antibodies have been demonstrated in dogs with this disease, but they have also been seen in other uveitis cases.[373,374] Histopathologic findings also suggest an active immune response, though the eye pathology may be more T_H2 driven and skin T_H1 driven, but these findings were based on only two cases.[375]

CLINICAL FEATURES

In dogs it appears more common in young to middle-aged dogs, with no apparent sex predilection.[376,377] Akitas have been reported most frequently, but other breeds including the Alaskan malamute, Australian shepherd, basset hound, Brazilian fila, chow chow, dachshund, German shepherd dog, Irish setter, Old English sheepdog, Samoyed, Shetland sheepdog, Shiba Inu, and Siberian husky have also been reported.[376-383] The authors know of cases in Bernese mountain dogs and a Labrador retriever. The syndrome is usually characterized by acute onset of bilateral uveitis, but unilateral uveitis may be seen in dogs with heterochromic irides.[378] Generally following, though occasionally concurrently or rarely preceding, the onset of uveitis there will be depigmentation of the hair, usually on the face and the skin of the nose, lips, eyelids and occasionally the footpads, scrotum, anus, and hard palate (Fig. 9-33, *A*). Generalized depigmentation was reported in one dachshund, and this as well as the eye lesions responded to immunosuppressive therapy.[379] Oral ulcerations may rarely be seen.[376,383] In one dog, a concurrent onychomadesis was present.[382] In most cases, skin lesions are mild, consisting of well-demarcated depigmentation with or without mild erythema and scale (Fig. 9-33, *B*). Some cases, however, progress or even rapidly develop more marked dermatitis, with depigmented areas developing varying degrees of erosion, ulceration, and crusting. Perhaps some of the dermatitis may be associated with exposure to sunlight (photodermatitis).[384] Patchy leukotrichia may be present in the areas surrounding the cutaneous depigmentation. Rarely, leukoderma and leukotrichia are widespread.[379,385] Clinical signs referable to the uveitis (anterior and posterior) may include photophobia, blepharospasm, lacrimation, conjunctival congestion, corneal edema, retinal detachment, glaucoma, cataract formation, and blindness.[381,386] Clinicopathologic evidence of a meningoencephalitic phase is rare in dogs, but one case with second cranial nerve deficits was reported.[387] One Parson (Jack) Russell terrier developed polymyositis following uveodermatologic syndrome.[388]

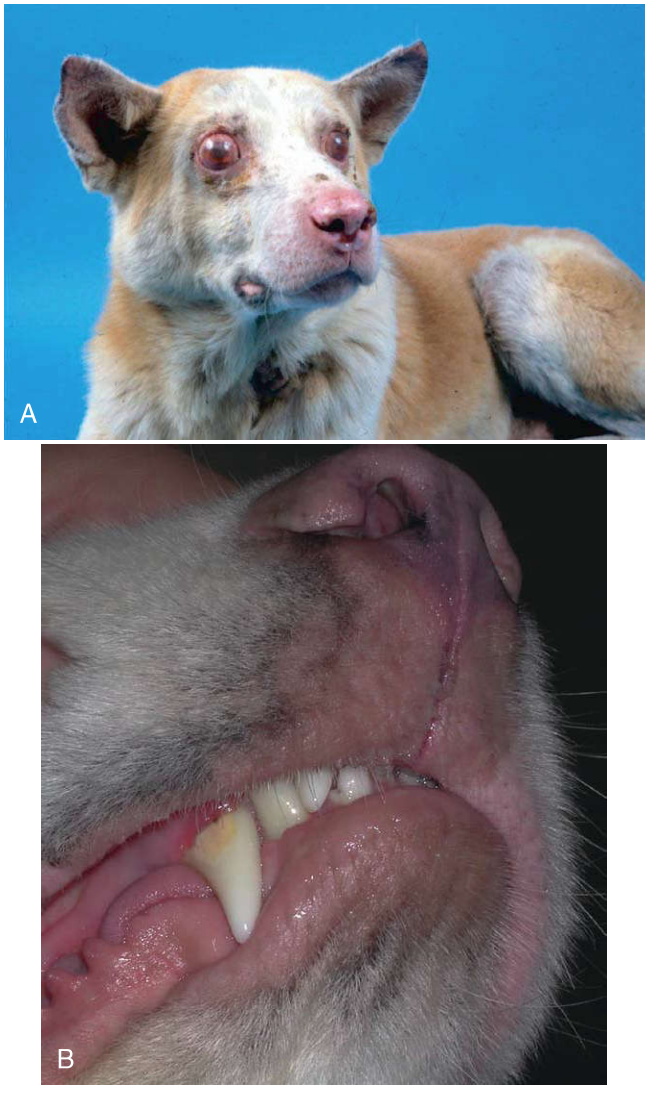

FIGURE 9-33 **A**, Uveodermatologic syndrome in an Akita. **B**, Uveodermatologic syndrome close-up photo showing depigmentation and erythema of the nose, anterior muzzle, and lips. (***A*** *From MacDonald JM: Uveodermatologic syndrome in the dog. In: Griffin CE, et al:* Current Veterinary Dermatology, *St. Louis, 1993, Mosby–Year Book.)*

DIAGNOSIS

The definitive diagnosis is based on history, physical examination, and skin biopsy. Histopathologic findings in specimens taken from early skin lesions are characterized by lichenoid interface granulomatous dermatitis with large histiocytes present.[376,377] Pigmentary incontinence is pronounced, but hydropic degeneration of epidermal basal cells is rare.[377] Cytologic examination of aqueous humor in one case revealed an infiltrate of predominantly macrophages.[387] Histopathologic findings in the eye include granulomatous panuveitis and retinitis, and degenerative changes of the optic nerve and tract may occur.[387] Results of direct and indirect immunofluorescence testing are usually negative.[25]

