Multimodal Management
of Feline Allergic Dermatitis
Bad Mood?

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THE STRESS RESPONSE

Stress is an altered state of homeostasis which can be caused by physical or emotional factors that trigger psychological, behavioral, endocrine and immune effects designed to handle stress.[1,2] Response to stress will vary between individuals and may be affected by breed, early experience, sex, age, health and the pet's behavioral profile. In cats, exposure to mild stressors and handling early in life stimulates hormonal, adrenal and pituitary systems that result in animals who perform better in problem solving tasks, have greater resistance to disease, and can better withstand stress later in life.[3,4]

The first component of the stress response is the HPA axis, in which the hypothalamus releases corticotropic releasing hormone (CRH), which stimulates the release of ACTH. The second component is the sympathetic-adrenal-medullary system, which releases noradrenaline and adrenaline. Noradrenaline is associated with sensitization and fear conditioning. If stress is persistent or chronic, there is continued stimulation of the HPA axis and an increase in cortisol with depression of the catecholamine system, leading to alterations in the immune system and possible development of stress-related diseases. Increases in dopamine may enhance aggressive behavior and lead to an increase in stereotypic and grooming behaviors. Canine studies have identified alterations in prolactin levels in fearful and anxious pets.[5,6] In one study, lower prolactin levels were associated with acute stress (fears and phobias) and higher prolactin levels associated with chronic stress (compulsive disorders).[5,6] Therefore, there can be marked differences in the effects of acute and chronic stress on health and behavior.[5-7]

STRESS AND PHYSICAL HEALTH

In humans, there may be a correlation between stress and poor immune function, skin and cardiovascular diseases, asthma, gastrointestinal disorders and cellular aging. Similarly in pets, stress may alter immune function and has been shown to be a contributing factor in gastrointestinal diseases, dermatologic conditions, respiratory and cardiac conditions, behavioral disorders and a shortened lifespan.[8]

With respect to the skin, stress leads to an immune response intended to enhance defense mechanisms; however, in some individuals, rather than helping to achieve homeostasis,

these stressors may contribute to inflammatory dermatoses.[9] This brain-skin connection is comprised of psycho-neuro-endocrino-immunological factors, which, under situations of stress, may play a role in the pathogenesis of dermatoses such as atopic dermatitis, psoriasis and urticaria.[10-12] In humans with atopic disease, stress has been shown to increase levels of IgE, eosinophils, cause an over-reactive sympathetic adreno-medullary system, and decrease hypothalamic-pituitary-adrenal responsiveness.[13-15] Stress may lead to increased release of vasoactive neuropeptides from dermal nerve endings that may contribute to atopic disease, psoriasis and other chronic skin diseases.[16-18] Opioid peptides released during stress may further potentiate pruritus.[19] In addition, an association between asthma and atopy has been demonstrated in humans.[20] A link has also been established between stress and increased epidermal permeability perhaps due to altered cortisol release.[10,11,21,22] A similar alteration in skin barrier function and an increase in epidermal permeability in pets might exacerbate atopic disease in a genetically predisposed individual. Therefore, stress intervention in humans can improve general health as well as cutaneous manifestations.[10,23] In dogs and cats, there is a similar interplay between the brain and skin including an increased severity and frequency of skin disorders in dogs with non-social fear and separation anxiety.[8] In one study of dogs with recurrent pyoderma, psychogenic factors were identified.[24] Psychodermatoses have also been reported in dogs.[25]

STRESS AND BEHAVIORAL HEALTH

Chronic anxiety, stress, conflict, and frustration may also lead directly to behavioral disorders in humans including separation anxiety, social and other phobias, panic, generalized anxiety, sleep, post-traumatic stress, obsessive-compulsive, and impulse control disorders which may all have animal correlates.[26] Self-traumatic disorders in humans in the obsessive-compulsive spectrum include impulse control disorders such as trichotillomania, skin picking and nail biting, and compulsive washing and grooming. Other psychiatric disorders may also lead to psychogenic excoriation.

