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Use of Low-dose Chlorpromazine in Conjunction with Environmental Enrichment to Eliminate Self-injurious Behavior in a Rhesus Macaque (*Macaca mulatta*)

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A 7-year-old, captive-bred, female rhesus macaque was placed in a quarantine facility upon arrival at our institution. At release from quarantine, she was observed pawing at and chewing on her left cheek. Physical examination revealed ulcerative lesions on the buccal surface of the left cheek. Initial differential diagnoses included *Cercopithecine herpesvirus 1* (B virus)-induced lesions and bacterial infection. Dental abnormalities and cheek pouch foreign body were ruled out during the physical exam. Treatment with 30 mg/kg cefazolin intramuscularly every 12 h was initiated. Twelve days later, the animal presented with a 2 × 2-cm, full-thickness erosion involving the opposite (right) cheek. Treatment with buprenorphine (0.1 mg/kg intramuscularly every 24 h) was initiated. Cultures for B virus were negative, and only nonpathogenic bacteria were isolated from swabs of the lesions. Hematology and serum chemistry profiles were normal. A wedge biopsy of the lesion revealed no definitive etiology. Further observation revealed that the lesions likely resulted from self-injurious behavior (SIB). Treatment with low-dose chlorpromazine (1 mg/kg intramuscularly once daily for 25 days, and then 0.5 mg/kg intramuscularly once daily for 25 days) was initiated. Bodyweight and condition were maintained during therapy, and serial hematology and serum chemistry profiles were normal. The animal was moved into a different room, and a toy "necklace" was created. The SIB was eliminated, and lesions healed within 35 days. Presently, 20 months after presentation, this animal remains in good health.

Nonhuman primates (NHP) serve as key animal models of human disease in biomedical research. NHPs are recognized as intelligent animals that are capable of exhibiting complex behaviors. For these reasons, high standards of care in captivity are mandated, and the maintenance of these animals' psychological well-being is a high priority (7). The phrase "psychological well-being" as it pertains to captive NHPs is not well-defined and certainly is debatable (2). Criteria to assess the psychological health of NHPs have been proposed as a means to help NHP caregivers promote psychological well-being to the highest degree possible (22). In 1991, the United States Department of Agriculture mandated through the Animal Welfare Act that facilities housing NHPs "must develop, document, and follow an appropriate plan for environmental enhancement adequate to promote the psychological well-being of nonhuman primates" (30). In addition, all facilities housing NHPs must institute measures that allow the expression of "noninjurious species-typical behavior" (30).

Many measures are taken at institutions with captive NHPs to promote psychological well-being. In the colonies at our institution, physical environmental enrichment takes the form of an array of manipulanda, toys, music, videos, and task-oriented feeding methods. The types of enrichment used by the animals are documented daily, and items are rotated between different animals to offer variety. Social environmental enrichment primarily consists of positive visual and auditory interaction with conspecifics as well as human caregivers to the greatest extent possible. Although pair-housing or protected contact between conspecifics also would be ideal forms of enrichment, current research protocol constraints, such as chronic catheterization, make this option unavailable. Despite the best efforts of caregivers, some NHPs exhibit behaviors that represent an abnormal or altered psychological state.

Abnormal behaviors that are thought to be indicators of poor psychological health in captive NHPs range from active whole-body and self-directed stereotypies to self-injurious behavior (SIB) (15). Stereotypical behaviors include acts such as pacing, flipping, rocking, hair-pulling, and finger-sucking. These behaviors rarely result in physical injury to the animal, but they are a cause for concern regarding the animal's psychological well-being (15). In contrast to most stereotypical behaviors which result in no physical harm, SIBs are defined as aggressive acts toward an animal's own body that may result in tissue damage (1) and most commonly manifest as self-biting of the extremities (6). Not every episode of SIB results in physical injury, and some episodes could be best described as self-abuse with no resultant injury. However, any self-abuse that becomes more rigorous has the potential to result in injury. Data regarding the prevalence of stereotypical behaviors in general is limited, but they have been reported to occur commonly in individually housed rhesus monkeys (3, 15). With respect to SIB specifically, a report of 188 individually housed rhesus monkeys stated that 14% of these animals, primarily males, engaged in some form of SIB that required veterinary care and that self-biting of extremities was the most common manifestation (20).