CLINICAL MANAGEMENT

Patients with poorly controlled uveitis often experience posterior synechiae with secondary glaucoma, cataracts, and vision loss. Also, since skin lesions may respond while eye disease remains active, it is important that routine monitoring of the eye and retina is done. Failure to stop eye lesions may result in blindness, so aggressive early treatment is essential. Topical or subconjunctival glucocorticoids and topical cycloplegics (e.g., atropine) are beneficial in patients with anterior uveitis. Systemic glucocorticoids and azathioprine or cyclosporine are needed to combat posterior uveitis and dermatologic signs. In humans, intravitreal triamcinolone and bevacizumab have been used with good results in difficult cases.[367] If the disease is treated early, variable degrees of cutaneous repigmentation (sometimes complete) usually occur. Occasionally, these cases may respond to systemic glucocorticoids alone, but because blindness may result from delaying an effective therapy, and because more aggressive therapy is often required, we recommend combination immunosuppressive therapy. Tetracycline and niacinamide have been reported to be effective in some cases.[389] Long-term therapy is usually indicated, and the response of skin lesions alone should not be used to assess response to therapy. Ophthalmic examinations should be periodically performed, even when the cutaneous changes are in remission and as therapy is tapered.

IMMUNE-MEDIATED SKIN DISEASES

CUTANEOUS ADVERSE DRUG REACTION

Adverse drug reaction (ADR) is any unintended effect due to the use of therapeutic drugs, drugs of abuse, or the

interaction of two or more pharmacologically active agents.[390] *Cutaneous adverse drug reaction* (CADR) is an ADR that primarily affects the skin. Other terms used to describe CADR include *cutaneous drug eruption*, *drug eruption*, *drug allergy*, and *dermatitis medicamentosa*. These other names suggest an immunologic cause of these reactions, though this has rarely been documented in veterinary cases. In humans, immune-mediated or idiosyncratic reactions that may be immunologic account for 25% of ADRs.[391] Despite the lack of proof that the immune system is the main cause for some forms of drug eruption, the immune system is at least involved in lesion development, and therefore we have elected to include this topic in the immunologic diseases.

CADRs are described as one of the most frequent forms of adverse drug reactions in humans, with incidence in hospitalized patients of 1% to 3%.[392] The incidence of CADRs in dogs and cats was reported to be 2% and 1.6%, respectively, of all the canine and feline dermatology cases examined at one university practice.[393,394] The true incidence in humans as well as veterinary medicine is unknown, but based on published cases, would be considered uncommon in dogs and cats.[202,395] Gastrointestinal signs are more prevalent, based on adverse event reporting of many FDA-regulated drugs. One study reviewing antibacterial therapy adverse events in dogs and cats showed that skin reactions are uncommon even for sulfonamides, which are considered one of the most likely antibiotics to induce cutaneous reactions.[396] Many cases of CADR go unreported, and this is especially true if the CADR is considered common or an unintended but expected event, such as dry skin or partial alopecia in a dog on glucocorticoids.

CAUSE AND PATHOGENESIS

Any drug may cause an eruption (Tables 9-5 and 9-6), though certain drugs are more frequently associated with CADRs. The drugs may be administered orally, topically, or by injection or inhalation. The most common drugs recognized to produce idiosyncratic CADRs in dogs are topical agents, sulfonamides (especially those that are trimethoprim-potentiated, such as Tribrissen), penicillins, cephalosporins, levamisole, and diethylcarbamazine.[394] In cats, the most common causes are topical agents, penicillins, cephalosporins, and sulfonamides.[28,393]

There are many pathological mechanisms for adverse drug reactions. CADR can be classified broadly into immunologic and nonimmunologic etiologies.[397] Nonimmunologic mechanisms include predictable reactions related to known activities of the drug that are not intended effects or related to overdose or drug-drug interactions and unpredictable reactions.[397] Unpredictable reactions may be idiosyncratic, pseudoallergic, or intolerance.

In humans, many factors may contribute to the development of drug reactions.[398] Genetics plays a role, because there are associations with human leukocyte antigens and certain drug reactions. Reactions also become more likely as more drugs are taken, demonstrating that drug-drug interactions play a role. Viral infections may also alter an individual's sensitivity to the development of drug reactions. Although the immune system is believed to contribute to most drug reactions, the actual pathogenesis is usually unknown.[398] Immunologic reactions that may occur are numerous and include types I to IV, as well as others such as FAS ligand activation inducing apoptosis.[391,392,397,399] The two most studied in humans are type I IgE-mediated reactions and delayed-type reactions. Since drugs are generally smaller molecules, they often react more as haptens and may have to bind to other proteins prior to eliciting a type I reaction. Adverse drug reactions may also be divided into two major groups: (1) *predictable*, which are usually dose dependent and related to the pharmacologic actions of the drugs, and (2) *unpredictable* or *idiosyncratic*, which are often dose independent and related to the individual's immunologic response or to genetic differences in patient susceptibility (idiosyncrasy or intolerance), often related to metabolic or enzymatic deficiencies. Drug metabolites are generated by cytochrome P450 mixed-function oxidases (phase I enzymes) but also by other oxidative metabolizing enzymes, some of which are present in skin.[400] Reactive drug metabolites must then be detoxified by phase II enzymes such as epoxide hydrolase or glutathione-S-transferase to prevent toxicity.

Thus, two places allow for inappropriate generation and/or accumulation of toxic reactants more toxic than the parent compounds. In humans, slow acetylation contributes to sulfonamide drug reactions, and familial anticonvulsant drug reactions are linked to inherited detoxification defects.[400] A hypothesis for the drug reactions associated with sulfonamides and anticonvulsants includes (1) oxidation by cytochrome P450 into chemically reactive metabolites (either in the liver by hepatic cytochrome P450, with secondary transfer to skin, or in keratinocytes by epidermal cytochrome P450), and (2) decreased detoxification of these reactive metabolites, which bind to proteins and induce an immunologic response.

