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Nutricional dermatoses and the contribution of dietetics in dermatology

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Nutritional dermatoses and the contribution of dietetics in dermatology

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Pascal Prélaud graduated in 1984 from the Ecole Nationale Vétérinaire in Toulouse. In 1987 he founded CERI, a veterinary biology laboratory in Paris, which he continues to direct. This laboratory was a pioneer in the field of allergic testing in Europe. Pascal has worked as a specialist in veterinary dermatology since 1987. He now works in the Paris region. A member of the International Task Force on Canine Atopic Dermatitis, he is the author of many scientific articles and lectures, mainly on allergic dermatopathies in dogs and cats. He has authored two books on veterinary allergies (1991, 1999) and a book on endocrinology (2002), which has been translated into several languages. Pascal Prélaud is co-author of the Guide de Dermatologie Féline (2000) with Dr. Eric Guaguère.

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The skin is a major organ both in terms of surface area ($1m^2$ for a 35-kg dog) and roles (social, maintenance of a stable internal environment, immune response, etc). In constantly rejuvenating itself the skin mobilizes a large part of the macro- and micronutrients provided by the food. An imbalanced intake of amino acids, fatty acids, vitamins or trace elements disrupts the barrier function (Table 1) and the immune protection provided by the skin. The dog may become more sensitive to infection and can develop allergic reactions more easily. The skin and the coat accordingly are the mirror of the dog's health and the quality of its food. There are many forms of nutritional dermatosis that frequently affect dogs (Table 2).

Nutrition has a special place in canine dermatology, not only as an essential factor in the prevention of skin diseases, but also as a therapeutic tool for allergy, keratoseborrheic and metabolic dermatopathies.

1 - Risk factors

The risks of developing nutritional dermatoses are not only related to the quality of the food, but also to individual factors in the animal such as the physiological stage, the type of hair and the predisposition to certain metabolic or allergic diseases.

► Breed specificities

There are many breed-related predispositions in canine dermatology that can be directly linked to nutrition **(Table 3)**.

The two main groups of nutritional dermatoses (zinc or vitamin A responsive dermatoses) are the major causes of keratinization problems in predisposed breeds (e.g. Nordic breeds with respect to zinc).

Table 1 - Nutrients that can influence the skin barrier function

Polyunsaturated fatty acids (PUFA) (e.g. linoleic acid)	They belong to the lipids produced by the sebaceous glands that form the hydrolipidic surface film
Proteins	Sufficient intake of all essential amino acids is necessary for the synthesis of keratocytes
Vitamin A	Essential to the maturation of keratocytes and so the formation of the keratinous layer
Biotin	Essential to PUFA metabolism
Vitamin C	Plays a key role in the formation of the lipids of the keratinous film layer
Zinc	A zinc supplement helps reduce water loss and deficiency leads to corneogenesis problems
Nicotinamide	Increases the free fatty acid and ceramide concentrations in the keratinous layer
Water soluble vitamins	Participate in PUFA metabolism
Vitamin E	Excreted by sebaceous glands, helps limit the oxidation of fatty acids

Table 2 - Possible signs of nutritional dermatology

- dull hair
- widespread scaling
- localized or mucocutaneous keratoses
- pruritus
- recurring urticaria
- chronic otitis
- recurring pyoderma

Table 3 - Breeds predispositions to nutritional dermatoses

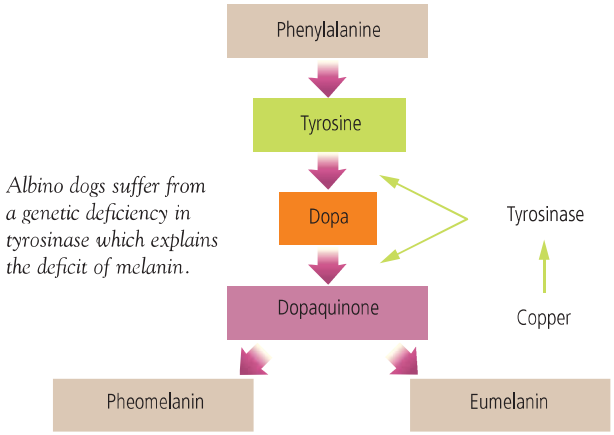
Deficiencies in intake or assimilation	
Zinc responsive dermatitis	Nordic breeds, large breeds
Vitamin A responsive dermatitis	Cocker Spaniel
Dietary hypersensitivity	
Predisposition or over-representation	Labrador Retriever
Predisposition associated with an atopic condition	American Staffordshire Bull Terrier, Beagle, German Shepherd, Boxer, Bulldog, Dalmatian, Fox Terrier, Bull Terrier Jack Russell Terrier, Labrador Retriever, Lhassa Apso, Pekingese, Shar-Pei, English Setters, Shi Tzu, West Highland White Terrier
Predisposition associated with malassimilations	German Shepherd, Irish Setters, Shar-Pei, Soft Coated Wheaten Terrier

There is a higher likelihood of dietary hypersensitivities in breeds suffering from malassimilation and atopy.

In dogs with a dense coat (e.g. Pomeranian, Spitz, Shih Tzu), the quantity of hair is such that skin and coat maintenance and rejuvenation of the skin and coat accounts for 30-35% of daily protein requirement *(Mundt & Stafforst, 1987)*. It is possible that the nutritional requirements of animals with a long coat and dense undercoat exceed that of shorthaired breeds.

► Coat

FIGURE 1 - SYNTHESIS OF MELANIN FROM PHENYLALANINE

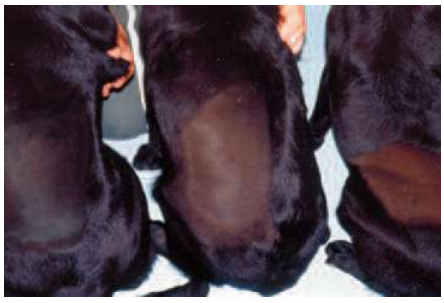


The influence of nutrients on the color of the coat is well known. The coat's pigmentation depends on the presence and the distribution of pheomelanin (yellow-red) and eumelanin (black) pigment grains in the cortex and/or the medulla of hairs and along the pilary stem. The synthesis of these pigments depends on the intake of aromatic amino acids (phenylalanine [Phe] and tyrosine [Tyr]) and the activity of the tyrosinases (cupric enzyme) **(Figure 1)**.

