VICAS Dermatology Module 2

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Module Outline

Immune-mediated dermatoses (allergic and autoimmune dermatoses)

Treatment of immune-mediated diseases

Keratinization disorders

Neoplasia of the Skin

Novel therapies for skin neoplasia
Immune-mediated Skin Disorders

A) Allergic or Hypersensitive skin diseases

Flea Allergic Dermatitis (FAD)

FAD is the most common hypersensitive skin disease reported in dogs and cats. In the cat, as well as the classical clinical presentation seen in the dog, FAD has been associated with many cutaneous reaction patterns, such as miliary dermatitis, symmetrical alopecia and feline eosinophilic granuloma complex.

Ctenocephalides felis is the species most frequently involved on a worldwide basis. Other species of flea, including hedgehog and rabbit fleas may be involved. Remember that in Ireland, the most common flea isolated on dogs is C. canis. The hypersensitive response develops following binding of haptens in flea saliva to dermal collagen. Whilst FAD can represent both a type I and type IV hypersensitive reaction in dogs, only the immediate-type reaction is currently recognized in cats. The development of hypersensitivity is not dependent on the number of fleas infesting or biting the host. In fact, dogs that are continually parasitized with a large flea burden, are often less likely to develop a hypersensitive response. It is postulated that the presence of atopy may predispose to the development of FAD. The clinical condition may be seasonal or perennial in individual animals, depending on geography and other environmental conditions. In multi-pet households, the role of other in-contact animals as a source of fleas must be considered, even if these pets are free from clinical signs.

Clinical Signs:

- Lesions principally seen on the dorsum, caudo-medial thighs, flanks and ventral abdomen, though individual lesions can occur in other sites.
- Pruritus is a classical feature. Be wary of histories taken from cat owners; not all owners are aware that their cat is scratching. A scratch reflex may be evident in dogs.
- Lesions present as a papulocrustous dermatitis, with alopecia, seborrhea and secondary infection, often characterized by pyotraumatic dermatitis.
- Severely affected animals may be depressed and inappetant, with occasional cases showing peripheral lymphadenopathy.
- Other cutaneous reaction patterns may be evident, as above.
- Some affected animals may also be infested with Dipylidium caninum.

Diagnosis:

- History and physical examination. Finding fleas on the animal is not essential, though obviously fleas (and flea faeces) will be present in some cases.
An intradermal challenge with commercially available flea saliva antigen is frequently used. An immediate reaction is normally seen. A second intradermal, consisting of whole flea extract, may also be attempted.

A peripheral blood eosinophilia and skin biopsy may alert suspicions to a diagnosis of FAD, but are not in themselves diagnostic.

Serology tests, based on such techniques as ELISA, are available although their sensitivity and specificity are still under some investigation. However, there is little doubt that some of these tests are becoming more reliable.

**Treatment:**

- See previous module on flea dermatitis for initial treatment and control measures.
- Systemic corticosteroids e.g. prednisolone (1-2mg/kg SID or divided BID in dogs and 2-4mg/kg SID in cats for 7-10 days), with gradual tapering of the dose to the lowest level which still controls clinical signs. Depot corticosteroid preparations and megoestrol acetate (cat) are sometimes used, but can be problematic.
- If prednisolone is unsuitable, then the anti-histamine chlorpheniramine can be used (4-8mg/dog BID PO). Results are not as good, in general.
- Topical or systemic antimicrobial therapy if required.
- Hypo sensitization has been attempted, but to date most case report studies have been disappointing. However, work is continuing with different vaccine antigens and future results may be more encouraging.

**Long-term control:**

- Adoption of control measures as reported in section on flea dermatitis.
- Intermittent or long-term use of prednisolone to control clinical signs.

**Atopic Dermatitis**

Atopic dermatitis (AD) was traditionally defined as a hereditary predisposition to forming reagenic antibodies against environmental allergens. However, much work has been undertaken in recent years in an effort to better characterize our understanding and definition of AD. An expert task force recently defined AD as:

“A genetically predisposed, inflammatory and pruritic allergic skin disease with characteristic clinical features most commonly (but not necessarily) associated with elevated IgE titres to environmental allergens.”

Some authors believe that only those patients with elevated IgE titres should be classified as atopic; others with the same clinical signs but no increase in IgE titres should be classified as “atopic-like”.
AD is the second most common hypersensitive skin disorder in the dog; many surveys suggest the incidence is as high as 10% of all dogs. The clinical syndrome is much less frequently diagnosed in the cat. The mode of entry of such offending allergens into the body was initially assumed to be by inhalation; whilst this is undoubtedly a potential route of entry, attention has increasingly focused on the huge significance of transdermal absorption. Entry via the GI tract is also possible. In susceptible patients, it appears that the immune responses to agents such as pollens, house dust mite faeces, dander etc., exceeds the pruritic threshold, and leads to the development of clinical signs. The precise pathogenesis is not as well understood in cats. A genetic predisposition is generally suspected, however.

The specific family of the reagenic antibody involved has traditionally been considered to be IgE. However, as stated above, not all atopic patients have an elevated IgE response to the causal allergens. Additionally, many clinically normal dogs have high IgE titres to various environmental agents, without having any signs of AD. More recently, attention has begun to focus on the possible role of IgG in the pathogenesis of this disease. Furthermore, whilst traditionally viewed as a Type I hypersensitive reaction (i.e. immediate), recent research would suggest that various components of the AD response (e.g. the late phase reaction) may in effect better resemble a Type IV delayed-type hypersensitive response.

Clinical signs may be seasonal or non-seasonal depending on the allergen(s) involved. Most cases first develop clinical signs before 3-4 years of age; onset beyond 7 years of age is very unusual. Although a survey in the USA showed the mean age of onset to be 18 months of age, some dogs exhibit signs within the first 6 months of life. No sex predilections exist. There are no known susceptible breeds in the cat. However, in the dog, breeds such as Westies, Cairms, Golden and labrador retrievers etc., are known to be predisposed.

**Clinical signs**

- Pruritus is a dominant sign in the dog. Although scratching may occur anywhere on the body, atopic dogs are frequently facial rubbers and pedal lickers. The ventral surfaces, particularly the axillae and groin are frequently involved. The flexor surface of the hock and the extensor surface of the carpus are also common sites.
- Self-trauma leads to erythema, alopecia, thickening and hyperpigmentation of the skin. Some affected surfaces become lichenified.
- Secondary bacterial and possibly yeast infections are common.
  - Whilst some cats have pruritus and papulo-crustous lesions, other cases are not seen to be pruritic by the owner, and may have no skin lesions.
  - Distribution of lesions in the cat not as well defined as in dogs, although the face and ears are frequently involved.
  - Several feline cases may present with a particular cutaneous reaction pattern, such as eosinophilic granuloma complex, symmetrical alopecia or miliary dermatitis.
  - Occasionally, peripheral lymphadenopathy is present.
If the offending allergen is present all-year round, then clinical signs will be present continually, unless treated.

**Diagnosis**

- Willemse’s criteria (1986).
- Exclusion of all resembling pruritic skin diseases.
- History of persistent or recurrent pruritus, with typical lesion distribution as above.
- If no history of pruritus in a cat, a trichogram and possible trial therapy with an Elizabethan collar should be considered to ensure the cat truly is non-pruritic.
- Histopathology of affected skin, whilst not diagnostic, may alert suspicions and can be used to rule-out other differentials.
- Intradermal skin testing – previously considered the method of choice. Allergens are selected based on geographical location and any particular suspicions.
- Serological tests (RAST, ELISA etc.) for the detection of allergen-specific IgE are available, but the sensitivity and specificity of these tests is somewhat controversial. More recent test kits e.g. Heska Allercept range, have offered improved reliability.

**Treatment**

- Prednisolone (initial dose of 1-2 mg/kg for dogs and 2-4mg/kg for cats per day) to control the clinical signs. The dose may be gradually tapered to the lowest level that still controls clinical signs. In some cases, periodic therapy may suffice.
- Topical glucocorticoids e.g. Cortavance spray
- Antihistamines such as chlorpheniramine (4-8mg/dog twice daily) may be effective in controlling clinical signs. Side-effects are possible.
- Cyclosporine (“Atopica”) – an inhibitor of cyclophilin in T lymphocytes (see later section on auto-immune dermatosis). Good success rate in about 70% of AD dogs.
- Other cyclophilin inhibitors e.g. Tacrolimus can be applied topically to local sites; efficacy is +/-
- Essential fatty acid supplements may help in treatment regimes (omega-3 and omega-6 fatty acids), particularly if combined with prednisolone or chlorpheniramine.
- Hyposensitisation is often the treatment of choice. An accurate diagnosis of the offending allergen(s) is essential. Success rates can be low (approximately 33%), but enhanced success rates have been reported with sustained use during the induction period (e.g. 9-12 months rather than the traditional 2-3 months).
- More recent agents to be tried include oxatomide, a mast cell stabiliser.
- Anecdotal evidence that some tyrosine kinase inhibitor drugs (e.g. for mast cell tumour therapy) can be highly effective in individual dogs.

**Prognosis**

- The prognosis for successful management is good, although on-going medication or hyposensitization, will be required.
If the allergen(s) can be successfully avoided e.g. tobacco smoke, then the prognosis is excellent.