Many cutaneous effects of certain drugs are predictable. For instance, many of the anticancer or immunosuppressive drugs can cause alopecia, purpura, poor wound healing, and increased susceptibility to infection through their effects on cellular biology. Doxorubicin typically causes alopecia that begins on the head and extends to the ventral neck, thorax, and abdomen.[401,402] Hyperpigmentation and pruritus may also occur. Glucocorticoids cause many adverse effects in the skin (see Chap. 3) including topical therapy inducing bullous lesions.[403]

CLINICAL FEATURES

CADRs can mimic virtually any dermatosis (see Tables 9-5 and 9-6). In humans, the most common morphologic patterns are morbilliform (pink macules and papules that may become confluent), pustular, bullous, nodular (even pseudoneoplastic, pseudolymphoma), urticaria or angioedema, fixed drug eruption, lichenoid, vasculitis, erythema multiforme, and Stevens-Johnson syndrome/toxic epidermolysis necrosis complex.[392,398] In dogs, the most common reactions were contact dermatitis, exfoliative dermatitis, pruritus with self-induced lesions, maculopapular eruptions, and erythema multiforme[394] (Fig. 9-34). In cats, the most common reactions were contact dermatitis and pruritus with self-induced lesions.[393] Other lesion morphology described in dogs and cats includes erythema multiforme, flea allergy–like, nodular, onychomadesis, pustular (sterile or pemphigus foliaceous), toxic epidermal necrolysis, vascular thrombosis, vasculitis, and vesiculobullous.[133,134,404-414] Two syndromes with severe skin disease and systemic signs, canine sterile neutrophilic dermatosis (Sweet syndrome) and canine eosinophilic dermatitis similar to Wells syndrome, have also been associated with drug reactions in dogs.[413,415-418]

No age or sex predilections have been reported for canine and feline cutaneous drug reactions, but young dogs and neutered dogs are more prone to ADR within 3 days of receiving a vaccine.[419] Breed predilection for CADR was reported in the Shetland sheepdog, dalmatian, Yorkshire terrier, miniature poodle, miniature schnauzer, Australian shepherd, Old English sheepdog, Scottish terrier, wirehaired fox terrier, and greyhound.[394] In addition, specific types of CADR are believed to have breed predispositions. Poodles, bichon frisés, Yorkshire terriers, silky terriers, Pekingese, and Maltese terriers ("fuzzy" hair coats) are predisposed to local injection reactions (especially with rabies vaccine),[410,420] Doberman pinschers to sulfonamide reactions,[421] and miniature schnauzers to sulfonamide,

Table 9-5 Cutaneous Adverse Drug Reactions in Dogs

Reaction Pattern	Frequency	Drugs
Urticaria-angioedema	R	Penicillin, ampicillin, cephalosporins, sulfonamides, tetracycline, ivermectin, moxidectin, levamisole, barbiturates, etoposide, neostigmine, xylazine, phenamidine, cyclosporine, amitraz, polyhydroxydine, vaccines, bacterins, antisera, blood transfusions, radiographic contrast media, allergen extracts, vitamin K, hypoallergenic shampoo
Maculopapular (morbilliform)	U	Penicillins, sulfonamides, amoxicillin clavulanate, griseofulvin, 5-fluorocytosine, diethylcarbamazine, hydroxyzine, procainamide, cimetidine, various shampoos, amitraz
Erythroderma/exfoliative dermatitis	C	Various topical agents, sulfonamides, quinidine, levamisole, lincomycin, itraconazole, hydroxyzine, chlorpheniramine, acepromazine
Autoimmune-like:	R	
Pemphigus foliaceus		Sulfonamides, ampicillin, penicillin, cephalosporins, diethylcarbamazine, metaflumazone/amitraz
Pemphigus vulgaris		Procainamide, thiabendazole, phenytoin
Bullous pemphigoid		Triamcinolone
Systemic lupus erythematosus		Sulfonamides, hydralazine, primidone, vaccines
Erythema multiforme	U	Sulfonamides, amoxicillin, amoxicillin clavulanate, cephalexin, chloramphenicol, enrofloxacin, erythromycin, gentamicin, lincomycin, tetracycline, aurothioglucose, diethylcarbamazine, ivermectin, levamisole, L-thyroxine, phenobarbital, chlorpyrifos, D-limonene, otic drops, itraconazole
Toxic epidermal necrolysis	R	Sulfonamides, ampicillin, penicillin, cephalexin, griseofulvin, levamisole, 5-fluorocytosine, D-limonene, aurothioglucose
Pruritus and self-induced lesions (allergy-like)	U	Sulfonamides, chloramphenicol, griseofulvin, acepromazine, primidone, levamisole, diethylcarbamazine, gentamicin, thyroid extracts, lincomycin, astemizole, phenobarbital, cephalexin, various topicals
Injection site reactions:	U	
Panniculitis		Rabies vaccine, others
Vasculitis		Rabies vaccine, others
Atrophy		Glucocorticoids
Contact dermatitis/otitis externa	C	Numerous topical (dermatologic and otic)
Vasculitis:	U	
Local		Injectables (especially rabies vaccine)
Multifocal		Sulfonamides, ampicillin, erythromycin, penicillin, chloramphenicol, amoxicillin, enrofloxacin, gentamicin, ivermectin, metronidazole, phenobarbital, furosemide, itraconazole, loperamide (Imodium), metoclopramide, vaccines, enalapril, phenylbutazone
Fixed eruption	R	Diethylcarbamazine, ampicillin, amoxicillin clavulanate, cephalexin, 5-fluorocytosine, aurothioglucose, thiacetarsemide, L-thyroxine
Granulomatous mural folliculitis	R	Cefadroxil, amitraz, shampoos, L-thyroxine
Lichenoid	VR	Drug combinations
Miscellaneous:		
Mucocutaneous dermatitis		Retinoids
Pressure point ulceration, onychomadesis		Bleomycin
Alopecia and increased susceptibility to infection		Glucocorticoids, numerous immunosuppressive agents
Flushing and pruritus		Doxorubicin
Hirsutism, papillomatosis, lymphoplasmacytoid dermatitis		Cyclosporine
Superficial suppurative necrolytic dermatitis		Shampoos
Epitheliotropic lymphoma-like		Ketoconazole, drug combinations
Subcorneal to follicular neutrophilic pustulosis		Sulfonamides, carprofen
Urticarial eosinophilic dermatitis		Diethylcarbamazine
Sterile abscess		Sulfonamides
Scabies-like		Amoxicillin-clavulanate
Follicular necrosis and atrophy		Sulfonamides, levamisole