The exact etiology of stereotypical behaviors and SIB in NHPs currently is not known, and, in fact, these behaviors should be

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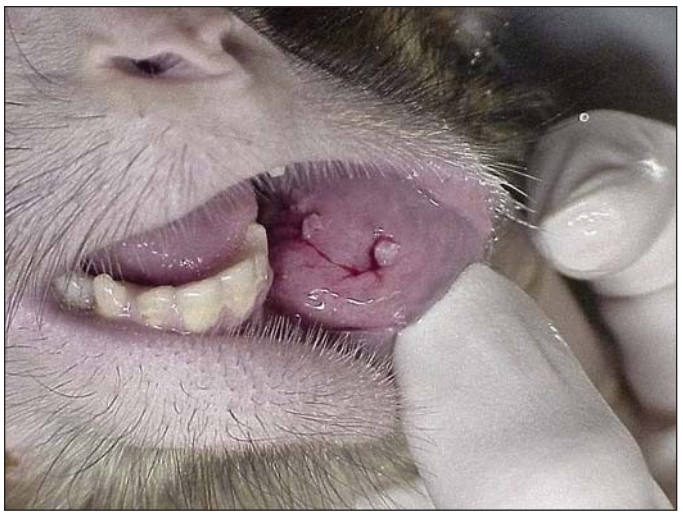

Figure 1. Clinical photograph of ulcerative lesion with hemorrhage on the buccal surface of the left cheek. This lesion was identified during physical examination on the day of the animal's exit from quarantine (day 0).

viewed as symptoms of another underlying problem (5). It is possible, then, that a single behavior might arise for a variety of reasons, and several predisposing factors have been identified. Age and sex of the animal, housing status (e.g., single versus group), and rearing history (e.g., mother versus nursery) all have been implicated as playing a role in the development of abnormal behaviors (3, 6, 20). Among these, individual housing, particularly at an early age, might be one of the best predictors of SIB (3, 20). There is also evidence that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis plays a role in the development of SIB in rhesus monkeys (28). Therapy reported in the literature consists of pharmacological intervention, manipulation of the physical environment, and changes in the animal's housing or social arrangement to reduce possible stress.

We report here a unique case of SIB in a female rhesus macaque that presented as repetitive chewing at the inside surface of the cheeks. This behavior eventually led to the development of a full-thickness erosive lesion in one cheek but did not involve the cheek pouch. To our knowledge, this is the first report of SIB presenting in this way. This case successfully was managed using analgesic and low-dose neuroleptic medical therapy, in combination with manipulation of the physical and social environment. This multi-faceted approach to therapy was the key to successful treatment. This animal showed no detrimental effects from the pharmacological agent used. Currently, approximately 20 months after initial presentation, this macaque is a healthy member of our institution's colony and participates in a research study approved by our institutional animal care and use committee.

Case Report

A 7-year-old, captive-bred, female rhesus macaque was sent to our institution as part of a group of ten animals from the Oregon National Primate Research Center (ONPRC), Beaverton, Oreg. Health records from the ONPRC indicated that this animal had been generally healthy but did show a single positive result on an enzyme-linked immunosorbent assay for *Cercopithecine herpesvirus 1* (B virus) approximately 3 years earlier. Upon arrival, the animal was housed singly for 45 days in an Association for the Assessment and Accreditation of Laboratory Animal Care,

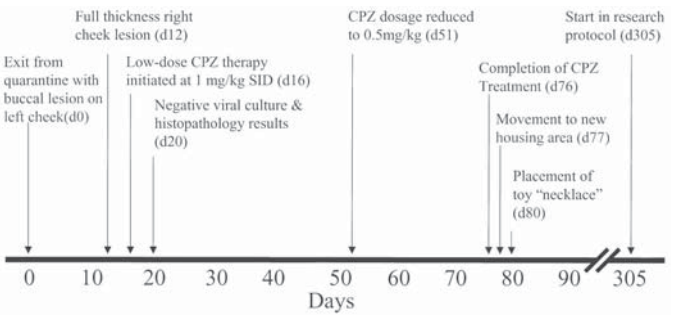

Figure 2. Timeline of medical therapy and enrichment for management of SIB.