In pets, situations of conflict (competing motivation), or frustration (where the pet is unable to achieve its goals or when the behavioral needs of the pet are not addressed), vacuum and displacement behaviors such as self-trauma, spinning, tail chasing or hyperesthesia might be exhibited. These signs are more likely to arise in pets that are

overly anxious or reactive and those that are genetically predisposed. Displacement behaviors that arise in response to a specific stimulus (e.g., visual, auditory, odor, tactile) or event (e.g., car ride, veterinary visit, owner departure or homecoming) might be resolved if inciting factors are avoided and with consistent and predictable owner responses. However, since self-traumatic disorders often develop secondary medical complications (pain, pruritus, infection), concurrent medical and behavioral therapy is often required.[25]

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Compulsive Disorders in Cats

SELF-DIRECTED BEHAVIORS:
- **psychogenic alopecia**
- **nail biting**
- **head and face scratching**

NEUROLOGICAL, HALLUCINATORY AND LOCOMOTORY SIGNS:
- **predatory sequences**
- **staring**
- **hyperesthesia**

INGESTIVE SIGNS:
- **picas**
- **licking**
- **polydipsia**
- **wool or fabric sucking**

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Compulsive disorders are those in which displacement behaviors are exhibited independent of the original context. The behaviors have no apparent goal and have an element of dyscontrol in either the initiation or termination of the behavior. They may be repetitive, exaggerated, sustained or so intense that they might be difficult to interrupt. The behavior becomes compulsive when it does allow the pet to settle (achieve behavioral homeostasis) and when the signs persist independent of the anxiety evoking events. Compulsive disorders are most commonly seen in genetically predisposed individuals that are subjected to chronic or recurrent stress or whose behavioral needs are not adequately met. A canine chromosome locus for flank sucking in Dobermans has recently been identified.[27] Other breed predispositions include wool sucking in oriental breeds of cats, spinning in bull terriers and tail chasing in German shepherds.

Compulsive disorders might include: a) self-directed behaviors such as psychogenic alopecia, nail biting and head and face scratching in cats and acral lick dermatitis in dogs; b) neurological, hallucinatory and locomotory signs such as predatory sequences, staring and hyperesthesia in cats and air snapping, spinning, pouncing, rhythmic barking, freezing, staring and chasing objects (real or imaginary) in dogs; and c) ingestive signs such as picas, licking, polydipsia and wool or fabric sucking in cats. Compulsive disorders may have a common pathophysiology; neurotransmitters may vary between presenting complaints (e.g., oral, locomotor, self-trauma, hallucinatory); or there may be changing involvement as the problem progresses. Beta-endorphins, dopamine and serotonin have all been implicated primarily based on evidence of response to therapy. Dopaminergic drugs such as amphetamines may induce stereotypies and narcotic antagonists may block the response.[28-30] Another possibility is that compulsive disorders may be mediated by opioid receptors since opioid antagonists such as naltrexone have been successful at reducing "stereotypies."[29,31] Altered glutaminergic neurotransmission may also be a factor, since blocking glutamate sensitive NMDA with drugs such as memantine or dextromethorphan may be effective.[32,33] Abnormal serotonin transmission has been identified as a primary mechanism by which stereotypies are induced.[34] As in humans with obsessive-compulsive disorders, drugs that inhibit serotonin reuptake (e.g., clomipramine, fluoxetine) have been shown to be most effective in the treatment of canine and feline compulsive disorders.[35-38]

SELF-TRAUMA — IS IT BEHAVIORAL OR IS IT MEDICAL?