**Prevention**

- Future episodes may be ameliorated by appropriate medication or hyposensitisation. In certain cases, anti-inflammatory medication may only be required on a seasonal basis.
- Affected dogs or littermates should not be bred from. Whilst a specific inherited predisposition has not yet been proven in the cat, judicious breeding programs may be appropriate.

**Food Allergy**

Food allergy is regularly incriminated in the aetiology of various pruritic skin disorders in the dog and cat. However, most surveys have shown that its true incidence is over-estimated, and in fact the condition probably only accounts for 1-2% of all canine and feline dermatoses seen in practice. Both immediate and delayed hypersensitive reactions have been reported. Ingestion of the offending allergen may occur for months to years before there is any clinical reaction. In many cases, it takes 12-24 months of feeding the diet before clinical signs appear. Therefore, the absence of a recent change in diet in the history does not rule out this syndrome. In some breeds, such as the Westie, clinical signs may appear earlier in life.

Food allergy, in which a true immune response exists, must be differentiated from food intolerance. In the latter syndrome, which is quite common in practice, some factor such as residues of antibiotics, metals etc. in the food lead to the development of clinical signs. The multitude of ingredients placed in commercial pet foods today has led to case reports of food allergy existing on virtually every protein source possible. There is no such thing as a “non-allergenic” protein. Remember also that simply changing the diet from one commercial source to another does not constitute a true exclusion diet, unless it can be shown that the raw ingredients are novel to that animal. Some controversy exists as to whether age or breed predispositions exist for food allergy. Although not all surveys would agree, many of the animals are relatively young and certain breeds e.g. Westies, Cocker spaniels, Collies etc. are over-represented.

**Clinical signs**

- Whilst the dominant clinical sign is pruritus, there are no skin signs which are diagnostic for food hypersensitivity.
- Erythema, papules, pustules, crusts and ulcers.
- Whilst any part of the body can be involved, the head and ears are common sites. Otitis externa is a frequent clinical finding.
- Secondary infection is a frequent complication.
GI tract and respiratory signs are very occasionally present e.g. vomiting /diarrhoea, or asthma.
Peripheral lymphadenopathy is rarely present.

**Diagnosis**

- Intradermal and scratch testing are of no practical benefit in establishing a diagnosis.
- Serology testing is available, but not currently recommended by most authors. Unlike the situation in humans, the results of such tests are not considered reliable.
- Feed a true elimination diet for a period of 6-8 weeks. **An accurate dietary history is essential** in order to perform this procedure efficiently. **No tit-bits are allowed.** The peak response to an elimination diet occurs after approximately 13 weeks, so don’t rule out food allergy prematurely.
- If the condition markedly improves following the novel diet, the diagnosis can be confirmed by provocative exposure to the previously incriminated diet. In practice, however, many owners are content to simply let their animal remain on the new diet.
- Occasionally, dogs subsequently become allergic to the new diet after a period of time. Thus, another novel diet is then required.

**Treatment**

- Continue feeding the elimination diet as outlined above. Home produced diets should be properly balanced to meet the animal’s requirements.

**Prognosis**

- The prognosis is excellent. However, some animals may later become hypersensitive to the new diet.

**Contact Dermatitis**

There are two basic forms of contact dermatitis – irritant and allergic. In the case of irritant contact dermatitis, there is no individual sensitivity or hypersensitive component to the disease entity. Basically, the offending substance is irritant and can be expected to induce a response in the vast majority of animals that come in contact with it e.g. urine scalding. Primary irritant contact dermatitis causes an inflammatory response in the majority of exposed animals. No prior sensitization is required. Highly corrosive compounds are typically involved and can cause significant lesions. Agents such as detergents, soaps, disinfectants etc. are commonly incriminated. In the case of contact allergic dermatitis, an individual sensitivity, immune-mediated, is the underlying mechanism of disease.
Irritant contact dermatitis appears more common than contact allergic dermatitis.
Reactions are also possible to thermal burns, plants etc. Whilst contact allergic dermatitis has traditionally been viewed as a delayed-type hypersensitive response, more recent studies in animals have shown that this may not be the case.

Clinical signs

- Initial erythema and papules at affected site.
- Lesions are common on contact surfaces or areas with little/no hair covering.
- Lesions may be widespread for an agent applied over most of the body e.g. shampoo.
- Pruritus leads to thickening, hyperpigmentation, crusts and excoriations.
- Alopecia, ulceration and secondary infection may also develop.
- Irritant contact dermatitis may occur as a single episode, whereas contact allergic dermatitis often has repeat episodes or is continually present.

Diagnosis

- Irritant contact dermatitis is often initially suspected on the basis of clinical signs and history.
- Response to symptomatic therapy and avoidance is helpful.
- Provocative exposure is possible, but often considered unnecessary.
- For contact allergies, the diagnosis may be confirmed by provocative exposure or patch testing.
- Biopsy of affected skin is non-specific.

Treatment

- Avoidance of the suspect irritant or allergen.
- Glucocorticoids (topical or systemic) are useful in managing the clinical signs.
- Symptomatic therapy if appropriate.

Prognosis

- Excellent, if avoidance possible.
- If not, then judicious glucocorticoid medication is indicated.

Prevention

- Try to avoid any offending irritants or allergens.

Drug Hypersensitivity

Reactions to drugs are classified as predictable or unpredictable. Unpredictable reactions may have an immunological or genetic basis. Predictable reactions include signs such as alopecia due to corticosteroids or anti-neoplastic drugs. Immunological reactions can be
Types I, II, III or IV hypersensitive responses. It should be remembered that virtually all drugs are capable of inducing an adverse reaction. Some cases of TEN, erythema multiforme and SLE may have an underlying drug etiology.

Certain drugs are over-represented in many surveys, including sulphonamides, penicillins and cephalosporins. This factor appears to arise for reasons other than simple frequency of use. Exposure to the drug could have been in the preceding weeks or months.

**Clinical signs**

- The clinical signs can mimic most, if not all, other types of skin diseases.
- Common lesions include erythema, papules, plaques, vesicles/bullae and urticaria. Many of the lesions may become annular or ulcerate.
- There may be necrosis and sloughing of affected skin.
- Common sites include the mouth, face, ears, mucocutaneous junctions, groin and feet.
- Some cases have signs similar to auto-immune dermatoses.
- Pruritus is variable, but can be severe.
- Some cases are manifested by a vasculitis reaction, and may exhibit necrosis and sloughing of the extremities e.g. tips of ears, nose etc.
- Systemic signs, such as inappetance, pyrexia etc., may be present.

**Diagnosis**

A definitive diagnosis is often difficult to make, and may only be confirmed retrospectively. Suspicious factors in the history include:

- Prior history of drug administration.
- The reaction pattern resembles one of hypersensitivity.
- The clinical signs resolve following withdrawal of the drug.
- Provocative exposure at a later date is theoretically possible to confirm the diagnosis, but this is not recommended, as it involves unnecessary risk.
- Histopathology of affected skin is not diagnostic from an aetiological point of view.

**Treatment and Prevention**

- Withdraw the suspect medication.
- Symptomatic therapy for any skin lesions.
- Do not use this or any cross-reacting drug at any future time point in that patient.

**Prognosis**

- Generally good, unless lesions affect a significant area of skin e.g. necrosis.
- The prognosis can be adversely affected by serious systemic involvement.
General Use of Corticosteroids in Veterinary Dermatology

The widespread use of corticosteroids in veterinary dermatology has led to a large amount of cynicism about the way in which skin cases are treated. The standard phrase from such cynics would be; “so how much prednisolone are you going to give this one, then?” However, it would be a huge mistake not to appreciate the incredible value and necessity of this class of drugs in our profession. Used judiciously, they can be life saving. Used inappropriately, they can be life threatening. The function of this section is not to detail every last product available on the market, as most of you have years of experience of their use. Rather, we should concentrate more on general principles of use, with particular reference to those factors that should influence your choice of formulation, the dosage selected, the dosage interval and overall duration of therapy. Appreciation of all the potential side-effects is also essential.

Natural corticosteroids

These hormones are naturally produced by the adrenal gland and divided into 3 major categories; glucocorticoids, mineralocorticoids and adrenal sex hormones. In the dog, the vast majority of the corticosteroids secreted by the adrenal gland are glucocorticoids. Natural glucocorticoids are not commonly used in veterinary dermatology, with the exception of hydrocortisone in topical preparations. Such products are normally indicated for focal inflammatory lesions and contact dermatitis cases. Cortisone tablets are available for use, and have been commonly used to control clinical signs in conditions such as hypoadrenocorticism. Cortisone is not normally used for dermatological cases, as it is less potent than the synthetic alternatives. Furthermore, cortisone could not be used topically, as it requires reduction of the keto group on C11.

Synthetic glucocorticoids

A whole range of synthetic molecules have been developed both for human and veterinary use. The natural steroid structure has been manipulated in several ways in order to facilitate the requirements for use. In other words, for our purposes, efforts have been made to increase the anti-inflammatory potency of the molecule, whilst at the same time reduce its mineralocorticoid activity. This is achieved by adding a double bond at C1-C2, hydroxylation of C16 or C17, methylation of C6 or C16 and flourination of C6 or C9. As a result of this, tables of anti-inflammatory and mineralocorticoid potency can be established, which can allow the clinician to decide which agent, with its consequent advantages and disadvantages, is most appropriate for a particular type of case.