International-accredited quarantine facility in accordance with the *Guide for the Care and Use of Laboratory Animals* (19). She was given a standard ration of LabDiet 5045 high protein monkey diet (PMI Nutrition International, Richmond, Ind.) appropriate for her bodyweight according to vendor guidelines, supplemental fresh fruits, and water ad libitum. Four days after arrival, the animal was anesthetized using 10 mg/kg ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa) given intramuscularly (i.m.) to allow physical examination (PE) and intradermal tuberculin testing, which were repeated biweekly over 4 weeks (total of three times). Thoracic radiographs were taken during the first examination, and a complete blood cell count (CBC) was performed as part of the final examination. PE, radiographic, and laboratory findings were within normal limits during quarantine. This animal's food consumption was inconsistent during the quarantine period, and her bodyweight decreased to 4.2 kg (compared with 4.8 kg at arrival). This weight loss was attributed to the inconsistent eating pattern because she showed no other abnormalities that would account for weight loss, such as diarrhea or reduced water consumption, and she maintained acceptable body condition.

On the day this animal was scheduled to leave quarantine and enter a new housing location (45 days after arrival), husbandry personnel observed her sitting in her cage, repeatedly rubbing and chewing her left cheek. This behavior had not been noted previously. She was anesthetized with ketamine for PE and for the previously scheduled transport from quarantine. Physical examination revealed bleeding ulcerations on the buccal surface of the left cheek (Fig. 1). No other abnormalities were noted. At this time, the lesions were swabbed so that bacterial and B virus cultures could be performed. In addition, a blood sample was collected from the femoral vein for the purposes of performing a CBC and serum chemistry analysis. The animal was transported as scheduled after PE and sample collection. The room into which she was transported housed approximately 16 rhesus monkeys, both males and females, ranging in age from approximately 6 to 12 years. All animals were individually housed in two-tiered cages, and the cages were in two rows facing each other so that animals could easily view conspecifics. Empirical therapy with cefazolin (30 mg/kg i.m. every 12 h; Ancef, GlaxoSmithKline, Pittsburgh, Pa.) was initiated to address the possible bacterial etiology of the lesion and reduce the risk of bacterial infection. CBC and serum chemistry results were within normal limits. In addition, after 6 days of growth, bacterial cultures identified a mixed flora of α-hemolytic *Streptococcus* spp. and gram-negative diplococci, which were presumed to be non-pathogenic flora.

For the purposes of clarity, all time points (in days) hereafter will be in reference to the day this animal exited quarantine,

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which is designated as day 0 (Fig. 2). On day 8, the animal was anesthetized for a recheck examination. In addition, laboratory personnel had noticed the animal pawing at her right cheek on occasion. PE revealed a small, pinpoint fistula on the left cheek, presumably a sequela to the lesion seen on the original examination on day 0. No other abnormalities were noted at this time. The lesion was cleaned using povidone–iodine. Carravet gel (Veterinary Products Laboratories, Phoenix, Ariz.), a wound dressing containing aloe vera extract and acemannan hydrogel, was applied to promote healing of the wound. On day 12, lab personnel reported a pronounced wound on the opposite (right) cheek of this animal. The animal was anesthetized for further examination, and the wound was found to be a 2 × 2-cm, full-thickness erosion of the right cheek (Fig. 3A). All other findings were normal, and the animal's bodyweight was 4.2 kg. The wound edges were scarified using a scalpel blade to stimulate a healing response, and the defect was closed using 3-0 polydioxanone (PDS) suture material (Ethicon, Somerville, N.J.) in a simple interrupted pattern. Suturing the wound closed was unsuccessful, however, as the animal removed the sutures approximately 1 day after they were placed. Concurrent with suture replacement, a small, wedge-shaped portion of the wound margin was excised and sent to the Michigan State University Diagnostic Center for Population and Animal Health, East Lansing, Mich. for histopathological analysis. To alleviate any discomfort associated with the lesion, buprenorphine (0.1 mg/kg i.m. once daily; Buprenex, Reckitt Benckiser Pharmaceuticals, Richmond, Va.) was administered. Therapy with enrofloxacin (5 mg/kg i.m. once daily; Baytril, Bayer Corporation, Shawnee Mission, Kans.) was initiated at this time, and cefazolin therapy was discontinued. We changed antibiotics at this point in order to continue to prevent secondary bacterial infection while mitigating the risk of wound colonization by bacteria resistant to cefazolin. Her food consumption continued to fluctuate daily during this period, although her bodyweight and condition were maintained.

