Pharmacology Biochemistry & Behavior, Vol. 24, pp. 1567–1572, 1986. 0091-3057/86 $3.00 + .00

The Effects of Clonidine on Food Consumption and Food Competition in Male Stumptail Macaques (*Macaca arctoides*)[1]

JENNIFER E. YOUNG, ANTHONY J. VERLANGIERI AND MARVIN C. WILSON[2]

Department of Pharmacology, School of Pharmacy, University of Mississippi, University, MS 38677

Received 15 August 1985

YOUNG, J. E., A. J. VERLANGIERI AND M. C. WILSON. *The effects of clonidine on food consumption and food competition in male stumptail macaques* (Macaca arctoides). PHARMACOL BIOCHEM BEHAV 24(6) 1567–1572, 1986.—The effects of clonidine on noncompetitive and competitive feeding were examined in three adult male stumptail macaques (*Macaca arctoides*). Noncompetitive feeding was examined when the subjects were individually-caged or group-caged. Clonidine (1.0 mg/kg) administered IM substantially increased food consumption over control values in all subjects in both housing situations. The effects of clonidine on competitive feeding behavior were evaluated in the group-caged environment. Food competition was assessed by recording the number of chows retrieved from a common food box by each subject. Food retrieval was increased in the lowest-ranking subject when clonidine was administered to all subjects. Retrieval decreased in the middle-ranking subject and was unchanged in the highest-ranking subject. Administration of clonidine to *individual* subjects did not increase food retrieval. It is concluded that since the hyperphagic property of clonidine was only apparent during noncompetitive food-getting, that other drug-behavioral interactions prevented an increase in food retrieval during competitive situations.

Clonidine *Macaca arctoides* Hyperphagia Competition Feeding Dominance

CLONIDINE is a derivative of the imidazoline family of compounds which have nasal decongestant properties. Clonidine was first synthesized in the early 1960's, and by the mid-1960's it was reported that clonidine had clinical efficacy as an antihypertensive agent [1]. Clonidine is currently used in the treatment of moderate to severe hypertension [5].

It has also been reported that clonidine is effective in treating anxiety associated with opiate withdrawal, mental depression, and phobic-panic anxiety [9]. Furthermore, there is evidence that clonidine might be useful in treating non-opiate withdrawal syndromes which are associated with anxiety, such as withdrawal resulting from cessation of chronic use of benzodiazepines, barbiturates, ethanol, and nicotine [10]. It has been suggested that clonidine may also be useful in treating eating disorders, such as anorexia nervosa [13]. It has been reported that hyperphagia resulted from clonidine administration to individually-caged [13–15] and group-caged monkeys [15]. Chronic administration of 0.1 mg/kg of clonidine significantly increased daily food consumption in individually-caged stumptail macaques [13–15]. Furthermore, in group-caged stumptail macaques, acute concurrent administration of 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg of clonidine significantly increased total food consumption in the subjects. This increase in food consumption was associated with significantly fewer episodes of social interaction [14].

The major goal of the present project was to verify the hyperphagic property of clonidine. Specifically, the purposes for undertaking this project were: (1) to confirm that clonidine induces hyperphagia in both individually-caged and group-caged monkeys; and (2) to examine whether clonidine-induced hyperphagia affects food competition behavior.

Three independent experiments were undertaken to accomplish these objectives. The purpose of Experiment I was to examine whether acute administration of clonidine would induce hyperphagia in individually-caged monkeys. Experiment II was designed to ascertain whether hyperphagia could be induced in a noncompetitive situation in group-caged monkeys following acute concurrent administration of clonidine. The effect of clonidine on food competition was examined in Experiment III.

[1]This research was supported in part by a grant from the American Health Assistance Foundation awarded to the second author, and in part by the Research Insitute of Pharmaceutical Sciences, University of Mississippi.

[2]Requests for reprints should be addressed to Marvin C. Wilson.