In general, the anti-inflammatory potency on an arbitrary scale of the available molecules goes like this;
Betamethasone> dexamethasone> triamcinolone> methylprednisolone> prednisolone> hydrocortisone> cortisone.
Agents like betamethasone and dexamethasone possess approximately 30 times the anti-inflammatory potency of hydrocortisone, whilst prednisolone is approximately 4 times more potent than hydrocortisone. In general, the synthetic glucocorticoids are considered to have little or no mineralocorticoid activity. In addition, the synthetic forms tend to have a lower binding affinity for plasma proteins and possess a longer duration of action (possibly due to increased receptor binding affinity and inhibition of hepatic degradation). In veterinary dermatology, prednisolone has established itself as the number one parenteral agent for a number of reasons;

* Relatively inexpensive  
* Poor mineralocorticoid activity  
* Short-intermediate duration of action  
* Can be administered ESD

Prednisone is a pro-drug of prednisolone. Following reduction of the keto group on C11 in the liver, it is converted into prednisolone. Prednisolone is a short-intermediate acting steroid, with a duration of metabolic effect of 12-36 hours. This is longer than hydrocortisone, but shorter than dexamethasone. Some companies are beginning to concentrate more and more on topical preparation of corticosteroids. As such, many formulations of topical betamethasone, dexamethasone and triamcinolone are currently available. A new topical formulation, containing resocortyl butyrate will shortly be marketed.

**Biological effects of glucocorticoids**

Corticosteroids are essential for life and have hugely significant effects on virtually every tissue of the body. In general, these molecules bind to specific receptors in the cell cytosol, and are subsequently transported to the nucleus Any relevant text can be consulted for a review of the metabolic effects of corticosteroids. The dose of prednisolone required to fulfill normal essential physiological functions is approximately $1/5$th that required for an anti-inflammatory effect. For the purpose of this talk, we will concentrate more on the anti-inflammatory and immunosuppressive effects of glucocorticoids.

The anti-inflammatory doses are well in excess of normal physiological doses, and are thus classed as pharmacological doses. Corticosteroids exert their anti-inflammatory affects through the following mechanisms;

- Steroids stimulate RNA transcription of lipocortin,
- Lipocortin inhibits phospholipase,
- This leads on to inhibition of prostaglandin, thromboxane and leukotriene synthesis,
- Steroids also appear to stabilize lysosomal membranes.

These effects result in;
- Suppression of the early and late phases of inflammation (and resultant clinical signs),
- Reduced febrile response,
- Decreased formation of inflammatory oedema, through effects on endothelial cell membranes,
- Decreased migration of polymorphs,
- Reduced deposition of fibroblasts.

The immunosuppressive properties of corticosteroids are largely attributable to;

- Suppression of lymphocyte and eosinophil counts in the peripheral blood,
- Inhibition of lymphocyte DNA synthesis,
- Decreased circulating T-lymphocytes and inhibition of lymphokine function,
- Decreased production of immunoglobulins,
- Suppression of bacterial processing by macrophages,
- Suppression of the margination, diapedesis and “inflammatory burst” of neutrophils,
- Suppression of cell-mediated and humoral immunity,
- Inhibition of complement activity.

The dose required for an anti-inflammatory effect with prednisolone is approximately 0.5-1.0 mg/kg bodyweight per day. Even at these dose levels, there will be inhibition of some, but not all, of the functions of the immune system. Immunosuppressive doses approximate to 2-4 mg/kg bodyweight per day. The higher end of the dose schedule is particularly required in the cat.

**Side-effects of glucocorticoid therapy**

Many of you will be very familiar with the side-effects associated with both the short and longer term use of glucocorticoids. In certain cases, these effects may lead on to the development of iatrogenic Cushings disease. Side effects include;

*PU/PD*  
*Polyphagia*  
*Weight gain*

*Hyperglycaemia/ DM*  
*Thin skin*  
*Alopecia*

*Comedones*  
*Prominent veins*  
*Hepatomegaly*

*Pancreatitis*  
*Osteoporosis*  
*Immune suppression*

*Inhibition of HPA-axis*  
*Electrolyte imbalance*  
*Protein catabolism*

*GI ulcers*  
*Calcinosi cutis*  
*Teratogenicity etc.*
**Which glucocorticoid to use?**

Various preparations are available. The major differences involve the dose required, route of administration and inter-dosage interval. Glucocorticoids are usually referred to as being short, intermediate or long acting. In general, prednisolone and methylprednisolone are considered to be short to intermediate in action. For most dogs the effects appear to last for 12-24 hours. However, in some cases, pharmacological doses can exert effects for up to 36 hours. Dexamethasone, betamethasone and triamcinolone are considered to be inherently long acting glucocorticoids, as their effects invariably last longer than 24 hours. It is obvious from your own experience in practice, however, that formulations (particularly in the forms of salts and esters) can be made that can greatly prolong the duration of effect of many glucocorticoids. Thus, methylprednisolone acetate (Depomedrone) would be expected to exert effects for 3-6 weeks in most patients. In products such as Voren and Voren 14, simply altering the size of the molecule (dexamethasone isonicotinate) can have a marked effect on the rate of absorption, and thus on the duration of efficacy.

The general rules of thumb are as follows;

- Sodium phosphate salts and succinate esters are soluble and may be administered intravenously. They are generally eliminated within 8-48 hours,

- Acetate, adamantoate and dipropionate esters of dexamethasone are intermediate to long-acting, generally exerting an effect for 4-14 days,

- Esters of methylprednisolone and triamcinolone are long acting, exerting their effects for 3-6 weeks,

- Topically applied valerate esters can have a varied duration of efficacy, generally averaging approximately 24 hours.

When presented with a patient with atopic dermatitis, the following factors would be considered important in deciding which active principle or formulation to use;

- Seasonal or perennial problem (long-term versus short-term therapy),
- Advantages and disadvantages of long-acting formulations,
- Ability to alter dose as required,
- Owner compliance (tablets versus injections, number of visits etc.),
- Side-effects and the speed of reversibility,
- Do you want to achieve an anti-inflammatory or immunosuppressive effect,
- Compliance with other medication e.g. desensitization,
- Cost.
For all of the above reasons, the preferred option in most cases is the use of oral prednisolone. This is my approach unless practical difficulties are encountered (such as above). Always remember that prednisolone is just one of the treatment options; it may just be used short-term whilst desensitization is attempted. Furthermore, following an initial dose of 1-2 mg/kg bodyweight per day, attempts are routinely made to wean the animal down to the lowest dose required to control clinical signs. Thus, in the later stages at least, we are relying more on the use of anti-inflammatory doses of prednisolone, not immunosuppressive doses. In my opinion, long acting preparations have been associated with a significant incidence of adverse effects. Therefore, the only indication for use is the treatment of seasonal atopics, in which owners have great difficulty in administering tablets. In general, I avoid them. Topical therapy should always be considered as an option. However, it is not a practical option in many cases, due to the large body surface area involved. Furthermore, it should be emphasized that topical steroids are absorbed into the systemic circulation, and can exert at least some of the side-effects listed above. They can also be absorbed percutaneously by the owner, if gloves are not worn.

**Golden rules for longer-term glucocorticoid therapy**

- Always try to minimize the dose and the dosage frequency,

- Gradually taper the dose and frequency downwards,

- Sudden withdrawals may precipitate an Addisonian crisis,

- Alternate day therapy is achievable in most atopic patients,

- Some authors recommend giving a double dose (ESD), but I usually do not find this necessary,

- Give a short-acting preparation, such as prednisolone or methylprednisolone,

- Administer the drug at the time of peak endogenous steroid activity i.e. morning time for dogs and evening time for cats,

- Constantly monitor these patients for adverse effects such as hyperglycaemia/ DM and Cushings disease,

- A clinical decision based on risk-benefit analysis must be made for each patient exhibiting significant side-effects,

- Always consider if other additional therapies may be indicated, and whether these may allow for a reduction in the glucocorticoid dose.
It must be remembered that the use of glucocorticoids will have detrimental effects on certain laboratory, immune and histopathological tests that may be required in the work-up of atopic dermatitis patients e.g. biopsies, intradermals. Therefore, a clear diagnostic strategy should be worked out before resorting to their use.

B) **AUTO-IMMUNE DERMATOSES**

This is a group of infrequent but not uncommon diseases, well recognised and reported in both dogs and cats, although most cases are seen in dogs.

The basic underlying aetiology and defects in the immune system which allow such diseases to develop have been dealt with previously in lectures on immunology and pathology. The relevant notes should be consulted as complimentary to this lecture.

The origin of an auto-immune disease normally arises from a breakdown in self tolerance due to interference with normal control mechanisms. The defects which may arise include:

1. Malfunction of T suppressor cells.
2. By-passing of T suppressor cell function.
3. Inappropriate activation of polyclonal B cells.
4. Auto-antigen modification, e.g. trauma to tissues etc.
5. Cross-reacting antigens.

The major diseases covered by this classification include:

1. Pemiphigus complex
2. Bullous pemphigoid
3. SLE
4. Discoid lupus erythematosus
5. Cold agglutinin disease

**1. PEMIPHIGUS COMPLEX**

Probably the most frequently seen of the auto-immune dermatoses. There are four distinct clinical forms of the disease.

