IT'S COMPLICATED

When an immune system’s ability to differentiate self from nonself is compromised, immune-mediated skin disorders can occur.
The immune system involves an extremely complicated process that serves as the body’s surveillance and defense systems. This process is continuously in flux and is still not completely understood. The immune system comprises 2 main components: innate (already present) and adaptive (created in response to a foreign substance in the body). Although each system works differently (the innate immune system is based on blockades, and the adaptive immune system is based on cellular defense), each system provides protection from foreign proteins (i.e., antigens) such as viruses, bacteria, parasites, fungi, or anything that could be considered harmful to the body.

The basic premise underlying the concept of protective immunity is the ability to differentiate self from nonself. When this ability is compromised, immune-mediated skin disorders can occur. Before we delve into specific immune-mediated skin disorders, we will start with a quick immunology refresher.

THE IMMUNE SYSTEM

Innate Immune System
All living organisms have an innate immune system. This immune system is not specific; it is made up of a series of very general blockades put in place to keep stuff out. It doesn’t really care who comes knocking—they just are not getting in. For example, trees have bark, dogs have skin, and even bacteria have cell walls.
(fluralaner topical solution) for Cats

Caution:
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
Each tube is formulated to provide a minimum dose of 18.2 mg/lb (40 mg/kg) body weight. Each milliliter contains 280 mg of fluralaner.

The chemical name of fluralaner is (S)-4-[5-(5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisooxazol-3-yl]-2-methyl-N-[1-oxo-2-(2,2,2-trifluoroethoxy)aminomethyl]benzamide. Inactive ingredients: dimethylethanolamine, glycoluril, diethyltoluamide, acetonone

Indications:
Bravecto kills adult fleas and is indicated for the treatment and prevention of flea infestations (Ctenocephalides felis) and the treatment and control of Ixodes scapularis (black-legged tick) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

Bravecto is also indicated for the treatment and control of Demodex variabilis (American dog tick) infestations for 8 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

Dosage and Administration:
Bravecto should be administered topically as a single dose every 12 weeks according to the Dosage Schedule below to provide a minimum dose of 18.2 mg/lb (40 mg/kg) body weight. Bravecto may be administered every 8 weeks in case of potential exposure to Demodex variabilis ticks (see Effectiveness).

Dosage Schedule:

<table>
<thead>
<tr>
<th>Body Weight Ranges (lb)</th>
<th>Fluralaner content (mg/tube)</th>
<th>Tubes Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6 – 6.2</td>
<td>112.5</td>
<td>One</td>
</tr>
<tr>
<td>&gt;6.2 – 13.8</td>
<td>250</td>
<td>One</td>
</tr>
<tr>
<td>&gt;13.8 – 27.5</td>
<td>500</td>
<td>One</td>
</tr>
</tbody>
</table>

* Cats over 27.5 lb should be administered the appropriate combination of tubes.

Step 1: Immediately before use, open the pouch and remove the tube. Hold the tube at the crimped end with the cap in an upright position (tip up). The cap should be rotated clockwise or counter clockwise one full turn. The cap is designed to stay on the tube for dosing and should not be removed. The tube is open and ready for application when a breaking of the seal is felt.

Step 2: The cat should be standing or lying with its back horizontal during application. Part the fur at the administration site. Place the tube tip vertically against the skin at the base of the skull of the cat.

Step 3: Squeeze the tube and gently apply the contents of Bravecto directly to the skin at the base of the skull of the cat. Avoid applying an excessive amount of solution that could cause some of the solution to run and drip off of the cat. If a second spot is needed to avoid run off, then apply the second spot slightly behind the first spot.

Step 4: The cat should be standing or lying with its back horizontal during application. Part the fur at the administration site. Place the tube tip vertically against the skin at the base of the skull of the cat.

Step 5: To avoid run off, then apply the second spot slightly behind the first spot.

Treatment with Bravecto may begin at any time of the year and can continue year round without interruption.

Contraindications:
There are no known contraindications for the use of the product.

WARNING
Human Warnings:
Not for human use. Keep this and all drugs out of the reach of children.
Do not contact or allow children to contact the application site until dry.

