Comparative Medicine
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Vol 59, No 1
February 2009
Pages 18–26

# Alopecia: Possible Causes and Treatments, Particularly in Captive Nonhuman Primates

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**Alopecia (hair loss) occurs in some nonhuman primates housed in captivity and is of concern to colony managers and veterinarians. Here we review the characteristics, potential causes, and treatments for this condition. Although we focus on nonhuman primates, relevant research on other mammalian species is discussed also, due to the relative paucity of studies on alopecia in the primate literature. We first discuss the cycle of hair growth and explain how this cycle can be disrupted to produce alopecia. Numerous factors may be related to hair loss and range from naturally occurring processes (for example, seasonality, aging) to various biologic dysfunctions, including vitamin and mineral imbalances, endocrine disorders, immunologic diseases, and genetic mutations. We also address bacterial and fungal infections, infestation by parasites, and atopic dermatitis as possible causes of alopecia. Finally, we examine the role of psychogenic factors, such as stress. Depending on the presumed cause of the hair loss, various treatment strategies can be pursued. Alopecia in nonhuman primates is a multifaceted disorder with many potential sources. For this reason, appropriate testing for various disease conditions should be completed before alopecia is considered to be related to stress.**

**Abbreviation:** VDR, vitamin D receptor.

Hair loss (alopecia) is a complex phenomenon that is not fully understood either in human or nonhuman primates. Hair loss can occur as the result of a congenital or genetic disorder, or it can develop during the lifetime of the animal. Hair loss occurring throughout life can be further divided into inflammatory and noninflammatory types. In this article, we focus on alopecia in nonhuman primates. We also will refer to humans and other mammals, given that mechanisms of hair loss and potential treatments for this disorder have been studied infrequently in nonhuman primates.

Patterns of hair loss can be categorized in various ways, and several different types of scoring systems have been developed for both animals and humans.[44,45,77] Most of these systems focus either on hair volume (referring to the number of hairs per unit area and often estimated along a 3- to 5-point scale) or distribution (referring to the size and location of bald patches) or some combination of both. Using rhesus monkeys as an example, typical patterns of hair loss include: 1) substantial whole-body hair loss (balding on the head, back, legs, and arms); 2) substantial hair thinning in various body regions (that is, hair is present but sparse); 3) extensive patches of bare skin, often bilateral in presentation, interspersed with normal hair; and 4) 1 or 2 small patches of bare skin on normally haired monkeys. A third dimension of hair loss is duration: hair loss can be short-term (less than 3 mo), long-term (lasting anywhere from 3 to 24 mo), or permanent. In the following paragraphs, we consider the typical hair cycle and various factors that can disrupt this cycle to cause loss of hair.

*Received: 17 Sep 2008. Revision requested: 05 Oct 2008. Accepted: 23 Oct 2008.*
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## The Hair Cycle

The hair follicle possesses a unique ability to regenerate itself throughout the life of the organism. Hair growth occurs in a series of stages, starting with the anagen (or growth) phase. During this period, cell division in the matrix of the hair bulb produces keratinocytes, which form the various layers of the individual hair shaft. Melanocytes in the hair bulb provide the keratinocytes with pigment. After the hair reaches a certain length, which varies depending on body region, it enters the catagen (or degradation) phase, when cell division and pigmentation cease. During the telogen (or resting) phase, a new follicle appears below the original follicle, the hair shaft grows back into the original follicle, and the previous hair shaft is shed. It is unclear whether the hair is lost simply as a result of the new hair shaft's upward trajectory or whether there is a separate active shedding (exogen) stage.[92,106] Studies on human head hair growth have shown that at any point in time, most (80% to 90%) of the hairs are in the anagen phase, with 1% to 2% in the catagen phase and the remaining 10% to 20% in the telogen phase.[117]

Dysfunctions during the telogen or anagen stages appear to result in hair loss. Some forms of hair loss are associated with excessive shedding of hair, a prolongation of the telogen phase commonly referred to as telogen effluvium.[43] Other forms of hair loss are related to a failure to produce viable hair during the anagen phase. Alopecia areata universalis is an autoimmune disease caused by a peri- and intrafollicular infiltratation of T lymphocytes and macrophages, thereby leading to defective anagen-stage hair shafts and miniaturization of the follicles.[15,112] Similar anagen dysfunction appears to underlie the best-known form of hair loss in humans, androgenetic alopecia (male pattern baldness). In this case, a dysfunctional anagen stage and miniaturization of the follicles presumably is caused by the effects of dihydrotestosterone on genetically susceptible hair follicles.[78]