EXPERIMENT I: THE EFFECTS OF CLONIDINE ON FEEDING BEHAVIOR IN INDIVIDUALLY-CAGED MONKEYS

METHOD

Subjects

Three drug-naive adult male stumptail macaques *(Macaca arctoides)* weighing 6.8, 11.3, and 12.6 kg served as subjects. The subjects were continuously housed in stainless steel individual primate cages, measuring 58.1 cm (W) × 88.9 cm (H) × 65.1 cm (D). A food box was attached to the front of each cage. A water device provided water ad lib. The colony room in which the cages were located was maintained on a 12-hour light/dark schedule. Temperature was maintained at 21±2°C and humidity at 50±5%.

Clonidine Solutions

Drug dosages were calculated on the basis of the hydrochloride salt. Clonidine HCl (Boehringer-Ingelheim, Elmsford, NY) was dissolved in sterile normal saline (0.9% Sodium chloride), and administered IM at a volume of 0.1 ml/kg of body weight. The doses of clonidine tested were 0.01, 0.1, and 1.0 mg/kg. Drug solutions were prepared every 2 weeks, shielded from light, and refrigerated between use.

Procedures

Prior to examining clonidine-induced hyperphagia, a 3-week acclimation period was provided to allow the subjects to adapt to the laboratory environment. Immediately following this acclimation period, there was a 4-week baseline period. During this period the subjects were familiarized with receiving IM injections and with the feeding regimen. Throughout the baseline period and remainder of the experiment, each subject was fed 50 chows (Purina Monkey Chow, Ralston Purina Co.) of uniform shape and size (6.6±0.5 g) twice daily, Monday through Friday at 8:30 a.m. and 9:30 a.m. On Saturday and Sunday at 2:00 p.m. each subject was fed the mean number of chows which he had consumed daily during the previous 5 days. Throughout the baseline period each subject was injected IM with saline Monday through Friday 15 min before the first feeding. At the completion of the baseline period, clonidine testing began.

Experimental sessions were conducted daily, Monday through Friday. Clonidine or saline was administered on Tuesday and Friday. All subjects were injected with an identical drug dose on a given day. Each clonidine dose was administered twice to each subject, and saline was administered prior to eight sessions. At least 96 hours separated successive administrations of clonidine. The clonidine doses and saline were administered in a random order, and the technician was unaware of the treatment schedule.

Hyperphagia was assessed by recording the number of chows consumed during a 3-hr feeding period which began 15 min following the administration of clonidine or saline. Fifteen min after the pretreatment, 50 chows were placed in each subject's food box. At the end of one hour, an additional 50 chows were placed in the food boxes, and the subjects allowed to feed for 2 additional hours. At the completion of the 3-hr feeding period, the biscuits remaining in the food box, on the floor of the cage, and in the tray below the cage were counted. Partial chows were counted as half a chow. Individual food comsumption was determined by subtracting this number of chows from the total number of chows (i.e., 100) made available to each subject.

Statistical analysis of grouped data was analyzed using ANOVA to compare the means of the data collected for each of the clonidine doses with the mean of the data collected during the saline sessions. Duncan's new multiple range test was used to compare means within the analysis [6].

RESULTS

Figure 1 illustrates the effects of clonidine on food consumption in three individually-caged subjects. When the subjects were administered either 0.01 or 1.0 mg/kg of clonidine, total food consumption for the group was significantly increased when compared to the mean control value ($p<0.05$). This increase was seen in each of the subjects following treatment with the 1.0 mg/kg (Fig. 2). Clonidine, 0.01 mg/kg, increased food consumption in only Tim and Bart, but not in Al. Tim was the only subject who exhibited a marked increase in food consumption following pretreatment with the middle dose.