Keep the product in the original packaging until use in order to prevent children from getting direct access to the product. Do not eat, drink or smoke while handling the product. Avoid contact with skin and eyes. If contact with eyes occurs, then flush eyes slowly and gently with water. Wash hands and contact skin thoroughly with soap and water immediately after use of the product.

The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

Precautions:
For topical use only. Avoid oral ingestion. (see Animal Safety).

Use with caution in cats with a history of neurologic abnormalities. Neurologic abnormalities have been reported in cats receiving Bravecto, even in cats without a history of neurologic abnormalities (see Adverse Reactions).

Bravecto has not been shown to be effective for 12-weeks duration in kittens less than 6 months of age. Bravecto is not effective against Demodex variabilis ticks beyond 8 weeks after dosing (see Effectiveness).

The safety of Bravecto has not been established in breeding, pregnant and lactating cats.

Adverse Reactions:
In a well-controlled U.S. field study, which included a total of 161 households and 311 treated cats (224 with fluralaner and 87 with a topical active control), there were no serious adverse reactions.

Percentage of Cats with Adverse Reactions (AR) in the Field Study

<table>
<thead>
<tr>
<th>Adverse Reaction (AR)</th>
<th>Bravecto Group: Percent of Cats with the AR During the 106-Day Study (n=224 cats)</th>
<th>Control Group: Percent of Cats with the AR During the 84-Day Study (n=87 cats)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>7.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>3.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3.1%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Scabs/Ulcerated Lesions</td>
<td>2.2%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

In the field study, two cats treated with fluralaner topical solution experienced ataxia. One cat became ataxic with a right head tilt 34 days after the first dose. The cat improved within one week of starting antibiotics. The ataxia and right head tilt, along with lateral recumbency, recurred 82 days after the first administration of the control. The cat recovered with antibiotics and was redosed with fluralaner topical solution 92 days after administration of the first dose, with no further abnormalities during the study. A second cat became ataxic 15 days after receiving its first dose and recovered the next day. The cat was redosed with fluralaner topical solution 82 days after administration of the first dose, with no further abnormalities during the study.

In a European field study, two cats from the same household experienced tremors, lethargy, and anorexia within one day of administration. The signs resolved in both cats within 48-72 hours.

In a European field study, there were three reports of facial dermatitis in humans after close contact with the application site which occurred within 4 days of application. For technical assistance or to report a suspected adverse drug reaction, or to obtain a copy of the Safety Data Sheet (SDS), contact Merck Animal Health at 1-800-224-5318. Additional information can be found at www.bravecto.com. For additional information about adverse drug reaction reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Clinical Pharmacology:
Peak fluralaner concentrations are achieved between 7 and 21 days following topical administration and the elimination half-life ranges between 11 and 13 days.

Mode of Action:
Fluralaner is for systemic use and belongs to the class of isoxazoline-substituted benzamide derivatives. Fluralaner is an inhibitor of the arthropod nervous system. The mode of action of fluralaner is the antagonism of the ligand-gated chloride channels (gamma-aminobutyric acid (GABA)-receptor and glutamate-receptor).

Effectiveness:
In a well-controlled European laboratory study, Bravecto killed 100% of fleas 8 hours after treatment and reduced the number of live fleas on cats by >98% within 12 hours after treatment or post-inestation for 12 weeks. In well-controlled laboratory studies, Bravecto demonstrated >94% effectiveness against Ixodes scapularis 48 hours post-inestation for 12 weeks. Bravecto demonstrated >99% effectiveness against Demodex variabilis 48 hours post-inestation for 8 weeks, but failed to demonstrate >90% effectiveness beyond 8 weeks.

In a well-controlled U.S. field study, a single dose of Bravecto reduced fleas by >89% for 12 weeks. Cats with signs of flea allergy dermatitis showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as a direct result of eliminating flea infestations.

Animal Safety:
Margin of Safety Study: In a margin of safety study, Bravecto was administered topically to 11- to 13-week (mean age 12 weeks-old)-kittens at 1, 3, and 5X the maximum labeled dose of 93 mg/kg at three, 8-week intervals (8 cats per group). The kittens in the control group (XO) were treated with mineral oil.

There were no clinically-relevant, treatment-related effects on physical examination, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, and urinalysis), gross pathology, histopathology, or organ weights. Cosmetic changes at the application site included matting/clumping/spiking of hair, wetness, or a greasy appearance.

