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Review Article

Hair Loss in Laboratory Bred Macaques: An Idiopathic Disorder of Major Consequence

David V. Gauvin*, Dale M. Cooper

Department of Neurobehavioral Sciences, MPI Research, Mattawan, MI, USA

***Corresponding author:** David V. Gauvin, Department of Neurobehavioral Sciences, MPI Research, Mattawan, MI 49071, USA. Tel: +12696683336 Ext. 1613; Email: david.gauvin@mpiresearch.com

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Abstract

In spite of the idiopathic nature of hair loss in non-human primates, the presentation of monkeys with hair loss has become a concern during site visits by Sponsors and federal regulatory authorities. This review attempts to define, describe, and somewhat defend the clinical findings of alopecia in colony-maintained nonhuman primates in research institutions and to allay any fears of maltreatment or neglect if the hairless monkey is found in the colony. Self-directed behaviors to the point of self-injury are common features of both nonhuman primates and humans. The etiology of alopecia in free-range and laboratory-maintained monkeys, as well as the human patient involves multiple factors, many of which are not in the direct control of behavioral management or therapy. Proper and complete documentation of initial observations, progression and recurrence, as well as active therapeutic interventions can go a long way to protect the laboratory from experiencing a "teaching moment" during regulatory agency inspections.

Keywords: Alopecia; Distress; Hair loss; Hair pulling; Self-aggression; Stereotypy; Well-being

Introduction

Hair loss is not uncommon in humans and nonhuman primates. Alopecia is a common problem with a poorly understood etiology that can have a variety of presentations. In laboratory bred NHPs, new molecular entities may be the source of alopecia identified during a study. Alopecia not only represents a concern for individual animal health and overall colony health but may also impact experimental work and has come under regulatory scrutiny. For matters of this review, drug-induced alopecia is considered a test-article adverse event and cessation of treatment or drug holidays may be imposed to circumvent the dramatic presentation on the study. Another common form of hair loss in research facilities is not necessarily metabolic - it is hair pulling. Trichotillomania is an impulse-control disorder in humans; treatment is aimed at controlling the underlying psychiatric condition. While "stress" has been proposed in the etiology of the "bald monkey" the spontaneous loss of hair and the intentional loss of hair may suggest separate factors of control.

There is currently no single or definitive cause of alopecia in laboratory animals [1] however, there have been some contributing factors identified such as seasonal variation, aging, rank status [2], sex [3,4], housing conditions, reproductive status, skin disorders [5-7], nutritional deficiencies [8], and behavioral/personality traits [9,10]. Other potential factors linked to alopecia include: endocrine disease, nutritional deficiencies or imbalance, behavioral abnormalities, aging, immunologic disorders, allergic disease, and stress. Some reports estimate the prevalence of alopecia at approximately 48% of animals exhibiting the symptoms at some point in their history [10] with incidents as high as 68% [7] to 86.5% [1,5] being reported in some populations. Despite the consensus of the idiopathic nature of alopecia it is generally presumed to be a sign of poor welfare. A default diagnosis of psychogenic self-inflicted alopecia often is reached in the absence of an evidence-based diagnostic approach [11]. The presence of alopecia in research facilities has been the subject of increased regulatory attention [3,4,12].

Hair Pulling

The prevalence of "hair pulling", which may be another cause of hair loss, has been estimated to be around 14% in individ-

ually housed rhesus monkeys and is associated with increasing age [13], but a more recent study by Luchins et al. [12] have reported overall rates of hair pulling as high as 33%. The incidence of hair pulling in rhesus is like that observed in the human disorder, trichotillomania, which also involves plucking out and sometimes eating hair [8,13,14]. In one study, Lutz et al. [1] reported an incidence of 49.3% of single-housed rhesus at four primate facilities in the U.S., showed some form of hair loss, with females (58.7%) exhibiting more hair loss than males. The incidence of hair pulling was significantly lower than that of hair loss with just under 8% of the total population demonstrating hair pulling and when hair pulling was documented it occurred more often in males rather than females. These authors concluded that the behavior of hair pulling, and the condition of a monkey's coat may not be as closely associated as previously believed. Therefore, the true cause and effect relationship between hair-pulling (trichotillomania) and alopecia remains unknown. While it is likely that hair-pulling produces hair loss in some monkeys it is unlikely that all cases of hair loss can be attributable to the hair-pulling syndrome [1].