Shortly after the cheek lesion was examined (day 12), the possibility that the wound in this animal was the result of SIB was discussed with laboratory personnel. SIB in this animal seemed likely in light of the repetitive behavior occasionally observed by the animal's caregivers. Therapy with the neuroleptic agent chlorpromazine (CPZ; 1.0 mg/kg i.m. once daily; Sigma–Aldrich, St. Louis, Mo.), reconstituted according to manufacturer's guidelines to achieve a concentration of 10 mg/ml, was initiated on day 16. CPZ was chosen because it has been used often in humans and to a lesser degree in NHPs to treat behavioral disorders (18, 20, 25, 26). In addition, CPZ is not a controlled substance, and laboratory personnel were comfortable administering the drug. A low dose was selected to reduce the risk of negative side effects reported to occur with higher doses (8, 9, 12, 17). Enrofloxacin and buprenorphine were continued at the doses and frequencies noted previously. CPZ was given in the morning, whereas buprenorphine was given only in the evening to prevent excessive sedation that we thought might be observed if both drugs were given concurrently.

Four days after initiating CPZ therapy (day 20), negative B virus culture results were received. In addition, the pathology report indicated that ulcerative dermatitis, likely secondary to trauma, was present, but no etiologic agent was identified. A veterinary pathologist at our institution corroborated these findings. Together, the negative viral culture and histopathology report