## Causes of Alopecia

Given the complex pattern of hair growth, it is not surprising to discover that there are many different factors that can contribute to the onset and maintenance of excessive hair loss in nonhuman primates. Although we will discuss these factors separately, hair loss in nonhuman primates very likely is a multietiologic phenomenon involving as-yet unknown combinations of factors that vary across subjects and settings. Hair loss itself has not been the focus of much research in monkeys. However, regulations to promote the psychologic well-being of captive primates along with the recent focus by regulators on alopecia as an area of concern make understanding hair loss in these animals essential.

**Naturally occurring hair loss.** Various naturally occurring changes, including seasonality and aging, are known to alter the hair cycle process.

***Seasonal variation.*** Many mammalian species undergo changes in hair production across seasons. A common pattern in some mammals (for example, ferrets)[74] involves 2 molting periods, wherein hair or fur is shed in early autumn replacing a summer coat with a winter coat and again in the spring replacing a winter coat with a summer coat. Some species also undergo a change in hair color (for example, the arctic hare whose coat is brown in the summer and white in the winter). These seasonally induced changes in hair are associated both with variations in day length and alterations in the levels of certain hormones.[47,74] In temperate regions, long days are associated with lower levels of melatonin and prolactin and shorter hair (that is, summer coat), whereas short days are associated with higher levels of both hormones and longer hair (that is, winter coat). Although little is known about the control of seasonal variation on pelage in nonhuman primates, the role of prolactin in affecting seasonal molting patterns has been well established for Djungarian hamsters,[34] goats,[32] sheep,[75] and deer.[25] Further support for the role of prolactin comes from an examination of hair regrowth cycles, which are delayed in prolactin-treated mice.[23]

Some species of monkeys appear to undergo seasonal changes in pelage. Seasonal hair loss has been reported for free-ranging vervet monkeys,[47] peaking in the months of November through January and being more obvious in subordinate monkeys. Such seasonal changes have also been observed in rhesus monkeys,[105] even when maintained under artificial light cycles. Hair loss was greatest during the winter and spring months and appeared to affect female rhesus monkeys more than males. Considerable individual differences in seasonal hair loss may occur, ranging from subjects that show no discernible pattern of hair loss (as determined by simple visual inspection) to others in which hair loss is noticeable and even extreme in nature. The causes underlying this individual variation are largely unknown. However, as noted previously, sex and dominance rank may explain some of the variance

***Aging.*** Hair loss has also been associated with the aging process. Even humans without visible hair loss show both a reduction in mean hair density and decreased growth rate of anagen hairs with increasing age.[110,113] The hair thinning that is characteristic of aged rhesus monkeys is shown in Figure 1. Two studies[45,46] have focused on age as a variable in hair loss in nonhuman primates. A comparison of geriatric and younger rhesus monkeys (mean ages, 25 and 10 y, respectively)[46] revealed that older monkeys showed skin abnormalities (that is, increased areas of reddened skin, scaling, wrinkling, and subacute dermatitis) and thinning hair. These

**Figure 1.** The left arms of 2 female rhesus monkeys, a 24-y-old (left) and a 9-y-old (right). Neither monkey has conspicuous bald spots on its torso. However, the aged monkey has thinner and shorter hair, which is particularly noticeable on her arms. The areas of skin seen on the 9-y-old monkey's arm are not due to alopecia but instead represent a normal parting of the hair produced by hair growing over the arm in one direction and under the arm in the other direction. This part, which varies in width, has been present in all rhesus monkey arms that we have photographed to date.

changes were not related to circulating concentrations of estradiol, thyroid stimulating hormone, triiodothyronine, thyroxine, and cortisol, nor were they a result of bacterial infections. An exploration of hair loss in a squirrel monkey colony[45] revealed that hair loss in female monkeys was associated with both older age (9.6 y for monkeys with hair loss versus 4.7 y for monkeys with a normal coat) and increased parity (4.2 versus 2.0, respectively). Hair loss was unrelated to body weight, serum chemistry (for example, hemoglobin, serum glucose, BUN), or free thyroxine. Monkeys with hair loss had more telogen hairs than did normally haired monkeys, suggesting an alteration of the hair cycle process consistent with chronic telogen effluvium.