Housing

There are ongoing investigations to determine the possible cause(s) of alopecia and while the literature on the subject is lacking overall, several recent reviews have focused on the issue [2,15]. Several large surveys have been published implicating time of year, time in the breeding cycle, living space, stress, housing conditions, age, and sex of the animal [6,7,16,17]. Monkeys housed outdoors tend to have healthier coats than monkeys housed indoors [6] and monkeys that originated from an outdoor colony before being moved indoors tended to have a lower incidence of alopecia than did those born and raised indoors and currently housed under the same condition [5]. Rhesus monkeys group-housed in enclosures with gravel substrates have been reported with significantly more severe alopecia than cohorts raised in grass-covered enclosures [17,18]. Pair-housed rhesus has been reported to have a better hair coat quality than single housed cohorts [19] however when pair-housed the low- or middle-ranking monkeys tend to have worse coats than do the high-ranking dominant cage mate [17, 20]. Coat condition has been reported to be worse with a decrease in available cage space per animal [6] and increasing animal density intensified the influence of pregnancy on hair loss [17]. There is growing evidence in the published literature appearing in peer-reviewed scientific journals that housing conditions alone are neither sufficient nor necessary conditions to induce alopecia in laboratory-maintained colonies [6,13,18].

Seasonal Variations

As indicated in these surveys, alopecia is often the result of normal seasonal or hormonal variations. Macaque hair coats demonstrate natural seasonal variation that may be associated with levels of circulating sex hormones [16,21]. In one large survey of free-ranging rhesus macaques, natural molting was seen in monkeys as young as 1 year of age and was associated with the period of the breeding season, implying an association with levels of sex hormones. The molt generally lasted from 4 to 16 weeks with replacement of old hair with new, darker hair. This should be considered as a potential cause of seasonal alopecia in male and female macaques and should spontaneously resolve [16]. Montagna [22] found that captive, indoor rhesus monkeys had profuse hair shedding throughout the year. This may explain the presentation of hair loss in indoor and mixed indoor-outdoor primate facilities. Similar, free-ranging vervet monkeys showed seasonal hair loss, and in this instance the hair loss was more severe in lower-ranked individuals [20]. Pregnancy may be associated with alopecia and hair loss may spontaneously resolve following parturition [17].

Comparisons of free-ranging macaques (*Macaca mullata*) roaming a governmental Forest Research Institute (FRI; India) and free-ranging macaques from an open forested area near the FRI was made by Lindburg [23]. Lindburg reported that many free-ranging individuals on the FRI property had "thin, matted coats throughout the monitoring period in contrast to the sleek full coats of forest groups. Some of the "wild" macaques on the institute property suffered moderate to severe loss of hair beginning in October and November [24]. New growth hair was reported to be evident by late December, but the most severe cases of alopecia were not yet completely recovered by May of the next year. No loss of hair was evident in free-ranging forest macaques. Regurgitation into the mouth and cheek pouches, following by chewing and reswallowing was seen in the free-ranging monkeys on the grounds of the FRI for over five months of the winter season. The highest frequency of hair loss was found in the free-ranging macaques on the grounds of the government land and not in free-ranging macaques just outside the fence of the FRI.

The high incidence of regurgitation and hair loss was in the group that sometimes picked through a garbage dump and consumed human food during the winter months. Regurgitation was not seen in the free-ranging forest troop residing just a few hundred meters outside of the institute-land troop. Johnson, Hill and Cooper [24] have reported a significant difference in the incidence of vomiting by free-ranging Indian bonnet macaques. Macaques that received food from tourists and relied heavily on trash generated by visitors and villagers, and stole food from houses and foraged on the natural vegetation were compared to a second group of macaques that lived in the Indira Gandhi Wildlife Sanctuary, nearby. Temple macaques vomited twice as often as their natural food source cohorts. These comparative findings suggest that the ethologically-normal food supply of the natural habitat may be somewhat more protective against vomiting and alopecia. In both studies, seasonal atmospheric conditions were identical between troops. The act of vomiting is aversive, a potential sign of physical weakness to both natural predators and within-troop familial

competitors for dominance in the maternal heirarchy, which are both stressful. The metabolic changes associated with a high incidence of regurgitation (i.e. acidosis) may also be contributing to the initiation of hair loss and not the ambient seasonal changes, themselves [25].

