Journal of the American Association for Laboratory Animal Science
Copyright 2011
by the American Association for Laboratory Animal Science

Vol 50, No 3
May 2011
Pages 396–400

Hyperhidrosis in Naïve Purpose-Bred Beagle Dogs (*Canis familiaris*)

Catherine A Carrier,[1,*] Jennifer L Seeman,[1] and Guenther Hoffmann[2]

This case study details the unusual clinical findings in a unique paw-pad disorder that recently emerged among 2 male and 1 female naïve purpose-bred beagle dogs (*Canis familiaris*) newly received into our facility. During acclimation period physical examinations, the affected dogs demonstrated constantly moist, soft paw pads on all 4 feet. No information was available regarding the epidemiology and pathogenesis of this pad condition in beagle dogs. Here, we report the results of physical examination, clinical chemistry analysis, hematology, histopathology, detailed observations, and novel testing techniques performed during the acclimation period. Histopathology of several sections of affected footpads was compared with that of an age-matched dog with clinically normal paw pads. We describe the morphologic features of a distinctive cutaneous canine footpad condition and discuss the possible differential diagnoses. The histologic and clinical features were most consistent with those of hyperhidrosis; to our knowledge, this report is the first description of hyperhidrosis as a distinct condition in purpose-bred beagle dogs.

Skin consists of the epidermis, basement membrane, dermis, appendageal system (hair and sweat glands), subcutaneous muscles, and fat.[14] The relative prominence of these components may vary depending on the anatomic location and amount of pressure or friction applied during normal use. The digital pads, on the plantar surface of the dog's foot, are specialized skin with a heavily keratinized epidermis and thick submucosal adipose layer, which provides additional protection and cushioning to these weight-bearing surfaces. In addition, paw pads in dogs are one of the few locations that contain eccrine sweat glands. In dogs, apocrine glands are the major type of sweat gland, and the distribution of eccrine sweat glands is limited to the footpads and nose.[14] Eccrine glands are unbranched, tubular in form, and open directly onto the surface of the skin.[14] They secrete a watery product that is hypotonic to plasma. Evaporation of this secretion on the surface of the skin aids in thermoregulation. However, the frequency of sweating and the circumstances under which sweating occurs in dogs is unclear.[14]

The cases we present here involve young beagles with constantly moist, soft paw pads with no other presenting signs. Conditions affecting the paw-pad surface typically can be divided into 3 main categories: congenital or hereditary, infectious, or traumatic. Congenital and hereditary disorders of the surface and follicular epithelium in dogs include a primary keratinization disorder, follicular parakeratosis, canine benign familial chronic pemphigus, epidermolysis bullosa, and familial canine dermatomyositis.[14] Infectious causes seen in the paw include viral (papilloma virus),[2,12] bacterial, and fungal agents, such as *Malassezia* spp. Trauma or overuse-related conditions include acute moist dermatitis, acral lick dermatitis, and simple abrasions. Given that all affected dogs in this case study were research-naïve (that is, never received any test compounds and were fed a standard certified canine diet while inhouse), we ruled out nutritional disorders and drug eruptions. The lesions on the paw pads did not appear to be trauma-related, because the surface of the skin was intact initially, with no bleeding or swelling. These findings lead to our main differential diagnoses of genetic or hereditary abnormalities.

Many hereditary disorders have been identified in dogs during the past few decades, and every year new disorders are discovered.[11] Historically, some breeds were developed by inbreeding a limited number of related founder dogs and then expanding the resulting population,[11] as is the case in the extensive breeding of beagle dogs for research purposes. In general, due to advances in veterinary medicine, surgery, and health surveillance, such as balanced nutrition, use of antimicrobials and vaccines, domestic dogs have experienced a diminished frequency or improved management of acquired conditions and consequently increased length of survival. The generally improved health conditions of pet animals also has lead to an overall increased recognition of genetic defects in dogs.[11]