Pathogenesis: an auto-antibody is produced to the glycocalyx of the keratinocyte. The antigens involved are heterogeneous, and may differ from one form of the disease to the next. When antibody binds to the antigen on the cell surface, it is thought to then internalise and bind with intracellular lysosomes. This leads to release and activation of a specific proteolytic enzyme which diffuses extra-cellularly and breaks down the glycocalyx. There is then a breakdown of the bridging network between neighbouring
cells, with the development of micro-vesicles or blisters. The vesicle represents fluid accumulation, with sloughed off keratinocytes. Histologically, the lesion is referred to as acantholysis and the cells are called acanthocytes. It is a Type II hypersensitive reaction, with no inflammatory cells or complement activation being required.

Some authors have proposed that other factors may be involved, particularly in a predisposing role, e.g. ultraviolet light and drug reactions etc.

A genetic predisposition is seen in some breeds, e.g. German shepherds.

**Clinical Signs**

Some signs are common to all four different forms of pemphigus and relate to the initial lesion type. Differences do exist in lesion location, severity and occasionally in the type of lesion.

Pemiphigus complex is a vesico-bullous, erosive to ulcerative skin disease. The vesicles, which are common in humans, are rarely seen in dogs/cats due to the thinness or reduced cell layer numbers of the canine/feline epidermis as compared to humans.

(a) **P. vulgaris**

One of the most common forms seen. Can occur at any age. The typical lesions are seen in the mouth and at mucocutaneous junctions, although lesions can occur elsewhere on the skin. The oral cavity is the most common site. The erosions/ulcers may show evidence of epidermal collarettes, and may be secondarily infected.

The nikolsky sign may be present, i.e. excessive wrinkling of the skin when linear pressure is applied, due to the loss of cohesion between neighbouring cells.

Pruritus and pain are variable, sometimes severe and sometimes non-existent.

(b) **P. vegetans**

Rare form. Most authors believe it represents a benign form of P. vulgaris. Similar sites to P. vulgaris. The lesions, however, are somewhat different in that they become verrucose or warty in appearance, and are frequently secondarily infected. Again, pruritus and pain are variable.

(c) **P. foliaceus**

Probably the form most commonly seen clinically. Certain breeds appear more predisposed.
Lesions may consist of vesicles/bullae or more commonly erosions/ulcers. These lesions quickly become secondarily infected, and thus at the time of consultation may consist of:
- erythema/crustiness
- pustules
- alopecia
- epidermal collarettes

The common sites include the body trunk (particularly hind limb region), face, ears and feet (including pads). It is normally not seen in the oral cavity. Lesions may become generalised in some animals, and have also been reported at mucocutaneous junctions in certain cases.

The bridge of the nose can be affected, and such animals may present with nasal depigmentation.

Whilst associated clinical signs are similar to above, if severely affected, anorexia and depression/lethargy are not unusual.

(d) **P. erythematosus**

Not as common. Some authors believe it represents a benign form of P. foliaceus. Lesions are commonly seen on face (nose, eyes) and ears. German shepherds and Collies are over-represented.

The clinical signs are similar to before, but nasal/ocular depigmentation and erosion/ulceration are often dominant features.

**Diagnosis**

The diagnosis of the various forms of pemiphigus rests on a combination of the following:

- History and clinical signs
- Biopsy – lesions of acantholysis etc.
- Immunoflorescence studies – can demonstrate the antibody in situ in some, but not all, cases. This is particularly true for P. erythematosus, but as some of these animals also have ANA titres, there could be an overlap between it and SLE/DL.

Routine bloods are usually unrewarding.

2. **BULLOUS PEMIPHIGOID**

Vesico-bullous, ulcerative skin disease, where the initiating pathology is based at the level of the dermo-epidermal junction, i.e. the basement membrane zone.
The auto-antibody attacks this junction and thus the vesicles or bullae develop sub-epidermally. Another difference between this and the pemiphigus complex is that complement fixation and neutrophil/eosinophil chemo-atraction are aspects of the pathogenesis in bullous pemiphigoid.

Predisposing factors are the same as before.

Clinical Signs

Certain breeds appear pre-disposed, e.g. Collies. Common sites include the mouth, mucocutaneous junctions and different parts of the body trunk (axilla and groin in particular). Many cases have lesions in the mouth. The foot-pads may be involved.

Clinical signs are similar to those for the pemiphigus complex, but the ulceration may be more severe.

Diagnosis

- History and clinical examination
- Biopsy – sub-epidermal lesions.
- Immunoflourescence tests – direct immunoflourescence testing for antibodies and complement at the b.m. zone.

3. SLE

This disease is covered in other lectures dealing with (systemic) auto-immune diseases – see relevant lectures.

The aetiology of this disease appears to be multi factorial. Auto-antibodies are formed against numerous different cell types, not just skin.

There are many theories on how skin lesions arise in this condition. One of the more popular theories suggests that:

(a) Ultraviolet light penetrates down to the basement membrane cells, and alters the keratinocyte surface to allow expression of previously hidden antigens (in cytoplasm or nucleus).
(b) Antibodies to these antigens attach to the keratinocyte surface.
(c) This induces cytotoxicity of the keratinocyte.
(d) Inflammatory mediators and immuno-modulatory agents are released.
(e) Infiltration of affected tissues occurs with lymphocytes and histiocytes.

Predisposed breeds include German shepherd, Collies and Shelties.
Clinical Signs

Somewhat variable compared to before – systemic; cutaneous. Vesicles/bullae and ulcers seen on face, ears and distal limbs. Foot pads and nasal planum commonly involved. Secondary pyoderma and sebborheic skin disease are occasionally present. Pruritus is variable, but on occasions can be marked. There may be ulceration or hyperkeratosis of the food pads.

Diagnosis

See other relevant notes on auto-immune diseases.

- History and clinical signs.
- Routine haematology/biochemistry and urinalysis, e.g. anaemia, thrombocytopenia, proteinuria, etc.
- Serology test for ANA – the current most accurate routine test.
- LE cells on smears.
- Skin biopsy – various lesions, the most common of which is an interface dermatitis.
- Immunofluorescence tests – antibodies and complement deposited at b.m. zone.

4. DISCOID LUPUS ERYTHEMATOSUS

Considered by many authors to be a benign form of SLE. There are no systemic signs present and lesions are confined to the skin.

Clinical Signs

Breed predisposition – German shepherd, Collies, Shelties and some husky breeds.

Lesions are usually confined to the face, although there can be exceptions to this rule.

Early signs include depigmentation, erythema and slight excess scale over the nasal region.

The lesions commonly erode/ulcerate and may crust over. Lesions extend along the bridge of the nose.

Lesions have also been reported around the eyes, ears and on the limbs. Mouth involvement and foot-pad involvement (hyperkeratosis) are also reported.

Pruritus/pain may or may not be present.

Ultraviolet light frequently causes a deterioration in this condition.

Diagnosis
• History and clinical examination.
• Skin biopsy – interface dermatitis. Lesions seen near b.m. zone, and around dermal blood vessels and adnexal structures.
• Immunoflourescence tests – antibody and complement deposited at b.m. zone.

5. COLD AGGLUTININ DISEASE

Certain proteins can be precipitated from blood by cooling, e.g. cryoglobulins, etc. These globulins can be monoclonal or polyclonal, and can be associated with disease processes as diverse as infections, autoimmune diseases and neoplasia.

The effect of precipitation of these proteins is to cause vascular pathology through obstruction, thrombosis, stasis of blood vessels etc.

As well as globulins, other proteins such as fibrinogen can also be involved.

Clinical Signs

As the auto-antibodies involved are cold reacting, cold agglutinin disease generally affects the extremities, i.e. paws, nose, etc. Skin lesions involve erythema, necrosis, purpura and ulceration. Exposure to cold is often a relevant factor in the history.

There may be signs of anaemia present.

It is a type 2 hypersensitive reaction, and has been associated with lead poisoning in dogs and upper respiratory infections in cats.

Diagnosis

• History and clinical signs.
• Serology – cold-reacting auto-antibodies (cold agglutinins)
• Haemagglutination on a slide at cold temperatures, e.g. 0°C, which can then be reversed by heating up to 37°C.
• Skin biopsy – necrosis/ulceration. Secondary infection.

Treatment

• Avoid exposure of the animal to cold.
• Follow the general principles outlined below.
General treatment of auto-immune dermatoses

The treatment of auto-immune dermatoses can be both rewarding and frustrating. In referral practice and University-type situations, we would see numerous cases of this nature on a yearly basis. Whilst the numbers reported in everyday practice may be less, the same difficulties apply in attempts to control such problems. It is not within the scope of this talk to explain the pathogenesis or clinical signs observed in auto-immune dermatoses. The aim is instead to explore the treatment options available once a diagnosis has been reached.

From the outset, it must be emphasized that the therapeutic approach to a case of auto-immune skin disease will be significantly influenced by the severity of the condition, and whether or not the disease process is confined to the skin e.g. is it part of an SLE complex. Many different treatment strategies can be attempted, but most of the emphasis rests with conventional medication. The role of, or overlap between, UV radiation and certain auto-immune skin diseases is well known. This knowledge allows us to consider the relevance of additional strategies such as avoidance of UV light during maximum periods of exposure, as well as therapies concentrating on the use of sun-blocks etc. Furthermore, many of the drugs that we discuss here would be more correctly labeled as immune-modulating compounds, rather than immunosuppressive agents.