**Nutritional and hormonal imbalances.** ***Nutritional factors.*** Although vitamin and mineral imbalances have been posited as causes of hair loss,[98] the nutritional parameters that might regulate hair production have not been evaluated comprehensively. Much of the focus has been on zinc, vitamin D, and protein. Studies of the role of zinc in hair loss demonstrate the principle that both too little and too much of a substance can have deleterious effects. Moderate to severe zinc deficiency has been associated with alopecia in rhesus and bonnet macaques,[109] marmosets,[20] talapoin monkeys,[48] and children.[4] In all of these cases, addition of zinc to the food or drinking water led to a substantial improvement of skin and hair. A milder deficiency that was sufficient to retard skeletal growth and maturation in adolescent rhesus monkeys did not reliably produce alopecia.[40] Conversely, exposure to toxic levels of environmental zinc has also been associated with alopecia, usually in combination with anemia and achromatricia (also called 'white monkey syndrome'). In 1 report,[38] elevated zinc levels and white monkey syndrome were found in young baboons housed in 1 of several galvanized metal and concrete cage units. This particular unit received significantly lower levels of sunlight than did other units, and the authors hypothesized that zinc leaching from the galvanized cage during cage rinsing led to contaminated standing water that did not dissipate quickly because of the low illumination. Removal of the animals from this particular cage led to a reversal of clinical signs in most cases.

Although vitamin D is thought to play a role in hair production, most of the evidence for this hypothesis comes from studies of mice lacking the vitamin D receptor (VDR) and humans with VDR mutations.[16,51] Targeted removal of the VDR in mice produces a cluster of clinical signs (including hypercalcemia, hyperparathyroidism, and rickets) that includes alopecia.[61] The alopecia appears to be the result of an inadequate response of hair follicles to anagen initiation.[100] Selectively restoring VDR to the keratinocytes by crossing VDR knockout mice with transgenic mice expressing the human VDR successfully prevented the development of alopecia.[21] Because the effect of the VDR on hair loss is ligand-independent,[99] the actual role of vitamin D in regulating hair growth remains elusive. Furthermore, little is known about the role of the VDR in hair loss in nonhuman primates.

Alopecia has also been associated with other deficiencies and overdoses. A syndrome of alopecia, weight loss, and hypoalbuminemia in Western lowland gorillas eventually was traced to protein deficiency.[70] This finding is consistent with the reported hair loss and hypoalbuminemia in young baboons experimentally exposed to a protein-deficient diet.[22] Hair loss has also been linked to folacin deficiency in squirrel monkeys.[93]

Two other nutritional factors merit some discussion, even though the influence of these factors has not yet been studied in nonhuman primates. An extensive literature in nonmenopausal women suggests that iron deficiency can result in alopecia.[28,98] However, reduced iron stores do not account for all forms of hair loss. One study[50] found a significant association of iron levels and hair loss in cases of androgenetic alopecia and alopecia areata but not in cases of alopecia universalis or telogen effluvium. Vitamin A also may have an effect on hair loss. Rats fed a diet deficient in vitamin A developed a constellation of clinical signs that included anemia and alopecia.[66] Conversely, a syndrome of severe emaciation and alopecia in calves was thought to be due to a vitamin A overdose.[118] Whether low iron stores or vitamin A levels affect hair growth in nonhuman primates is largely unknown. However, the designated requirements for vitamin A in Old World monkeys have recently come under scrutiny as possibly being too high.[68,85,86]

***Hormonal imbalances or changes.*** Changes in hormone levels have long been known to play a role in hair loss, particularly in humans. Perhaps the best known example is male pattern baldness (androgenetic alopecia), which is caused by the conversion of androgens into dihydrotestosterone within genetically vulnerable hair follicles. Dihydrotestosterone shortens the anagen phase and causes follicles to become miniaturized.[78] This condition appears to have no nonhuman primate homologue, although the stumptailed macaque with its characteristic bald forehead has been used as a model for studying the effects of minoxidil on hair growth.[30,31] However, other hormones can be linked to hair loss in both humans and animals. Here we focus on the possible roles of hypothyroidism, tumors of the pituitary or adrenal causing hyperadrenocorticism, and pregnancy in hair loss.