Dietary imbalances in animals with a dark or black coat may provoke the reddening of the coat *(Busch-Kschiewan et al, 2003)*. This was initially shown in cats. In cats a slight imbalance in the aromatic amino acid intake may provoke the appearance of neurological problems (sensorial neuropathy) *(Dickinson et al, 2004)* and lightening of the coat in red cats, or the reddening of the coat in black cats *(Yu et al, 2001)*.

Reddening is also a common pigmentation anomaly in large dogs with a black coat. Work conducted on Newfoundland puppies and black Labrador puppies *(Zentek et al, 2003)* shows that, in canines too, the level of phenylalanine and tyrosine needed to guarantee optimal coat pigmentation is twice that of the minimum requirements to ensure the puppy's optimal growth. They also showed that tyrosine supplementation in food helps increase the intensity of coat color **(Figure 2)**. The nutritional recommendations based on the study of growth (NRC, AAFCO) do not allow estimation of the requirements necessary for some metabolically intense functions such as the production of melanine.

FIGURE 2 - INFLUENCE OF DIETARY TYROSINE INTAKE ON COLOR INTENSITY IN BLACK DOGS



Over a 6 month period, these dogs have consumed the same diet, differing only in tyrosine and phenylalanine content (Tyr + Phe). From the left to the right, the (Tyr + Phe) intake represents 3.2, 2.6 and 1.9 times the estimated AAFCO requirement for growth. The effect of the diet is obvious: the black color is more intense in the dog on the left whereas, on the right, the growing hair have a reddish color.

► Age and physiological condition

The age or the physiological condition may influence the relationship between skin homeostasis, coat quality and food.

In dogs, immaturity of the immune system and high intestinal permeability may to some degree explain the prevalence of dietary hypersensitivities in the young animal *(Day, 1999; Prélaud, 1999)* as it does in humans *(Chehade & Mayer, 2005)*. These phenomena may be more common during weaning.

Nutritional deficiencies appear more readily when the dogs' nutritional requirements exceed simple maintenance requirements: for example chronic disease, during gestation, lactation and growth, and especially in large-breed dogs. These deficiencies in protein, essential fatty acids and zinc, may result in keratinization defects.

In aging dogs, malassimilation is characterized by imbalances in the intake of polyunsaturated fatty acids.

► Concurrent diseases

Any disease that disrupts the assimilation of nutrients may have direct and indirect consequences on the quality of the coat and favor the development of concurrent diseases. Malassimilation is frequently associated with a dull and dry hair coat or even recurrent bacterial infections. Defective protein digestion may cause a decrease in immune tolerance as clearly demonstrated in human and murine models.

In dogs, this phenomenon is frequently described in German Shepherds with exocrine pancreatic failure *(Biourge & Fontaine, 2004; Wiberg et al, 1998)* and Soft Coated Wheaten Terriers suffering from protein-losing enteropathy *(Vaden et al, 2000)*, which often develop digestive hypersensitivities with cutaneous manifestations (pruritus, recurring pyoderma). Chronic digestive problems or prolonged use of antibiotics may also provoke a deficiency in B vitamins and a secondary deficiency in polyunsaturated fatty acids (PUFA).

At birth the skin is very supple and the number of hair follicles is low. The fragility of the skin and the coat means that the puppy is very susceptible to attacks on the skin by parasites or infections.
During growth the dermis thickens, the sebaceous glands increase in size and the hair follicles multiply: they increase by 50% in the Miniature Poodle between week 10 and 28 *(Credille et al, 2002)*. The composition of skin lipids is also modified *(Dunstan et al, 2002)*.

TABLE 4 - THE MOST COMMON DIETARY IMBALANCES WITH CONSEQUENCES FOR THE QUALITY OF THE SKIN AND COAT

Type of food	Particulars	Nutritional consequences	Dermatological consequences
Low-end generic food	Indigestible proteins	Protein deficiency	Xerosis Keratoseborrheic conditions
	Low fat content	Insufficient energy intake Essential fatty acid (EFA) deficiency	-
	Mineral excess (calcium and phytates)	Zinc deficiency	Generic dog food disease
Home-prepared diet (no supplementation)	PUFA deficiency	EFA deficiency	Xerosis Keratoseborrheic conditions
	Trace element deficiency	Zinc, vitamin E deficiency of water soluble vitamins	-
Vegetarian diet	Restricted protein intake	Sulfur amino acid deficiency	Dull, brittle coat
	PUFA deficiency	EFA deficiency	Xerosis Keratoseborrheic conditions
Excessive mineral supplements	Calcium excess	Zinc deficiency	Generic dog food disease

► Dietary balance

Poorly balanced nutritional intake may generate spectacular dermatological imbalances. The most common are due to generic foods that are low in fat with excessive mineral supplementation, the most common being surplus calcium which inhibits the absorption of zinc **(Table 4)**.

2 - Nutritional dermatoses

Nutritional dermatoses may be specific (identified deficiency of a particular nutrient or group of nutrients) or non-specific: associated with general underfeeding, poor digestibility of the food or a gastrointestinal absorption problem.

► Specific deficiencies

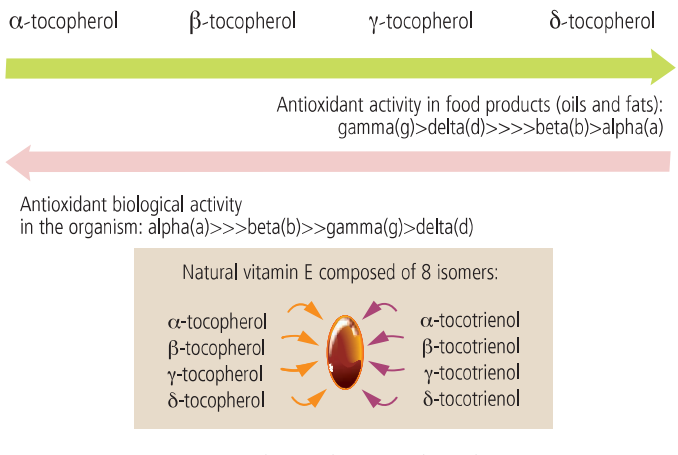
Nowadays, specific nutritional deficiencies are rare. They may, however, be observed in dogs fed with a poor-quality commercial food or an unbalanced homemade food.