Corticosteroids

Glucocorticoids again represent a very important avenue of treatment for the auto-immune skin case. Reference should therefore be made to the notes on the use of corticosteroids in the treatment of the allergic patient. Certain significant differences should be highlighted:

- As stated previously, the immunosuppressive doses of prednisolone are higher than the anti-inflammatory dose,
- As several cases of auto-immune dermatoses are not particularly pruritic, the clinician needs a clear understanding of the goals of therapy e.g. allow all ulcers to clear up? This will influence the dose selected and the frequency of administration,
- In most cases, the clinical condition will be perennial and therapy is often life-long,
- For conditions such as pemphigus erythematosus, sun-block etc. may play an additional pivotal role,
- Corticosteroids can often be combined with other immunosuppressive or immun-modulating agents to achieve better overall control. This may allow for the dose of steroid to be reduced.

In earlier times, corticosteroids alone represented the major treatment strategy for auto-immune skin disease. Now certain classes of drugs, and other individual agents, have established clear roles in such treatment protocols.
Azathioprine

This purine analogue (trade name = **Imuran**) has a long history of use in human medicine, in which it has been utilized in the treatment of various immune-mediated diseases. In veterinary medicine, azathioprine has been routinely used in the treatment of diseases such as SLE and inflammatory bowel disease. In more recent times, we have experimented more and more with its use in veterinary dermatology, with increasing evidence of success. However, many of the limitations on its use in other areas of human and veterinary medicine have been additionally encountered in our dermatology cases.

The single biggest limitation to the use of this agent is its unreliability as a single agent treatment. Practice experience would dictate that it often requires to be combined with another agent, usually prednisolone. Many cases are treated initially with corticosteroids, and if a remission is not obtained or the steroid medication causes undue side-effects, azathioprine is then often added to the protocol. A further limitation to its use is the lag phase commonly encountered prior to its full beneficial effects being experienced. Thus, the initial dose is normally set at 2 mg/kg bodyweight per day, and after a period of approximately 4-6 weeks, this can then be reduced to 2 mg/kg bodyweight every second day. In some cases, the dose itself can also be halved. As the drug takes more and more effect, the dose of prednisolone is usually reduced. Thus, in the authors’ experience, it is possible after about week 6 to have the animal on alternate day doses of steroid and azathioprine.

The adverse effects of azathioprine can be potentially serious. Myelosuppression can occur, and it is advised that the CBC and platelet count be routinely monitored. The author suspends use of this drug if the neutrophil count goes below 4-5 x 10^9 cells/l. Effects on the liver are also reported, and ALT, GGT and AP concentrations should also be monitored (beware an expected rise if also on steroid therapy). Some dogs vomit following oral administration of the drug. In general, azathioprine is not recommended for use in cats, as it is particularly myelosuppressive in this species.

Gold therapy (chrysotherapy)

Initial uses of gold salts concentrated on conditions such as rheumatoid arthritis in man. Following early work in cats and dogs, it was discovered that gold salts were also efficacious in conditions such as the pemphigus complex and plasma cell lesions in the cat (e.g. feet and mouth). There is a lag phase encountered before these drugs generally kick in, usually in the region of 8-12 weeks. As a consequence of this, steroid medication is usually combined with gold salts during this initial treatment period. The actual mode of action of gold salts on the immune system is incompletely understood. We know that these salts are capable of inhibiting many mediators of inflammation, including prostaglandins, lysosomal enzymes and histamine. They also interfere with neutrophil function and complement activity, but the precise mechanism is not understood. Gold salts can be administered by the oral and intramuscular routes. The author normally uses the intramuscular formulation, sodium aurothiomalate (Trade name = Myocrisin). Bioavailability is very high by this route, with a half-life of approximately 6 days. The
The drug is highly protein-bound (approximately 95%). Other formulations are additionally available in different countries. Some animals are particularly sensitive to the side-effects of gold therapy. Such side-effects include severe ulceration of skin and mucosal surfaces, proteinuria and bone marrow suppression. With this in mind, I usually give prospective patients 1-2 trial doses of 1 –5 mg sodium aurothiomalate at weekly intervals. If no adverse effects are evident, a full course of weekly injections are given at the RTD of 1 mg/kg bodyweight IM for 8-12 weeks. The IM administration of product does tend to cause pain on injection. At the end of this period, the response is assessed, and if appropriate, the frequency of administration can be reduced to fortnightly, and then monthly. Oral formulations are available in certain countries, but GI tract side-effects tend to be more frequent. The author has limited experience of using Auranofin (Trade name = Ridaura), at a dose rate of 0.2 mg/kg bodyweight bid, but has found it to be less efficacious than the parenteral form. Gold therapy should not be used in auto-immune skin diseases that are part of the SLE complex, as it may elicit or worsen renal damage and bone marrow abnormalities. Additionally, gold salts should not normally be combined with other cytotoxic drugs, apart from steroids. Patients on long term therapy require regular blood counts and urinalysis (for proteinuria). In some cases, gold therapy may be discontinued if all signs resolve after several months of treatment. However, this is done more in hope than with confidence.

**Chlorambucil**

This alkylating agent has a similar mode of action to the commonly used anti-neoplastic drug, cyclophosphamide. Thus, it leads to the addition of alkyl groups onto various bases on the DNA molecule, creating false base pairs that prevent successful replication of DNA in affected cells. This interference on cell division in rapidly dividing cells also makes chlorambucil ideal for modulating the immune system in diseases like pemphigus foliaceus. Chlorambucil is suitable for use in felines. However, as with previous agents, it normally requires to be combined with prednisolone. The RTD is 0.1-0.2 mg/kg bodyweight once daily or ESD, by the oral route. Initial improvement of clinical signs normally takes 6-8 weeks, at which point the medication can be reduced to alternate day therapy. From then on, the dose of steroid and chlorambucil are tapered down to the least effective level. Side-effects include GI tract upsets, inappetance and bone marrow suppression. Thus a CBC and platelet count should be performed periodically. In some cases, if the response is particularly good, then it may be possible to maintain the animal on prednisolone alone, in the longer term.

**Cyclosporine**

Cyclosporine is a potent modulator of the immune system, with particular effects on specific T lymphocyte and T- associated B lymphocyte responses. Its initial use in graft rejection procedures in humans is well documented. Cyclosporine does not inhibit migration of leucocytes into damaged tissue, nor does it affect virgin or naive lymphocytes. Thus, it does not predispose to the same incidence of secondary infections that some other agents do. The cyclosporine molecule is a small cyclic peptide, consisting of only 11 amino acids. Oral tolerance of the human formulation is not always high in
dogs and cats. Initial veterinary treatment concentrated on the topical use of this product for the treatment of dry-eye, but in recent years, cyclosporine has become a standard treatment for canine AD. Individual case reports also exist for its use in cases of autoimmune skin disease and a variety of other conditions including anal furunculosis and sebaceous adenitis. The author has used this preparation on a number of cases, although expense has been a problem. Initial dose selection has been difficult to standardize. In general 5 mg/kg SID has been required. Once a clinical remission has been obtained, the dose was reduced down to 2.5 mg/kg SID or even every second day. Nephrotoxicity is a reported side-effect, although the author has not experienced this in the cases that he has treated. It is possible to use this drug topically for discrete lesions of the nose, eyes etc. Clinical response has been highly variable, with the best results being obtained for anal furunculosis and some cases of sebaceous adenitis. For anal furunculosis, initial debridement was also required, and some cases had surgery later on to try and maximize lesion healing. The biggest concern was the incidence of relapse, which was actually quite disappointing. However, larger case numbers and better controlled trials are required before a definitive position can be adopted on the use of cyclosporine for such indications. It should also be emphasized that one of the more critical aspects for success in humans depends on maintaining the plasma concentration of the drug within a certain therapeutic window; however, recent evidence may suggest that this factor is not so critical in the dog.

Miscellaneous drugs

Certain other drugs have been employed to treat smaller numbers of individual cases of auto-immune skin disease. In my experience, these have been employed when a satisfactory response was not obtained with more conventional agents, or when the side–effects were unwarranted. Some are still at an experimental phase, or may have been attempted in very small case numbers due to expense. Included in this category are;

- **Interferon** – Interferon α-2a has been used in conditions which are thought to have an immune component e.g. eosinophilic granuloma complex, as well as for the treatment of cutaneous lymphoma. Availability and expense are two critical issues. Anecdotal evidence of its use for auto-immune dermatoses, particularly in the cat, is available, but case numbers are very low. No recommendation can currently be made for this compound for conditions such as DLE etc.

- **Vitamin E** – this fat soluble vitamin has been used to treat a variety of auto-immune skin diseases in addition to conditions such as dermatomyositis and steatitis. There is little hard scientific evidence to conclusively prove its value for the auto-immune diseases, but many authors recommend it for cases of DLE in the dog (200-400 iu per dog bid or tid). Excess vitamin E has been associated with hypertension in humans. The formulation normally employed in veterinary dermatology is natural α-tocopherol. Vitamin E on its own would be insufficient for clinical control of the disease, but is rather employed as additional therapy.
• *Tetracycline and Nicotinamide* – this combination has been employed by some authors to control cases of DLE, although I have no personal experience of using this protocol. Tetracycline has been known for some time to possess certain anti-inflammatory properties, in addition to its antibacterial effect. The combination of drugs is also believed to inhibit neutrophil migration and histamine release from mast cells. The dose rate employed is 100-500 mg of each drug per dog tid. Clinical resolution is expected after a lag phase of several weeks. Depression and vomiting are occasional side-effects.