C, common; R, rare; U, uncommon; VR, very rare. Data from Matus RE, et al: Plasmapheresis in five dogs with systemic immune-mediated disease. *J Am Vet Med Assoc* 187:595–599, 1985; Mason KV: Fixed drug eruption in two dogs caused by diethylcarbamazine. *J Am Anim Hosp Assoc* 24:301–303, 1988; and Fritsch PO, Ruiz-Maldonado R: Erythema multiforme. In Freedberg IM, et al, editors: *Fitzpatrick's dermatology in general medicine*, ed 5, New York, 1999, McGraw-Hill, p 644.

Table 9-6 Cutaneous Adverse Drug Reactions in Cats

Reaction Pattern	Frequency	Drugs
Urticaria-angioedema	VR	Tetracycline, penicillin, ampicillin, vaccines
Maculopapular (morbilliform)	R	Cephalexin, sulfonamides, penicillin, ampicillin, griseofulvin
Erythroderma/exfoliative dermatitis	U	Various topicals, penicillin
Autoimmune-like pemphigus foliaceus	R	Ampicillin, cimetidine, doxycycline, cephalexin, sulfonamides
Erythema multiforme	R	Cephalexin, penicillin, aurothioglucose, amoxicillin, sulfonamides, griseofulvin, propylthiouracil
Toxic epidermal necrolysis	R	Cephaloridine, hetacillin, ampicillin, griseofulvin, penicillin, aurothioglucose, cephalexin, FeLV antiserum
Pruritus and self-induced lesions (allergy-like)	U	Methimazole, amoxicillin clavulanate, propylthiouracil, ampicillin, hetacillin, gentamicin
Injection site reactions:	U	
Panniculitis		Vaccines, glucocorticoids
Vasculitis		Vaccines, ivermectin, antibiotics
Atrophy		Glucocorticoids, progestationals
Contact dermatitis/otitis externa	C	Numerous topicals (dermatologic and otic)
Vasculitis:	R	
Local		Injectables
Multifocal		Penicillin, fenbendazole
Fixed eruption	VR	Clemastine, enrofloxacin
Lichenoid	VR	Drug combinations
Miscellaneous:		
Pinnal erythema		Ciprofloxacin, enrofloxacin
Generalized atrophy and fragility		Glucocorticoids, progestationals, phenytoin

C, common; FeLV, feline leukemia virus; R, rare; U, uncommon; VR, very rare.Data from Matus RE, et al: Plasmapheresis in five dogs with systemic immune-mediated disease. *J Am Vet Med Assoc* 187:595–599, 1985; and Mason KV, Rosser E: Cutaneous drug eruptions. In *Advances in veterinary dermatology*, von Tscharner C, Halliwell REW, editors: *Philadelphia*, 1990, Baillière-Tindall, p 426.

gold, and shampoo (superficial suppurative necrolytic dermatitis) reactions.[394,422]

Although humans with human immunodeficiency virus (HIV) infection are at increased risk for drug reactions, cats with CADRs were not feline immunodeficiency virus (FIV) positive or feline leukemia virus (FeLV) positive.[393]

No specific type of reaction is related to only one drug, but certain reactions are more common with certain drugs. The syndrome of *superficial suppurative necrolytic dermatitis of miniature schnauzers* has been associated with shampoos and in one case was documented by patch testing with the shampoo.[422,423] There is reference to anecdotal reports of this syndrome occurring in schnauzers that have not been shampooed.[409] Adult miniature schnauzers of either sex show cutaneous and systemic signs within 48 to 72 hours after shampooing (usually insecticidal). Lesions, which may be widespread or primarily ventral, include erythematous papules and plaques that develop pustulosis, becoming painful, necrotic, and ulcerative (Fig. 9-35). Lesions regress spontaneously within 1 to 2 weeks with symptomatic therapy. Systemic signs include pyrexia, depression, and neutrophilia.