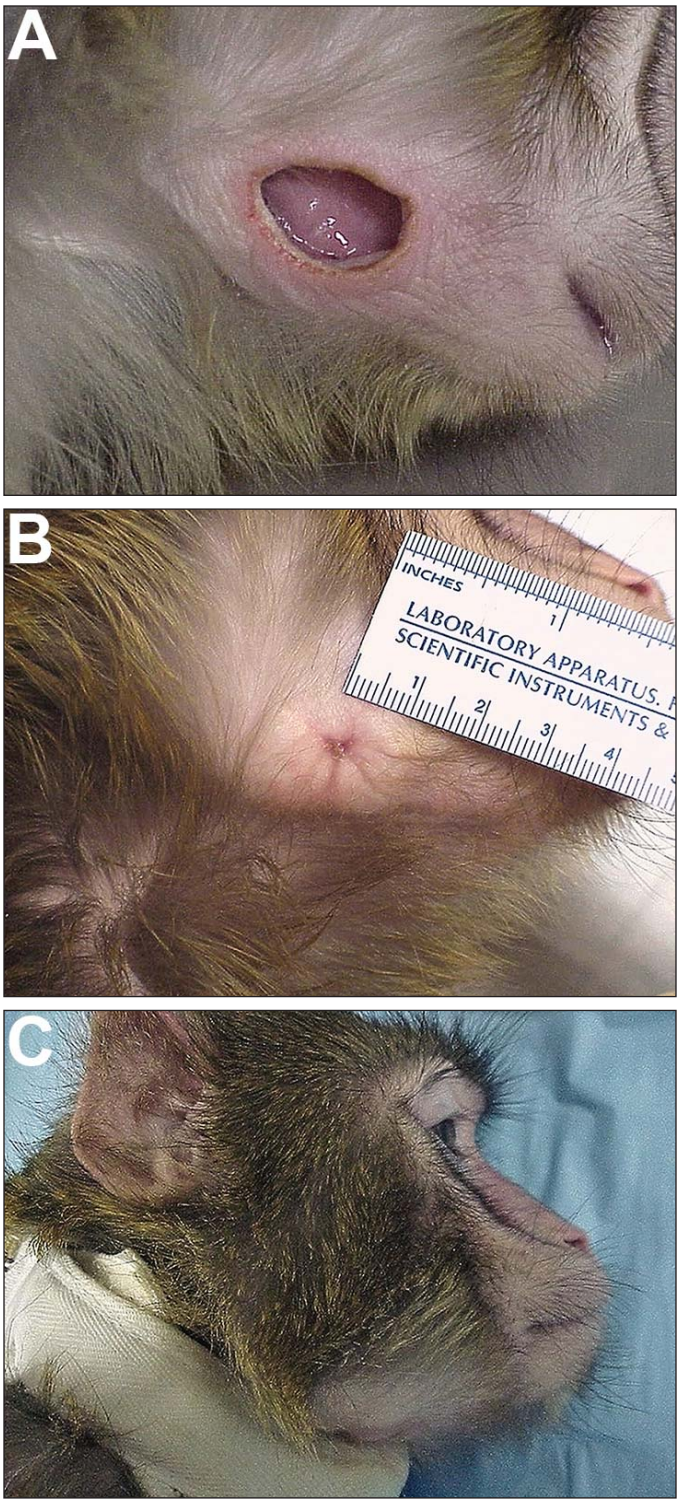

Figure 3. Clinical photographs of the full-thickness lesion on the right cheek at (A) initial presentation on day 12, (B) on day 51 (at 35 days of CPZ therapy), and (C) approximately 10 months after the completion of CPZ therapy. Note the complete resolution of the wound and initial regrowth of facial hair. Note also that this lesion did not involve the cheek pouch.

further confirmed our suspicion that lesions seen in this animal were the result of SIB. In addition to the described medical therapy, this animal received environmental enrichment, primarily

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Figure 4. Clinical photographs. (A) Macaque wearing the environmental enrichment necklace designed to divert residual SIB from cheek tissue to this chewable, rubber toy. (B) Macaque using the chew necklace while under observation in the housing room.

various manipulanda, from lab personnel as would be standard under the institutional animal care and use committee-approved research protocol pertaining to this animal.

During the period from day 16 (initiation of CPZ therapy) to day 67, the animal was observed daily and underwent ketamine anesthesia for five complete physical exams. Blood was collected twice during this period (days 24 and 33) for CBC and serum chemistry profiles, both of which showed no abnormalities except for mild hypoglycemia on one occasion. This abnormality presumably was due to the animal's inconsistent eating pattern. It was not attributed to CPZ therapy, because human subjects undergoing CPZ therapy tend to be hyperglycemic (25). The right cheek lesion showed consistent improvement during therapy. Enrofloxacin administration was discontinued after the second examination on day 24, thus constituting 12 days of therapy. This duration was within the originally prescribed range of time, and the risk of secondary infection was thought to be low. Buprenorphine was discontinued on day 48 because we felt the lesion was no longer causing discomfort. The original lesion, which had measured 2×2 cm (Fig. 3A), had decreased to a 0.1×0.1-cm pinpoint lesion (Fig. 3B) on day 51, at which time we decided to start weaning the animal from the CPZ and reduced the dosage to 0.5 mg/kg once daily. CPZ therapy was discontinued completely on day 76. Within a few months of the completion of CPZ therapy, the area of the cheek with the lesion had visible regrowth of facial hair (Fig. 3C). Although the volume of food consumed by this animal continued to be somewhat variable, her bodyweight had increased to 4.4 kg when measured on day 76.

During the time this animal received the reduced CPZ dosage, laboratory personnel occasionally observed her pawing at her cheeks as she did prior to the start of therapy. They noted that she appeared sensitive to frequent changes in colony structure that were inherently part of her physical environment. The cheek-pawing behavior seemed to correlate with direct visual access to certain conspecifics, and there was concern that she would cause self-injury again if her exposure to such environmental stressors could not be reduced. On day 76 (completion of CPZ therapy), space became available in another housing location where changes in colony dynamics could be more tightly controlled, and arrangements were made to move this animal there on the following day. In addition, rubber toys that could withstand chewing were attached to the animal's collar in the form of a toy "necklace" (Fig. 4A). This animal appears to preferentially chew on these toys when excited or anxious, particularly in the presence of unfamiliar individuals (Fig. 4B). This necklace is replaced as it becomes worn from usage. This animal currently weighs approximately 7 kg and has not exhibited further episodes of SIB.

Discussion

This report describes a unique presentation of SIB in a young, female rhesus monkey. SIB most commonly takes the form of self-biting of the arms, hands, legs, and feet. In this case, however, wounds were seen only on the cheeks. She was never observed biting any other portion of her body nor were any other wounds noted on PE. Mild ulcerations of the buccal surface of the left cheek were the first lesions noted. However, a full-thickness erosion involving the tissue of the right cheek ultimately developed. These lesions were a result of this animal's repetitive pawing and chewing at the inside surface of her cheek.