Oral Safety Study: In a safety study, one dose of Bravecto topical solution was administered orally to 6- to 7-month-old-kittens at 1X the maximum labeled dose of 93 mg/kg. The kittens in the control group (X0) were administered saline orally. There were no clinically-relevant, treatment-related effects on physical examination, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, and urinalysis), gross pathology, histopathology, or organ weights. All treated kittens experienced salivation and four of six experienced coughing immediately after administration. One treated kitten experienced vomiting 2 hours after administration.

In a well-controlled field study Bravecto was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics, steroids and sedatives. No adverse reactions were observed from the concurrent use of Bravecto with other medications.

Storage Conditions:
Do not store above 77°F (25°C). Store in the original package in order to protect from moisture. The product should not be opened and should be stored in a cool, dry place.

How Supplied:
Bravecto is available in three strengths for use in cats (112.5, 250, and 500 mg fluralaner per tube). Each tube is packaged individually in a pouch. Product may be supplied in 1 or 2 tubes per carton.

NADA 141-459, Approved by FDA
Distributed by: Intervet Inc (d/b/a Merck Animal Health), Madison, NJ 07940
Made in the USA.

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Rev. 09/16
to protect them. The innate immune system serves as both first and second lines of defense.

**First Line of Defense**
This defense system is a pretty simple barrier system. It serves to keep foreign substances out of the body and includes the skin, chemical properties (e.g., the acidity of skin or stomach fluids), and sticky mucous membranes.

**Second Line of Defense**
This defense system comes into play after something has gotten past the first line of defense and entered the body. It includes the inflammatory response (which brings blood to the area so that white blood cells can get to work) and phagocytosis (the process by which cells remove pathogens and cell debris). Phagocytosis occurs when cells with receptors on their surfaces bind with antigens: in effect, trapping them. When these receptors become bound to antigens/pathogens, phagocytes are activated to wrap around the offenders to engulf and then digest them. The phagocyte will take some of the digested antigen/pathogen and bind it to a protein of its own, forming what is called a major histocompatibility complex (MHC) type II. MHCs type II are primarily present on antigen-presenting cells (i.e., macrophages and Langerhans cells that have engulfed foreign particles), whereas MHCs type I are present in nearly all nucleated cells in the body.

MHCs are kind of like name tags. Their presence on the surface of phagocytes enables other cells to determine whether they know what that phagocyte has killed. If it is something that they have seen before (i.e., if a memory cell for that antigen exists), they jump into action.

Several types of cells are capable of phagocytosis; after they have phagocytized pathogens or debris, they are called antigen-presenting cells (FIGURE 1). Neutrophils are usually the first on the scene as part of the inflammatory response, macrophages are slower to respond but can engulf more than neutrophils, and dendritic cells (in the skin, these are Langerhans cells) (FIGURE 2) are best at stimulating the adaptive immune system.

**Complement System**
Within the innate immune system is the complement system, which is composed of over 30 proteins and protein fragments. The adaptive immune system activates the complement system to enhance (i.e., complement) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from the body; it also promotes inflammation and attacks the pathogen’s cell membrane.

The complement system consists of a number of small proteins synthesized by the liver, which circulate in the blood as inactive precursors. When stimulated by one of several triggers, proteases cleave specific proteins to release cytokines (chemical messengers that communicate with cells) and activate the complement cascade, resulting in the 3 functions described above (clearing foreign material, inflammation, and cell membrane destruction).
The antigen-antibody binding site is called an epitope and is very specific for just 1 protein, very much like a lock and key.

Adaptive Immune System
The adaptive immune system is the body’s specific response to each individual antigen or potential pathogen encountered. This response begins when a dendritic cell (i.e., Langerhans cell) engulfs an antigen and then presents it to a lymphocyte. There are 2 types of lymphocytes: B lymphocytes (also known as plasma cells) and T lymphocytes. Lymphocytes are found primarily in lymph nodes but also throughout most of the body.

B Lymphocytes
B lymphocytes, also called B cells, are produced in the bone marrow and are responsible for the humoral (antibody) response. The humoral response occurs throughout the body, in the fluids between cells.