Drug eruptions associated with systemic signs and a fatal outcome were reported in two dogs after carprofen (Rimadyl) therapy.[293,415] Skin lesions included small pustules, erythematous macules, crusts, and erosions that histologically had dermal neutrophilic infiltrates. Both dogs died despite immunosuppressive therapy. Both had neutrophilic infiltrates of the respiratory tract. It was proposed that these two cases had a carprofen-induced condition similar to Sweet syndrome in humans. Another case was reported that had concurrent vasculitis and survived the reaction with treatment.[413]

Drug-induced pemphigus foliaceous has been reported in 12 dogs and was associated with sulfonamides in 8.[132-134,408,424] It was also seen in a cat on trimethoprim-sulfadiazine[389] (Fig. 9-36, *A*). Vasculitis and ischemic dermatopathy (discussed later in this chapter under "Vascular Diseases") are more often associated with vaccine reactions, though Doberman pinschers may be genetically prone to type III reaction with vasculitis from sulfadiazene.[421,425,426] Erythema multiforme was associated with trimethoprim combined with a variety of sulfa drugs in 13 of 26 drug-induced cases.[47] Though a common form of drug eruption in humans, fixed drug eruptions are rare in dogs and have not been reported in cats. Aurothioglucose, diethylcarbamazine, thiacetarsemide, and 5-fluorocytosine have been associated with fixed drug eruptions; in two of the five cases, the scrotum was reported affected (Fig. 9-36, *B*).[427-430] Several other localized drug reactions are now well recognized. Feline vaccine induced sarcoma will be discussed in Chapter 20, Neoplastic and Non-Neoplastic Tumors. Focal vasculitis and panniculitis (see discussion of vasculitis this chapter and panniculitis, Chap. 18) sometimes follows subcutaneous administration of vaccines, most commonly the rabies vaccine.

Cyclosporine has been reported to cause lymphoplasmacytoid dermatitis with malignant features (usually appear as plaques or nodules) and gingival hyperplasia in dogs and humans (Fig. 9-37).[431-434] Methimazole may produce severe pruritus and excoriations of the face and neck of cats that are only partially responsive to glucocorticoid treatment and mimic food hypersensitivity.[435] Ketoconazole has been rarely reported to cause pruritus and erythema.[436] Drug reactions (associated with ketoconazole in one case, multiple drugs in others) that were clinically and histologically indistinguishable from epitheliotropic lymphoma have occurred in dogs, as has also been reported with various drugs in humans.[394,398] Lesions resolved spontaneously when the drugs were stopped. Granulomatous mural folliculitis is a rare cutaneous reaction pattern apparently associated with drug administration (amitraz, cefadroxil, topicals, L-thyroxine).[437] Lesions consist of large areas of well-circumscribed coalescent alopecia, scaling, and hyperkeratosis (Fig. 9-38). Foci of papules, plaques, erosions, and crusts may occur. Chronic lesions often have a smooth, shiny, cicatricial appearance.

Drug eruption may occur after a drug has been given for days or years or a few days after drug therapy is stopped. It is possible to have had the drug with no reactions on prior use; this is common because some reactions require that the patient becomes sensitized to the drug. This is especially true of allergic and immunologic-mediated reactions, which also are more likely to be reproducible with subsequent exposure.[397] In some cases, the drug will only cause a reaction once, and repeat exposure may not result in a reaction, or the reaction may