In field observations reported by Poirer [26] self-grooming in Nilgiri Langurs of India (*Presbytis johnii*) was limited to body parts where visual inspection could accompany the grooming. Legs and thighs are areas most often in the focus. As in social grooming the hand was typically the grooming agent; the mouth is occasionally employed to free debris. Individual monkeys observed in the wild sit while self-grooming, but occasionally they did so while lying down. Monkeys may groom themselves intently, but rarely continued the activity longer than 5 minutes. Interestingly, the sight of a monkey picking through its own hair appeared to be stimulate other monkeys to self-groom. Poirer reported that on occasion an animal watching another groom itself interrupted and assumed the "groomer" role. The interruption of self-grooming in free ranging animals was never rejected [26]. Poirer [26] also observed that pair-grooming was obviously pleasurable for the animal being groomed. The groomed animal was relaxed, often closed its eyes, and during longer bouts typically prone or supine on a branch, both male-male and male-female sequences were observed. Poirer reported that the relaxed attitude of the groomed animal was "marked". The animal being groomed, especially if it was lying down, was in a very vulnerable position but an attack never occurred during a grooming sequence. More interesting with respect to this review, Poirer reported no observation of a grooming animal being attacked because it pulled too hard on the hair of the groomed animal [26].

While alopecia can be a natural phenomenon, it can also be a manifestation of more systemic disease, a manifestation of social hierarchy, or due to behavioral abnormalities. On report linked alopecia in a large cohort of animals with cutaneous hypersensitivity reactions [5]. Low-ranking individuals have been shown to higher incidences of alopecia in several surveys [17,20]. Some patterns of alopecia, specifically distal limb alopecia, have been linked to psychogenic causes, analogous to similar conditions in cats and human [11]. There are many individual case reports of alopecia as a manifestation of other diseases including alopecia areata [27], latex sensitivity [28], atopic dermatitis [29,30], telogen effluvium [31], seborrheic dermatitis [32], protein malnutrition [33,34], folate deficiency [35], and zinc deficiency [36] which present primarily or secondarily as alopecia. Housing in galvanized steel cages has been associated with achromotrichia and alopecia in one group of rhesus macaques and a group of baboons, a condition known as "white monkey syndrome" [37,38]. Rarely, infants may present with total alopecia. A mutation in the rhesus "hairless" gene was identified in one such case [39,40]. A similar condition was identified in chimpanzee though the mutation was not found [41].

Management of alopecia is a challenge due to the variety of underlying conditions that are present. Regardless of the cause(s) documentation of alopecia should be present in animal's medical records. Ideally a scoring system should be implemented to categorize and track individual animals and to provide possible triggers, etc. [42]. For severe cases or those for which physical examinations suggest causes other than seasonal influences, pregnancy, or advanced age, or more intensive diagnostic evaluation is recommended to rule out underlying disease syndromes.

Initial work up of all cases should include a thorough physical exam and complete bloodwork aimed at identifying any comorbidities and possible underlying conditions. Further diagnostics can include skin scrapings to identify parasites, trichograms for hair development abnormalities or signs of hair damage, skin culture and dermatophyte culture for bacterial and fungal identifications, skin biopsy, and possibly intradermal or serum allergy testing. Stress hormones can be measured by serum, feces and hair and can be used to help determine if stress is an underlying factor. Endocrine disease, infectious disease, and allergic disease should be ruled out before a diagnosis of stress-induced hair loss is made. Treatment should be aimed at any underlying conditions identified during the diagnostic workup.

Macaque Hair and Nutrition

Rhesus monkey hair has been analyzed for 8 core elements on the Cayo Santiago macaques, by Marriott et al. [43]. Analysis of hair has been commonly used in both humans and animals as an indicator of exposure of the animals to essential and nonessential elements [44]. As in humans, element concentrations of monkey pelage are generally 10 times higher than that found in plasma or serum [45] (Table 1).

Mineral (µg /g)	Males		Females		Overall	
	Mean	SEM	Mean	SEM	Mean	SEM
Calcium	453	24.1	384	13.7	415	13.4
Phosphorus	185	4.4	200**	3.8	193	3.0
Magnesium	174**	11.17	109	6.8	138	6.7
Manganese	3.29	0.280	2.46	0.129	2.84	0.15
Iron	65	7.6	60	4.4	62	4.2
Copper	8.32	0.199	8.82	0.168	8.59	0.13
Zinc	161	4.6	158	2.9	159	2.6
*** $p < 0.001$; ** $p<0.01$						

Table 1: Hair mineral concentrations (mean +/- SEM) in rhesus monkeys from Cayo Santiago [43].