A simplistic approach to this question would be to look at the behavioral presenting signs and do a comprehensive diagnostic assessment to determine if there are is an underlying medical cause. However, the simple question of whether the problem is behavioral or medical is complicated by the fact that primary behavior problems can lead to secondary medical problems such as pain, inflammation and deep pyoderma, which would need to be treated concurrently.[24] In addition, as discussed, there may be a psycho-neuro-immuno-endocrinological component in which stress contributes to the onset or maintenance of medical conditions such as atopy.[25] Further complicating the matter is that cutaneous sensory disorders may be responsible for some causes of self mutilation and hyperesthesia.[39]
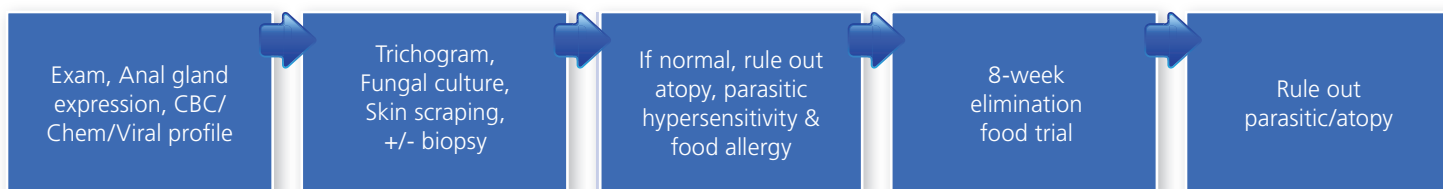
| Exam, Anal gland expression, CBC/ Chem/Viral profile | → | Trichogram, Fungal culture, Skin scraping, +/- biopsy | → | If normal, rule out atopy, parasitic hypersensitivity & food allergy | → | 8-week elimination food trial | → | Rule out parasitic/atopy |

Figure 1 - *Diagnostic evaluation for cats presented for alopecia*

DIAGNOSTIC WORKUP FOR PSYCHOGENIC ALOPECIA

When presented with a cat who has hair loss or licking, the diagnostic workup should begin with an examination, anal gland expression, blood and urine testing and a viral profile **(Figure 1)**. The dermatologic evaluation would continue with a trichogram, fungal culture, skin scraping and possible biopsy. Assuming no abnormal findings, this does not confirm a behavioral cause since parasitic hypersensitivity needs to be ruled out with a parasiticide trial and food intolerance with a food elimination trial. If improvement is significant, the cat should be challenged with its original diet to confirm whether food is indeed a factor. Finally, since hypersensitivity to environmental allergens can also lead to self-trauma, a steroid response trial (e.g., two injections of medroxyprogeserone acetate three weeks apart) can help to determine whether the problem is due to pruritus. Cats with partial improvement with diet can be maintained on the diet during the steroid trial. Using this protocol in 21 cases presented for psychogenic alopecia, 76.2% had a medical etiology, 9.5% were compulsive and 14.3% were combined medical and behavioral **(Figure 2)**. Adverse food reaction was the most common finding in 57% of cases, with a combination of adverse food reaction and atopy (6 cases) the most common diagnosis **(Figure 3)**. Some cats had atopy, parasitic hypersensitivity, or an adverse food reaction alone. Although biopsies indicated an inflammatory response for most medical cases, some cats with histologically normal skin had a medical cause. Average duration of signs was 13 months.[40] Following the publication of the study, one additional case was diagnosed as having a medical cause, since it had improved entirely with a food trial and change in litter.
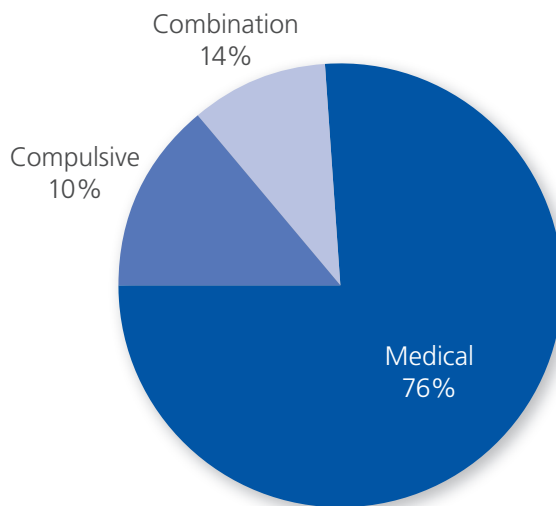
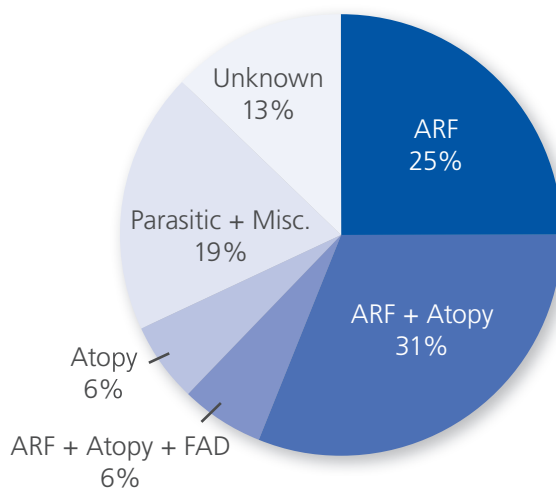Figure 2 - *Final diagnosis of 21 cats presented for psychogenic alopecia*[40]