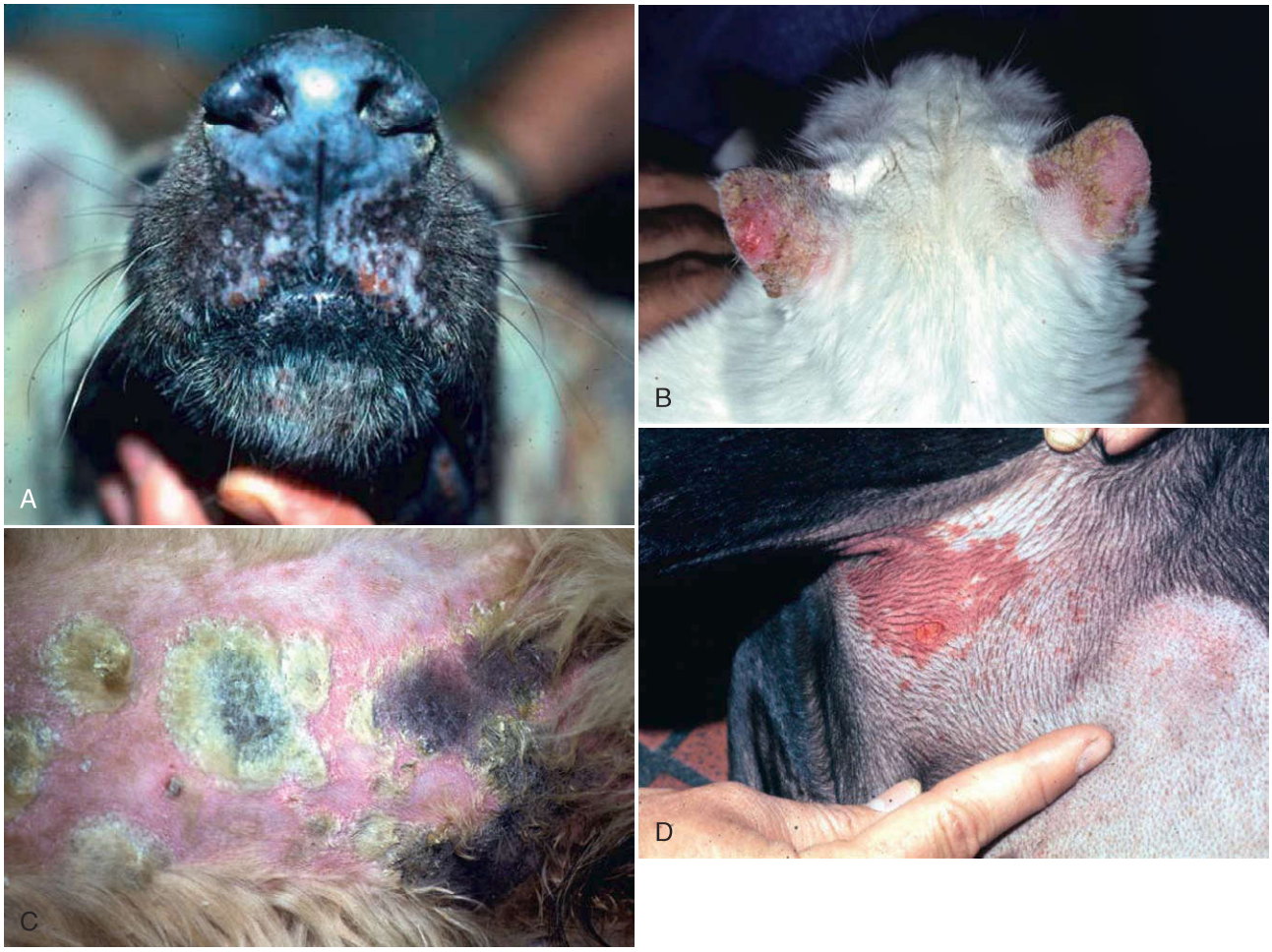

FIGURE 9-34 **A,** Mucocutaneous depigmentation and ulcers due to triple sulfa. **B,** Pinnal erythema, crusting, and alopecia due to Tresaderm. **C,** Exfoliative erythroderma due to Tribrissen. **D,** Vasculitic purpura due to chloramphenicol.

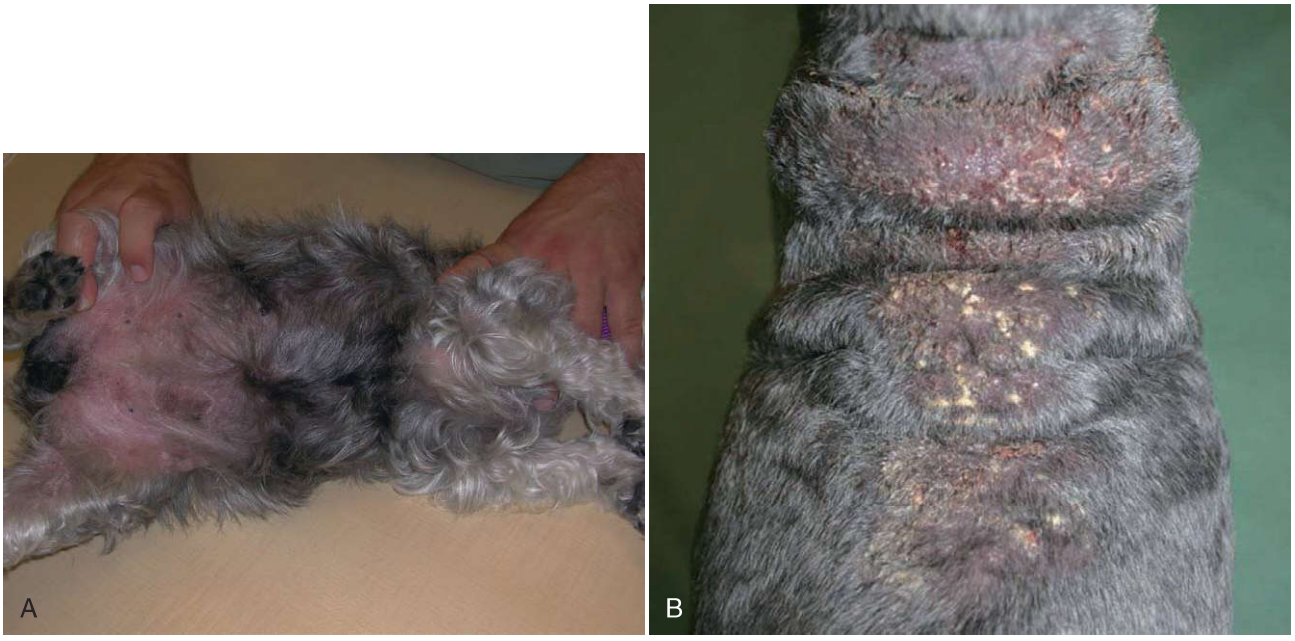

FIGURE 9-35 **A,** Schnauzer with early stages of superficial necrolytic dermatitis, showing total body erythema and scale. **B,** Superficial suppurative necrolytic dermatitis with severe necrotic and ulcerative lesions that develop over a few days following shampoo exposure. ***(B** Courtesy of N Murayama.)*

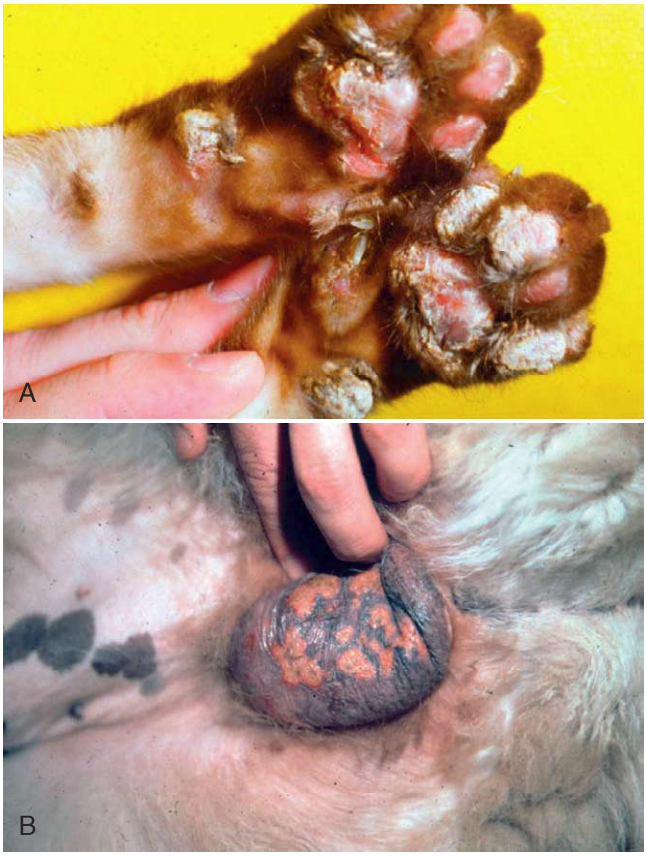

FIGURE 9-36 **A,** Pemphigus foliaceus on footpads of a cat in association with trimethoprim-sulfadiazine. **B,** Fixed drug eruption associated with diethylcarbamazine on scrotum of a dog. Well-circumscribed ulceration and depigmentation.