Beagles are rarely reported in the literature as having footpad conditions of genetic origin, like epidermolysis bullosa and familial canine dermatomyositis. Epidermolysis bullosa simplex has been reported to occur in collie dogs[15] and 4 other cases.[3] Epidermolysis bullosa is a group of genetic conditions caused by mutations in keratin or anchoring filament genes, resulting in a separation of the epidermis and dermis that causes the skin to be very fragile, such that erosions and blisters form easily in response to minor injury or friction, such as rubbing or scratching. Epidermolysis bullosa simplex is a leading form of epidermolysis bullosa. In humans, multiple clinical subtypes are recognized, and lethal and nonlethal variants are described in the dog.[14] In mild cases, blistering may primarily affect the hands and feet, and the blisters usually heal without leaving scars. In dogs, erosive to ulcerative lesions are most marked on the pinna, bony prominences of the face, pressure points on the limbs, and footpads.[14] Furthermore, familial canine dermatomyositis has been identified in collies.[8] In this condition, cutaneous lesions present at 7 to 11 wk of age on the face, lips, ears, and skin over boney prominences of the limbs, feet, sternum, and tip of the tail. Lesions often involve muscle in addition to the

Received: 18 Aug 2010. Revision requested: 27 Sep 2010. Accepted: 22 Nov 2010.
[1]Veterinary Services and [2]Pathology Services, Nonclinical Safety Assessment, Covance Laboratories, Madison, Wisconsin.
[*]Corresponding author: Email: Catherine.Carrier@covance.com

skin and lead to muscle atrophy.[8] The presentation and histologic findings described for epidermolysis bullosa simplex and familial canine dermatomyositis vary considerably from those of the beagles we examined in this case study, suggesting that a different condition was present.

Hyperhidrosis is characterized by sweating in excess of the amount that is necessary to maintain thermal homeostasis. This condition has not previously been reported in beagle dogs as a distinct condition but has been reported as a minor feature in some dogs with atopic dermatitis, often associated with yeast overgrowth.[10,14] In addition, hyperhidrosis may be present in 10% to 20% of atopic dogs.[14] In previous reports, hyperhidrosis was noted in conjunction with other signs of atopic dermatitis, including areas of pruritus, intermittent otitis externa, conjunctivitis, secondary bacterial or *Malassezia* infections in self-traumatized areas of skin, which usually occur on the feet, face, distal extremities, anterior elbows, and ventrum or some combination thereof.[14]

However, hyperhidrosis in people is a common, distinct medical condition affecting an estimated 2.8% of the population.[6] It is likely a heritable condition, in that 30% to 50% of affected patients have a positive family history.[6] There are 2 main categories of hyperhidrosis. In primary hyperhidrosis, sweating is usually focal, typically affecting localized areas of the body such as the axillae, palms, perineal–inguinal area or soles, although any area on the body can be affected. Secondary hyperhidrosis usually has a generalized distribution, with sweating over the entire body from secondary causes, such as malignancies, drugs, or endocrine conditions.

Primary hyperhidrosis in people has the following characteristics: sweating impairs daily activity; has an age of onset of less than 25 y; is associated with a positive family history; distribution is bilateral and relatively symmetrical; and focal sweating ceases during sleep. Histologic studies have shown no increase in the number or size of eccrine glands in patients who have hyperhidrosis.[6] Because eccrine glands are innervated by sympathetic nerve fibers, hyperhidrosis is thought to be due to sympathetic overactivity in affected people.[6]

The cases described here represent a new hyperhidrosis-like condition in the footpads of purpose-bred beagles. No information regarding the epidemiology and pathogenesis of this condition in beagles is currently available. We present findings from physical examination, clinical chemistry analysis, hematology, histology, detailed observations, and novel testing techniques performed during the acclimation period that support the likelihood of these dogs having hyperhidrosis.

Case Study

Clinical history and histopathologic evaluation. Initially, 2 naïve purpose-bred beagle dogs (*Canis familiaris*), one male and one female, both younger than 1 y and newly received into our facility, were identified during the acclimation period, initial evaluations, and baseline data collection. Evaluation of dogs during their 2-wk acclimation period to the facility before inclusion in a study included the following procedures: initial detailed physical examination, clinical pathology (CBC and clinical chemistry panels on 2 occasions), and detailed daily observations to identify any aberrations such as fecal abnormalities or problems with food consumption; actual protocols may have varied depending on study requirements. These 2 initial dogs had permanently moist paw pads on all 4 feet, and this moisture on the pad surface consistently returned when dried with a towel during physical examination. All other physical examination findings for these 2 dogs were considered to be within normal limits. The dogs did not demonstrate any limited use of the limbs or pain on palpation of the affected footpads. Paw surfaces were intact, with no gross ulcerations, fissures, abrasions, or erosions. These dogs had multicolored black and white footpads.