**Additional strategies for controlling auto-immune disease**

• If pyoderma is present, appropriate use of systemic and topical antibacterial agents should be employed.

• Some animals may develop excess scale and seborrhea as part of the treatment strategy. Appropriate shampooing etc. may be indicated.

• IF UV light is considered to be an eliciting or complicating factor in the pathogenesis of the disease, then the use of appropriate sun-block preparations and avoidance of peak-time exposure to UV light should be instigated.

• Tattooing has largely fallen out of fashion, due to the danger of ink penetrating beneath the skin surface, and eliciting a foreign-body type reaction.
Anal Furunculosis

- Disease of large breed dogs, and the German shepherd in particular.
- The cause is basically unknown. Many theories have been proposed relating to initial pathology of the anal sacs, immune-mediated disease etc. The condition is probably multifactorial in aetiology. Certainly, poor ventilation under the tail and accumulation of secretions are common findings in clinical cases.

Clinical signs

- Excess moistness in the region around and under the tail.
- Erythema and purulent infection. Numerous sinus tracts may be evident.
- Furunculosis and fissuring or ulceration of the skin under the tail and peri-anally.
- Foul smell from affected region. Necrosis and sloughing of affected tissue.
- Pain and discomfort are variable. In some cases the condition is only noticed incidentally. Other dogs are depressed and in obvious discomfort.

Treatment

- The response to antibiotics and corticosteroids is invariably disappointing. This is not to say that antibiotics should not be used to control any secondary infection.
- Trials have been conducted in the recent past with the use of cyclosporine. Results have been variable, and further work is necessary before any final recommendations can be made.
- Topical tacrolimus applied once daily can also work in some cases, but patient compliance with topical application is often a limiting factor.
- Combined therapy with metronidazole and azathioprine has been successful in approximately 50% of cases.
- Although surgery is usually not the best first treatment option, surgical intervention to debride affected tissue after initial medical therapy has been of benefit in some cases.
**Keratinization Disorders**

**Seborrhoea**

Extremely common problem in canine practice (less commonly seen in felines). Seborrhoea is characterized by the presence of excess scale on the skin and coat. In addition, the coat is either excessively dry (seborrhea sicca) or greasy (seborrhea oleosa). In certain forms of the condition, the affected skin may be inflamed, giving rise to the term seborrhoeic dermatitis. Lesions of seborrhoeic dermatitis are often described as “target lesions”, and must be differentiated from other causes of “target lesions”, such as staphylococcal dermatitis and ringworm etc. Seborrhea can be classified as primary or secondary.

In primary seborrhea, the condition appears relatively early in life (often below 1 year of age). It is an inherited disorder and therefore certain breeds are known to be predisposed e.g. Cocker and Springer spaniels, Basset hounds and Irish setters. Many other breeds can be affected also. Affected animals typically exhibit clinical signs whilst young, with other diagnostic tests e.g. skin scrapes, intradermals etc., all yielding negative results. Many primary cases are greasy or oily in nature.

Secondary seborrhea is the more common clinical form of the two. In this condition, the presence of excess scale is associated with another underlying skin disorder. The underlying causes include pruritic skin diseases, endocrine dermatoses, nutritional and environmental factors. Endocrine diseases e.g. hypothyroidism or hyperadrenocorticism are common underlying causes. The fact is that virtually any skin disorder may give rise to seborrhea. If the underlying disorder can be corrected, then the seborrhea usually resolves. Most cases of secondary seborrhea are dry in nature.

**Clinical signs**

- Excess scale or flakiness of the skin and coat.
- The coat feels abnormally dry or oily. Oily cases frequently present with pronounced mal-odour.
- Lesions may be focal or diffuse.
- Secondary infection (bacterial or yeast) is not uncommon.
- In cases of secondary seborrhea, clinical signs related to the underlying cutaneous disease are usually present.
- Seborrhea may be a manifestation of internal, metabolic or immunosuppressive diseases, and systemic signs of disease may be evident.
- In seborrhoeic dermatitis, target lesions consisting of alopecia, epidermal coallarettes, erythema and hyperpigmentation are usually seen.

**Diagnosis**

- History and clinical signs.
• It is essential to rule in or out, any underlying skin disorder. Therefore, a complete skin work-up is required.
• Skin biopsy may help to diagnose various underlying disorders and can be helpful in confirming seborrheic dermatitis.
• Various tests e.g. bloods, radiographs etc., are required to diagnose underlying systemic diseases.

Treatment

• Treat or correct any underlying skin or systemic disorder that is predisposing to the development of the seborrhea. This may lead to resolution of secondary seborrhea.
• Primary cases cannot be cured, but can be successfully managed with on-going therapy.
• Topical shampoos (see lecture on pharmacology of the skin) are very beneficial in treatment. The choice of shampoo and the frequency of treatment will depend on the individual case. Agents frequently used include benzoyl peroxide, selenium, sulphar, coal tar etc. **Do not bath the dog too frequently.** Bath oils and humectants can be very useful in dry seborrhea.
• Some authors advocate the use of EFAs in the treatment of dry seborrhea. Results to comprehensively prove a beneficial response are not available.
• Secondary infections will require appropriate therapy.
• In refractory cases (and in cases of seborrhoeic dermatitis), the judicious use of corticosteroids may be indicated.

Seborrhoea in the cat is rare; when it does occur, it invariably is secondary in origin and “dry” in nature. Greasy seborrhea has been reported in cats with severe systemic disease. The approach to the seborrhoeic cat is similar to that for the dog; whilst shampoos are not commonly used, it is important to avoid those that contain tar, selenium or phenols.

**Canine and feline acne**

Canine acne is a common sub-clinical disorder. The condition is manifested in the form of lesions around the chin and lips of young dogs primarily. Residual lesions are often seen in adulthood, but rarely cause a problem. In the past, the lesions were referred to as comedones (blocked hair follicles, with accumulation of sebaceous secretion beneath the blockage. More recent work has shown that the lesions more likely resemble infected papules or furuncles. Diagnosis is confirmed on clinical signs alone in the vast majority of cases. Treatment involves the use of topical agents such as benzoyl peroxide on an intermittent or regular basis. More aggressive therapy e.g. systemic antibiotics etc., is rarely required.

Feline acne is rare. Lesions are generally confined to the chin and upper or lower lips. The disease can manifest as recurrent bouts. Adult cats are commonly affected. Both sexes are equally affected. Whilst many underlying diseases are suspected, the condition is basically idiopathic. The lesions in feline acne more commonly resemble true comedones. Secondary infection may lead to pustules developing. The chin (and possibly
the lips) may become grossly swollen. Pruritus can be a common feature in advanced cases. Regional lymphadenopathy may be evident clinically. Residual scarring may develop. The diagnosis is often made clinically, but can be confirmed on histopathology. Conditions to rule out include ringworm, demodicosis and the eosinophilic granuloma syndrome.

Topical therapy is frequently beneficial in cats. Benzoyl peroxide may be irritating in some cats, so agents such as sulphur or ethyl lactate can be used instead. Systemic antibiotics are indicated if pustules are present. Vitamin A derivatives and even short courses of prednisolone may be required for severe cases. The need for on-going therapy varies from cat to cat. Some cats only have one bout of disease, others have several bouts or continual disease.

**Vitamin A-responsive dermatosis**

Primarily a disease of cocker spaniels (other breeds can be affected). Generally reported in adulthood, and characterized by marked seborrhea and follicular plugging affecting the ventral and lateral chest/abdominal walls. It is not unusual for the follicular plugs to take on a “frond-like” appearance. Additional clinical signs typically include:

- crusting/scaling,
- alopecia (often dry, easily epilated coat)
- papular dermatitis,
- skin malodour,
- ceruminous otitis externa,
- pruritus.

Treatment involves supplementation with vitamin A (10,000 IU) every day in a fatty meal; the response to synthetic vitamin derivatives (e.g. isotretinoin) is very good, but such agents are often restricted to hospital use because of potential side effects. Treatment is life-long.

**Nasodigital hyperkeratosis**

Characterized by excessive amounts of horny, keratinized (stratum corneum) tissue on the footpads +/- nasal planum. The excess keratin can vary markedly in terms of size, shape, ridging and fissuring. The surface invariably feels rough/hard and dry to touch. Pad cracks can result in lameness; in certain circumstances, the keratin can develop into a corn that pushes into the surrounding pad.

Common causes include the following:

- zinc-deficiency/generic dog food dermatosis (rare when animal on balanced diet),
- autoimmune dermatoses,
- hepatocutaneous syndrome,
- infection e.g. CDV, Leishmaniasis, papillomavirus
- familial (pads only),
- idiopathic (quite common).

Diagnosis, treatment and management depend on which specific aetiology is involved. Excess keratin can be trimmed back accordingly in severe cases; however, in less severe cases. Use of keratolytic/softening agents (following initial soaking or hydration of the foot/nose) can be beneficial in some cases e.g. petroleum jelly, salicylic acid, propylene glycol gel etc.) - use as frequently as required. Steroid/antibiotic gels can be applied if fissuring occurs with secondary infection.