Hypothyroidism has been most well studied in dogs in part because of the high prevalence of this endocrine disorder in a variety of breeds.[24,33] Primary hypothyroidism, which is associated with a gradual decline in functional thyroid tissue,[37] gives rise to alopecia in about 25% of cases.[82] The hair loss appears to be a result of telogen effluvium, and treatment with thyroxine generally induces hair regrowth and improved skin.[24] In comparison to humans with hypothyroidism, dogs with this endocrinopathy require a substantially higher dose of thyroxine because of decreased rates of absorption and increased rates of clearance.[72] Less is known about hypothyroidism and its link to hair loss in other species. However, hypothyroid-related hair loss has been reported for a gorilla,[60] an orangutan,[108] and a chimpanzee.[67] Treatment with thyroid hormone reversed the alopecia in all cases except for the chimpanzee, for which hormone treatment was planned, but the effects were not described.

Hyperadrenocorticism (Cushing syndrome) has been studied extensively in both humans and canines. In dogs, this endocrinopathy is associated with excess glucocorticoids either from therapeutic administration of glucocorticoids (iatrogenic disease) or from excess adrenocorticotropic hormone secretion by the anterior pituitary, most often due to tumor of the pars distalis region. One of the classic signs of pituitary-dependent hyperadrenocorticism in dogs is a symmetrical pattern of hair loss that affects nearly the entire body except for the head or lower extremities.[37] Typically pituitary-dependent hyperadrenocorticism is differentiated from stress-induced elevations in cortisol by means of several screening procedures, including the adrenocorticotropic hormone stimulation and dexamethasone suppression tests. Treatment of pituitary-dependent hyperadrenocorticism generally involves surgical removal of the tumor in humans, whereas both surgical treatment and drug administration have been used in dogs. Dogs have been treated successfully with lysodren (a relative of DDT),[88] which suppresses the production of cortisol in the adrenal cortex and causes progressive destruction of adrenal tissue. Dogs must be monitored closely, and cortisone supplements must be available to reverse the suppression if necessary. Currently, trilostane is used increasingly to treat pituitary-dependent hyperadrenocorticism and appears to have fewer side effects than does lysodren.[95] Although the incidence of pituitary-dependent hyperadrenocorticism in nonhuman primates is largely unknown, a recent case report of hair loss in a Japanese macaque was attributed to hyperadrenocorticism on the basis of changes in skin morphology and various endocrine and hematologic parameters.[56]

Hair loss has been associated with pregnancy and the postpartum period in both humans and animals. Pregnancy can induce telogen effluvium in some women;[71] however, this form of hair loss is associated more commonly with the postpartum period, occurring in about 30% to 50% of women.[27] In most women, the hair loss is temporary, and regrowth occurs in about 3 to 6 mo. Little is known about the causes or possible treatments for this condition.[35] Both pregnancy and lactation have been associated with diffuse telogen effluvium in some breeds of dog.[19] Furthermore, a recent report[26] links hair loss to pregnancy in some rhesus monkeys. During gestation, 10 breeding female monkeys, housed in an indoor-outdoor run, showed substantial hair loss that was unrelated to seasonal influences. After parturition, hair grew quickly, and full coats were restored within 2 mo (Figure 2 ). As for humans, there is no established treatment for this condition in nonhuman primates, but vitamin, mineral, and hormonal imbalances should be ruled out.

**Immunologic and genetic factors. *Autoimmune hair disorders.*** Alopecia areata is an immunologic disorder that generally affects men and women between the ages of 20 and 40 y.[117] The disease

**Figure 2.** Depicted is the change in hair condition in a female rhesus monkey over the course of her pregnancy. The top and bottom photos, in which the hair condition is normal, were taken at the time of conception and 2 mo after parturition, respectively. The middle photo, showing total-body alopecia, was taken during the month when parturition occurred. These photographs are courtesy of E Davis (NIH Animal Center, National Institute of Child Health and Human Development, Poolesville, MD).

starts with rapid patchy hair loss, which can spread to the entire scalp (alopecia areata totalis). In rarer cases, alopecia areata can involve hair loss over the entire body (alopecia universalis).[84] The typical pattern involves the development of only a few patches that disappear very slowly as a result of regrowth from the periphery. Alopecia areata is characterized by a dysfunctional immune response, in which the hair follicle is invaded by lymphocytes (primarily CD4-positive T lymphocytes) and macrophages that target specific antigens of the anagen hair follicle. The occurrence of a similar kind of immune-mediated hair disease has been noted both in rhesus monkeys and chimpanzees. One reported case involved a female rhesus monkey presenting with total hair loss since infancy.[15] Based on clinical examination, serologic testing, and histologic and immunocytochemical examinations of the skin showing perifollicular lymphocytic infiltration, the authors concluded that the monkey had alopecia universalis. A similar conclusion was reached in determining the cause of total body hair loss in a female chimpanzee.[36]