There is large variability of mean values related to both sex and age and juvenile monkeys have higher concentrations of calcium, copper, and iron [43]. Magnesium is significantly higher in males when compared to female age-matched cohorts, but phosphorus concentrations were found to be higher in female rhesus. Any deleterious or unexpected effects induced by test article administration on one of the contributing factors of alopecia may result in hair loss.

Vitamin and mineral imbalance have been suggested to be factors in hair loss [46], however the specific role of nutrients which might influence hair growth or loss in macaques has yet to be disseminated. As stated above, the hair follicle cells have a high turnover. A caloric deprivation or deficiency of several components, such as proteins, minerals, essential fatty acids, and vitamins, caused by genetic errors or reduced uptake, can lead to structural abnormalities, pigmentation changes, or hair loss, although exact data are often lacking. Zinc, Vitamin D, and proteins have been implicated in the general health of the hair coat. Moderate to severe zinc deficiency has been associated with hair loss in rhesus monkeys [36] and humans [46,47,48] that often recover with replacement therapies. However, in 2017 there is no definitive evidence to support the popular view that low serum zinc concentrations cause hair loss [46].

Age-related iron deficiencies [46,49]; as well as a surfeit of Vitamin A have been also being proposed [50-55] as significant factors in hair loss. According to the National Research Council (NRC), the minimal requirements for vitamin A are not well established. According to Tilden & Miller [56], reported that control monkeys weighing 2 to 3 kgs. and receiving 175-700 IU of vitamin A per day appeared to be in satisfactory health. O'Toole et al. [57] reported that 400 IU/day of vitamin A will maintain plasma concentrations at approximately 10 µg/dl. Transport of vitamin A in plasma and its metabolism by NHP is like humans [58-60] so the NRC has concluded that it is reasonable to set the daily requirements that are comparable to humans.

The Estimated Average Requirement (EAR) to meet the needs of an adult male human is approximately 625 µg of all-trans-retinal which is roughly equivalent to 4,000 IU/kg of dietary materials. The Recommended Daily Allowance (RDA) for human adult male is 900 µg per day which is equivalent to 6,000 IU/kg of dietary materials [61].

The NRC has concluded that this RDA should meet or exceed the needs of NHPs. Commercial NHP diets containing 20,000 to 30,000 IU/kg support normal growth, good health, and reproduction with 10,000 IU/kg considered safe and adequate to meet the needs of laboratory NHPs.

One IU of vitamin A is equal to 0.3 micrograms of all-trans-retinal; 10,000 IU / kg is equal to 3,000 micrograms or 3 milligrams per kg. As can be seen in (Table 2), the standard high-fiber primate chow contains 149 micrograms per pellet of Vitamin A. Monkeys receiving 8 to 16 pellets per day in two divided meal rations receive 3 mg of retinal, the recommended 3 mg/kg by the NRC. It is standard procedures in research laboratories conducting studies with NHPs to supplement the daily meal rations with food enrichments (i.e., Prima Treats). The laboratory food supply industry has responded to the admonishments of published reports highlighting hypervitaminosis A as a precipitating factor in NHP hair loss [50-55] (Table 2)

Vitamin	mg from Prima Treats	mg from 4 biscuits	mg from 8 biscuits	Total Intake 4 biscuits	Total Intake 8 biscuits
Vitamin A_1	0.2276	1.1962	2.3923	1.4238	2.6199
Vitamin B_1 (Thiamine)	0.072	1.3670	2.7341	1.439	2.8061
Vitamin B_2 (Riboflavin)	0.162	0.9683	1.9366	1.1303	2.0986
Vitamin B_3 (Niacin)	0.806	12.5312	25.0624	13.3372	25.8684
Vitamin B_5 (Pantothenic Acid)	0.46	6.7213	13.4426	7.1813	13.9026
Vitamin B^6 (Pyridoxine)	0.066	1.2531	2.5062	1.3191	2.5722
Vitamin B_7 (Biotin)	0.004	0.0262	0.0524	0.0302	0.0564
Vitamin B_9 (Folic Acid)	0.12	1.1392	2.2784	1.2592	2.3984
Vitamin B_{12} (Cyanocobalamin)	0.004	3.1898	6.3795	3.1938	6.3835
Vitamin C	87.68	85.4400	170.8800	173.12	258.56
Vitamin D_3	40.32	0.0188	0.0376	40.3388	40.3576
Vitamin E_3	0.844	5.1139	10.2277	5.9579	11.0717
Vitamin K	.016	0.3532	0.7063	0.3692	0.7223

Table 2: Vitamin content delivered to NHPs in daily rations of certified food/chow and standard food enrichments.