**Canine ear margin dermatosis**

Common cornification disorder primarily seen in the Dachshund (though other breeds can be affected as well, particularly those with pendulous ears). Occasionally, seen as a manifestation of hypothyroidism, although other skin lesions will typically be observed at other body sites in such cases. Keratin deposits and alopecia typically present on the ear margin – often greasy and crusty. When the crusty material is pulled off, the underlying tissue may bleed. The disease may extend quite far from the pinnal margin. Secondary infection and fissuring also occurs and may lead to significant pruritus (milder cases may have minimal pruritus). The ear margin can have a “moth-eaten” appearance as if affected tissue has become necrotic and died-away. The main differentials are sarcoptic mange and vasculitis reactions that target areas with poor peripheral circulation.

The above syndrome must also be differentiated from the pinnal alopecia observed as a form of “male pattern baldness” in male Dachshunds; this latter syndrome is non pruritic and simply involves alopecia and hyperpigmentation of the entire pinna.

**Ichthyosis**

Uncommon, hereditary disorder that is typically sub-divided into epidermolytic and non-epidermolytic forms in the dog (latter more common in the dog). Affected animals suffer from a wide variety of cornification defects including alterations in lipid structure within the outer stratum corneum or the desmosomal bridges that bind the epidermal cells together. Thus, the keratin breaks off the skin surface far too easily compared to normal.

Affected dogs present with thick scales that attach to the hair coat and skin surface; in severe cases, the scale can form mats around growing hairs. The skin thus takes on a typical “fish-scale” appearance, hence the name of the disorder. Alopecia is observed in affected areas. The thick scale can often be dark brown-light black in colour, and the skin surface feels rough and uneven to touch. Flexure surfaces and the pads are often targeted. Fissuring and crateriform lesions may be seen, which may become secondarily infected.

Affected breeds include terrier breeds and golden retrievers. Cases can vary from mild to severe. Mild cases may have focal involvement (e.g. face, ventral abdomen) with some periods of normalcy (i.e. the disease “waxes and wanes”). The lesions may simply consist of fine, white, powdery scale that is loosely adherent to the skin/haircoat (e.g. golden
retriever). Severe cases have generalized involvement with constant clinical signs (typically the smaller terrier breeds). Symptomatic treatment with appropriate de-scaling shampoos (e.g. sulphur, salicylic acid), antimicrobials (if secondary infection) and EFAs are indicated.

Refractory cases will often respond, at least partially, to synthetic retinoids (e.g. isotretinoin), but availability of such agents is a major issue in many countries.

**Tail gland hyperplasia**

The tail gland (preen gland) is located on the dorsal border of the tail in dogs (a few cm down from the base of the tail). This gland is composed of modified sebaceous and perianal glands, along with compound hair follicles). In male dogs it is under the influence of androgen stimulation. Thus, chronic stimulation in older male dogs (or elevated androgen levels in some dogs) may result in hyperplasia of the gland. This is manifested clinically as a thickening and elevation of the skin in the affected area in mild cases; the gland may appear swollen, nodular or even tumourous in more severe cases. with alopecia, keratin debris on the surface and secondary infection.

No treatment may be necessary in asymptomatic cases. Castration will prevent any further gland enlargement, as will anti-androgen or progestigenic therapy. Treatment of more severe cases (in addition to castration) includes the use of anti-seborrheic shampoos and antibiotics. Surgery is reserved as a last resort for cases that do not respond to castration, and is rarely undertaken in modern-day practice.
NEOPLASIA OF THE SKIN

Skin tumours are extremely common in dogs and cats. Whilst many are benign and can be left alone, others are malignant or of marked discomfort to the animal, and may require surgical removal and/or chemotherapy. Appropriate diagnosis depends on accurate biopsies, and on occasions, more advanced histopathological techniques including immunostaining to identify particular cell types.

Certain skin tumours, e.g. cutaneous T-cell lymphoma, have a very poor prognosis and warrant prompt action. The treatment modality chosen for each particular case will depend on the tumour type, stage of the disease, knowledge of tumour biology (particularly the cell / tissue type) and the general health of the animal.

The following notes do not represent an exhaustive list of all possible skin tumours, but rather represent the most common skin tumours of dogs and cats and details on their main biological characteristics:

1. Cutaneous papillomas

These tumours arise from squamous epithelial cells. Viral papillomatosis is mainly seen in young dogs. A Papovavirus has been detected in affected cells. The incubation period is reported to be about 30 days, and the condition is highly contagious through communal feeding bowls, toys, etc. Lesions are usually multiple and can vary from small plaques/papules to large cauliflower-type growths. Common sites include the mouth, lips, peri-ocular region and elsewhere on the skin. Squamous papillomas in which no viral cause can be identified are reported rarely in dogs and cats.

In older dogs, cutaneous papillomas can be found around the head, eyelids and feet, as well as elsewhere on the body trunk. A viral aetiology does not occur in those older cases. Inverted papillomas are sometimes seen on the ventral abdomen. They are solid raised lesions, often with a central pore that opens to the surface.

Histologically, papillomas can normally be classified as squamous or fibromatous. All of the above papillomas are usually benign, but can rarely transform into squamous cell carcinomas.

Treatment
- Benign neglect - if viral, lesions normally regress within 3-4 months.
- Surgery - if problematic.
- Immunotherapy - vaccine (autogenous) for viral cases. Not as commonly used nowadays due to manufacture/supply issues.
2. **Squamous cell carcinoma**

Common malignant growth of the squamous epithelium surface layer that is observed in both dogs and cats. Although the aetiology is unclear, UV light is a known predisposing factor in cats and dogs (particularly in relation to actinic keratosis lesions and areas of depigmentation). Thus, white cats/dogs are more prone to the condition; one typical presentation involves SCC of the ears or nose in white cats.

SCCs are most common in the age range of 7-11 years. The clinical presentation is typically proliferative and ulcerative in nature. Some SCCs are particularly destructive in nature, giving a lytic appearance to the tissue affected (e.g. mucous membranes in mouth). Lesions are usually solitary, although multiple lesions are possible; typical locations in dogs include the trunk/extremities/mouth region. Lesions on the digits are also common, in which case they must be differentiated from pododermatitis or nail bed infections. In cats, they often occur around the head (i.e. ears, nose, lips and eyes) with a proliferative, cauliflower appearance. Surface ulceration and secondary infection are common. Some affected animals develop cutaneous horns on the surface of the SCC.

SCCs are locally invasive tumours that are slow to metastasize.

**Treatment**

Surgical excision - needs to be aggressive with appropriate margins. This represents the best chance of a cure. If surgery is not an option, consider cryosurgery/radiotherapy. Chemotherapy protocols have proven to be of limited benefit, but a protocol using carboplatin and mitoxantrone has given some encouraging results even with pulmonary metastases. Because of their solitary nature, intra-lesional administration of agents like cisplatin or 5-FU have been beneficial.

3. **Basal cell tumour**

Despite their nomenclature, BCCs are normally benign (not a carcinoma). Traditionally, these tumours were thought to arise from basal cells of the epidermis, hair follicles and adnexal glands both in humans and animals; however, recent re-classification in humans means that most follicular/gland tumours are now not included as BCCs. The picture, unfortunately, is not so clear in veterinary medicine. Thus, with restricted classification, some authors believe they are very uncommon in dogs and cats.

The aetiology of BCCs is unknown, although in humans, UV light is an important factor. Mainly observed in middle to older aged animals. As with SCCs, they are usually solitary, but several may occur on one animal. Predilection sites in dogs include the head, neck and shoulders; BCCs can range in size from small to 10 cm in diameter. Cocker spaniels and poodles are particularly predisposed.

No site predilections are known in the cat, but they are the most common melanotic skin disorder in the cat (not melanomas). BCCs are typically firm and elevated above the skin;
they often ulcerate and may even appear cystic. Lesions in cats are usually very small, but more likely to be multicentric.

**Treatment**

- Benign - could leave alone or perform surgery if problematic.

4. **Mast cell tumours**

MCTs are one of the most common skin tumours in the dog (most common in some reports, representing approximately 27% of all malignant skin tumours); cats are also affected, but less commonly so. In practice, all MCTs must be considered at least potentially malignant until proven otherwise (30-40% actually are malignant).

Whilst any breed can be affected, Boxers, English bulldogs, mastiffs, retrievers, dachshunds and Weimaraners are considered predisposed breeds. The aetiology of MCTs is uncertain, although the occurrence in certain breeds does raise a question in relation to genetics. The proto-oncogene c-KIT codes for a tyrosine kinase receptor on the mast cell surface (called the KIT protein); mutations in this oncogene have been associated with abnormal proliferation of mast cells in both humans and dogs. The importance of this KIT receptor has recently been underlined by the introduction of novel therapeutic agents that block this tyrosine kinase as treatment for MCTs (e.g. Masivet, Palladia).

MCTs primarily occur in older animals (> 8 years old). In cats, MCTs are reported more commonly in older males. Cases vary a lot in presentation - the typical presentation in the dog involves a single, solitary tumour on the body trunk, perineal area or the limbs. The mass is often nodular and may even be pedunculated. Texture can vary from soft-to-firm, and the variation in size can also be marked. An interesting feature of MCTs is that due to their potential to degranulate vasoactive amines, MCTs can vary in size by up to 30% on a daily basis. MCTs can be found in the skin or S/C tissue, and may commonly ulcerate or become melanotic. A pin-feathered appearance is characteristic of this tumour in some affected dogs.

In cats, MCTs often appear on the head and neck, and can occasionally be plaque-like or nodular in appearance. Flushing of the skin is reported (histamine release), but is rare. Systemic signs may appear following degranulation e.g. GI tract ulcers, clotting defects etc. MCTs must be differentiated from systemic mastocytosis.