Several other autoimmune disorders are associated with alopecia. Lichen planus is an inflammatory disorder affecting the follicles and inducing hair loss.[6] Lupus erythematosus is associated with nonscarring alopecia in 40% of cases, but in a small percentage of cases (14%), a scarring alopecia can develop secondary to discoid lesions.[119] At present, lichen planus has not been reported in nonhuman primates; however, a systemic lupus erythematosus-like syndrome occurred in a rhesus macaque,[5] and a similar syndrome was observed in cynomolgus monkeys maintained on a 40% alfalfa sprouts diet.[64]

***Mutations of the hairless gene.*** Certain forms of hair loss have been linked to mutations in the hairless (*hr*) gene in mice and humans. Atrichia with papular lesions is a rare genetic disorder in which organisms are born with hair which, once shed, is never replaced.[2,18] An examination of the skin reveals the absence of normal hair follicles and the presence of papular cysts. Permanent and total hair loss occurs between days 14 to 21 of postnatal life in mice and during the first year of life in humans.[83] Mutations of *hr* also can produce hair loss in rhesus macaques. An infant rhesus macaque was born fully haired at the Tulane Primate Center but lost all of its hair and eyelashes within the first week of life.[94] Analysis of its skin showed an absence of hair follicles and the presence of dermal cysts. Subsequent genetic evaluation revealed mutations in the *hr* gene.[1]

**Inflammatory hair loss.** A variety of skin conditions are associated with inflammation and pruritis and may also result in hair loss. These etiologies include bacterial infections, either primary or secondary to some other disease process, parasitic infections, and allergic processes (for example, dermatitis).

***Bacterial infections.*** Several different bacteria affect the skin, producing lesions and hair loss. *Staphylococcus* bacteria can produce a scarring alopecia (folliculitis decalvans) in middle-aged adults.[79] *Staphylococcus* infections have also been shown to produce skin lesions and alopecia in sheep,[59] horses,[29] and dogs.[90] Furthermore, induction of chronic salmonellosis in guinea pigs was associated with hair loss that varied across subjects as a function of the route of administration and the strain of *Salmonella*.[102] Although bacterial infections should be ruled out as a possible source of hair loss, no available report suggests that bacterial infections are a leading cause of hair loss in captive nonhuman primates.

Bacterial skin infections also can develop as a secondary consequence of other diseases. Most relevant for nonhuman primates are the skin infections that can develop in monkeys with diabetes. Humans with either type 1 or type 2 diabetes are at increased risk for skin infections that can lead to hair loss.[69] Skin infections were noted in mandrills with a syndrome similar to type 2 diabetes.[91]

***Parasitic infections.*** Fungal infections can cause hair loss that generally is associated with pruritis. Tinea capitus is a disorder that produces scalp eruptions and hair loss in both children and adults.[65] The infection typically is caused either by *Microsporum canis* or *Trichophyton tonsurans*. Fungal infections (usually caused by *M. canis*) have also been detected in rhesus monkeys,[13,81] chimpanzees,[57] and gibbons.[111] Treatment with oral antifungal preparations (for example, griseofulvin and itraconazole) was generally effective in reducing or eliminating the infection. Recent research suggests that topical treatment with a sustained-release preparation of clotrimazole can effectively eliminate *M. canis* infection in gibbons.[12]

Several insect parasites can produce oozing skin eruptions and hair loss. Prominent among these is the sarcoptic mange mite, which has a worldwide distribution. *Sarcoptes scabiei* mites parasitize many different mammals. However, evidence suggests that mites have species-specific hosts and that cross-transference to a nonspecific host produces a pseudosarcoptosis, which is transient and self-limiting.[11] Diagnosis can be established from microscopic examination of skin scrapings. Sarcoptic mange is quite rare in nonhuman primates and appears to be limited to monkeys maintained in natural or seminatural settings. Sacaroptic mange was identified in 5 juvenile, human-habituated mountain gorillas in Bwindi Impenetrable National Park, Uganda,[41] and in an adult female bonnet monkey maintained in an open enclosure in a seminatural environment.[73] In both cases, sarcoptic mange was treated successfully with ivermectin.