EXPERIMENT II: THE EFFECTS OF CLONIDINE ON NONCOMPETITIVE FEEDING BEHAVIOR IN GROUP-CAGED MONKEYS

METHOD

The subjects used in the previous study were used in this experiment. They were continuously housed in a group cage, measuring 3.13 m (W) × 2.29 m (H) × 2.44 m (D). The back wall and right side wall of the cage were lined with formica; the ceiling and left side wall were constructed with a 5×15 cm, 4-gauge wire. The front wall was constructed with Plexiglas. Several perches were located at various heights on both the formica constructed walls. A single food box was attached to the wire constructed wall. A watering device provided water ad lib. A standard stainless steel individual primate squeeze cage, measuring 61 cm (W) × 71 cm (H) × 75 cm (D) was mounted adjacent to the back wall of the group cage, and was equipped with a sliding door which allowed passage through the side wall into the group cage. This smaller cage was used for administering all injections. The group cage was maintained on a 12-hr light/dark schedule. Temperature was maintained at 21±2°C, and humidity at 50±5%. Drug solutions were prepared and administered in the same manner as in Experiment I.

Procedure

Prior to examining hyperphagia in the group-caged monkeys, a 3-week acclimation period was provided to permit the subjects to adjust to the group cage. This acclimation period also provided time to train the subjects to enter the administration cage. A 4-week baseline period immediately followed the acclimation period. During this period the subjects were familiarized with receiving IM injections in the administration cage and with the feeding regimen to be used to examine hyperphagia. During both the baseline period and the clonidine treatment, the subjects were fed 200 chows at 8:30 a.m. on Monday, Wednesday, and Thrusday, and 300 chows once daily at 8:30 a.m. on Tuesday and Friday. On Saturday and Sunday at 2:00 p.m. the group was fed the

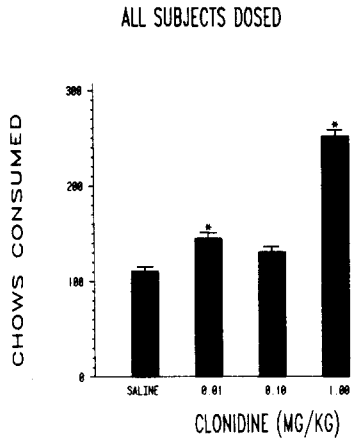

FIG. 1. The effects of clonidine on total food consumption by three individually-caged stumptail macaques. Each bar represents the mean (±SEM) of the number of chows consumed by all subjects from a possible total of 300 chows following pretreatment with saline (8 sessions) or clonidine (2 sessions per dose). An asterisk (*) denotes those values significantly ($p<0.05$) different from control values.

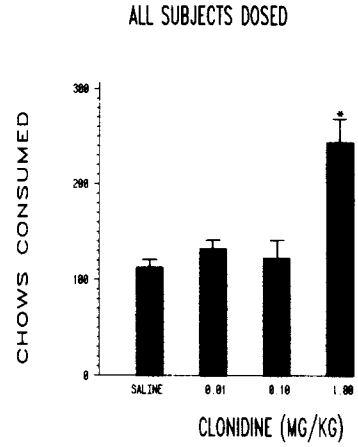

FIG. 2. The effects of clonidine on total food consumption by three group-caged stumptail macaques. Each bar represents the mean (±SEM) consumed by the subjects from a possible total of 300 chows following indentical pretreatment of all subjects with saline (8 sessions) or clonidine (2 sessions per dose). An asterisk (*) denotes those values significantly ($p<0.05$) different from control values.

mean number of chows that they had consumed daily during the previous 5 days. Throughout the baseline period each subject was injected IM with saline Monday through Friday prior to being fed. At the completion of the baseline period, clonidine testing began.

Hyperphagia was assessed by recording the number of chows consumed by the subjects following the administration of clonidine or saline. Both individual and group food consumption were recorded following a 3 hr feeding period. Fifteen min after all subjects had received an injection, 300 chows were scattered on the cage floor, enabling all subjects to obtain food in a non-competitive manner. At the end of 3 hr, the chows remaining on the cage floor were removed and counted and subtracted from 300 to ascertain total consumption by the group. Group consumption was determined during 8 saline control sessions and 2 sessons following pretreatment with each dose of clonidine. Individual food consumption was determined by videotape monitoring, once for each clonidine dose and twice for saline.

Analysis of individual food consumption involved separately comparing the total number of chows consumed by each subject for each of the 3 clonidine doses with the mean of the data collected during 2 clonidine control sessions. Group food consumption was analyzed statistically as described above.