Combination 14%
Compulsive 10%
Medical 76%

Figure 3 - *Medical diagnosis of cats presented for psychogenic alopecia*[40]
ARF = Adverse reaction to food

Unknown 13%
Parasitic + Misc. 19%
Atopy 6%
ARF + Atopy + FAD 6%
ARF 25%
ARF + Atopy 31%

Wrong food?

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FOOD ALLERGY

Food allergy is often used to describe any adverse reaction to a food. An adverse reaction to food is an abnormal response to an ingested food or food additive and may include both immunologic and nonimmunologic reactions. Most of the reported adverse food reactions causing dermatoses have been termed food allergy or food hypersensitivity; although no specific tests were performed to confirm an immunologic basis for the clinical signs. Ideally, the terms food allergy and food hypersensitivity should be reserved for those adverse reactions to food that have an immunologic basis. Food intolerance is more appropriate for the large category of adverse food reactions due to nonimmunologic mechanisms. True prevalence of food allergies is difficult to determine. However, food allergy is considered to be one of the most common causes of hypersensitive skin disease in dogs and cats and is estimated to cause 10 to 49% of allergic responses in dogs and cats.[41,42] Several investigators have suggested that adverse food reactions are relatively more common in cats than in dogs.[19,43]

Adverse reactions are more common in cats than dogs.

Adverse reactions to food have been reported to occur in cats between 6 months and 12 years of age with no gender predilection.[44-46] In one study, approximately half of the cats with adverse reactions to food were less than 2 years of age.[47] In food allergies the onset of clinical signs is not typically associated with recent food changes. Studies suggest that dogs and cats may develop food allergies after prolonged exposure to one brand, type or form of food. In contrast, adverse reactions due to food intolerance may occur after a single exposure to a food ingredient because immune amplification is unnecessary.[48]
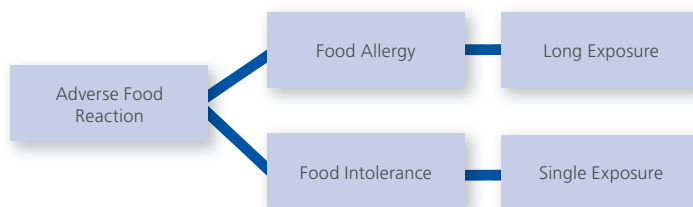
Food allergies present as nonseasonal skin or gastrointestinal (GI) disorders. While nonseasonal pruritus is the most commonly reported sign, cats with food allergy may present with a variety of clinical reaction patterns including: 1) severe, generalized pruritus without lesions, 2) miliary dermatitis, 3) pruritus with self-trauma centered around the head, neck and ears, 4) self-induced alopecia, 5) pyotraumatic dermatitis and/or 6) scaling dermatoses **(Figure 4).**[19,43,45-47] In one study, angioedema, urticaria or conjunctivitis occurred in one-third of cats with food allergies.[47] Food allergies may also be implicated in cats with the so-called eosinophilic skin diseases such as eosinophilic plaques, eosinophilic granulomas and indolent ulcers of the lips.[19,40,43,46] Concurrent flea-allergy or atopic dermatitis triggered by environmental allergens may occur in up to 30% of cats with suspected adverse food reactions.[44,47] Cats with concurrent allergic diseases may be pruritic year

Figure 4.
Five-year-old female spayed, domestic short-hair with severe head and neck pruritis.