The true etiology of SIB is uncertain. In the human population, it is observed in approximately 5 to 17% of individuals with intellectual and developmental disabilities, but has also been observed in humans suffering from schizophrenia, bipolar dis-

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order, and various forms of depression (24). SIB also occurs in a small percentage of the general human population (27), and it is therefore quite likely that there is no single cause for the behavior. The incidence in NHPs, specifically singly housed macaque species (*Macaca spp*.), was reported to be as high as 14% in one study and 15% in another (6, 20). The condition is identified most frequently in males (20), but wounds tend to be more severe in females exhibiting SIB (4). As is suspected in humans, the etiology of SIB in NHPs is almost certainly multifactorial (20). One study by Bayne and colleagues (4) found no discernable influence of rearing history, whereas Bellanca and Crockett (6) found that nursery-reared animals displayed more abnormal behaviors, including self-abuse. In general, singly housed animals exhibit more abnormal behaviors than those housed in groups (3). Interestingly, it seems that the amount of time housed alone at an early age is a more important predictor for the development of abnormal behaviors than is simply being housed individually as an adult (6, 15). A recent study of the pathophysiology of SIB in rhesus monkeys showed that animals with SIB had lower mean cortisol levels, suggesting that these animals have some dysfunction of the hypothalamic-pituitary-adrenal axis and thus might respond to stress differently than other animals (28). In the case we present, the animal's records indicate that she was captive-bred and individually housed until arrival at our facility. Extensive detail about rearing is not available. There was no history of SIB prior to her arrival. Evidence in this case indicates that multiple events perceived as stressful by this animal, such as transport and subsequent placement into a housing location with unfamiliar conspecifics, elicited the SIB. In addition, because of experimental needs, animals were frequently moved into and out of the postquarantine housing room, a situation that was potentially an additional stressor.

Successful management of SIB in NHPs usually requires several approaches. Therapy reported in the literature consists of pharmacological intervention, manipulation of the physical environment, or changes in the animal's housing or social arrangement. Among pharmacological agents, chlorpromazine (18), guanfacine (16), and cyproterone acetate (10), a synthetic progestin, have been used successfully for the treatment of SIB in rhesus monkeys. Supplementation with oral L-tryptophan also has been used successfully (32). Manipulation of the physical environment through the introduction of puzzle feeders was effective in eliminating several stereotypical behaviors in common marmosets (*Callithrix jacchus jacchus*) (23). One study of pair-housed female squirrel monkeys found that artificial turf forage boards failed to reduce the frequency of stereotypical behaviors significantly (11). Furthermore, introduction of puzzle feeders to rhesus monkeys with a history of SIB did not reduce the behavior, and some animals continued to injure themselves while they manipulated the boards (21). In general, manipulation of the physical environment alone is not very effective in managing SIB (17). Placement of females with vascectomized male rhesus monkeys with a history of SIB was effective in ameliorating the condition (31). Considering the evidence as a whole, pharmacological intervention and manipulation of the social environment can be effective measures for managing SIB, whereas alterations in the physical environment alone are much less effective.

In this case, we combined medical therapy with manipulation of the physical and social environment to eliminate this animal's SIB. For medical therapy, we chose to use the neuroleptic agent CPZ at a lower dose than what had been reported previously. Our goal was to manage the SIB while avoiding side effects that have been reported when higher dosages were used (9, 17, 18). We started with a dosage of 1 mg/kg for approximately 35 days, decreased the dosage to 0.5 mg/kg for approximately 25 days, and then discontinued therapy completely. We found only one report in which CPZ was used specifically to treat behavioral disorders in NHPs. In this study, a group of four rhesus monkeys were treated with 10 mg/kg orally once daily for 1 week and then 7.5 mg/kg once daily for 11 weeks (18). At a dosage of 10 mg/kg, all animals exhibited noteworthy extrapyramidal and sedative side effects, but these diminished at the lower dosage in all but one animal. Therapy was successful in these animals, but no data beyond 4 weeks post-CPZ therapy were presented, therefore conclusions about long-term success cannot be made. We did not observe any extrapyramidal or sedative-like side effects in this animal. The animal typically appeared to be alert, and food consumption generally improved during CPZ therapy, which was reflected by her slight weight gain during that time.