RESULTS

Figure 2 illustrates the effects of clonidine on total food consumption by 3 group-caged subjects. Total food consumption was significantly ($p<0.05$) increased following treatment with 1.0 mg/kg of clonidine. Administration of 0.01 mg/kg increased food consumption in two subjects, Al and Bart. Tim and Bart exhibited increases in food consumption when administered 0.1 mg/kg of clonidine. However, all subjects demonstrated a substantial increase (intake at least doubled) in food consumption following pretreatment with 1.0 mg/kg of clonidine.

EXPERIMENT III: THE EFFECTS OF CLONIDINE ON FOOD COMPETITION

METHOD

The subjects used in the two previous experiments were also used in this experiment, and were housed in the group cage previously described. The same clondine doses used in the previous experiments were also tested in this study.

Procedure

A 4-week baseline period familiarized the subjects with the feeding regimen to be used to examine food competition. Throughout this baseline period the subjects were fed 75 chows at 9:00 a.m. and 50 chows at 3:00 p.m. on Monday through Friday. The chows were placed in the single food box to enhance food competition. The chows were provided in 25-chow allotments at 5 min intervals. At the completion of the 30-min feeding period, chows remaining in the food box and on the cage floor were removed. On Saturday and Sunday the subjects were fed 100 chows at 2:00 p.m. During the baseline period each subject was injected IM with saline on Monday, Tuesday, and Friday 15 min prior to the 9:00 a.m. feeding.

Food competition was assessed by recording the feeding order and number of chows retrieved by each subject from the food box. Retrieval of food required that the subject place his hand into the food box, grasp a chow between his fingers, and withdraw his hand with the chow. The chow did not have to be consumed or placed in the mouth to be counted as a retrieval.

In addition to examining feeding order and food retrieval during the food competition test, the frequency and dyadic nature of supplanting at the food box were recorded. Supplant was defined as a subject leaving the area of the food box in response to the approach of another subject.

Two clonidine treatment schedules were evaluated: (1) concurrent treatment in which all subjects were identically

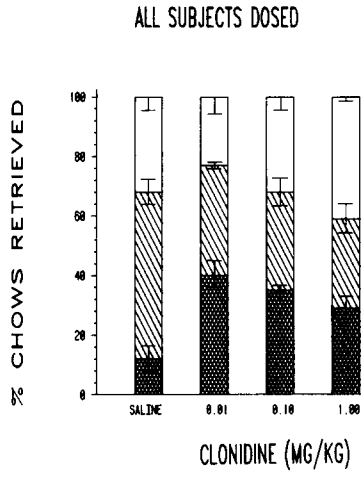

FIG. 3. The effects of concurrent administration of clonidine on food competition in three group-caged stumptail macaques (cross-hatched bars—TIM, hatched bars—AL, open bars—BART). Each bar is subdivided into 3 means (±SEM), converted to percentages, and represents the percentage of chows retrieved by each subject from a possible total of 75 chows. The data were obtained from 6 saline sessions and 2 sessions per dose of clonidine.

TABLE 1

ALTERATIONS IN THE PERCENT OF THE FIRST 10 CHOWS RETRIEVED BY THREE GROUP-CAGED STUMPTAIL MACAQUES DURING FOOD COMPETITION TESTING FOLLOWING CONCURRENT ADMINISTRATION OF CLONIDINE*

	Tim	Al	Bart
Saline			
6 sessions	0%	53.33 ± 8.03%	46.67 ± 8.03%
0.01 mg/kg Clonidine			
1st session	30%	20%	50%
2nd session	100%	0%	0%
0.1 mg/kg Clonidine			
1st session	70%	0%	30%
2nd session	60%	0%	40%
1.0 mg/kg Clonidine			
1st session	100%	0%	0%
2nd session	80%	0%	20%

*Each saline value represents the mean (±SEM) number of the first 10 chows retrieved by each subject converted to percentages. Each clonidine value represents the percentage of the number of the first 10 chows retrieved by each subject during each clonidine session.