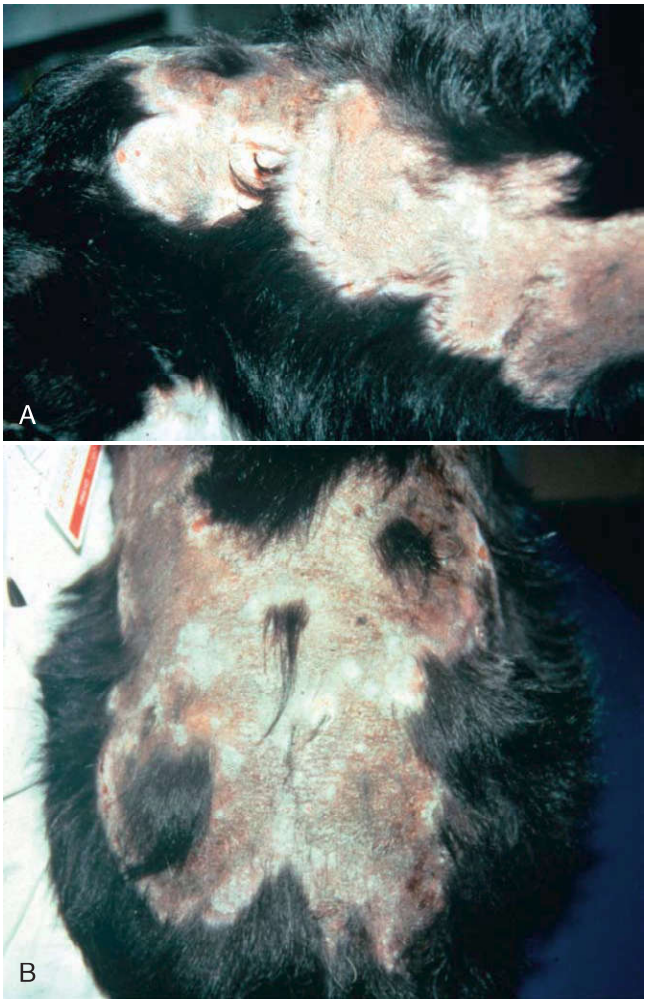

FIGURE 9-38 Granulomatous mural folliculitis in a dog, associated with L-thyroxine. **A,** Well-circumscribed alopecia, scaling, and mild hyperpigmentation over dorsolateral thorax. **B,** Similar lesions including hyperkeratotic plaques over dorsal lumbosacral area.

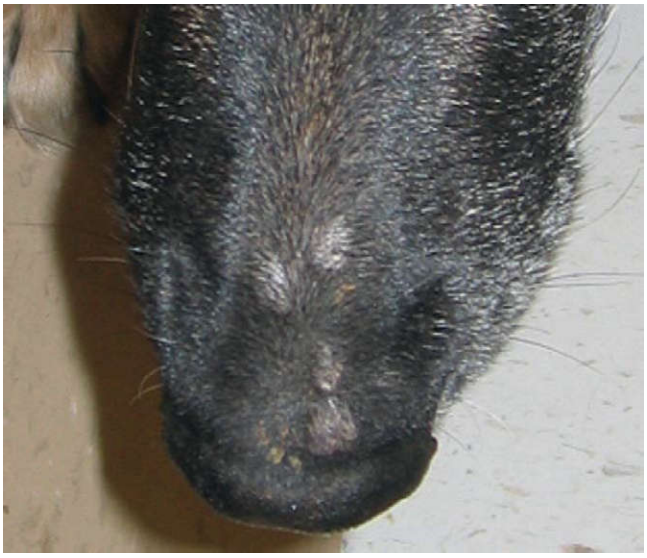

FIGURE 9-37 Lymphoplasmacytoid plaques in a dog on cyclosporine.

resolve even while still taking the offending drug.[392,398] This may be more common when the mechanism is nonimmunologic and when another inciting cofactor must be present at the same time, such as another drug or virus infection. Age and the presence of malignant diseases are also believed to result in changes in the nature of drug reactions.[398] Lack of recurrence with repeat vaccinations has been anecdotally recognized in dogs with rabies vaccine reactions, but this may also reflect that the initial reaction occurred when multiple vaccines were given at the same visit, and the repeat vaccination was limited to the rabies vaccine only. Eruptions most commonly occur within 1 to 3 weeks after initiating therapy.[393,394] Some reactions (vasculitis, atrophic dermatosis, nodules, rabies vaccine reactions) may occur weeks to months after the drug is administered.[420] Discontinuing the drug usually results in disappearance of the eruption within 1 to 2 weeks.[397] Occasionally, however, drug eruptions persist for weeks to months after the offending drug is stopped (e.g., reactions to vaccines and other injectables, lichenoid reactions).[420,430]

DIAGNOSIS

As discussed, certain presentations such as erythema multiforme and localized nodules and alopecia at areas where vaccines are given are more likely to reflect a drug reaction, but many lesions and patterns suggestive of many dermatoses can be due to a drug reaction. Therefore the differential diagnosis is extensive because CADR may mimic virtually any dermatosis. An accurate knowledge of the medications given to any patient with a dermatologic disease is imperative because drug eruption should be considered possible for most initial presentations of a dermatologic disorder, especially when they are new or of acute onset. This is not only important at

initial visits but at subsequent presentations or any time there is a change in the signs of the disease. In some cases, a dog or cat may be presenting for a dermatologic disease, and during treatment for that disease a drug eruption may occur. The relationship between the new eruption and the drug that was given for the dermatologic disease is what should be considered. The history is critical for tentatively diagnosing a drug reaction. Features that are considered helpful to make a diagnosis include:

1. A drug not taken before is given more than 7 days prior to onset of the eruption, but repeat drug exposure can occur sooner.
2. The eruption is occurring while the patient is on the drug or the drug has only recently been discontinued.
3. Stopping the drug results in resolution of the lesions, generally rapidly or within 7 to 14 days.
4. If repeat exposure occurs generally a similar reaction occurs. (This is generally only done when reactions are mild, because serious reactions should be avoided and rechallenge is contraindicated. This also occurs when the role of a drug was unknown, and repeat exposure induces the same reaction.)
5. Other causes for the eruption are ruled out as a cause of the eruption.

One other criterion often used in human medicine for the tentative diagnosis of a drug reaction is:

6. Features of the eruption are considered consistent with a drug reaction and correlate to eruptions the suspect drug is known to cause.

Unfortunately, their is not enough experience with the number and type of drugs causing reactions in veterinary medicine as they have in humans. Therefore, our list that fits this last criterion is relatively smaller. Comparing suspect cases to what has been described in humans may be helpful.

In general, no specific or characteristic laboratory findings indicate drug eruption. Results of in vivo and in vitro immunologic tests depend on the mechanism of action and have been shown to have some use in humans.[392,397] Tests used include intradermal testing, patch testing, lymphocyte transformation (blastogenesis), toxicity testing, and dermatopathologic analysis. Sensitivity and specificity of such testing is generally unknown, although there is evidence they have value in diagnosing some CADR.[438,439] How helpful they may be in veterinary medicine has not been evaluated. One report of a dog with Sweet syndrome did use lymphocyte transformation (blastogenesis) assays to suggest that two antibiotics being given with carprofen were less likely to be the cause of the drug reaction.[413] Since these tests are rarely used and of unknown specificity and sensitivity in dogs and cats, the diagnosis of CADR is based on clinical findings and the association with the drug history and eruption as described earlier.

Since the diagnosis is often based on the history, a variety of diagnostic algorithms and drug scoring systems were described for CADR in humans[440-443] and have been modified and applied to dogs.[416,444] The following section lists the most recent drug score criteria described in a study of 29 dogs that assessed the possibility for drugs causing severe eosinophilic dermatitis.[416]

DRUG SCORE

This system assigns a numerical score (+3 to –3) based on the following criteria:

1. A score of +1 (suggestive) was given if the lesions appeared more than 7 days after first administration of the drug or less than 1 day after readministration.
2. A score of +1 was given if the lesions resolved after removal of the drug, with no other therapeutics. A score of 0 (inconclusive) was assigned if other drugs were given simultaneously. A score of –1 (incompatible) was given if the lesions persisted despite drug withdrawal or if the patient improved without drug withdrawal.
3. A score of +1 was assigned if the drug was readministered and the patient relapsed, a score of 0 if no rechallenge occurred, and a score of –1 if no recurrence was seen after challenge.
4. A positive drug score was deemed suggestive of a casual drug association. A zero score was inconclusive. A negative score indicated that a drug association was unlikely.

The value of these drug scoring systems in humans is questioned, and their accuracy has been shown to vary, with studies showing the sensitivity and specificity ranging from 0% to 50% and 53% to 100%, respectively.[439,445] Since even less is known about the use of drug score values in dogs, they may be interesting to use but certainly can not be relied upon to determine when the diagnosis is appropriate.

Just as the clinical morphology of drug reactions varies greatly, so do the histologic findings. Histopathology is most helpful to diagnose specific syndromes that are known to have an association with drug eruptions and have a specific set of histopathologic changes required for a tentative diagnosis. Such syndromes include erythema multiforme, toxic epidermal necrolysis, sterile neutrophilic dermatosis, eosinophilic cellulitis, superficial suppurative necrolytic dermatitis, and vasculitis. The most important aspect of getting histopathologic support for a diagnosis of cutaneous drug reaction is that the pathologist is given the drug history when biopsies are submitted, and they should be alerted whenever a drug reaction is suspected.

CLINICAL MANAGEMENT

The prognosis for drug reaction is usually good unless other organ systems are involved or there is extensive epidermal necrosis. Therapy of drug reaction consists of (1) discontinuing the offending drug, (2) treating symptoms with topical and systemic medications as indicated, and (3) avoiding chemically related drugs. Drug reactions may be poorly responsive to glucocorticoids, although some immunologically mediated reactions respond to glucocorticoids, cyclosporine, pentoxifylline, or immunosuppressive regimens. Another option for severe or poorly responsive cases is IVIG, which was reported effective in two severe cases.[446]

ERYTHEMA MULTIFORME

Erythema multiforme is described as an uncommon disease in dogs and a rare disease in cats, characterized by acute onset of a cutaneous inflammatory reaction featuring epidermal apoptosis and lymphocytic satellitosis.[447] In humans, it is a disease clinically characterized by acute onset of typical lesions (target lesion) and a usually mild and self-limited but commonly recurrent mucocutaneous rash that is associated with infections, the most frequent being herpesvirus infections.[448-450] These clinical features are not usually seen in the dog or cat, where the number one association described is drug reaction and not infectious disease.[444,447] The question is what relationship there is between erythema multiforme and Stevens-Johnson syndrome. Toxic epidermal necrolysis has been described for years in human and veterinary medicine and at times considered similar to erythema multiforme. In human medicine, these diseases are now considered separate entities.[449-452] It is still controversial in veterinary medicine, with