***Atopic dermatitis.*** Atopic dermatitis, a common cause of hair loss in cats and dogs, is a chronic skin condition that appears to be precipitated by exposure to allergens. The condition is associated invariably with pruritus, which sometimes results in oozing sores that can lead to secondary bacterial infections. The dermatitis may be caused by airborne allergens (for example, dust mites), food sensitivity, or direct skin contact with allergens in cleaning agents, toys, and bedding products. Atopic dermatitis was identified as the cause of skin inflammation and alopecia in 2 case studies involving rhesus monkeys.[63,80] An allergen-specific IgE antibody test was used to screen for potential allergens. In 1 case, a possible latex allergy was identified and confirmed through skin prick tests. Replacement of latex gloves with vinyl gloves led to a marked improvement in the skin condition of this monkey.[63] In the other case, the source of the allergic reaction could not be identified with an allergen-specific IgE antibody test.[80] This outcome is not uncommon, in that the source of the allergic reaction can be difficult to identify. Despite this difficulty, several treatments have proven somewhat effective. Essential fatty acids are now being used to treat atopic dermatitis. This treatment appears to have few side effects and is effective in reducing inflammation, skin lesions, and pruritis in dogs[99] and humans.[49,58] Furthermore, oral administration of a fatty acid (dihomo-gamma-linolenic acid) to NC/Nga mice that spontaneously developed atopic dermatitis resulted in a marked dose-dependent reduction in the severity of the lesions.[54] Steroids have also been used to treat atopic dermatitis and may be the pharmacotherapy of choice in some cases, despite the possibility of considerable side effects.[3] However, recent reports indicate that cyclosporine, a macrolide calcineurin inhibitor, may be as potent as glucocorticoids in eliminating atopic dermatitis.[76] Cyclosporin successfully reduced skin lesions and pruritus and produced hair growth in dogs,[76] cats,[114] and in the described rhesus monkey for which no specific allergen was identified.[80]

**Psychologic factors and hair loss.** The role of psychologic factors in hair loss is not well understood. Here we focus on various behavioral characteristics that may lead to hair loss and examine the concept of stress-related hair loss.

***Self-induced hair loss.*** Monkeys and apes can develop an abnormal pattern of behavior in which they pluck their hair.[14] Some animals pull their hair, out creating bald patches, whereas other hair pullers show little evidence of hair loss. This disorder shares some similarities with the human pathologic disorder trichotillomania.[116] In both cases, the act tends to be highly ritualized and repetitive: after the hair is pulled, it usually is manipulated and then ingested. Some investigators speculate that hair pulling is brought about by environmental stressors or by exposure to impoverished captive environments.[96] Indeed, 14% of rhesus monkeys housed in individual cages developed this pathology.[62] However, other medical conditions may underlie the development of hair pulling, and therefore a health exam is necessary to rule out physical causes. This point was underscored in a recent study of psychogenic alopecia in cats. Cats that had previously been diagnosed with psychogenic alopecia (an apparent compulsive licking or grooming associated with hair loss) were reevaluated. Of the 21 cats in the study, 16 actually had a medical disorder, the most common being atopic dermatitis, leading the authors to conclude that psychogenic alopecia is overdiagnosed.[115]

Currently, no established treatment for hair pulling reliably reduces or eliminates this behavior. Little substantiated evidence indicates that environmental enrichment routinely alleviates this behavior, although exercise cages[107] or social housing.[104] may provide some benefit. The failure to reduce or eliminate this perplexing behavior in captive primates underscores the need for future research to determine the underlying causes and identify effective treatments.

***Hair pulling by others.*** Nonhuman primates living in social groups may be vulnerable to having their hair pulled out by other animals. In a study of 2 breeding groups of rhesus monkeys, monkeys pulled hair at the rate of 2.3 episodes per hour. Most of the episodes were directed to other monkeys rather than to self (97% versus 3% respectively).[97] Reduction in socially directed hair pulling in group-housed monkeys was noted after provision of a foraging task.[17] However, in our experience, the problem may be more difficult to extinguish in pair-housed monkeys and may not necessarily be eliminated with new partners. In this situation, the only known successful treatment is separation of animals; therefore, the risk of alopecia induced by hair pulling has to be weighed against the cost of individual cage housing.