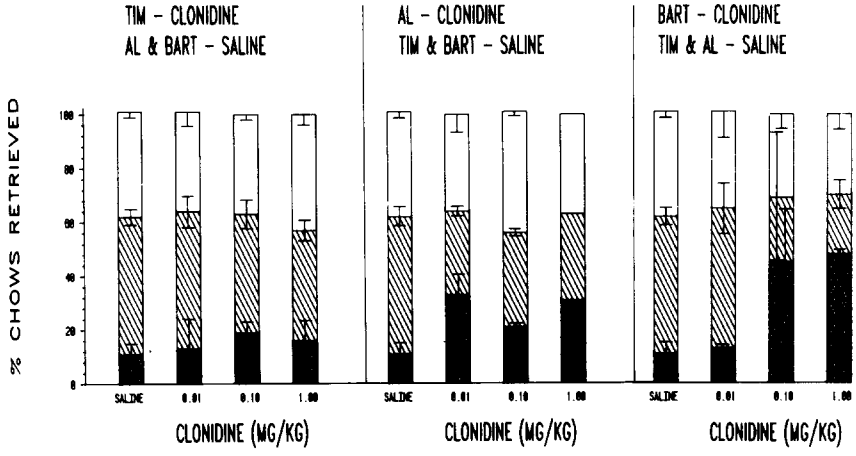

FIG. 4. The effects of individual administration of clonidine on food competition in three group-caged stumptail macaques (cross-hatched bars—TIM, hatched bars—AL, open bars—BART). Each bar is subdivided into 3 means (±SEM), converted to percentages, and represents the percentage of chows retrieved by each subject from a possible total of 75 chows following pretreatment of all subjects with saline (6 sessions) or a single subject with clonidine and the 2 remaining subjects with saline (2 sessions per dose per subject). Clonidine, 1.0 mg/kg, was administered individually only 1 time to Al and 3 times to Bart.

treated prior to a given session; and (2) individual treatment in which one subject was administered clonidine and the remaining two subjects treated with saline. Experimental sessions were conducted daily, Monday through Friday during both clonidine treatment schedules. Each subject was tested with each dose of clonidine on two occasions under each treatment regimen. Six saline control sessions were conducted in which all subjects received saline. At least 72 hr separated successive clonidine sessions or clonidine and control sessions.

RESULTS

The effects of concurrent clonidine pretreatment on food retrieval during food competition testing are illustrated in Fig. 3. When all 3 subjects were pretreated with saline, Al retrieved the greatest percentage of the chows and Tim the lowest percentage. Following the administration of each of the clonidine doses, however, there were alterations in food retrieval. In particular, the percentage of chows retrieved by Al was reduced. Conversely, the percentage of chows re-

trieved by Tim was increased following concurrent administration of each dose. Bart's food retrieval was not significantly affected following concurrent clonidine treatment.

Figure 4 reveals the effects of clonidine on food retrieval during competition testing following administration of clonidine to individual subjects in the group. Individual treatment of Tim with each of the clonidine doses resulted in no significant change in the percentage of chows retrieved by any subject. When Al was individually treated with each of the clonidine doses his food retrieval percentages decreased. These decreases were offset by increases in Tim's retrieval (0.01 and 1.0 mg/kg of clonidine); whereas, Bart's retrieval was unaffected. Administration of 0.1 and 1.0 mg/kg of clonidine to Bart resulted in a decrease in Al's food retrieval, whereas Tim's food retrieval increased. However, Bart's food retrieval remained unchanged. Therefore, clonidine did not consistently result in enhanced feeding in a given subject in a competitive situation even though it had significantly increased noncompetitive feeding by the same subject.

In addition to examining each subject's food retrieval from a possible total of 75 chows, each subject's retrieval was also examined for only the first 10 chows from the common food hopper (Table 1). Following concurrent administration, the percentage of the first 10 chows retrieved by each subject was dramatically altered. For example, Tim, who had retrieved 0 chows when administered saline, retrieved the greatest percentage of the first 10 chows when treated with clonidine (5 of 6 sessions). Al, the subject who had retrieved the majority of the first 10 chows when adminstered saline, retrieved the lowest percentage of these chows when given each of the clonidine doses. Bart's food retrieval of the first 10 chows, however, was not consistently affected following the administration of clonidine, although the largest dose appeared to decrease this parameter.