Each B cell has on its surface about 10,000 glycoprotein molecules, called membrane-bound antibodies or immunoglobulins (FIGURE 3). When a potential pathogen enters the body, membrane-bound antibodies will bind with the antigen (e.g., virus, bacteria, foreign protein). The antigen–antibody binding site is called an epitope and is very specific for just 1 protein, very much like a lock and key.

After a B cell becomes bound to the antigen at the epitope, the cell becomes activated, but only with the help of T helper cells (a safety feature, so the body does not attack just anything, including itself).

After activation, a B cell will start cloning itself. Some clones will become memory cells (which can hang around for 10 years or more, so if the same antigen/pathogen comes along, they are ready in large numbers to bind it and tag it for removal), and others will become effector cells (also called plasma B cells), which act as antibody factories, churning out as many as 2000 free-floating antibodies per second. These antibodies then bind to the pathogens, tagging them for destruction by phagocytosis (opsonization) (FIGURE 3).

When a B cell becomes activated (i.e., attached to the epitope on the antigen/pathogen), it will engulf the potential pathogen, digest it, and take some of the digested remains (a peptide chain made up of amino acids) and bind it to a protein of its own, forming an MHC type II. This is the phagocytosis we have already talked about, but these phagocytes are very specific, compared with other phagocytes (neutrophils), which are nonspecific. Helper T cells will activate the B cell, based on what they “think” of the MHC, and tell the B cell to clone itself into memory cells and effector cells (to produce those free-floating antibodies).

Before B cells are released from the bone marrow to perform the functions just described, they first go through “basic training and testing.” Any B cell that reacts to self proteins (almost all of the body’s proteins are available in the bone marrow for testing) will die. B cells that survive head to other parts of the body, including the lymph nodes. Unfortunately, this system is not foolproof and occasionally a B cell that reacts to self gets out into circulation. What happens then?

When a B cell that reacts to self escapes from the bone
marrow, it still needs a specific T cell (with the same specific receptor) to find it and activate it before it can act against its own body, thereby acting as a backup safety mechanism.

**T Lymphocytes**

T lymphocytes, also called T cells, are produced in the bone marrow and mature in the thymus. As they mature, similar to B cells they undergo basic training and testing. Any T cell that fails testing and either binds too strongly, or not at all, to self MHC antigens, is destroyed (i.e., undergoes apoptosis). T cells that can recognize self and do not bind strongly enough to elicit a cytotoxic event are retained.

T lymphocytes are activated after an antigen/pathogen has gotten inside a cell, at which time they trigger a cell-mediated response. There are 2 types of T cells: helper and cytotoxic.

**Helper T Cells**

Like B cells, the surfaces of helper T cells are covered in thousands of receptors, which are specific to each T cell. After binding to the presented antigen MHC II, a T cell is activated. Also like B cells, after activation, T cells clone themselves, with some becoming memory cells and some becoming effector cells.

Unlike B cells, however, T-cell effector cells do not make antibodies; instead, they release cytokines, which are chemical messengers that tell other cells to take specific actions (like ramping up the activities of B cells or starting an inflammatory or allergic cascade).

**Cytotoxic T Cells**

Cytotoxic T cells also have receptors all over their surface and are activated by binding to MHC I (MHC I is found in all nucleated cells in the body, as opposed to MHC II, which is found only in antigen-presenting cells). When a cell in the body is altered by a pathogen or neoplasia, it sends out a message via MHC I. This process is kind of like waving a flag that says, “There is something terribly wrong with me. Please kill me so that the rest of the body can survive.” Activated cytotoxic T cells clone into memory cells and effector cells. The effector T cells are the natural killer cells, which use proteins and enzymes to kill a cell when something has gotten inside that cell and it has become compromised in some way (i.e., neoplasia; virus).

### Autoimmune diseases are a subset of immune-mediated diseases, the result of the immune system overreacting and attacking the body itself.