> Vitamin deficiencies

• *Vitamin A*

Retinol, a fat soluble vitamin, is essential to the differentiation of epithelial cells. As a consequence, retinol deficiency causes a general keratinization problem, with scaling. In the only case in dogs described in the literature, these problems were associated with visual deficiencies and digestive problems *(Scott et al, 2001)*.

FIGURE 3 - TOCOPHEROL ISOMERS



• *Vitamin E*

Vitamin E is a generic term covering two classes of fat soluble molecules: tocopherols (α, β, γ, δ) and tocotrienols (α, β, γ, δ). Each of these eight different forms has a specific biological activity. α-tocopherol is the most widespread form of vitamin E in animal foods and organisms: it is the form with the greatest biological antioxidant activity in the cell membranes **(Figure 3)**.

Deficiencies of vitamin E are rare and usually due to foods whose fats are poorly stabilized *(Scott & Shelfey, 1987)*. Vitamin E is actually a natural antioxidant, being consumed during oxidation. An experimental deficiency in dogs provokes the appearance of dry seborrhea, diffuse alopecia, erythroderma, secondary pyoderma and anomalies of the immune system.

• *B vitamins*

B vitamins are water soluble and play a role as coenzymes for the cellular enzymes involved in energy metabolism and tissue synthesis. They are provided in food and some are synthesized by gastrointestinal flora. Deficiencies are rare. A correctly formulated commercial food stored in good conditions contains vitamins in sufficient quantities and supplementation is not necessary.

The dermatological manifestations of such deficiencies vary depending on the vitamin:
- **Riboflavin deficiency** (vitamin B_2), sensitivity to light: xerosis localized to the periorbital and abdominal regions

- **Niacin deficiency** (nicotinamide or vitamin PP), occurring with food low in animal nutrients: pruriginous dermatitis of the abdomen and hind limbs.
- **Biotin deficiency** (vitamin B_8 or H), mainly described in animals fed with an excess of egg whites, which contain avidin, a molecule that complexes the biotin and prevents its absorption in the intestine: erythema, facial and periorbital alopecia, generalized scaling, leukotrichia, dull and brittle hair.

> Trace element deficiencies

Trace elements are mineral substances that act at very low concentrations in the organism. The trace elements most directly related to the beauty of the coat are iron, zinc and copper.

• *Zinc*

Deficiencies in zinc intake are typically caused by foods high in phytates, which chelate zinc. These are most often foods of poor quality that are high in whole meal cereal containing a lot of bran. This intake deficiency is also observed with foods oversupplemented with calcium or in breeds with an inability to absorb zinc.

Zinc is a cofactor in a very large number of metabolic pathways, and a deficiency provokes immunity problems and keratinization with scaly, crusty periorificial thickening observed in the skin. The differential diagnosis is not always easy. Therefore it is important to confirm the clinical diagnosis in a histopathological biopsy. Zinc deficiency is characterized by major parakeratosis in the epidermis and the follicles.

In contrast to other types of dermatopathies related to metabolic disorders of zinc **(Table 5),** a simple deficiency can be controlled by rebalancing the diet and controlling secondary infection. In previous classifications, this deficiency is termed generic dog food disease or type-2 zinc responsive dermatitis (common in large-breed dogs) **(Figure 4)**.

TABLE 5 - CLASSIFICATION OF DERMATOSES IMPROVED BY ZINC
(Roudebush & Wedekind, 2002)

Abnormal nutritional intakes
- Primary zinc deficiency
- Secondary zinc deficiency
- Polyunsaturated fatty acid deficiency

Genetic abnormality
- Lethal acrodermatitis

Malabsorption of zinc

• *Copper*

Copper is a component of many carrier enzymes or proteins. A deficiency is observed mainly in puppies fed a homemade food without supplementation or with excessive zinc, calcium or iron content. The deficiency leads to changes in the coat with discoloration beginning in the face, and a thin coat with dull and brittle hairs **(Figure 5)** *(Zentek & Meyer 1991)*.

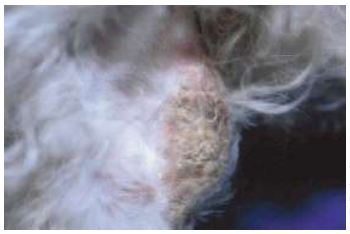

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***Figure 4** - Hyperkeratosis of the elbow in a Fox Terrier due to zinc deficiency.*


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***Figure 5** - Leukotrichia (pilary depigmentation) in a Scottish Terrier puppy due to malnutrition.*

• *Iodine*

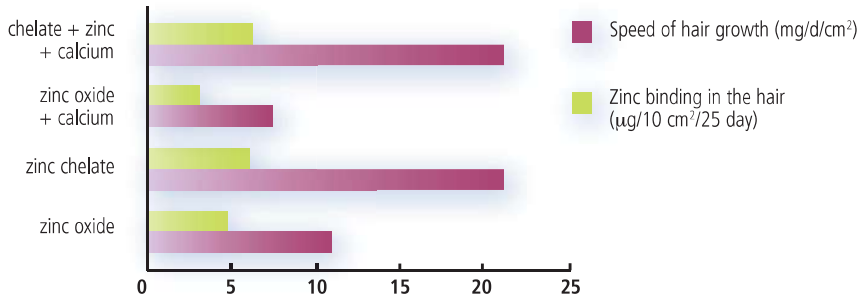
While an iodine deficiency could theoretically disturb the synthesis of thyroid hormones, these phenomena are unusual in dogs and generally without clinical consequence. The daily iodine requirement of a beagle is in the order of 140 µg. A reduction in total thyroxin is only observed when concentrations are under 20-50 µg/day, there is no however, in free thyroxin and no signs of a hypothyroidism *(Feldman & Nelson, 2004)*.