As a result of these findings, the dogs (nos. 1 and 2) were excluded from future studies and underwent veterinary histopathologic evaluation of the paw pads. At the same time an age-matched control dog (no. 3) was selected for comparison purposes. All dogs were euthanized with an intravenous overdose of sodium pentobarbital (Fatal-plus, Vortech Pharmaceuticals, Dearborn, MI). Review of baseline hematology and clinical chemistry collected on all 3 dogs during acclimation was unremarkable and did not identify any underlying disease (Table 1). For this case study, 'control dogs' are those with footpads that appear grossly normal on examination by a veterinarian.

Housing. All dogs in this case study were on IACUC-approved protocols and were housed indoors at Covance Laboratories, a facility that is fully AAALAC-accredited. Environmental conditions, including temperature, humidity, and lighting, were in accordance with the *Guide for the Care and Use of Laboratory Animals*,[9] and animals were managed consistent with all applicable regulations as prescribed in the *Animal Welfare Regulations*.[1] Dogs were housed in 1188-in.^{2} (7659.3-cm^3) stainless steel, suspended, 2-tier dog racks with 4 cages per unit. All cages were equipped with a removable side panel for social housing, tilt pans, built-in resting boards, and a chew toy. Flooring was a removable metal slatted grate 31 × 35 0.75 in. (78.7 × 90.8 cm). Slats were 1 in. (2.54 cm) wide with 0.75 in. (1.9 cm) of space between each parallel metal slat. Dog caging in the facility was washed in a rack washer that used acid and neutralizer cycles with a water rinse, and no changes in the cycle or chemicals were instituted during the past year. In addition, no particular area of the facility was noted with an increased incidence of affected animals, a situation that might have suggested that a particular rack washer was a cause of the condition. Animals were fed a commercial chow (Certified Canine Diet no. 2027C, Harlan Teklad, Madison, WI) ad libitum, with supplemented food treats offered daily.

Histologic methods. The gross cutaneous changes consisted largely of moist soft to weepy paw pads on all 4 feet. Several foot pad tissue sections were taken from dogs 1, 2, and 3 at necropsy by using a scalpel blade. The sections were fixed with 10% formalin and embedded in paraffin for routine histologic examination. Paraffin sections (thickness, 2 to 4 µm) were stained with hematoxylin and eosin.

Histopathologic findings. Specific pathologic changes associated with areas of antemortem seepage were not identified during histopathologic examination. Incidental findings consisted of inflammatory foci of variable chronicity in the dermis of both affected and unaffected carpal, tarsal, or digital pads. These foci were interpreted to be unrelated to chronic antemortem fluid seepage because they were absent from some clinically affected areas and were also present in some unaffected control pads. Specifically, there were no histologically apparent changes in the appearance or number of the eccrine glands. The sections taken from affected digital, carpal, and tarsal pads from dogs 1 and 2 were histologically comparable to similar sections taken from unaffected control dog 3.

Additional testing. Because postmortem findings were inconclusive, another dog (no. 4) was selected for additional diagnostic evaluation. This male dog was used for training purposes and treatment-naïve except for having undergone surgery for vascular access port implantation into his jugular

Table 1. Summary of evaluations of the 5 dogs presented

	Sex	Date of birth	Feet affected?	Histology performed?	Hematology and clinical chemistry results	Starch iodine test performed?	Paw fluid sample obtained?
1	Female	6-3-09	Yes	Yes	Normal	No	No
2	Male	6-8-09	Yes	Yes	Low-normal hematocrit (37.8%; normal, 35.0% to 47.5%)	No	No
3	Female	6-9-09	No	Yes	Low albumin (2.8 g/dL; normal, 2.9 to 3.6 g/dL)	No	No
4	Male	3-18-09	Yes	No	Normal	Yes	Yes
5	Male	3-21-09	No	No	Normal	Yes	Insufficient

vein. All infusions during training involved sterile water or standard locking solutions, after sterile preparation of the vascular access port site in the scapular region. All 4 feet of dog 4 were mildly moist and multicolored (Figure 1 B). The moisture appeared clear and nonviscous as it seeped from the pad surface. Dog 4 had no history of veterinary treatment associated with his feet or for other spontaneous conditions and was otherwise normal on physical examination. The veterinary team performed further detailed observations of the feet and collected seeped material for analysis, and applied the topical starch iodine test (Delasco, Council Bluffs, IA). Tests were done on affected dog 4 and an age-matched control animal (dog 5; Figure 1 A). Results from all 5 dogs (Table 1) and a proposed diagnosis are discussed in following sections.