### THE IMMUNE SYSTEM GONE AWRY

In a perfect world, the immune system works very well. However, when B and T cells do not work as intended, the body can run into real trouble; the immune system can target the body itself rather than an invader. This
results in immune-mediated or autoimmune diseases, which can affect different things in the body, including the skin. Immune-mediated diseases result from abnormal activity of the immune system. Autoimmune diseases are a subset of immune-mediated diseases, the result of the immune system overreacting and attacking the body itself. Fortunately, this does not happen very often! There are a number of autoimmune skin diseases that may occur in our veterinary patients, but most of these are rare. However, a few (pemphigus, lupus erythematosus, and vasculitis) occur more commonly, and we will focus on those.5

Pemphigus Complex
This complex of diseases includes pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris, and pemphigus vegetans. These are vesiculobullous (blistering) and pustular disorders characterized by acantholysis (breakdown of cellular adhesions). The immune system, for various and often unknown reasons, starts to produce antibodies against parts of the desmosomes (the bridges that connect adjacent epithelial cells). The antibodies produced by the subtypes of pemphigus are directed against different antigens of the desmosomes, which determines the location of the vesicles/pustules and the various clinical signs. After the antibody is bound to the part of the desmosome, the antigen–antibody complex triggers intracellular reactions, leading to the release of plasminogen activators, which subsequently cause the conversion of plasminogen to plasmin. The production of plasmin causes disruption of the desmosome attachments and therefore loss of keratinocyte adhesion. This loss of adhesion between adjacent cells is called acantholysis.6 The resulting acantholytic cells are large, round epithelial cells with a large, dark-staining nucleus (Figure 4); they occur most often as single cells or in rafts of a few cells still partially joined together, in vesicles or pustules, formed by the destruction of the intercellular connections.7

The immunopathogenesis of all diseases in the pemphigus complex seems to be the same, but the target proteins vary according to the type of pemphigus. Therefore, location of the bullae or separation within the epidermis differs; for example, the bullae of pemphigus foliaceus are more superficial than those of pemphigus vulgaris.8

In dogs, the most common autoimmune disease is pemphigus foliaceus (Figure 5). Pemphigus erythematosus is considered a mild and benign variant of pemphigus foliaceus because its lesions affect only...
the head (nose, face, and ears) (**FIGURE 6**). Hallmarks of pemphigus vulgaris are vesicles, erosions, and ulcers of the oral cavity and mucocutaneous junctions (**FIGURE 7**). Pemphigus vegetans is an extremely rare and milder variant of pemphigus vulgaris; it is distinguished clinically from other autoimmune diseases by production of lesions that are vegetative (proliferative) rather than pustular, vesicular, or ulcerative. All forms of pemphigus seem to be exacerbated by UV light.

Pemphigus foliaceus lesions usually start on the face and pinnae, then appear on the feet (crusting and sometimes fissuring of the footpads). If the disease is not treated, lesions can also appear in the inguinal region and become multifocal or generalized. Pustules are large (spanning more than 1 hair follicle) and fragile, resulting in dry, yellow to brown crusts (**FIGURE 5**). Other lesions include erythema, scaling, alopecia, and epidermal collarettes. Lesions are often symmetric and include the head, which helps to differentiate pemphigus foliaceus from pyoderma. Depigmentation of the nasal planum (**FIGURE 6**), and footpads is common, as is waxing and waning of symptoms such as lethargy and anorexia. Pemphigus foliaceus is most common among Akitas, chow chows, cocker spaniels, dachshunds, and Labrador retrievers. Most patients are middle aged. The diagnostic procedure of choice is skin lesion biopsy, preferably of intact pustules, which enables the histopathologist to see the entire disease process; crusted lesions are not as telling. Simple in-house cytology taken by performing impression smears from lanced pustules or lifted crusts will reveal a sea of neutrophils with acantholytic keratinocytes. Eosinophils are also often seen.

**Lupus Complex**

In terms of lupus, animals are much more fortunate than people because lupus rarely produces systemic diseases in dogs. Genetic factors seem to play a role; breeds that are predisposed to lupus include collies, Shetland sheepdogs, German shorthaired pointers, Siberian huskies, and Brittany spaniels.