The quantity of trace elements provided in the food does not correspond to the quantity actually available to the organism. The level of absorption depends on the chemical form in which they are provided and their dietary environment. There are interactions between the different elements. So calcium absorption competes with the absorption of zinc, copper and iodine. The percentage of trace element absorption is often under 30%.

When the trace elements are provided in the organic form chelated with amino acids their absorption is clearly improved. Therefore they are better utilized by the organism. For example, in the presence of an excess of calcium in the ration, which inhibits zinc absorption, loss of zinc in the feces increases. Conversely with the chelated form, assimilation is not affected **(Figure 6)** *(Lowe & Wiseman, 1998)*.

A chelated trace element is made up of a metallic ion linked to three amino acids. This element weighs less than 1500 Daltons. Normal trace element absorption efficiency varies from 5% to 30%. When trace elements are chelated, the absorption efficiency can be in excess of 60%.

FIGURE 6 - INFLUENCE OF THE FORM OF ZINC INTAKE ON HAIR GROWTH
(From Lowe et al, 1998)



Chelated zinc binds to hair more avidly than zinc in mineral form (zinc oxide) and the speed of hair growth is significantly faster. Because calcium binds zinc, excessive calcium in the ration leads zinc oxide to bind to a lesser degree in the hair. Zinc binding is unaffected when zinc is provided in chelated form.

> Essential fatty acid deficiency

Essential fatty acids are so termed because they are not synthesized by the organism. As is the case with most vitamins they must be provided by the food. They are primarily the precursors of two families of PUFA, omega 6 fatty acids and omega 3 fatty acids.

- **Linoleic acid,** a precursor of fatty acids of the omega 6 family, is abundant in most vegetable oils. It represents more than 70% of the fatty acids in evening primrose oil and more than 50% in sunflower oil, wheat, corn and soy.

- **Alpha linolenic acid**, a precursor of fatty acids of the omega 3 family, is found in green vegetables, fruits, grasses and plankton, and is found in concentrated form in the oil of plants like soy and flax. The oils of fish from cold waters contain very high levels of two long-chain fatty acids derived from alpha linolenic acid: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These two fatty acids participate in the fluidity of the cell membranes.

PUFA fulfill four main functions:
- Incorporation in the structure of the cell membrane, which gives it its flexibility and permeability
- Production of eicosanoids (leukotrienes, prostaglandins)
- Maintenance of the skin barrier permeability (especially omega 6)
- Cholesterol metabolism and transport

PUFA deficiencies are observed only in animals suffering from malassimilation or animals fed with poor-quality diets or diets that have been overheated for a lengthy period. The cutaneous signs include xerosis, dull hair and a keratoseborrheic disorder. The response to PUFA supplementation is rapid.

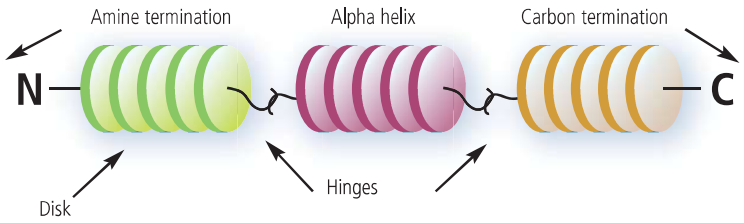
> Overall protein deficiency

Low-quality or overcooked food will undergo modification due to Maillard reactions and the digestibility will be reduced. Hair growth and the regeneration of the skin mobilizes almost 30% of protein intake and such protein deficiency leads to keratinization problems and diffuse alopecia with dull, brittle hair. Protein deficiencies are also observed in dogs presented with a chronic debilitating disease or bitches at the end of gestation or in lactation, if the dietary intake is not adapted.

The low digestibility of proteins may favor the development of dietary hypersensitivity *(Cave & Marks, 2004)*.

FIGURE 7 - STRUCTURE OF A KERATIN MOLECULE

(From Credille, 2002)



The word keratin comes from the Greek keratos, which means horn. There are several types of keratin, each with the same basic helicoidal structure. Inside the molecule, their hinges allow them to be flexible and to interconnect to form resistant filaments.

> Specific amino acid deficiencies

- ***Aromatic amino acids: tyrosine, tryptophan***

These amino acids are essential to the synthesis of the melanins responsible for hair pigmentation: pheomelanin (red, brown) and eumelanin (black). A dietary deficiency leads to a lightening of the coat or the reddening of black hairs **(see above)**.

- ***Sulfated amino acids: methionine, cystine***

Methionine and cystine are essential to the growth of hair, as they participate in the production of keratin **(Figure 7)**. These amino acids are abundant in animal proteins and are rarely deficient in dog food, with the exception of non-supplemented vegetarian diets.

Dogs are however less sensitive than cats to such deficiencies.

► Metabolic diseases

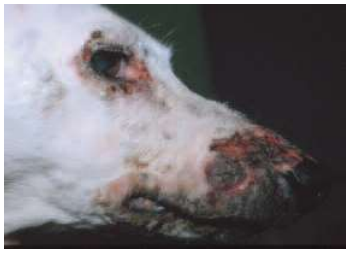
> Migratory necrolytic erythema

Migratory necrolytic erythema (or superficial necrolytic dermatitis, hepatocutaneous syndrome) is a serious dermatosis due to a severe amino acid deficiency. It originates from chronic liver dysfunction (tumor, cirrhosis, functional failure induced by the administration of Phenobarbital *(March et al, 2004)*) or less commonly from a pancreatic tumor (glucagonoma). It is most often a deficiency of amino acids, essential fatty acids and zinc *(Campbell & Lichtensteiger, 2000; Scott et al, 2001; Outerbridge et al, 2002; Turek, 2003)*.

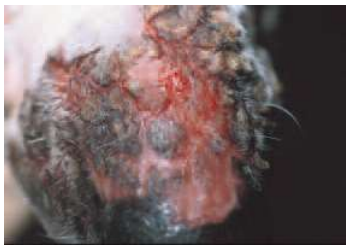
There is no breed or sex predisposition. The patients are usually old. Dermatological lesions are mucocutaneous and pedal in distribution, and are characterized by erythema associated with major, painful hyperkeratosis **(Figures 8 A-D)**. The diagnosis is based on skin biopsies and the identification of the cause of the deficiency (prolonged Phenobarbital intake, biochemical imbalance, liver and pancreatic ultrasound, biopsies). If the cause cannot be treated, the prognosis is poor.