According to the most recent supplier certificate of analysis (March 17; http://www.bio-serv.com/pdf/PRIMA-Treats.pdf) the contemporaneous supply contains 37,935 IU/kg of vitamin A in the bulk product. Each PrimaTreat™ wafer weighs 5 grams. At 37.9 IU/gram, each treat delivers 189.5 IU per wafer; at 0.3 micrograms per IU, each PrimaTreat™ delivered to monkey provides an additional 56.85 micrograms of vitamin A. A standard ration of six PrimaTreats™ per day, provides only an additional 341 micrograms (0.341 mg) of vitamin A to each monkey. Based on these nutritional values, vitamin A concentrations are most likely not a precipitating event for hair loss in standard NHP colonies in the U.S in today's laboratory. The cost of a standard vitamin A serum panel is expensive and cost prohibitive. The addition of blood concentrations of vitamin A to assist in the determination of the general health status of the hair deficient monkey may not add much to a well conducted physical examination.

The NRC [62] has concluded that appropriately formulated nutritionally complete diets best serve the health and welfare needs of most captive monkeys. Standard feeding schedules of primates in captivity can fulfill their nutrient and energy needs in just a few minutes [62]. Environmental enhancement is generally accomplished through the means of providing the standard primate diet rather than through addition of treats that might be nutritionally incomplete. It should also be noted that botanic classification of wild foods in the natural habitats of macaques such as fruit, has commonly led to the misuses of cultivated fruits (for example, bananas, oranges and apples) as though they were comparable with their wild equivalents in nutrient composition, color, texture, and proportion of edible husks or shells. The NRC has highlighted that wild plants and their various parts are quite different from the cultivated plants used for human food [62-65]. The wild foods tend to be higher in fiber, and that fiber is often of low digestibility. Nutrient bioavailability also varies with source and can be different between wild foods and cultivated foods [66]. These differences may not help to explain differential alopecia within a given research laboratory, but differential food-based nutrient sources may come into play when comparing hair loss in two similar troops of free-ranging macaques living in forested versus industrial plots of land (discussed above) or between institutional and free ranging macaques.

Pharmacology of Hair Loss

One of the most common causes of hair loss in humans is dose administrations of antineoplastic (cancer) agents such as methotrexate, 5-fluorouracil, cyclophosphamide, vincristine, etc. Hair loss is evident within days to weeks following the beginning of chemotherapy. The condition is usually a diffuse, non-scarring loss of hair that is commonly reversible upon discontinuation of the medicine. Hair growth resumes approximately 2 months after treatment cessation. This is anagen effluvium, described as an event that impairs the mitotic activity of the hair follicle.

In humans, Telogen effluvium, the non-scarring, non-inflammatory alopecia with relatively sudden onset can be triggered by prescribed medications such as mood stabilizers or antidepressants including valproic acid (Valproic™), lithium, gabapentin (Neurotin™), vigabatrin (Sabril™), and carbamazepine (Tegratol™). Mercke et al. [67] highlight other, older antidepressants, such as amitryptiline (Elavil™), imipramine (Tofranil™), nortryptiline (Pemalor™) and doxepin (Silenor™) as causative factors in hair loss, which worsens with the duration of treatment. The efficacy of these older antidepressants was attributed to the blockade of synaptic reuptake of norepinephrine, which provided for a surfeit of this neurotransmitter within the synaptic cleft to improve post-synaptic receptor binding. More interestingly, the monoamine oxidase inhibitors (MAOIs) which block the degradation of all monoamine neurotransmitters (epinephrine, norepinephrine, and dopamine) are not known to induce hair loss. Other drugs whose efficacy has been linked to monoamine function such as the dopamine antagonists, haloperidol (Haldol™), olanzapine (Zyprexa™) and respiridone (Risperdal™) are also associated with hair loss [68,69]. The loss of hair following the initiation of treatment in a comorbid state of depression is a major contributor to patient noncompliance. Drug development programs and Contract Research Organizations that routinely conduct preclinical safety studies for Investigational New Drug (IND) application submission are particularly vulnerable to similar drug exposures to new molecular entities that may have similar mechanisms of actions.