However, when only individual subjects were treated with clonidine, there were no consistent changes in the retrieval of the first 10 chows by the treated subject.

GENERAL DISCUSSION

Administration of clonidine resulted in hyperphagia in food deprived stumptail macaques when individually-caged and group-caged. This effect was seen in each of the three subjects under both housing conditions, and occurred when food retrieval was noncompetitive. These results support the previous reports of hyperphagia resulting from chronic administration of clonidine to satiated individually-caged stumptail macaques [13–15] and concurrent administration to satiated group-caged stumptail macaques [15]. Therefore, the occurrence of clonidine-induced hyperphagia appears to be independent of the deprivation state in this species.

Similar effects on feeding did not occur when feeding was competitive. In contrast to all other reports by investigators at this facility [2, 8, 18, 19] the highest-ranking subject in the present study did not retrieve the majority of chows on control days. Instead, the middle-ranking subject always retrieved the majority of the chows on these days. Although it is generally assumed that the subject who retrieves the majority of chows during competitive food-getting is the highest-ranking subject [11,17], in the current study this subject (Al) was always supplanted at the food box by another subject (Bart). It was, therefore, concluded that Al was not the highest-ranking subject. Closer examination of the dyadic relationships among all 3 subjects revealed that on all control days, Tim emitted submissive behaviors to both Al and Bart, Al emitted submissive behaviors to Bart, and Bart did not emit any submissive behaviors. The fact that Al always yielded to Bart at the food box, and also was the subordinate animal in all other dyadic interactions with Bart, supports the contention that Bart was the highest-ranking subject. Approach/withdrawal interactions have previously been undertaken to assess the dominance ranking in primate social groups [3, 4, 7, 12, 16].

Although 1.0 mg/kg of clonidine had substantially increased food consumption in both the middle-ranking and highest-ranking subjects during noncompetitive food-getting, this dose, when concurrently administered, did not increase either subject's food retrieval during competitive food-getting. In the competitive feeding situation only the lowest-ranking subject demonstrated an increase in feeding following concurrent administration of clonidine.

A similar increase in competitive feeding did not occur in the lowest-ranking subject when only he was administered clonidine. This is not surprising since on control days little opportunity was provided by the other subjects for this animal to retrieve chows. The lack of enhanced feeding when either of the other subjects were individually treated with clonidine during competitive feeding also suggests that other drug-behavioral interactions may be preventing the increase in food retrieval in a competition setting, which had characteristically occurred in noncompetitive feeding. A possible inhibitory effect of clonidine on competitive feeding is suggested by the ability of the lowest- and middle-ranking subjects, when not dosed, to retrieve food despite the presence of the dosed, highest-ranking subject at the food box. Throughout the food competition period, the highest-ranking subject, when dosed, sat directly in front of the food box. When either the lowest- or middle-ranking subject approached the food box, the highest-ranking subject made no physical attempts to interfere with their retrieval. On control days, however, when the highest-ranking subject was at the food box, neither of the other subjects made any attempts to approach the food box. It would appear, therefore, that the lowest-ranking subject's increase in food retrieval, when concurrently dosed, was perhaps the result of a greater incentive to obtain food and a possible behavioral disruption induced by clonidine in the highest-ranking subject.

In conclusion, clonidine produced hyperphagia in stumptail macaques when food-getting was noncompetitive. Concurrent administration of clonidine increased food retrieval during competitive food-getting, but in only the lowest-ranking subject. Individual administration of clonidine did not increase food retrieval by the treated subject during competitive food-getting; instead, food retrieval was increased in nondosed subjects. Perhaps during competitive food-getting where food is not plentiful, other drug-behavioral interactions prevent an increase in food retrieval which characteristically occurred in noncompetitive situations. Hence, further investigation is necessary to determine if dominance is causally related to either of these presumed effects of clonidine. Such a hypothesis is suggested by the results of this preliminary investigation of the action of clonidine on food competition behavior.