FIGURES 8A TO D - MIGRATORY NECROLYTIC ERYTHEMA

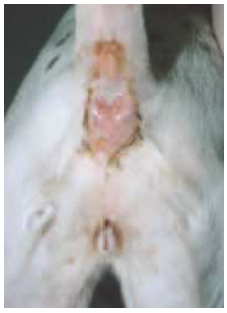
8A - Hyperkeratosic, ulcerated foot lesions.



8B- Ulcerated, crusty perioficial lesions.



8C- Close-up of the lesions in figure 8B: wide ulcers on the face and firmly attached scabs.



8D- Perianal erosions.

TABLE 6 - SYMPTOMATIC AND NUTRITIONAL TREATMENT OF NECROLYTIC MIGRATORY ERYTHEMA

Amino acid intake
White cheese, egg yolk (1/10 kg body weight/day)
Slow intravenous infusions containing all essential amino acids at 10% every day

Polyunsaturated fatty acid intake
Egg yolk
Omega 3 fatty acids (fish oils, rapeseed oil)

Zinc intake
Zinc gluconate 10 mg/kg/day;
avoid zinc methionine

Multiple meals per day

Treatment of infectious complications
Empirical antibiotic therapy (e.g. cephalexin)

Analgesics
Opioid injections or patch

However, with appropriate nutrition intervention the condition of these animals can be quickly improved, and in some cases recovery or a very long remission is possible. Treatment involves intravenous infusion of amino acid solutions **(Table 6)** or administration of egg yolks and supplementation of essential fatty acids and zinc, at the same dosages as for zinc responsive dermatosis **(Table 7)**.

Zinc gluconate is preferable to zinc methionine complex, as it is less hepatotoxic. These nutritional measures are associated with a discontinuation of antiepileptics, antibiotic therapy and administration of analgesics (opioids), especially when the foot lesions affect locomotion.

> Lethal acrodermatitis in the Bull Terrier

Lethal acrodermatitis in the Bull Terrier is a rare autosomal recessive genetic dermatosis. It is probably a disorder of zinc metabolism, rather than a problem with zinc absorption. The animals present in poor general condition from a very early age (two weeks), with erythematous and keratoseborrheic lesions in the extremities of the limbs **(Figure 9)** and the face. The digits are thicker. There are serious systemic symptoms including bronchopneumonia, bone deformation, cataracts, and gastroenteritis. This disease is accompanied by a severe immune deficiency and is fatal in all cases.
The diagnosis is based on anamnestic data and histopathological confirmation. The supplementation of zinc is ineffective.

> Zinc responsive dermatosis

Type 1 Zinc responsive dermatosis is not a metabolic disease as such, but results from an abnormality in the intestinal absorption of zinc. It is mainly observed in Nordic breeds of dogs, but many other canine breeds can be affected, including Beaucerons, German Shepherd dogs, Boston Terriers, Bull Terriers and Great Danes.

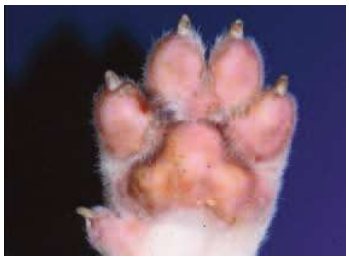

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***Figure 9** - Erythema, scaling and ulcers on the extremities of a Bull Terrier puppy suffering from lethal acrodermatitis.*

The initial lesions are localized to the periorificial zones and the digits: erythema, scaling, which progress to firmly attached crusts **(Figures 10 & 11)**. Pruritus is present in the case of secondary infection. A febrile syndrome is sometimes associated with the condition. The diagnosis must be confirmed by histopathological examination of a biopsy. The differential diagnosis is sometimes difficult. It includes leishmaniasis in endemic areas, scabies, pemphigus foliaceous or dermatophysis *(White et al, 2001)*.

Zinc supplementation is generally sufficient and a clinical improvement follows in less than a month. In case of failure, the administration of low-dose glucocorticoid therapy for three weeks will achieve a rapid improvement in the clinical signs (e.g. oral administration of prednisolone at 0.1-0.2 mg/kg/day for three weeks). The treatment is usually lifelong *(White et al, 2001)*.


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***Figure 10A** - Hyperkeratosis of the pads of a Siberian Husky presenting with zinc responsive dermatosis; note the cracking on one of the pads.*


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***Figure 10B** - Periocular Hyperkeratosis (firmly attached crusty scaling) on a Siberian Husky presented with zinc responsive dermatosis.*

TABLE 7 - DOSAGE OF THE VARIOUS ZINC SALTS USED IN THE TREATMENT OF ZINC RESPONSIVE DERMATOSIS

Zinc (dosage by weight of zinc)	Dosage	Administrations per day
Zinc methionine	4 mg/kg/day	1
Zinc gluconate	5 mg/kg/day	1 to 2
Zinc sulfate	10 mg/kg/day	1 to 2

The various types of dermatitis due to zinc deficiency (food high in phytates or calcium and low in essential fatty acids) have several features in common including an identical histological appearance, hyperkeratosis of the mucocutaneous junctions and the pads. Treatment is based on balancing the diet and administering zinc for three to four weeks **(Table 7)**.

► Dietary hypersensitivities

The term dietary hypersensitivity covers all the dermatoses caused by the ingestion of a food that provokes a harmful reaction in a healthy individual. These hypersensitivities, also termed intolerances, can be of non-immunological or immunological origin *(Johanson et al, 2001)*. An immunological hypersensitivity is a dietary allergy. The clinical manifestations are highly diverse and include gastrointestinal, respiratory, cutaneous, renal or generalized involvement **(Figure 12)**.