Other published studies of the effects of CPZ on NHPs are concerned with the effect of varying dosages of the agent on normal behavioral and physiologic parameters. As little as 0.1 mg/kg CPZ given intravenously to rhesus monkeys significantly affected performance on an operant behavioral test battery (12). Similarly, an effect on short-term memory was seen when dosages of CPZ between 0.5 and 1.5 mg/kg were administered subcutaneously to rhesus monkeys, however the authors concluded that CPZ does not have specific disruptive effects on memory (13). CPZ administered to chimpanzees (*Pan troglodytes)* at a dosage of 1 mg/kg given i.m. twice weekly significantly lowered water consumption (8). Rhesus monkeys receiving between 5 and 10 mg/kg of CPZ i.m. once daily exhibited many abnormal social behaviors, decreased drinking and eating, and even a cataleptic state at a higher dosage (14). Rhesus monkeys that were given CPZ orally at a dosage range of 8 to 40 mg/kg exhibited a wide range of dyskinesias and alterations in social behavior (17). Most of these effects subsided after CPZ was withdrawn. A study of the effects of CPZ on body temperature found that between 0.1 and 8 mg/kg given intravenously to Formosan macaques (*Macaca cyclopis*) induced hypothermia in a dose-dependent manner (9).

We observed no detrimental or unwanted effects in our animal for the duration of CPZ administration. The monkey's behavior was considered normal during the course of therapy. We cannot comment on the effects of CPZ on this animal's memory or performance on tests because she is not involved in activities that specifically yield such information. As mentioned, food consumption was more consistent during CPZ administration compared with time prior to therapy. We use automatic watering systems in our facility, therefore water intake was not measured directly, but we assumed water consumption was normal during therapy in light of acceptable urine output. This animal's body temperature was normal on PEs performed during the course of therapy. In addition, bloodwork performed during therapy showed no abnormalities that could be attributed to the use of CPZ.

When transition to the decreased dosage of CPZ (0.5 mg/kg) was made, this animal occasionally was observed rubbing at her cheeks, the behavior that was originally described. This behavior indicated that medical therapy alone was not likely to be curative and that unwanted behaviors might return when the CPZ was discontinued. As a result, we included manipulation of this

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animal's physical and social environment as the other portion of the management plan. This animal, along with all NHPs at our facility, received a wide and constantly varying array of manipulanda and other forms of physical environmental enrichment. To reiterate, most commonly used forms of enrichment such as puzzle feeders and toys do not effectively eliminate SIB in NHPs (21, 29). For this reason, in addition to commonly used enrichment devices, we designed a toy necklace by attaching a chew toy to a modified vest so that the toy hung around the animal's neck (Fig. 4). It appeared that the accessibility and proximity of the necklace encouraged the animal to chew the toy instead of her cheeks.

Probably more important than alterations in the physical environment are changes in the social environment for managing SIB. It is well established that housing condition and social environment are important factors in the development of abnormal behaviors, including SIB (3, 6, 15, 20). In the case we present, it appeared that visual and auditory contact with certain conspecifics and frequent changes in social dynamic within the housing room were a source of stress for this animal. It was important, therefore, to identify a more suitable housing location. We could have considered co-housing this animal with another NHP, as social housing may be effective in eliminating SIB (31). However, in this situation, pair-housing was not possible because of NHP study protocol constraints. A new housing location became available on day 77 (one day after completion of CPZ therapy), and this animal was moved. The room was smaller and had a more stable social structure because animals were involved in long-term research projects. This relocation presumably eliminated some of the triggering events that would have continued to elicit SIB in this animal in the housing location into which she was moved immediately after the quarantine period.

We believe that SIB in this animal was eliminated due to the combination of approaches used in the case management. Therapy with low dosages of CPZ was important to help acutely alleviate stress. Stress reduction was crucial because no other housing locations were available at the time of initial diagnosis, a situation that limited our options for the manipulation of the social environment. We believe the CPZ diminished this animal's response to stress, thus eliminating the SIB and allowing the cheek lesion to heal. Once medical therapy was completed, the implementation of a novel enrichment toy and the change in housing location were vital to the successful long-term management of this monkey's SIB.

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