**Discoid Lupus Erythematosus**

One of the more frequently encountered autoimmune skin disorders of dogs is discoid lupus erythematosus. In patients with this disease, lesions can start as areas of depigmentation or erythema on the nasal planum (**FIGURE 8**) or footpads (**FIGURE 9**) that slowly progress to loss of the normal cobblestone appearance as plasma cells take over and actually push structures apart. Eventually, erosions, ulcers, and crusts develop.
The area most commonly affected is the nasal planum, although lesions can extend up to the dorsal and lateral part of the haired muzzle. Without treatment, the alar wings will erode away. Scarring may occur in severe and chronic cases. Lesions have also been noted on the eyelids, lips, foot pads, and concave surface of the pinnae and in the oral cavity. Minor trauma to the nasal planum may trigger profuse hemorrhage. Sunlight exacerbates the lesions and may play a role in the pathogenesis of discoid lupus. The diagnostic procedure of choice is skin lesion biopsy, preferably of areas that are graying, because histopathologic findings will be most fruitful in areas where depigmentation is actively going on. Any fully depigmented areas should be avoided because the depigmentation process has finished. Ulcerated lesions (deep erosions that extend all the way to the basement membrane) should also be avoided because they destroy the dermal-epidermal junction, which is the site of active disease.

**Systemic Lupus Erythematosus**

Dog breeds that are predisposed to systemic lupus are collies and Shetland sheepdogs. Systemic lupus affects multiple organs, including the skin for 40% to 50% of affected dogs. Systemic lupus is characterized by production of a variety of autoantibodies that form circulating immune complexes. These complexes can become “stuck” in different parts of the body, including organs. Signs and symptoms are often nonspecific and can wax and wane. Cutaneous signs associated with systemic lupus include ulcerative stomatitis, mucocutaneous erosions and ulceration, foot pad ulceration, seborrhea, panniculitis, urticaria, and purpura (bleeding into the skin manifested as petechiation and/or ecchymosis). Noncutaneous signs include polyarthritis, fever, glomerulonephritis, hemolytic anemia, thrombocytopenia, polymyositis, neurologic abnormalities, pleuritis, myocarditis, and lymphedema.

**Vasculitis**

Vasculitis is inflammation of blood vessels, which can result from physical trauma but most often results from an immune response to an infection or a drug reaction (including vaccines). Breeds that are predisposed to vaccine reactions include poodles, silky terriers, Yorkshire terriers, Pekingese, and Maltese. Histopathologically, the inflammatory response targets blood vessel walls, leading to destruction and ischemic changes, which in turn affect surrounding tissues. Vasculitis can involve just the skin but can be systemic. Although the disease process is not fully understood, theories include circulating immune complex formation and deposition in the vessel wall (type III hypersensitivity, in which the immune complex “clogs things up”) and direct binding of antibodies to the vessel wall antigen (type II hypersensitivity).

Clinical findings include erythema, plaques, scaling, alopecia, and purpura. Diascopy is a simple and helpful method for differentiating between erythema and ecchymosis. Also seen are ulcers, wheals, nodules, dependent edema, acrocyanosis, panniculitis (if deeper vessels are involved), and even tissue necrosis. Lesions are found on the distal extremities.
tail tip, ear tips, nail beds, footpads, nose, prepuce, scrotum) and pressure points. Systemic disease (e.g., hepatopathies, glomerulonephritis, synovitis–arthritis, gastroenteritis, pleuritis/pericarditis) may be a consequence of the vasculitis and/or of the underlying disease (e.g., anemia and/or thrombocytopenia of systemic lupus).

PUTTING THE PIECES OF THE PUZZLE TOGETHER

All of the conditions described here can look similar to pyoderma, especially mucocutaneous pyoderma around the nasal planum, alar wings, and periocular region (FIGURE 12). TABLE 1 contains tips to help you distinguish between immune-mediated and infectious conditions.

In addition, look for any possible triggers in your patient's history (e.g., vaccination, drugs, illness, seasonality, or changes in diet). Patient history should be thorough and include a timeline for clinical signs, response to medications, progression of lesions, and any other clinical signs such as fever, loss of appetite, or decreased activity. Paying attention to your patient's history and clinical signs should help you recognize immune-mediated or autoimmune disorders.