Photo courtesy of Dr. Phil Roudebush

around but exhibit increases in the intensity of pruritus associated with the seasonal disease (flea allergy dermatitis, atopic dermatitis). Additionally, since cats tend to be fed (or if allowed to roam can acquire) a more varied diet than most dogs, their pruritus may wax and wane. Adverse reactions to food can have widely variable clinical presentations should be considered in the differential diagnosis of any pruritic cat.

In one study of chronic idiopathic GI problems in cats, 16 of 55 cats (29%) were diagnosed as food sensitive by elimination-challenge tests.[49] The wall of the digestive tract is the largest surface of the body exposed to the environment. The GI tract has to differentiate between nutrients, which have to be tolerated, and potential harmful substances (bacteria, viruses, parasites), which need to be expelled.[48] The gut associated lymphoid tissue (GALT) accomplishes this double function. GALT is composed of four distinct lymphoid compartments: Peyer's patches (PP) and aggregates of lymphoid follicles throughout the intestinal mucosa, lymphocytes and plasma cells scattered throughout the lamina propria, enterocytes with intraepithelial lymphocytes (IELs), and mesenteric lymph nodes. Four mechanisms ensure the conflicting functions of tolerance and exclusion of antigens: (1) the mucosal barrier, (2) regulation of the immune response, (3) elimination and (4) tolerance of antigens reaching the mucosa. Impairment of this GI defense predisposes patients to food allergy. Every level of the GI tract can be affected by food allergies. In dogs, cats and people, clinical signs usually relate to gastric and small-bowel dysfunction, but colitis can also occur.[50,51] Vomiting and diarrhea are prominent features. The diarrhea can be profuse and watery, mucoid or hemorrhagic. Intermittent abdominal pain, intermittent diarrhea, weight loss, flatulence, irritable demeanor, soft feces and increased frequency of defecation are also seen.[42,49] GI disturbances occur in up to half of dogs and cats with cutaneous manifestations of food hypersensitivity.[19,42,43,52]

DIAGNOSIS

Currently, intradermal testing, RASTs and ELISAs for food hypersensitivity are considered unreliable for patients with dermatologic disease. Adverse reaction to a food is best confirmed by elimination-challenge trials.[53] Correct design of elimination-challenge trials is critical for reliable diagnosis. Accurate design requires a thorough nutritional history. The nutritional history should include a complete list of the foods used in the cat's regular feeding plan or as treats including: 1) specific commercial foods, 2) commercial snacks and treats, 3) supplements, 4) chewable medications, 5) human foods and 6) access to other food sources. It is often helpful to have the pet owner keep a diary for several weeks documenting the types of food and other items the cat ingests daily. Ingredient statements on commercial pet food labels may provide information for identifying all the food ingredients that might cause adverse reactions. However, this information may be misleading. A study of over-the-counter limited protein source dog foods found that 75% of the diets tested were positive for soy, poultry and/or beef, despite the fact that their ingredient lists did not include sources of soy, beef or poultry.[54] Virtually any pet food ingredient may cause an adverse reaction. However, particular attention should be directed at those ingredients that contain protein. Beef, dairy products and fish are most commonly reported as ingredients causing adverse food reactions in cats.

Elimination diets can be homemade diets, commercial novel protein diets or commercial hydrolyzed protein diets. A diet can only be "hypoallergenic" if the animal was never exposed to the food components before. The identification of what is truly a novel protein for any given individual is entirely dependent on the accuracy and extent of the dietary history obtained.