By placing the spotlight on central nervous system monoamine function as a precipitating factor in hair loss are there other data to support it? While consumption of caffeine is enjoyed by millions, it is not a simple drug. Caffeine is a phosphodiesterase inhibitor, that also enhances noradrenergic (norepinephrine; [70]) and serotonergic activity [71] and functions through adenosine, as well [72]. Caffeine is a psychomotor stimulant and has been linked to self-biting, hair-pulling (barbering), and self-injury in rodents. Other CNS active stimulants such as amphetamine and pemoline can also induce these dysfunctional behaviors, albeit through other mechanisms of action [73-76]. The retrospective linkage of pharmaceuticals to changes in behavior seems logical, but no clear consensus of cause-and-effect relationships between any of these drugs and hair loss in humans or animals has been established. The monoamines may be involved in some aspect of hair loss, but all drugs have multiple effects and, as such, a direct connection may never be confirmed.

Psychological Well-being

There is often no pathology underlying alopecia and it is often assumed to be caused by "stress". Focally extensive alopecia affecting the distal limbs is a common clinical pattern in research facilities across the world [11]. As described in the literature, these macaques have irregularly shaped patches of hair loss on their forearms, lower legs, or both that is not necessarily associated with diffuse hair loss on other anatomic sites. While the hair loss may have been locally extensive, non-inflammatory alopecia was the only presenting clinical sign that initiated a request for medical/behavioral evaluations. Novak et al. [77] reported a positive correlation between hair cortisol and the degree of hair loss in caged monkeys, however these authors admonish that there was no clear evidence that stress caused the hair loss. In other published studies conducted by Sarnowski et al. [78], Steinmetz et al. [6], and Luchins et al. [79] there were no positive correlations between cortisol and hair loss. Monkeys with hair loss in these latter studies had no other biomarker for stress such as hyperglycemia, hypercortisolemia, or a stress leukogram [79]. Additionally, animals with damaged coats were reported to have lower fecal glucocorticoid levels than those with no hair loss [6].

Lutz et al. [80] have highlighted that hair loss may be self-induced. Significantly more monkeys with hair loss were reported to hair pull than those with little or no hair loss [81] and more severe cases of hair loss were associated with hair pulling [19]. Dorsal alopecia is over twice as prevalent on the right side of the animal as on the left, while limb alopecia was more than twice as common on the left than on the right side of the animal. A right-handed monkey would be expected to preferentially pull hair from the left side of the body, especially hair of the abdomen and dorsal aspects of left rib cage. There may be an overlooked, but significant, role played by the laterality of handedness that increases the likelihood of asymmetrical hair loss.

The majority of free-ranging and laboratory bred rhesus monkeys are left handed [82,83], however the animal's posture alters both the direction and strength of hand preference with monkeys showing a significant shift toward greater use of the right hand for bipedal vs. quadrupedal reaching [84]. Most monkeys are quadrupedal within the home cage, and by suggestion left-handed. In comparison, neither juvenile nor adult cynomolgus monkeys exhibited manual or positional bias at the group-level [85,86].

The focus on laterality or handedness data are relevant to the present discussion on alopecia because a significant positive correlation has been reported between cortisol levels sampled in

juveniles and the frequency of right- versus left-hand use sampled in monkeys during adulthood [87,88]. Right-hand preference is negatively correlated with stress reactivity. These data are consistent with the view that stress reactivity and function are associated with the development of hemispheric specialization in primates. It is also relevant that behavioral lateralization of handedness is associated with immune functioning and behavioral reactivity in monkeys [89].

The frequency of right- versus left-hand use was significantly positively correlated with cerebrospinal fluid concentrations of monoamine metabolites 5-hydroxyindoleacetic acid 5-HIAA (serotonin), Homo Vanillic Acid (HVA), and 3-Methoxy-4-Hydroxyphenylglycol (MHPG), plasma concentrations of the hormones cortisol and Adrenocorticotropic (ACTH), and multiple indices of social behavior, including occurrences of proximity to other animals, grooming, submission, and aggression [82,90] (but see discussion above regarding the role of amines and hair loss).