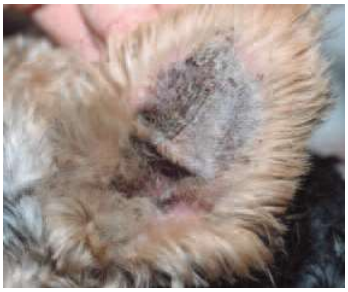


***Figure 11A** - Crusty scaling in a Fox Terrier presented with generic dog food disease.*

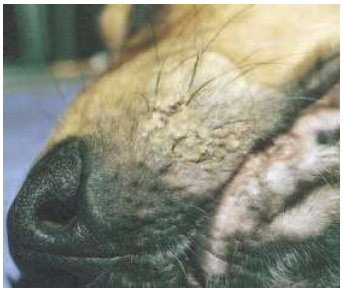


***Figure 11B** - Crusty perioral scabs in a Basset Hound fed with a generic food (generic dog food disease).*

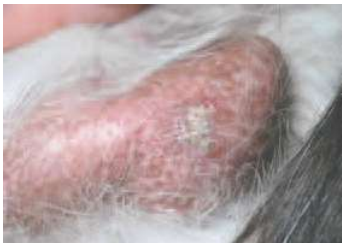


***Figure 11C** - Localized scrotal hyperkeratosis of zinc responsive dermatosis.*

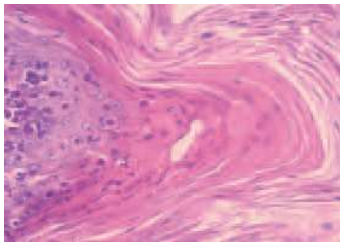
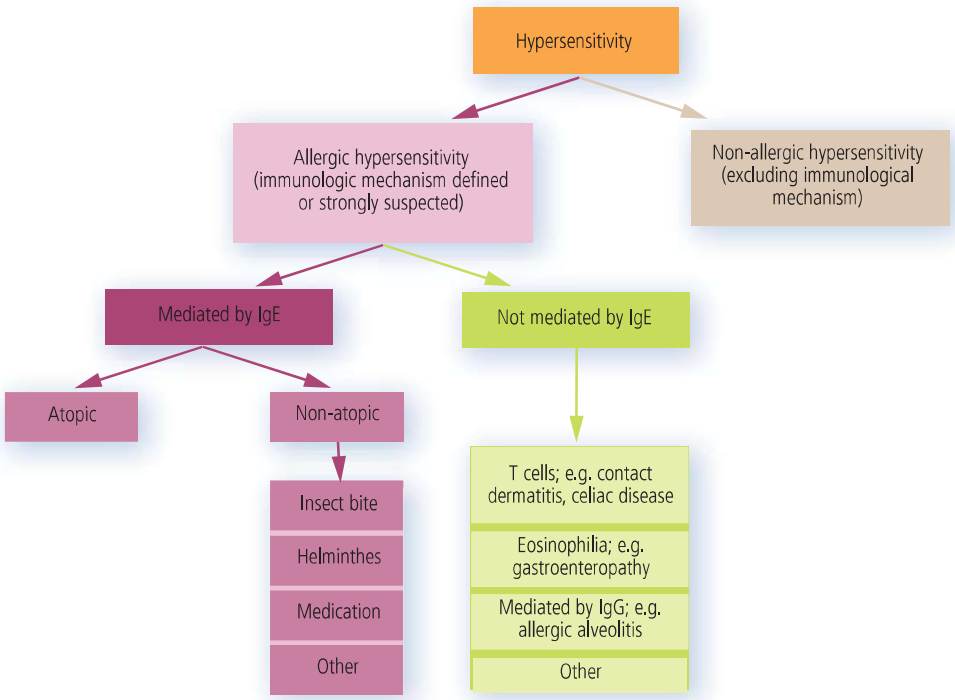


***Figure 11D** - Zinc responsive dermatosis: skin biopsy of crusty squama lesions (X 400, HE): note the major parakeratotic hyperkeratosis (persistence of knots in the corneocytes).*

FIGURE 12 - CLASSIFICATION OF HYPERSENSITIVITY REACTIONS DEFINED BY THE EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY (EAACI)



> Etiology

• *Non-immunological hypersensitivity*

The non-allergic reactions are highly diverse. Some foods may cause urticaria or aggravate an atopic dermatitis if they are high in:

- **histamine**: tomatoes, spinach, beef, pig liver, fresh crustacea, tuna, dry sausage, cheese
- **histamine liberator compounds**: chocolate, strawberries, fish, pork, ovomucoid
- **tryptamine**: chocolate, cooked cheese *(Prélaud, 1999)*.

• *Gastrointestinal allergies*

The development of an allergic reaction depends on the nature of the dietary antigens, their presentation to the digestive immune system and genetic factors.

Break in immune tolerance

The immune response to ingested antigens is generally an immune tolerance reaction. The immune reaction is inhibited when the antigens are present in low concentrations.

When the antigen concentration is high, anergy or even deletion phenomena may occur *(Chehade & Mayer, 2005)*. This immune tolerance is an active phenomenon that depends on several factors related to the individual and the antigen **(Table 8)**.

A hypersensitivity reaction may be triggered by the following factors: augmentation of intestinal permeability, chronic digestive problems, high insoluble antigen content, and individual predisposition to hypersensitivity reactions.

Dietary allergens

The foods most often implicated in the studies on dietary hypersensitivity in dogs are meat (beef, chicken, lamb), eggs, dairy products and soy, but any dietary protein is potentially allergenic. The very nature of the allergens implicated in these allergies is well known in human medicine, where the major allergens and their structural particularities have not been defined in the dog *(Breiteneder & Mills, 2005)*.

When it comes to dogs, our knowledge is very limited. The overwhelming majority of allergens identified in dogs are proteins of large molecular weight – 40-70 kD. The main allergens of beef and cow's mild for dogs may be heavy chains of immunoglobulin G *(Martin et al, 2004)*. There were however crossed sensitivities between cow's milk and beef in dogs. The allergy to casein in cow's milk has also been demonstrated in the animal models presenting spontaneous dietary allergies *(Jackson & Hammerberg, 2002)*. Lastly, some muscle enzymes common to many species of mammal could explain the crossed reactions between lamb's meat and beef in dogs. This is the case for phosphoglucomutases *(Martin et al, 2004)*.