Fluid collection and analysis. To identify the nature of the fluid seeping from of the pad surfaces of affected dogs, we placed all 4 feet of dog 4 into plastic bags and covered them with standard dog protective boots. The bags were left in place for 1 h while dog 4 was monitored to ensure the boots stayed in place during fluid collection. The fluid from all 4 bags was transferred into a single 2-mL serum tube for clinical pathologic analysis. The cloudy, red to brown fluid was centrifuged for 5 min to remove desquamated cells. The sample was analyzed for electrolytes and protein in an automated clinical chemistry analyzer (Modular Analytics, Roche Diagnostics, Indianapolis, IN; Table 2). Dog 5 underwent the same sample collection process, but no fluid (except for some condensate on the inside of the bags) could be collected.

Topical starch iodine test. The topical starch iodine test is considered diagnostic in humans with hyperhidrosis. The test kit (Starch Iodine test kit, Delasco) consisted of iodine tincture (2% in ethanol) and a 20% starch suspension. The starch iodine test is based on the reaction of starch and iodine in the presence of sweat.[6] We conducted the test according to the manufacturer's instructions. Briefly, the area to be tested was dried and the iodine solution applied. After a few seconds, the starch suspension then was applied to the area. In a positive reaction, the starch and iodine interact in the presence of sweat to generate a purple color. For a negative reaction, the area remains orange to brown in color, as is the iodine tincture solution.

Because of the continuous fluid seepage from the pads of the right front paw of dog 4, the surfaces of the paw pads could not be dried fully as directed, complicating the test. The continuous flow of fluid from the surface of the paw pads washed away the iodine as it was applied. No reaction was noted on the surface when the starch was applied to the pads. However, when the paw was dried after the apparently failed test, a purple color was noted along the edges of the pads and extending onto the adjacent haired skin, suggesting a partially positive but inconclusive reaction for sweat. In dog 5, the topical starch iodine test yielded no color change (that is, negative result for sweat) after application of the starch solution to its right front foot. The test was repeated on the right hindfoot of dog 5, and again no color change was observed.

Other observations. When dog 4 was sleeping and his feet were examined before awakening, the pad surfaces were dry on all 4 feet. Once the dog was awake, the pad surfaces began to become moist after approximately 1 min. This result was considered a characteristic observation regarding the most likely cause of the seepage. Cessation of seepage during sleep suggests a physiologic nature to the defect rather than a local effect, as also supported by the normal histology of affected paw pads. Additional observations were that the feet were constantly moist while the dog was awake, and despite intensive efforts at drying the pads, the moisture consistently returned within seconds in all affected dogs. All 4 feet were equally affected in all 3 affected dogs, indicating a bilaterally symmetrical distribution. Our experience with dogs with this condition is that they do not present with a single affected foot; typically all 4 feet are affected at presentation or rarely either the forefeet or hindfeet only. In addition, the condition appears to have an early onset, as all dogs in the current report were younger than 1 y.

Discussion

Hyperhidrosis was suspected in these purpose-bred beagles, given the clinical and histologic findings. In these cases, the dogs displayed many similarities to humans with hyperhidrosis including: affected areas were bilateral and symmetrical; subjects were otherwise apparently normal; feet were constantly sweaty and moist; sweating ceased during sleep; and histology of affected skin was normal (that is, no change in the number or size of the eccrine glands or a defect in the dermal or epidermal layers of the footpads). This abnormality appears to be a distinct condition in these lines of purpose-bred beagles, suggesting that these affected dogs could serve as a valuable animal model for studying hyperhidrosis in humans.