Most common food allergens in cats

| FISH | DAIRY | BEEF |

HOMEMADE DIETS

Homemade diets (HMDs) are frequently recommended as initial test diets for dogs and cats with suspected food allergy. In one survey veterinarians prescribed HMDs in 72% of dogs and 86% of cats with suspected food allergy.[55] Typically, HMDs include a single protein source or a combination of a single protein source and a single carbohydrate source. Ingredients typically recommended for homemade feline foods include lamb baby food, lamb, rice and rabbit. HMDs can be composed based on the individual patient's nutritional history and provide the advantage of allowing the owners to feel more involved. The disadvantages of HMDs include increased expense and preparation time. Poor palatability and initial digestive upsets may also occur. Perhaps the most important drawback is the majority of HMDs are nutritionally inadequate for growth and maintenance. One study documented that of the commonly recommended HMDs

Types of Elimination Diets

Homemade → Novel Protein → Hydrolyzed Protein

for cats, 92% were nutritionally inadequate.[55] In general, homemade foods often lack a source of calcium, essential fatty acids, certain vitamins and other micronutrients, and contain excessive levels of protein, which are contraindicated in food allergy cases. Even when fed for short durations these imbalances may have a clinical effect. Cats develop anorexia and vomiting within one to two weeks of feeding foods deficient in thiamin (vitamin B_1). Importantly for cats, many of these HMDs were taurine deficient, which may be of concern for foods fed longer than three to four weeks. Foods with a severe imbalance of minerals can cause skeletal diseases in young animals within four weeks.

92% percent of homemade elimination diets recommended for cats are nutritionally inadequate.

These diets often lack a source of calcium, vitamins, essential fatty acids and, importantly for cats, many are deficient in taurine.

Cats develop anorexia and vomiting within two weeks of eating foods deficient in thiamin.

COMMERCIAL NOVEL PROTEIN DIETS

A variety of novel protein diets (NPDs) are available for dogs and cats. NPDs are easy to obtain and practical in use and are nutritionally complete and balanced for the intended species. Unfortunately, few of these commercial foods have been adequately tested in cats with known adverse food reactions; only a limited number of foods (approximately 15 of more than 50 veterinary therapeutic foods marketed for adverse food reactions) have undergone the scrutiny of clinical trials using patients with dermatologic or GI disease.[42,47,49,52,56-61] In these published clinical trials 66%-75% of patients with suspected adverse food reactions had significantly improved clinical signs when fed commercial veterinary therapeutic elimination-type foods. The lack of an accurate individual dietary history can explain why the diet was not effective in some of the patients. Recently, the use of veterinary therapeutic novel protein foods has been complicated by the availability of many over-the-counter limited ingredient foods. Protein sources in these over-the-counter foods include sources that are commonly used in veterinary therapeutic foods: rabbit, pork, lamb, venison, bison and duck. The availability of these foods as well as the documented 'cross contamination' of over-the-counter single protein source foods[54] complicates determining a truly novel protein for many clinical cases. Novel or unique protein sources are less important when protein hydrolysates are used.

OVER-THE-COUNTER PROTEIN SOURCES	THERAPEUTIC PROTEIN SOURCES
Rabbit	Rabbit
Lamb	Lamb
Venison	Venison
Bison	Duck
Duck	