The frequency of right- versus left-hand use was significantly negatively correlated with the frequency of submissive behavior, and with the frequency and intensity of bouts in which animals received aggression. We suggest that handedness may be associated with an array of biological and behavioral processes in free-ranging adult male rhesus macaques and that left-handedness may be used to identify individuals at increased risk for impaired functioning of the serotonin, norepinephrine, and hypothalamic-pituitary-adrenal systems, and for social isolation and susceptibility to violent attack. This series of studies suggest that future examinations and interventions for alopecia should include the documentation of handedness as a possible predictive index for future studies on the topic.

With that said, Coleman et al. [91] recently used the Human Intruder Test to compare psychological aspects related to "temperament" in rhesus macaques to see if general "traits" or behavioral characteristics related to "stress" or anxiety may covary with the degree of hair loss. There have been suggestions in the published literature that certain temperamental constructs, such as behavioral inhibition, may be associated with increased vulnerability to stress and its concomitant physiological measures (refer to [92-94]). The four primate facilities described in the Coleman et al. paper experienced hair loss of 0 to 80% of total body hair in the study monkeys. Video clips were rated by two independent observers during four periods of recorded human-monkey interactions. Behaviors quantified included: 1) time spent in the back of the cage, 2) the amount of time freezing, 3) the time each subject spent engaged in stereotypical pacing and self-directed behaviors (scratch, yawn, etc.), and 4) the number of threat responses such as: a) open mouth threat, b) cage shaking, c) fear grimacing, d) lip-smacking, and e) teeth grinding when there was eye-to-eye contact between a human intruder into the colony room and the monkey. There was a significant negative correlation between hair loss and self-directed behaviors ($p < 0.001$), freezing ($p < 0.001$), defensive behaviors ($p < 0.001$) and the time spent in the back of the cage ($p < 0.05$) and pacing ($p < 0.001$). Coleman et al. [91] reported that monkeys that engaged in "stress-like" behaviors had less hair loss than those that did not express these behaviors. There was a negative relationship between the expressions of "defensive behaviors", such as lip smacking and fear grimacing, and the degree of hair loss. Stereotypical pacing was not correlated with hair loss, either. In this study behavioral expression of "anxiety-like" behaviors were not related to hair loss in rhesus monkeys.

Intervention & Treatment

Kramer et al., [11] examined and analyzed tissues from macaques diagnosed with focal distal alopecia at the New England Primate Research Center (Southborough, MA) and reported that the hair loss was not associated with bacterial, fungal, or parasitic agents. Comparative analysis of biopsies taken from affected and non-affected areas of each macaque confirmed non-inflammatory dermatosis with mild hair follicle pathology with some evidence of hair follicle damage, consistent with "presumptive psychogenic alopecia". Some of the monkeys were more dramatic hair loss were found to have skin pathology consistent with a cutaneous hypersensitivity reaction [5]. These biopsies were characterized by prominent perivascular mononuclear inflammation composed of increased numbers of mast cells, lymphocytes, and histiocytes, together with mild to moderate acanthosis and hyperkeratosis. In these latter cases, the inflammation caused pruritus resulting in self-inflicted hair loss.

Environmental and behavioral interventions may be somewhat effective in reducing the incidence of hair loss. If hair pulling is observed because of "grooming" in pair or group housed monkeys, individual housing exception from "The Guide" may be requested from the IACUC. However, current mandates within many primate facilities prioritize paired- or group-housing over single cage housing, so retaining animals in contact with social partners may well outweigh the health concerns presented by dominance-submissive over-grooming.

If a single monkey is witnessed to hair pull, distractor environmental enrichments may be delivered into the cage area, such as canvas covered fire hose sections, a braided length of nontoxic material (braided tail), steam-treated tree branches (sterilized tree branches with bark are available), or even coconuts that have been drained of milk. Our experience is that if undrained coconuts are used, they are often broken within a few minutes and are simply a fomite for bacterial growth in the cage. The inclusion of environmental enrichments as "distractors" may be minimally effective because "hair pulling" is a self-directed behavior. The placement of environmental enrichments into the cage does not target the

underlying neurological aspects of self-directed automatisms and are, therefore, not generally diminished by these types of external "distractors".