We determined that the footpads in affected dogs were histologically normal, with a normal number and appearance of sweat glands. This finding is similar to the condition in humans where, in areas of hyperhidrosis, the skin is histologically normal.[6] In addition, we confirmed that the fluid seeping from the paw pad surface had a similar composition to human sweat,[16] with high and equal amounts of sodium and chloride, although we found no published composition of dog pad sweat. The sodium, chloride, and potassium concentrations of sweat from cat paw pads are much higher than those in human sweat; and the sodium and chloride concentrations increase as the rate of sweating increases.[5] In addition, the composition of human sweat can differ due to the collection method used. For the purposes of this case study, we accepted that local sweat samples might yield higher concentrations of electrolytes than would those collected by washing down the entire body. For this report, we collected local sweat samples from the feet, and

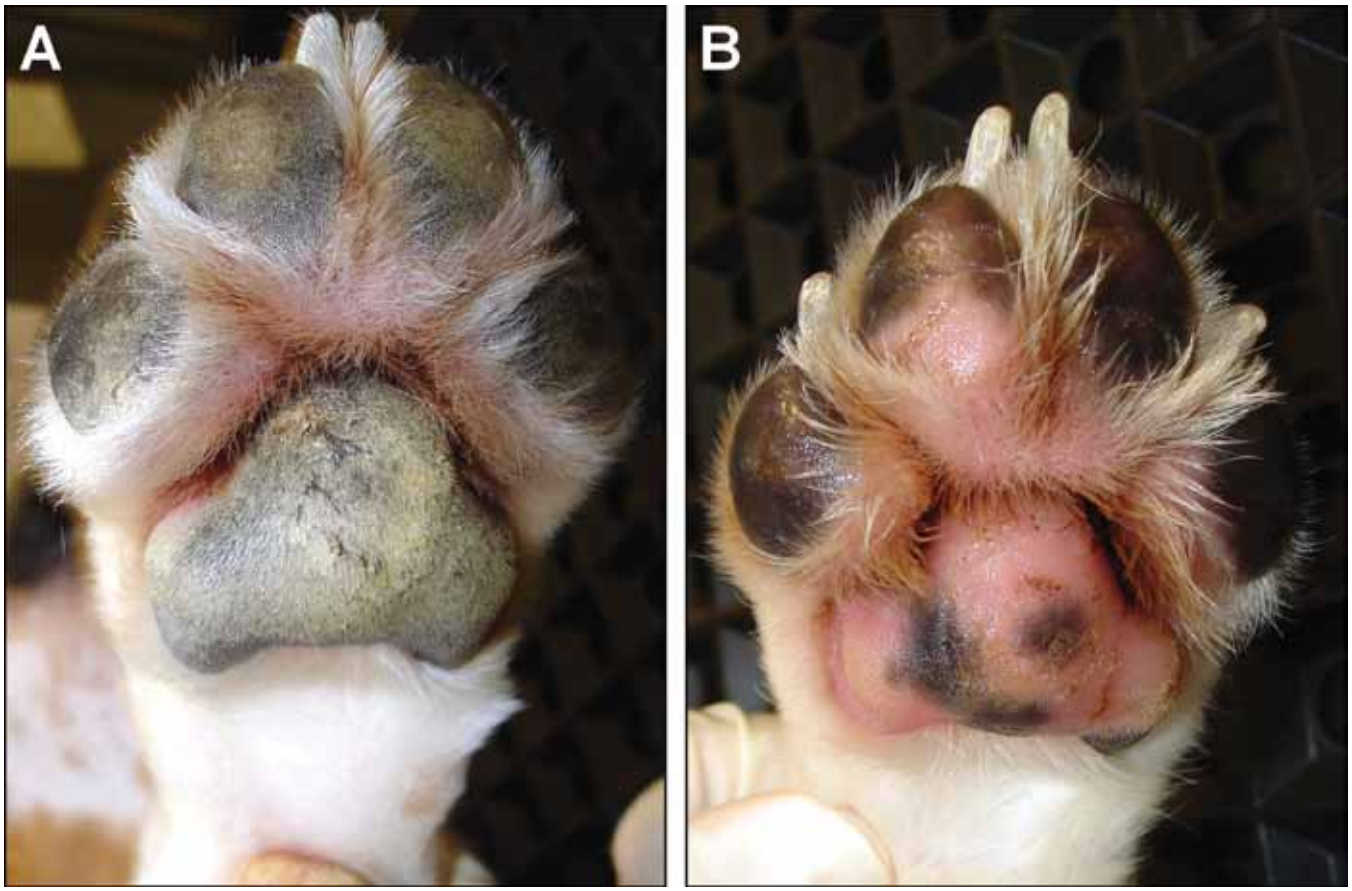

Figure 1. A side-by-side comparison of (A) normal plantar surface of dog 5 and (B) affected moist sweaty surface of the paw pads of dog 4.

