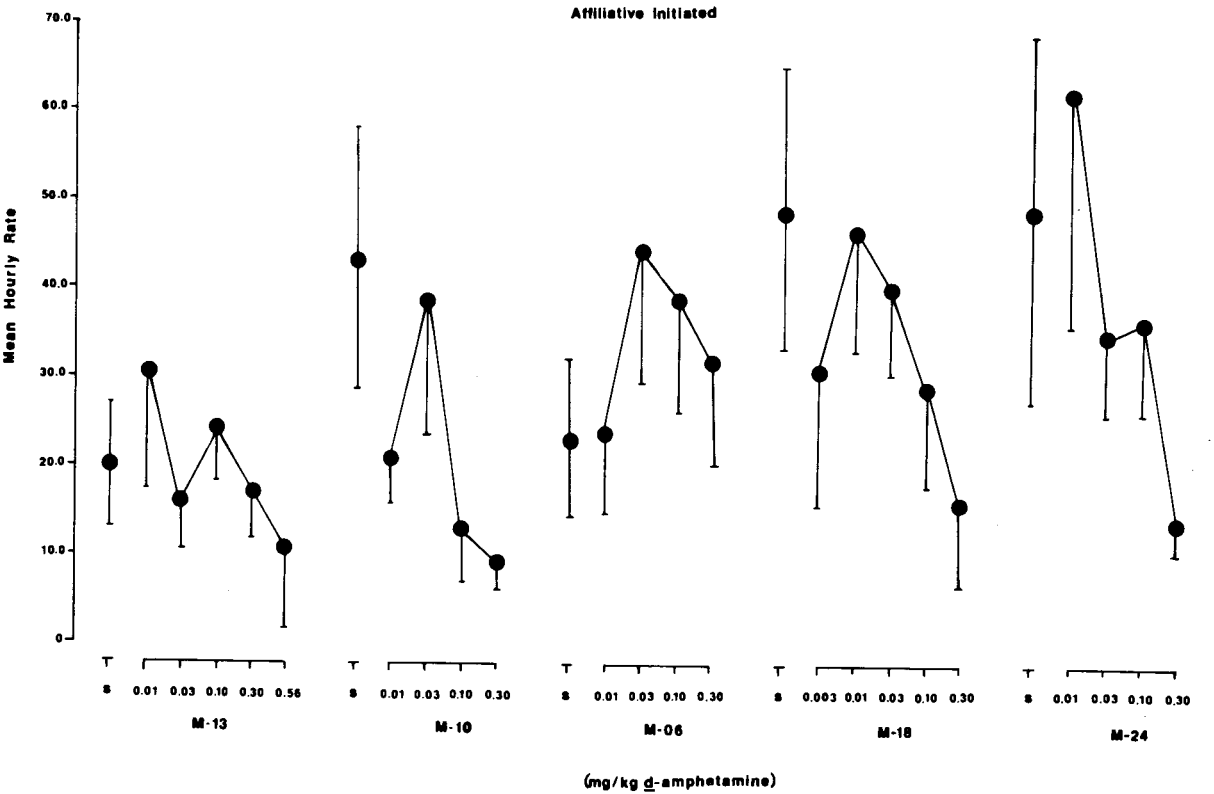

Fig. 7. Effect of *d*-amphetamine on rate of affiliative behavior initiated in five adult male stumptail macaques. Each data point is the mean + SEM based on three adminstrations (except the highest dose for monkey M-13 and the lowest dose for monkey M-18 are based on only one administration). Data ponts to the left of the dose-effect curves were obtained when saline was administered as a control.