REFERENCES

1. Barchas, J. D., J. Madden, IV and I. N. Mefford. Clonidine: basic and clinical perspectives. *J Clin Psychiatry* **43:** 47–48, 1982.
2. Bellarosa, A., J. A. Bedford and M. C. Wilson. Sociopharmacology of d-amphetamine in *Macaca arctoides*. *Pharmacol Biochem Behav* **13:** 221–228, 1980.
3. Bernstein, I. S. Primate status hierarchies. In: *Primate Behaviour. Developments in Field and Laboratory Research*, vol I, edited by L. A. Rosenblum. New York: Academic Press, Inc., 1970, pp. 71–109.
4. Bernstein, I. S. and L. G. Sharpe. Social roles in a rhesus monkey group. *Behavior* **26:** 91–104, 1966.
5. Blaschke, T. F. and K. L. Melmon. Antihypertensive agents and the drug therapy of hypertension. In: *The Pharmacological Basis of Therapeutics*, 6th edition, edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: MacMillan, 1980, pp. 793–818.
6. Daniel, W. W. *Biostatistics: A Foundation for Analysis in the Health Sciences*, 2nd edition. New York: John Wiley and Sons, 1978.
7. Kaufmann, J. H. Social relations of adult males in a free-ranging band of rhesus monkeys. In: *Social Communication Among Primates*, edited by S. A. Altmann. Chicago: University of Chicago Press, 1967, pp. 73–98.
8. Lovell, D. K., J. A. Bedford, L. Grove and M. C. Wilson. Effects of d-amphetamine and diazepam on paired and grouped primate food competition. *Pharmacol Biochem Behav* **13:** 177–181, 1980.
9. Redmond, D. E., Jr. Does clonidine alter anxiety in humans? *Trends Pharmacol Sci* **3:** 477–480, 1982.
10. Redmond, D. E., Jr. and Y. H. Huang. New evidence for a locus coeruleus-norepinephrine connection with anxiety. *Life Sci* **25:** 2149–2162, 1979.
11. Richards, S. M. The concept of dominance and methods of assessment. *Anim Behav* **22:** 914–930, 1974.
12. Rowell, T. E. Hierarchy in the organization of a captive baboon group. *Anim Behav* **14:** 430–443, 1966.
13. Schlemmer, R. F., Jr., R. C. Casper, N. Narasimhachari and J. M. Davis. Clonidine-induced hyperphagia and weight gain in monkeys. *Psychopharmacology (Berlin)* **61:** 233–234, 1979.
14. Schlemmer, R. F., Jr., J. K. Elder, R. C. Casper and J. M Davis. Clonidine-induced hyperphagia in monkeys: evidence for α-noradrenergic receptor mediation. *Psychopharmacology (Berlin)* **73:** 99–100, 1981.
15. Schlemmer, R. F., Jr., R. C. Casper, J. K. Elder and J. M. Davis. Hyperphagia and weight gain in monkeys treated with clonidine. In: *Psychopharmacology of Clonidine*, edited by H. Lal and S. Fielding. New York: Alan R. Liss, Inc., 1981, pp. 197–210.
16. Struhsaker, T. T. Social structure among vervet monkeys (Cercopithecus aethiops). *Behavior* **29:** 83–121, 1967.
17. Syme, G. J. Competitive orders as measures of social dominance. *Anim Behav* **22:** 931–940, 1974.
18. Wilson, M. C., L. Bailey and J. A. Bedford. Effects of subacute administration of amphetamine on food competition in primates. In: *Ethopharmacology: Primate Models of Neuropsychiatry*, edited by K. Miczek. New York: Alan R. Liss, Inc., 1982, pp. 293–305.
19. Wilson, M. C., G. Nail and J. A. Bedford. Alterations in nonhuman primate food competition induced by d-amphetamine. *Res Commun Subst Abuse* **3:** 467–482, 1982.