Table 2. Comparison of dog and human sweat

	Sweat from dog 4 (affected)	Human sweat (from reference 16)
Sodium	108 M	58 ± 16 M
Potassium	28.9 M	10 ± 2.4 M
Chloride	101 M	45 ± 16 M
Color	Cloudy red to brown	not available
Volume	approximately 1 mL	not available
Protein	0.141 g/dL	not available

A sufficient sample could not be collected from dog 5, which had normal-appearing footpads.

due to the lack of published dog pad sweat composition values, compared our data with published human sweat values.

The composition of the fluid we collected from the dogs' paw pads was similar in composition to human sweat and supports our assumption that it is sweat. Human sweat contains 58 ±16 M Na^+, 45 ± 16 M Cl^-, and 10 ± 2.4 M K^+.[4,16] The sample from dog 4 yielded 108 M Na^+, 101 M Cl^-, and 28.9 M K^+—all of which values were more concentrated that those in human sweat[16] but similar to concentrations found in cat pad sweat[5] (Table 2). The protein value in the fluid collected from the dogs' feet supports sweat excretion rather than an inflammatory exudative process. The protein content of dog sweat was 0.141 g/dL; this value is much lower than normal serum protein levels in dogs and lower than that defining transudates (about 2.5 g/dL protein).[13]

In addition, we attempted using a topical starch-iodine test as a diagnostic test for sweat. Although the testing process was complicated by the high volume of seepage, we obtained a positive (purple) reaction along the periphery of the pads, another result indicating that the fluid was sweat. Like affected dogs, normal age-matched controls had normal paw pad histology and number and appearance of sweat glands. However, we were unable to collect sufficient fluid from feet of an age-matched control dog, and the topical starch iodine test had no color change to purple after application of the starch solution.

In humans the cholinergic sympathetic nervous system controls sweating.[7] In response to heat, the adrenergic activity of the sympathetic nervous system, which controls cutaneous vasoconstriction and metabolic rate, is inhibited, resulting in cutaneous vasodilation and a reduced metabolic rate. These responses increase heat loss from the skin and decrease heat production in the core. If heat is sufficiently intense, a particular component of the autonomic nervous system—the cholinergic sympathetic fibers, which innervate the sweat glands—is stimulated, and acetylcholine is released.[7] This process leads to sweating. Sweating markedly increases heat loss from the skin and is an involuntary cooling response in humans. In patients with hyperhidrosis, sympathetic hyperactivity is suspected.[6] The mechanism of the hyperhidrosis in these dogs is unknown but may be similar to that in humans, and more work should be done by using affected dogs to elucidate the mechanism of this condition.

Care should be taken when using dogs with this hyperhidrosis-like condition in long-term studies because in our experience,

Early onset (all dogs reported here are younger than 1 y old)
Constantly moist paw pad surfaces, even after drying
Bilateral and symmetrical
Cessation of sweating when dog is sleeping
Dogs are otherwise normal
Skin components and eccrine glands are normal on histopathologic examination
Progressive in some dogs due to maceration and breakdown of tissue and development of painful lesions
Only dogs from 2 sources presented with these signs, even though all dogs were housed under the same conditions, suggesting possible genetic origin

Figure 2. Characteristics of hyperhidrosis in beagles.

some dogs eventually have a breakdown in the paw pads and an inability to control the development of painful secondary complications, which are refractory to treatments. Suspected increased hydration of the skin may be a contributing factor in various signs noted in chronic cases but not discussed in detail here. In severe cases, the skin of affected dogs may become macerated and weakened, leading to tissue breakdown and development of fissures and sometimes painful erosions and abrasions.

Mildly affected dogs usually require no additional treatment because their secondary pad lesions are limited to mild abrasions and appear nonpainful. Other dogs may show progression to fissures, cracks, and painful erosions or ulcers.[14] Over time and with widespread lesions on all 4 feet, dogs may become reluctant to ambulate. Although large doses of nonsteroidal antiinflammatory drugs may relieve some of the pain associated with the secondary skin lesions, it is difficult to maintain animals at these dose levels for the duration of the study protocol, and eventually humane euthanasia may become preferable. Some dogs require only episodic courses of treatment with nonsteroidal antiinflammatory drugs to control the transient pain. Other dogs, especially those with severe disease, need near-constant treatment. The cyclic nature of the disease can complicate the management of affected dogs used in toxicologic studies, leading to their exclusion from study.