### TABLE 1 Diagnostic Tips for Distinguishing Immune-Mediated Skin Disorders From Pyoderma

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>IMMUNE-MEDIATED</th>
<th>PYODERMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Breed predilection, triggers</td>
<td></td>
</tr>
<tr>
<td>Clinical progression</td>
<td>Waxes and wanes</td>
<td>Gradually progresses</td>
</tr>
<tr>
<td>Response to antibiotics</td>
<td>Negative</td>
<td>Positive (based on culture)</td>
</tr>
<tr>
<td>Lesions</td>
<td>Symmetric distribution, affects the head</td>
<td>Asymmetric distribution, usually spares the head</td>
</tr>
<tr>
<td>• Pemphigus</td>
<td>Yellow crusts (ruptured pustules); large pustules spanning &gt;1 hair follicle</td>
<td>Usually small pustules incorporating only 1 hair follicle</td>
</tr>
<tr>
<td>• Lupus</td>
<td>Depigmentation, loss of cobblestone appearance</td>
<td>May have depigmentation after severe inflammation</td>
</tr>
<tr>
<td>• Vasculitis</td>
<td>Affects extremities (including tail tip) and pressure points</td>
<td>Usually localized to 1 area</td>
</tr>
<tr>
<td>Ideal biopsy sites</td>
<td>Biopsy not required for pyoderma</td>
<td></td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>Intact pustules</td>
<td></td>
</tr>
<tr>
<td>Discoid lupus erythematous</td>
<td>Faded (gray/blue) depigmenting areas</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Multiple lesions at different stages</td>
<td></td>
</tr>
<tr>
<td>Cytology findings</td>
<td>No bacteria (unless secondary infection)</td>
<td>Inflammatory cells, bacteria</td>
</tr>
<tr>
<td>• Pemphigus foliaceus</td>
<td>Sea of neutrophils, acantholytic keratinocytes; eosinophils often present</td>
<td>Occasionally single acantholytic keratinocytes in cases of deep pyoderma; eosinophils rarely seen</td>
</tr>
</tbody>
</table>

References
Immune-Mediated Skin Disorders of Dogs

LEARNING OBJECTIVES
The objective of this article is to help veterinary nurses better understand the immunology involved in immune-mediated skin disorders of dogs and to recognize these disorders in their patients.

TOPIC OVERVIEW
The immune system is an extremely complicated process that is continuously in flux and is not completely understood. The article provides a refresher on immunology and describes what happens when the immune system targets the body itself, rather than an antigen or pathogen. The reader will understand that’s when immune-mediated and autoimmune diseases result, including skin diseases. The article details how the reader can use a patient’s history and clinical signs to narrow in on a diagnosis of immune-mediated or autoimmune disease.

1. Which distribution pattern is most consistent with autoimmune skin disease?
   a. Pinnae, inguinal region, paws
   b. Muzzle, lymph nodes, pinnae
   c. Paws, nasal planum, pinnae
   d. Mucocutaneous junctions, axillae, pinnae

2. Vasculitis is a result of damage to blood vessels, as a result of
   a. the formation of immune complex
   b. opsonization
   c. a response from the innate immune system
   d. complement

3. Discoid lupus erythematosus is exacerbated by
   a. corticosteroids
   b. ultraviolet radiation
   c. exercise
   d. poor nutrition

4. The optimal area to biopsy for suspected pemphigus foliaceus is
   a. the footpad
   b. the nasal planum
   c. an intact pustule
   d. an ulcer

5. The most diagnostic biopsy sample for suspected discoid lupus erythematosus is collected from areas
   a. faded to grey/blue
   b. of full depigmentation
   c. of crusting
   d. of ulceration

6. Typical impression smear cytology for pemphigus foliaceus reveals
   a. plasma cells mixed with neutrophils
   b. eosinophils engulfing microorganisms
   c. acantholytic keratinocytes in a sea of neutrophils
   d. eosinophils and degranulating mast cells

7. Pemphigus erythematosus is considered a benign form of pemphigus foliaceus because
   a. the history of clinical symptoms waxes and wanes
   b. lesions affect the head only
   c. it is not complicated by systemic disease
   d. it is another form of mucocutaneous pyoderma

8. Discoid lupus erythematosus is characterized by
   a. loss of cobblestone appearance of the nasal planum
   b. acantholytic keratinocytes on cytology
   c. acute onset of clinical signs
   d. accompanying systemic disease

9. The best samples to collect for cytology when considering pemphigus foliaceus are
   a. direct smears from the top of crusts
   b. fine needle aspirates from lymph nodes
   c. impression smears from epidermal collarettes
   d. impression smears from lanced pustules or lifted crusts

10. Vasculitis affects which areas of the body?
    a. distal extremities and pressure points
    b. ventral abdomen and dorsal pelvis
    c. mucocutaneous junctions
    d. soft and hard palates