TABLE 8 - FACTORS INVOLVED IN IMMUNE TOLERANCE
(Chehade & Mayer, 2005)

Antigen dose
Strong dose: lymphocytic deletion or anergy
Weak dose: activation of regulating T cells
Antigen form
Soluble antigens are more tolerogen than particulate antigens
Host genetics
Commensal floral
Age of the host
Newborns present stronger immune reactions.

In contrast to humans, there are no cross reactions between pollens and food (with the exception of the cross reaction between tomato and the Cryptomeria japonicum pollen) *(Fujimura et al, 2002)*.

> Predisposing factors

All the factors contributing to immune tolerance can favor the development of dietary hypersensitivity.

• *Maldigestion*

The great majority of dietary proteins, which are allergens or potential allergens, are broken down by the gastric and intestinal enzymes, although only amino acids or small peptides are normally assimilated by the mucosa of the small intestine. If digestion is defective, the quantity of antigens in the digestive immune system and their molecular weight is much greater, which is conducive to the break in tolerance. This explains why a chronic intestinal inflammatory disease or exocrine pancreatic failure is conducive to the development of dietary hypersensitivity.

• *Intestinal permeability problems*

An increase in intestinal permeability, by greatly increasing the quantity of allergens presented to the immune system, can break the condition of tolerance and induce deleterious immunological reactions. The inflammatory reaction increases the intestinal permeability and a vicious circle of maintenance of the phenomenon is maintained.

• *Vaccinations*

Vaccinations provoke an increase in the synthesis of IgE in dogs *(Hogen-Esch et al, 2002)*. This increase of IgE synthesis to dietary allergens in the experimental models of dietary allergy is however not accompanied by the appearance of symptoms.

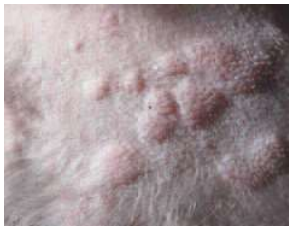


Figure 13A *- Urticaria visible only after clipping in a Yorkshire Terrier.*

Figure 13B *- Chronic urticaria on the abdomen of a dog presented for dietary hypersensitivity.*

Figure 13C *- Facial angioedema due to a vaccine allergy in a French Bulldog puppy.*

• *Atopy*

By definition, an atopic condition predisposes the animal to the development of allergic reactions, be they aeroallergens or dietary allergens *(Prélaud & Olivry, 1998)*.

> Symptoms

The skin symptoms of dietary hypersensitivity are highly variable and sometimes rather vague. The clinical presentation may be that of atopic dermatitis, general or local pruritus, or major acute (skin rash, urticaria) or chronic keratinization problems **(Figures 13 A-C)**.

• *Urticaria and angioedema*

The most common causes of urticaria in dogs are allergies to medication (vaccines, anti-inflammatory drugs, anti-infection drugs including antibiotics, anti-viral, anti-fungal agents, allergens, etc) or reactions to anthropod bites **(Table 9)**. A dietary cause is less commonly identified. In this case, it may be due to an immunological phenomenon (immediate allergic reaction), the ingestion of a food that is high in vasoactive amines or anaphylactiod reactions (mastocyte degranulation without IgE intervention).

The allergic reactions to vaccines have some things in common with dietary allergies, in that, in the majority of cases, the allergy is due to residues of calf fetal serum in cell cultures (IgG bovines) or to protein additives (casein, gelatins) *(Ohmori et al, 2005)*. As a consequence, it is possible that these vaccine reactions are due to dietary sensitivities to these same proteins, as some vaccinal allergic reactions are observed during initial vaccination, so theoretically without prior sensitivity to the vaccine.

• *Atopic dermatitis and atopic-like dermatitis*

Atopic dermatitis is a chronic pruriginous dermatitis of the face and the extremities, characterized by a genetic predisposition to developing hypersensitive

TABLE 9 - MAIN CAUSES OF URTICARIA DESCRIBED AND SUSPECTED IN DOGS

Food
Medication: penicillin, ampicillin, tetracycline, cephalexin, vitamin K, oxopirvedine, vaccines, diethylcarbamazine, amitraz, doxorubicin
Radiolographic contrast agents
Antiserums
Allergenic extracts
Arthropod bites: bees, wasps, mosquitoes, caterpillars, termites, spider crabs, fleas
Plants
Intestinal parasites
Heat, cold
Dermographism
Aeroallergens

Figure 14A - *Periocular erythema and alopecia in an atopic dog presented with dietary hypersensitivity.*

Figure 14B - *Erythema of the surfaces of the concha auriculae showing the existence of otitis externa in an atopic Labrador.*

Figure 14C - *Perioral erythema in an atopic dog.*

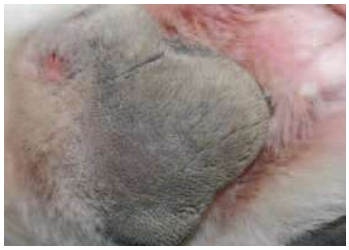


Figure 14D - *Interdigital erythema in an atopic dog.*

Figure 15A - *Abdominal and stifle fold erythema in an atopic Fox Terrier (classic form of atopic dermatitis).*

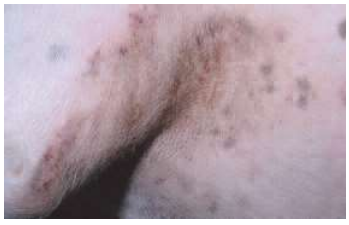


Figure 15B - *Erythema, papules and excoriations in the groins of a French Bulldog presented with a classic form of atopic dermatitis.*

Figure 15C - *Severe form of atopic dermatitis in a Cairn Terrier: major lichenification, and abdominal and inguinal hyperpigmentation.*

Figure 15D - *Severe form of atopic dermatitis, with widespread alopecia, erythema and lichenification lesions in a Poodle (complication of Malassezia dermatitis).*

reactions to environmental allergens. The allergy to aeroallergens is not however demonstrated in 20-25% of referred or university atopic dermatitis cases.

This phenomenon, which is also described in humans, has led the European Academy of Allergy and Clinical Immunology (EAACI) to propose the term atopic dermatitis syndrome, covering all cases of atopic dermatitis of whatever cause, with or without a demonstrated allergy.