***Stress.*** Increasing evidence suggests that stress may be associated with hair loss. This notion began with early uncontrolled studies and, in some cases, anecdotal reports that alopecia areata in humans might be due to stressful life events. A review of this body of information[89] pointed out the noteworthy limitations of such approaches. Subsequent studies that were better controlled did find some evidence for a role of stress in precipitating episodes of hair loss. Nevertheless, the authors of the review[89] urged caution regarding assuming a definite association between stress and either the onset or exacerbation of alopecia areata.

Thee possible relationships between stress and hair loss in humans have been proposed:[42] 1) stress (either acute or chronic) could be a primary causal factor in triggering hair loss by telogen effluvium; 2) stress could be a secondary factor in exacerbating hair loss due to a preexisting disorder, such as endocrine imbalance, toxin exposure, nutrient deficiency, or autoimmune disease; and 3) stress could be induced by the psychologic effects of losing one's hair, which then might exacerbate the problem in a classic 'vicious circle.' Only the first 2 hypotheses would seem to pertain to nonhuman primates, because the relevance of alopecia as a stressor for nonhuman primates is questionable at best.

The primary effects of stress on hair growth or loss have been explored most fully in mice. Mice exposed to footshock or noise exhibit hair loss as a result of prolonging the telogen phase, thereby delaying anagen phase induction,[7,52] or by prematurely terminating the anagen phase, leading to more rapid development of the catagen phase.[9] The mechanisms responsible for these effects appear to be complex, involving multiple biologic pathways.[10] At a cellular level, various stressors may induce a local inflammatory response that leads to an inhibition of keratinocyte proliferation as well as an increase in apoptotic death of keratinocytes in telogen-stage hair follicles.[8] The signaling pathways mediating these effects are thought to involve the peptide substance P acting on neurokinin 1 receptors,[9,52] nerve growth factor,[87] and possibly glucocorticoids due to activation of the hypothalamic–pituitary–adrenocortical axis. Moreover, elements of the skin (including hair follicles) appear to have their own endocrine-like system that includes local synthesis and expression of corticotropin-releasing hormone and its receptors, adrenocorticotropic hormone, and cortisol.[10,103] Some evidence indicates that this system is upregulated in affected areas of skin in patients with alopecia areata.[53,55]

Alopecia in captive macaque monkeys, at least as related to hair-pulling behavior, has been attributed to stress.[44] Nevertheless, currently little, if any, evidence supports a direct association between stress and alopecia in nonhuman primates and certainly no mechanistic information is available. In fact, 1 recent study found a reduction rather than an increase in fecal levels of the cortisol metabolite 11-oxoetiocholanolone in rhesus monkeys with alopecia.[105] Clearly, more research in this area is needed before any reliable conclusions can be drawn.

If alopecia is due to stress, pharmacologic treatment might be beneficial. One report[39] cites anecdotal data suggesting that alopecia areata may respond positively to treatment with antidepressant or anxiolytic drugs, but the authors also note the need for appropriately controlled clinical trials to substantiate such observations. A retrospective study of 11 cats investigated psychogenic alopecia related to overgrooming (potential biologic causes of hair loss were ruled out by examining veterinarians). Consistent with the anecdotal reports regarding alopecia areata, most of these animals responded positively to antidepressant or anxiolytic drug administration.[101] We know of no reports of successful treatment of alopecia in nonhuman primates with psychoactive medications.

## Managing Alopecia in Laboratory Primates

Because monkeys in captivity can develop alopecia, it is important to determine the likely causes and identify effective treatments. As we have discussed, many different factors contribute to hair loss in nonhuman primates. But clearly some of these factors are quite rare (for example, mutations of the hairless gene), whereas others may be more common. Here we present a possible strategy for determining the causes of and managing alopecia in nonhuman primates.