Self-directed behaviors in a NHP refers to an attentional engagement towards itself, not other NHPs or objects within the close environment. Self-directed injurious behaviors have been found to reduce anxiety in the monkeys [13,95-97] and humans [98-101]. What appears to be a subjectively painful or distressful action to a naïve human observer is most likely not to the monkey. The monkey appears to find self-injury to be a "rewarding" event. This is not surprising since it has been demonstrated over 40 years ago that NHPs will lever press to receive electric shock [102,103]. Aversive stimuli can serve as positive reinforcers. The hedonic valence (euphoria vs dysphoria) of self-directed behaviors to the point of self-injury is a function of experimental, social, and life history of the patient [97,100,101,104-106]. Reward bias is not generally predictive of therapeutic outcome by standard "distractors" that are added to a monkey cage [95,97]. This finding is supported by studies that show that these primate patients exhibit long-lasting disturbances in central and peripheral opioid and stress response systems with comorbid HPA-axis and 5-HT system functions. These monkeys have a more profound disorganization of brain function involving many neurohormonal and transmitter systems related to the hedonic valence attributed to stimuli [107,108]. Basically, the self-injuring monkey is "wired differently". The source of these alterations in brain function have been linked to their personal history including nursery rearing, single housing, and time spent in single housing [97-101,104-106]. The presence of a kong toy, food, or coconuts near fail to provide the stimulus salience that the monkey's own internal milieu provides during self-injury. This is often held true of children diagnosed with an autistic spectrum disorder and has important implications for understanding the development and maintenance of substance use disorders and potentially their treatment and prevention [109].

In cases of non-study, colony-maintained monkeys, Macy et al. [110] has reported that medical intervention with guanfacine (Intuniv ER™, 0.5 mg/kg/daily in 2 divided doses) has shown some efficacy in reducing self-injury and hair pulling.

Educating the Share Holders

The field of captive macaque management is accumulating a large body of applied research that examines common factors associated with abnormal behaviors displayed by these animals that are used in nonclinical safety assessments. A complete physical examination to assess the overall health of the animal should always be conducted that also documents the extent of the hair loss. Targeted care and case documentation is essential to maintain an institutional standard of care required by the AWA [111,112]. A standardized dermatological examination should document: 1) the lesion type, 2) distribution, 3) and both the type of additional diagnostics and location at which these were performed [113-115]. In some cases, the staff veterinarian may request blood samples for a Complete Blood Count (CBC), clinical chemistry panel, and a comprehensive metabolic profile. At the first consult the medical staff may also perform skin scrapings, surface cytology preparations, surface bacterial culture, and dermatophyte cultures. Skin scrapings are used to collect surface crust material, epidermal cells, and contents of hair follicles for analysis. Surface preparations can be conducted using standard "double-sided" tape and stained with modified Wright-Giemsa stain and evaluated under a microscope for evidence of fungal and bacterial infection. Bacterial cultures can be processed as well. In more severe cases, skin biopsies may be appropriate during the initial anesthetic episode – these can serve as the animal's own control baseline. Tissue can be processed for mast cell analysis, dermal and perifollicular fibrosis, and cellular infiltrates. While financially costly, immunohistochemistry for T cells ($CD3^+$) may also be requested.

Despite the research, behavioral managers in primate facilities have had only limited success in preventing and treating these behaviors [116-118]. Behavioral interventions require a thorough knowledge of macaque ethology (natural behaviors in the wild and natural behaviors exhibited within the closed confines the research laboratory). The science of animal welfare is not served by a "notion" that stress causes all anomalies in the colony. The automatic or reflexive presumption of a diagnosis of "stress", "distress", or altered "psychological well- being" should not be accepted within the research facility. Heagarty et al. [119] have provided a convincing argument that social hair pulling is not an aggressive behavior. Though stress may be one potential factor of behavior related hair pulling and subsequent alopecia, this should be a diagnosis of exclusion and based on sufficient diagnostic data to rule out other potential causes. Earlier this year İslamoğlu & Unal [120] reported a study of human patients experiencing alopecia areata and concluded that genetic factors may influence the development of the hair loss. This does not hold true, of course, for hair pulling that is witnessed or visualized in some manner by technical or medical staff. Government regulatory inspections can initiate unfounded fears and anxiety throughout the research institute. Proper and complete documentation of initial observations, progression and recurrence, as well as active therapeutic interventions can go a long way to protect the laboratory from experiencing a "teaching moment" during these regulatory agency inspections.

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