**Diagnosis**

- Biopsy - characteristic findings; some authors place great emphasis on the Patnaik grading system of Grades 1, 2 and 3 (increasing malignant potential as you go up the scale).
Treatments

- Surgery - wide excision. Surgical resection is always the treatment of choice. As large percentages re-occur, however, a guarded prognosis is often warranted.

- If disseminated or non-resectable (N.B. referral to a surgical specialist should always be considered before determining the MCT as non-resectable), chemotherapy can be attempted:
  - glucocorticoids and H₂ blockers commonly used in the past as a simple, non-expensive protocol. The steroids inhibit degranulation of the mast cells and the H₂ blockers counter the ulcerogenic effects of histamine.
  - Vinblastine and prednisolone
  - Lomustine (CCNU – alkylating agent)
  - Tyrosine kinase inhibitors - big area of development in veterinary medicine. Agents such as Masivet and Palladia block this key receptor that plays a prominent role in regulating MC proliferation. Therapy is usually continuous if the MCT proves static or reduces in size. Side effects are common, particularly affecting the GI tract and bone marrow. However, side effects appear to diminish after 8-12 weeks, once a large percentage of responding cells have finished undergoing apoptosis. Expensive.

5. Tumours of the Hair Follicle

Usually benign in the vast majority of cases.

(a) Trichoepithelioma – common in dogs (arises from keratinocytes of hair follicle). In humans, considered hereditary at times. Typical presentation is in animals > 5 years of age; seen on head and back mainly. Usually solitary, though not always so. Firm, rounded and up to 10 cm in diameter. Often ulcerate and develop alopecia.

Treatment
If benign, leave alone. Otherwise surgical removal, if problematic.

(b) Tricholemma - similar origin and appearance to above. Benign.
(c) Pilomatrixoma - benign. Arises from hair matrix. Similar approach to above.

6. Tumours of Adnexal structures

(a) Sebaceous glands:
These growths are common in dogs; not in cats. Cause unknown. Generally observed in dogs > 9-10 years of age. Single/multiple. Can occur anywhere, but especially common on the head.

Sebaceous hyperplasia - nodular in clinical appearance. Most common type seen in practice. Firm, but small and often alopecic (may be cauliflower-like; 2-10mm in diameter). Obviously benign.

Sebaceous adenomas are larger and not as lobulated (not cauliflower-like) (up to 3 cm in diameter). Adenocarcinomas are larger still, tend to ulcerate and are firm to the touch.

Most sebaceous gland problems are benign, even the adenocarcinomas are slow to spread to distal sites. Many have sebum-type material within, which can be seen at the time of surgical removal or if they rupture.

Treatment: remove or observe. Vitamin A is reported to be effective in humans. Synthetic retinoids not readily available in veterinary medicine.

(b) Sweat glands.
Apocrine/eccrine glands (now known as epitrichial and atrichial glands, respectively). Rare tumours in the dog and cat. Occur at >8 years of age.

Apocrine tumours could arise due to cystic hyperplasia/adenoma/carcinomas. The problem is that the carcinomas are highly invasive and metastatic. Hyperplasia occurs on head/neck and is often multiple. Adenomas and carcinomas on the other hand, tend to appear on flanks and along the back.

Eccrine gland tumours arise from foot pads and often ulcerate. Fortunately, they are very rare.

7) Histiocytomas.

Common benign tumour of the dog, though very rare in cats. Cause is unknown. Previously thought to be viral in aetiology, but this is not proven. Predominantly seen in young dogs mainly under 2.5 years old (occasionally reported in older dogs). This tumour consists of a large accumulation of histiocytes, usually with some lymphocyte/plasma cell infiltration also. Most often solitary. Found on head/tail/limbs. Can vary quite a bit in size, but are usually firm like a button. Frequently ulcerate.

Treatment: most regress within 3 months; could be surgically removed if deemed necessary. Some authors believe that the malignant forms could represent a form of lymphosarcoma. Furthermore, there are additional variants including histiocytic sarcomas and systemic histiocytosis that have a significantly poorer prognosis.
8) **Lipomas.**

Extremely common in older dogs. Rare in cats. Found on thorax, sternum, abdomen and front legs.

Soft, flabby, non-painful. If hard, they usually contain a large amount of connective tissue. If painful, probably have a large blood supply and are referred to as angiolipomas. Although generally harmless, lipomas can occasionally grow very large and could interfere with nerves etc. The malignant form (liposarcoma) is rare but can have a poor prognosis due to marked local infiltration.

**Diagnosis**
FNAs – typical lipid appearance even on gross inspection.

**Treatment:**
- 10% CaCl₂ injection in smaller tumours to decrease size.
- Benign neglect.
- Surgical removal if problematic.

9. **Fibrosarcoma**

Common in dogs and cats; malignant. Can arise from dermal and s/c fibroblasts. In cats, a virus has been isolated but only in kittens (FeSV – mutant of FeLV). It is not associated with solitary masses in older age.

Clinically, these tumours are usually solitary - mainly found on limbs/trunk. Nodular appearance, but frequently slightly irregular. Often ulcerate. Although they infiltrate locally, only 25% metastasize. Thrombocytopenia (immune-mediated) has been associated with this tumour type.

**Treatment**
- Surgery. Often recur, and if so, chemotherapy can be attempted. However, prognosis with chemotherapy, is not that good.

10. **Circum-anal adenomas**

Derived from modified sebaceous and epirichial glands located around the anus (i.e. the circum-anal hepatoid gland). It should be noted that such tumours can also be found some distance from the anus e.g. tail-head, genitalia etc.
These are very common and are predominantly seen in males due to the effect of androgenic stimulation on this glandular tissue. Most animals are above 8 years of age and virtually all breeds are affected. The lesion may ulcerate and cause some discomfort. Diagnosis is based on clinical signs and cytology from either an aspirate or biopsy. Management is normally by surgical removal and castration to try to prevent recurrence (not always successful). Castration should at least arrest further growth, unless malignant. Various progestagens have been used to chemically reduce their size, particularly if surgery is not indicated. Oestradiol benzoate, though used previously, is not recommended anymore due to potential side-effects.

The malignant circum-anal adenocarcinoma grows more rapidly, tends to ulcerate more frequently and may metastasize to distant sites. These occur equally in males and females. This tumour can be associated with systemic hypercalcaemia. Diagnosis is based on aspiration cytology or biopsy. A more radical surgical excision is indicated and prognosis is guarded.

11. Melanomas

Common in dogs, not in cats. May be benign or malignant. These tumours arise from melanocytes and melanoblasts.

The underlying cause in dogs is unproven; in man, UV light is an important factor. In cats, FeSV has been shown to reproduce this tumour type. However, the suspicion is that many melanomas in dogs/cats represent spontaneous transformation of either previously normal melanocytes or the transformation of benign melanocytic proliferations.

Melanomas occur mainly above 9 years of age. Common in Terrier and Spaniel breeds. More common in males, and typically solitary in nature. Found on the face, trunk, feet and scrotum. Cutaneous form – 25-50% malignant (digits and scrotum have a worse prognosis). A major practical problem is that the histopathological picture does not always correlate with the prognosis.

If benign, they appear as brown/black macules to firm nodules (up to 3 cm in diameter). Malignant ones grow rapidly, appear bigger and ulcerate frequently. Malignant forms are common only found in the mouth (90% malignant) and at mucocutaneous junctions.

**Treatment**

- Radical surgery. If malignant, average survival is only 1 year. If in mouth, it may be only 3 months. Poor response to chemotherapy, but radiotherapy may shrink the tumour well in some cases (metastases still a major problem). A melanoma vaccine has received a conditional license in the USA for therapeutic indications – further safety and efficacy data awaited. Preventive claim – not assessed yet.
12. **Cutaneous lymphosarcoma**

Such tumours of the skin can be of either the B cell or T cell type. In the case of B cell lymphoma (usually non-epitheliotropic), lesions may be confined to the skin or may be multicentric e.g. lymph nodes, spleen etc. Skin lesions appear as nodules, plaques or a maculo-papular rash. Diagnosis is based on biopsy or aspiration cytology. The therapy of this disease is similar to that for the lymph node form etc.

In the case of T cell lesions (usually epitheliotropic), the disease process may be limited to skin. The clinical presentation is highly variable. Some animals present with local or generalized erythroderma that may have been mistaken for an allergic skin disease. In other cases, the lesions may develop through a papular/plaque type phase into nodular lesions that frequently rise above the skin in a horse-shoe or arcuate shape and may ulcerate. Some cases present with mucocutaneous ulceration, similar to an autoimmune disease. The progress of this condition can be relatively quick. Histopathological findings are diagnostic in most cases. Pruritus is variable. Whilst combination chemotherapy has been tried for this condition, most cases are fairly far advanced by the time of diagnosis. Secondary infection is not uncommon at this stage.

Local therapy can include the use of topical steroids, mechloretamine (Nitrogen mustard – itself carcinogenic) or radiotherapy. Systemic therapy usually involves steroids, retinoids (if available), **lomustine** (alkylating agent commonly used) or CHOP protocols typically used for lymphoma (poorer response than for lymph node lymphoma cases)

The long-term prognosis is grave. However, some authors describe cases with a very protracted course stretching over years in certain cases, whilst the median survival time reported is often 7-11 months. In my experience, however, many cases are euthanized earlier due to poor quality of life.