The first step in the process is assessment. As part of regular health exams, animals' hair and skin conditions should be routinely assessed. Quantifying the hair loss and evaluating the skin surface may be useful in determining whether the condition is improving or deteriorating from one health exam to the next. Photographs to document progression can be a useful tool. The second step is to determine whether immediate medical evaluation is necessary. In this regard, dividing cases of alopecia into 2 categories may be helpful. The first is the 'wait and watch' category which would include cases of minor hair loss (one or more small patches) as well as hair loss associated with seasonal or reproductive factors that would be expected to resolve on its own without significant consequence. The second is a medical evaluation category which would include alopecia associated with reddened and inflamed skin, extensive whole-body hair loss that cannot be attributed to seasonal and reproductive factors, and excessive hair plucking. For cases requiring medical evaluation, the third step is to obtain skin biopsies for evaluation of inflammation, bacterial, fungal, or parasitic infections. Biopsies also can provide information on hair follicle condition. This information should be supplemented with behavioral observations to determine the incidences of scratching and presence or absence of hair pulling by self or others. This determination can often be made by animal care technicians, who are most familiar with the animals, but these determinations also can be made by environmental enrichment technicians by using direct observation or video recordings of subjects with alopecia along with room-matched controls. The fourth step, if necessary, is to obtain blood samples for routine screening and assessment of relevant hormone levels. The final step is to narrow the range of possibilities and consider treatment options. Here we consider 3 scenarios representing what might be the more common causes of hair loss in nonhuman primates and possible treatments.

**Scenario 1.** If increased scratching is observed along with reddened skin, and biopsies have ruled out bacterial, fungal, or parasitic infections, then the most likely diagnosis is atopic dermatitis. If the source of the allergen cannot be identified and removed, then several treatment options are available depending on the research protocol. For nonhuman primates, treatment with oral steroids or cyclosporine should be considered. We successfully treated 1 aged female monkey with pronounced total-body hair loss, inflamed skin, and pruritis by administering dexamethasone orally for a period of several months, during the latter part of which the dosage was gradually reduced. Treatment was effective in restoring full body hair, and her coat has been maintained for well more than 1 year after treatment.

**Scenario 2.** If the hair loss is self-induced (by hair pulling) and skin biopsies have ruled out inflammation and bacterial, fungal, and parasitic infections, then a tentative diagnosis is psychogenic or stress-induced hair loss. If the stressor cannot be identified and removed (possible sources include experimental procedures, husbandry practices, and other animals, among others), then 2 strategies might be useful. The first is an enrichment strategy in which the environment is modified to provide the animal with greater stimulation. Such changes might include pair housing. The second is a pharmacotherapeutic strategy in which the animal is treated for anxiety by using anxiolytic drugs such as diazepam. However, no systematic studies show that either of these strategies is completely effective in eliminating hair-pulling behavior. Moreover, any proposed treatments for alopecia must be compatible with the research protocol under which the animal is being studied.

**Scenario 3.** If behavioral correlates of the hair loss are not apparent and skin biopsies reveal no evidence of skin inflammation or the presence of bacterial, fungal, or parasitic infections or alterations in hair follicle biology, then other factors have to be considered in the diagnosis. Three such factors include seasonal variation, reproduction, and age. Seasonal or pregnancy related-hair loss should resolve within 4 to 8 mo without treatment. If none of these factors is related to the hair loss or if the hair loss does not resolve, then hormonal imbalances and nutritional deficits should be ruled out. If the hair loss appears to be a natural consequence of aging, no treatment is currently available to ameliorate this condition in nonhuman primates.

## Conclusions

A variety of factors are known to produce hair loss in mammals and, more specifically nonhuman primates. Some of these factors are rare, accounting for only a small percentage of monkeys that show alopecia; others are probably much more common. In general, little is known about the prevalence of different types of hair loss in captive nonhuman primates, in part because of a tendency to view hair loss in this mammalian order as a unitary phenomenon related to stress. Identifying the causes of hair loss in individual primates depends on an assessment approach involving health exams, skin biopsies, blood screening, and behavioral observations. Knowing the cause is crucial to establishing effective treatment regimens. However, hair loss also can result from several causative factors working in concert. Furthermore, much remains unknown about treatment. Whereas some forms of alopecia can be treated (for example, hair loss associated with hypothyroidism), well established treatments are not available for other forms (for example, hair loss associated with hair pulling). In fact, simply monitoring the animal may be the best approach when underlying medical causes are ruled out and other clinical signs such as dermatitis or pruritus are absent. Finally, some forms of hair loss cannot be remediated (for example, mutations of the hairless gene, hair loss in some animals as a result of old age), and therefore alopecia most likely will never completely be eliminated from captive nonhuman primate populations. These problems underscore the need for future research on the causes of hair loss in nonhuman primates, not only to benefit their condition but also to develop new biomedical models to advance our understanding of alopecia in humans.

## Acknowledgments

The preparation of this manuscript was supported by grants RR11122 (to MAN) and RR00168 (to the New England Primate Research Center) from the National Institutes of Health.

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