In conclusion, apparent hyperhidrosis has emerged as a new distinct condition seen in beagles at our facility. This case study underlines early findings and characteristics of this paw pad condition, and further work is needed to understand the nature of the condition, including its possible mode of inheritance and treatments. Currently, we suspect that apparent hyperhidrosis in beagles is a genetic condition because genetic defects often cause clinical signs early in life and usually are chronic and progressive.[11] Studies to determine the mode of inheritance or disease frequency in the breed have not been done or are inconclusive. If a genetic basis to the condition can be proven and localized to specific genes, future investigation into the development of a DNA-based test to identify affected dogs may be useful. We have listed general characteristics (Figure 2) that our staff considers representative for apparent hyperhidrosis in purpose-bred beagles. This case study highlights the need to consider excluding from research dogs with hyperhidrosis, due to progression to painful lesions that are refractory to treatment. This condition in beagles may prove to be a valuable model for investigators researching hyperhidrosis and its treatments in people, given the apparent similarities to the human condition.

Acknowledgments

We thank K Gerbick, H Schroeder, the Covance–Madison Clinical Pathology Lab staff, and S Van Adestine for their technical assistance. The views in this article are those of the authors and do not necessarily reflect the views or positions of Covance.

References

1. **Animal Welfare Act as Amended.** 2007.7 USC §2131-2159.
2. **Balara JM, McCarthy RJ, Kiupel M, Buote MA, Wise AG, Maes RK.** 2009. Clinical, histologic, and immunohistochemical characterization of wart-like lesions on the paw pads of dogs: 24 cases (2000–2007). J Am Vet Med Assoc **234:**1555–1558.
3. **Cerquetella M, Spaterna A, Beribe F, Mechelli L, Tesei B.** 2005. Epidermolysis bullosa in the dog: 4 cases. Vet Res Commun **29:**289–291.
4. **Diem K, editor.** 1962. Documenta Geigy scientific tables, 6th ed. Ardsley (NY): Geigy Pharmaceuticals.
5. **Foster KG.** 1966. Composition of the secretion from the eccrine sweat glands of the cat's footpad. J Physiol **184:**106–119.
6. **Haider A, Solish N, Lowe NJ.** 2005. Management of hyperhidrosis, p 91–100. In: Carruthers A, Carruthers J, editors. Procedures in cosmestic dermatology series: botulinum toxin. Philadelphia (PA): Elsevier.
7. **Hankey GJ, Wardlaw JM.** 2002. Clinical neurology. New York (NY): Demos Medical Publishing.
8. **Hargis AM, Haupt KH, Hegreberg GA, Prieur DJ, Moore MP.** 1984. Familial canine dermatomyositis: initial characterization of the cutaneous and muscular lesions. Am J Pathol **116:**234–244.
9. **Institute for Laboratory Animal Research.** 1996. Guide for the care and use of laboratory animals. Washington (DC): National Academies Press.
10. **Olivry T, DeBoer DJ, Griffin CE, Halliwell REW, Hill PB, Hillier A, Marsella R, Sousa CA.** 2001. The ACVD task force on canine atopic dermatitis: forewords and lexicon. Vet Immunol Immunopathol **81:**143–146.
11. **Ostander EA, Giger U, Lindblad-Toh K.** 2005. The dog and its genome, 1st ed. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press.
12. **Plattner BL, Hostetter J.** 2009. Cutaneous viral papilloma with local extension and subungual cyst formation in a dog. J Vet Diagn Invest **21:**551–554.
13. **Raskin R, Meyer DJ.** 2001. Atlas of canine and feline cytology, 1st ed. Philadelphia (PA): WB Saunders.
14. **Scott DW, Miller WH, Griffin CE.** 2001. Muller and Kirk's small animal dermatology, 6th ed. Philadelphia (PA): WB Saunders.
15. **Scott DW, Schultz RD.** 1977. Epidermolysis bullosa simplex in collie dog. J Am Vet Med Assoc **171:**721–727.
16. **Verde T, Shephard RJ, Corey P, Moore R.** 1982. Sweat composition in exercise and in heat. J Appl Physiol **53:**1540–1545.