COMMERCIAL HYDROLYZED PROTEIN DIETS

Protein hydrolysates offer several advantages over intact protein sources. Protein hydrolysates of appropriate molecular weight (<10,000 daltons) are less likely to elicit an immune-mediated response **(Figure 5)**. Several published clinical studies document the efficacy of foods containing protein hydrolysates in veterinary patients. When fed a protein hydrolysate diet, clinical improvement was seen in 50 to 80% of dogs allergic to the intact protein.[62-66] Additionally, several clinical trials with protein hydrolysate-type foods have been conducted in canine and feline patients seen in general and specialty practices with dermatologic or GI disease. The results of these studies show similar efficacy of hydrolysates as compared with the more traditional novel protein sources.[42,52,67-69] Protein hydrolysate foods have also been used successfully in cats with self-inflicted alopecia and chronic GI disorders.[40,70]
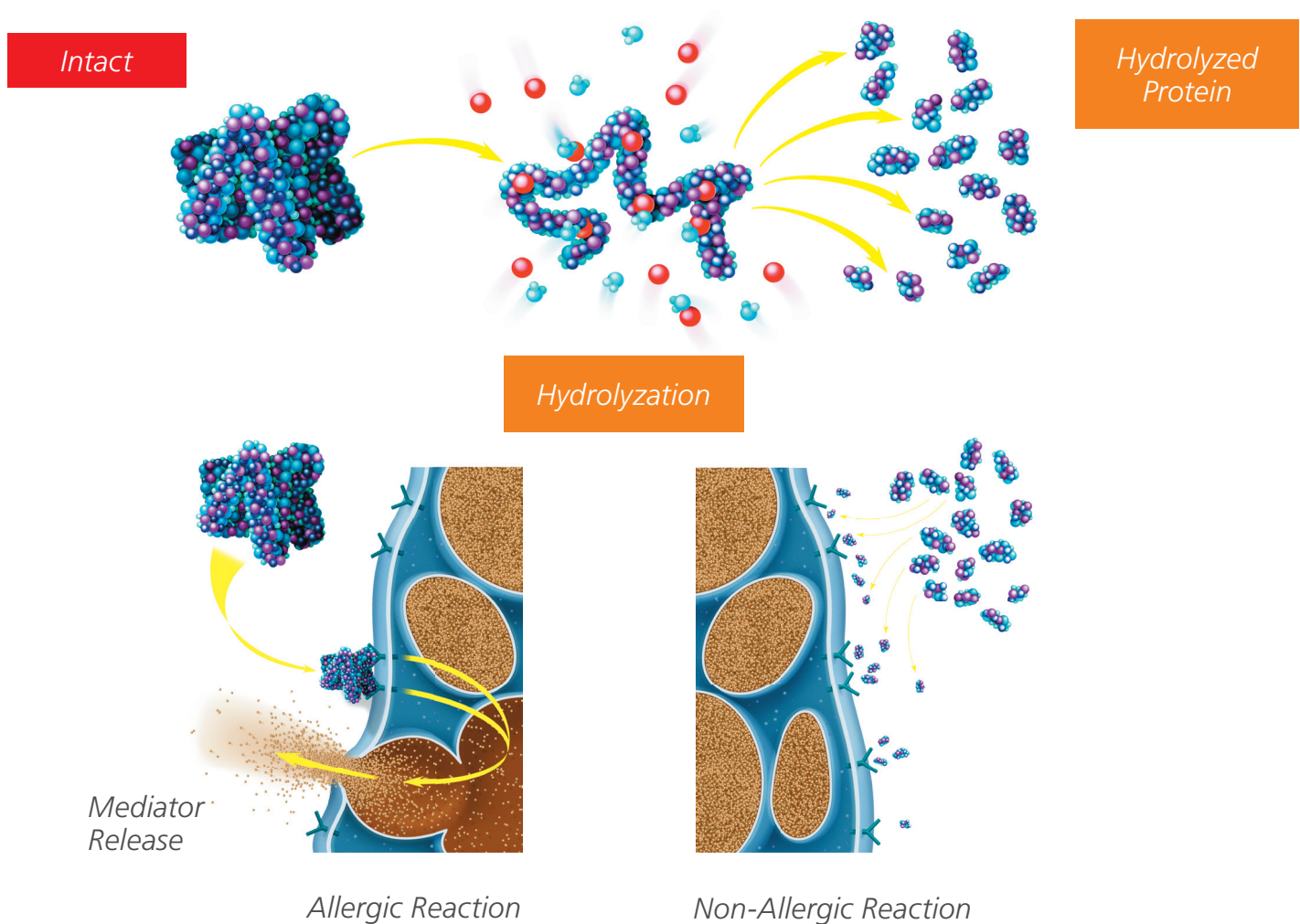
Figure 5 - *Hydrolyzed proteins are less likely to elicit an immune response.*

ELIMINATION TRIAL

A controlled elimination food should be fed for six to 12 weeks. Prior to beginning an elimination trial, the clinician should discuss potential sources of food allergens with the client. Clients must understand that diagnosis is based on the exclusion of all other potential sources of allergens, not just the addition of the elimination food. It is critical that no other substances should be ingested including treats, flavored vitamin supplements, chewable medications, fatty acid supplements, and chew toys. Cats should be confined to indoors to minimize exposure to other food sources. A daily food diary will aid in documenting the progression of clinical signs and if a strict elimination trial was performed in the home environment.