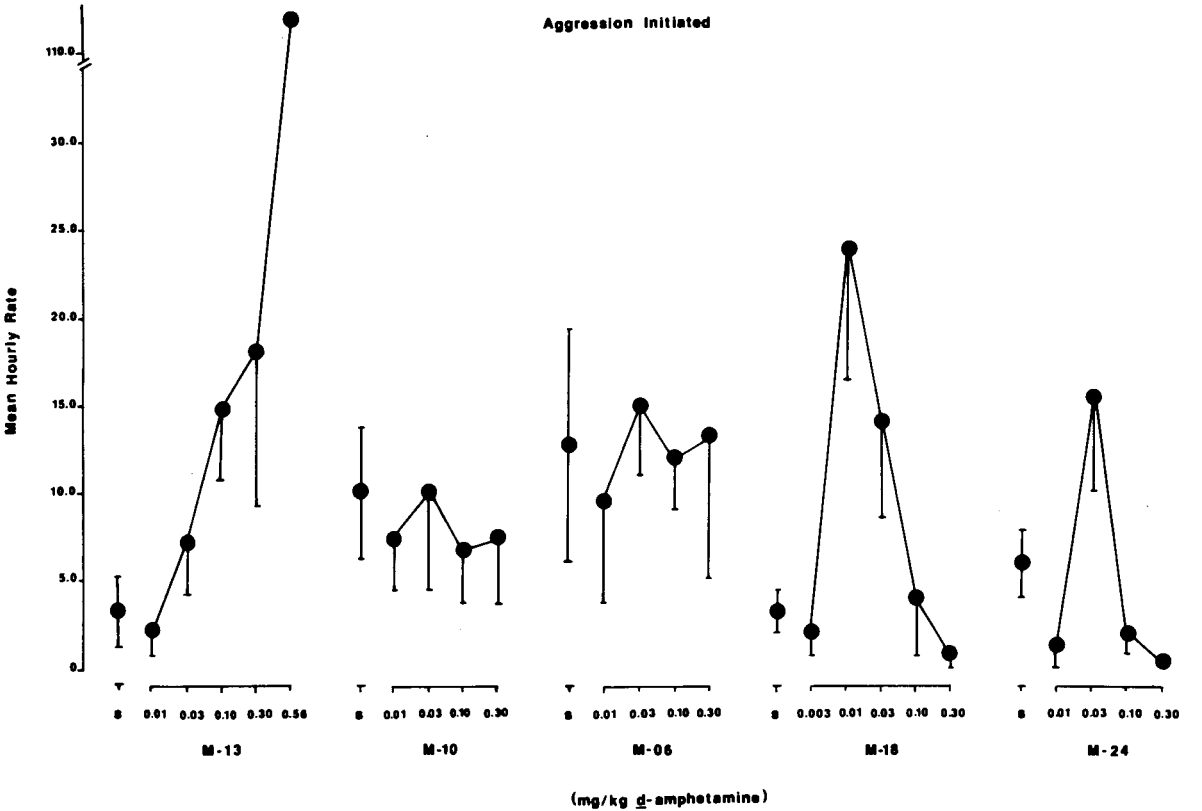

Fig. 8. Effect of *d*-amphetamine on rate of aggressive behavior initiated in five adult male stumptail macaques. Each data point is the mean + SEM based on three administrations (except the highest dose for monkey M-13 and the lowest dose for monkey M-18 are based on only one administration). Data points to the left of the dose-effect curves were obtained when saline was adminstered as a control.

large, heterogeneous social group, and that the enhancing effect is dose-dependent. The effect of *d*-amphetamine on self-directed aggression in group-living monkeys resembles the effect of *d*-amphetamine on conditioned or learned behavior in a variety of animal species. Low doses have little or no effect, higher doses result in an increase in the rate of the behavior, and still higher doses decrease or increase less the rate of the behavior (Byrd, 1973, 1981; Clark and Steele, 1966; Dews and Morse, 1958; Kelleher and Morse, 1968; McMillan, 1969). These results are also consistent with other reports of amphetamine in group-living monkeys (Bellarosa et al., 1980; Miller et al., 1973; Schlemmer, 1977; Schlemmer et al., 1980a; Scraggs and Ridley, 1978, 1979). The similarity of our results and those from laboratories in which individual animals are studied alone suggests a generality of effect of *d*-amphetamine that encompasses a wide range of behavioral conditions.

The foregoing indicates that the observation of nonhuman primates living in a group under seminatural conditions can represent a powerful paradigm for studying the behavioral effects of drugs. We have succeeded in developing a research design that allows for controlled experimentation within a stable, heterogeneous group of nonhuman primates, yet provides quantitative measures of behavior that are precise and readily amenable to a variety of analyses. More importantly, the data presented above show that a drug like *d*-amphetamine can have effects that depend qualitatively on the type of behavior under study and may depend on the social or dominance position of the subject in the group. These phenomena could not easily be studied in individual subjects removed from the group environment, and therefore these results lend credence to the value and importance of studying the behavioral effects of drugs under conditions that more closely approximate those of the human population. The research design we have described allows for closer parallels between animal experiments and the real world of human primates.

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