A tentative diagnosis of an adverse food reaction in dermatologic patients is made if the level of pruritus markedly decreases. This improvement may be gradual and may take four to 12 weeks to become evident. Ideally, the diagnosis of an adverse food reaction is confirmed if clinical signs reappear after the patient's former food is offered as a challenge. Clinical signs may be evident within hours of a challenge or take up to 14 days. Reinstituting the elimination food should resolve the clinical signs induced by the food challenge. Food challenges can be performed in an "open," "single-blind" or "double-blind" manner. In an open food challenge, both the client and veterinarian are aware that a specific food or previous food is being fed. In a single-blind food challenge, only the veterinarian is aware of what food is being given. In a double-blind food challenge, neither the client nor veterinarian is aware of whether a specific food is being given. Double-blind, placebo-controlled food challenges are considered to be the "gold standard" for the diagnosis of adverse food reactions in people.[71] Only half of human patients thought to be allergic to a food react to the food when challenged in controlled, blinded conditions. Unfortunately, all reports and most food challenge recommendations in the veterinary literature have been open challenges. Open challenges will continue as the most practical method of establishing tentative diagnoses of adverse food reaction in dogs and cats, but are subject to false interpretation by clients and veterinarians.

Provocation involves introducing single ingredients until as many positive reactions as possible can be documented. Clients and veterinarians are often reluctant to pursue challenge and provocation after clinical signs have improved or have been eliminated. Provocation may also be difficult because commercial pet foods contain large numbers of ingredients and feeding the same ingredients often cannot be duplicated in challenge studies. As an example, use of chicken meat in a provocative food challenge may not duplicate the types or levels of antigens found in poultry by-product meal. Elimination trials are often difficult to interpret because of concurrent allergic skin disease. These patients may only partially respond to an elimination trial. Flea-allergy and atopic dermatitis triggered by environmental allergens are the most common concurrent diseases and should be eliminated through other diagnostic testing.

Failure to challenge a suspected food-sensitive patient will lead to marked over diagnosis of food sensitivity.[49] However, whether to challenge the patient or not is a decision that needs to be made collectively with the owner. Many owners are happy with a presumptive diagnosis of food sensitivity and do not wish to undertake a challenge test. After a diagnosis of food sensitivity is made, further cycles of elimination-challenge trials may then be undertaken in an attempt to identify the responsible food ingredients. It is noteworthy that dietary trials confirm or rule out adverse reactions to food but do not indicate the underlying mechanism (allergy or intolerance).

MANAGEMENT

The only effective way of managing genuine cases of food intolerance is to avoid the foodstuffs that are involved. Long-term feeding of commercially available limited ingredient or hydrolysed diets are the most appropriate options. Most cats with adverse reactions to foods do not respond well to routine anti-inflammatory dosages of corticosteroids in comparison to cats with flea allergy dermatitis or atopic dermatitis. Antihistamines are rarely effective in managing food allergy associated pruritus in the cat. Omega-3 (n-3) fatty acids exhibit multiple anti-inflammatory and immunomodulating effects. They have the potential to affect allergic and other inflammatory diseases through modulating cytokine production, inhibiting cellular activation and cytokine secretion, altering the composition and, in the case of dermatologic disease, function of the epidermal lipid barrier.[72] Veterinary therapeutic foods for dogs and cats with inflammatory disease related to adverse food reactions should provide 0.35 to 1.8% DM of total omega-3 fatty acids. However, because of their potential benefit in inflammatory diseases, inclusion of omega-3 fatty acids could confuse the diagnostic phase of managing food sensitivity. The ratio of omega-6 to omega-3 fatty acids that should be included in foods for patients with adverse food reactions is currently unknown.

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