In canine medicine, the term atopic-like dermatitis was recently proposed by the International Task Force on Canine Atopic Dermatitis (ITFCAD) to designate cases of atopic dermatitis without a demonstrable allergy. All these variations of definition are the origin of confusion and controversy. If the results of allergological explorations are taken into account, as they are in human medicine, it is impossible to differentiate an atopic dermatitis due to aeroallergens from an atopic dermatitis due to dietary allergens *(Hillier & Griffin, 2001; Jackson et al, 2005)* **(Figures 14-16)**.

As a consequence, its diagnosis may be based on criteria tied to anamnesis and clinical signs comparables to those proposed in human medicine *(Prélaud et al, 1998)* **(Table 10)**.

In approximately 30% of atopic animals, the condition is significantly improved by an elimination diet. This suggests that dietary hypersensitivities could be considered as major factors in the etiology of canine atopic dermatitis *(Chesney, 2001 & 2002)*. As a consequence, when confronted with all the symptoms of canine atopic dermatitis, it is necessary to envisage the existence of dietary hypersensitivity in patients with the following clinical signs *(Prélaud, 2004)*:

- Bilateral otitis externa
- Bilateral cheilitis
- Bilateral pododermatitis
- Local or widespread Malassezia dermatitis

TABLE 10 - DIAGNOSTIC CRITERIA FOR CANINE ATOPIC DERMATITIS

The observation of more than three criteria in the following list enables a diagnosis with 80% discriminating firmness and 80% specific variance:

- Age of first symptoms: between 6 months and 3 years
- Steroid responsive pruritus
- Bilateral otitis externa
- Anterior erythematous pododermatitis
- Bilateral cheilitis

Table 11 - Various clinical forms of atopic dermatitis and therapeutic consequences

Clinical form	Clinic particularities	Common therapeutic bases	Therapeutic particularities
Benign	Localized lesions (e.g. otitis, pododermatitis, anitis) Moderate pruritus	- Complete and continued external anti-parasite treatment - Essential fatty acids if they lead to improvement - Hypoallergenic diet or highly digestible diet where possible	Local care often sufficient: emollients and anti-inflammatory drugs (corticoids or tacrolimus)
Classic	Multiple localizations Pruritus necessitating generalized treatment		- Early allergen immunotherapy - Control of secondary infections - Brief corticotherapy - Cyclosporin A
Serious	Very widespread localization of lesions, secondary infections Widespread pruritus		- Importance of local care (clipping and antiseptic shampoo and emollients) - Lengthy anti-infection treatments - Corticosteroid therapy most often contraindicated - Allergen immunotherapy - Cyclosporin A

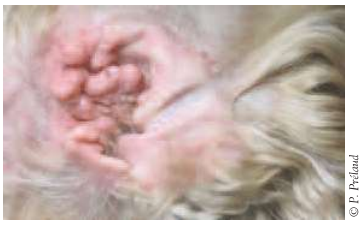

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Figure 16A *- Chronic recurring otitis externa in an atopic Poodle.*

- Erythematous or lichenified dermatitis of the large folds
- Hyperhidrosis

Regardless of whether the clinical form is benign, classic or severe **(Table 11)**, a hypoallergenic and highly digestible elimination diet is mandatory.

• *Local or general pruritus*

Dietary hypersensitivity may also manifest itself in the form of local pruritus, which is most often bilateral. The lesions generally consist of erythema associated with a self-induced alopecia **(Figures 17 A-B)**.

• *Pyotraumatic dermatitis (hot spots)*

Dietary hypersensitivity is one of the causes of recurring pyotraumatic dermatitis. This diagnostic hypothesis must however be envisaged after the infection has been controlled **(Figure 18)** and the most common hypotheses such as demodetic mange (especially in Labrador Retrievers and Rottweilers), flea allergy dermatitis (FAD) and lack of hygiene in dogs with a dense undercoat have been eliminated.

• *Recurring superficial pyoderma*

Atopy and less often food allergy is the most common underlying cause of recurrent superficial pyoderma. No specific breed or age group is predisposed. Generally, the lesions (papules, pustules, crusts, epidermal collarettes) are first observed in the regions of predilection: abdomen and inguinal region **(Figures 19 A & B)**. They can spread all over the body. The response to antibiotic therapy is always good, but recurrence will be rapid after the antibiotic therapy has been stopped.

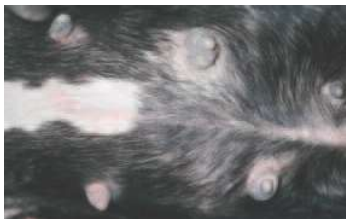
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Figure 16B *- Perinipple lichenification, a minor form of atopic dermatitis in a French Bulldog.*

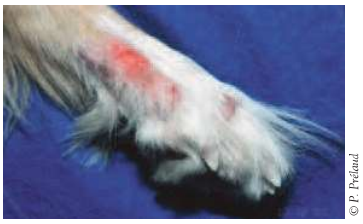
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Figure 17A *- Local pruritus in the extremity of limbs leading to alopecia and erythema in a Collie presented with dietary hypersensitivity.*

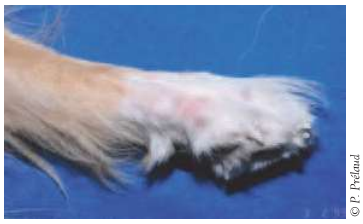
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Figure 17B *- Same dog as in figure 17A after a month-long elimination diet.*


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Figure 18 *- Pyotraumatic furunculosis in a Retriever; note the papules and furuncles around the hot spot, which are visible only after clipping.*


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Figure 19A *- Papular lesions of recurring superficial pyoderma in a German Shepherd.*


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Figure 19B *- Papular lesions of superficial pyoderma in an atopic French Bulldog.*

The diagnosis is based on identifying the lesions and conducting a cytological test to find neutrophilic leukocytes with some evidence of cocci phagocytosis. The differential diagnosis is that of all recurring superficial pyoderma and comprises at least the exclusion of an ectoparasitic or another allergic dermatitis (FAD, atopic dermatitis). Once all the causes of recurrence have been ruled out **(Table 12)**, an elimination diet must be initiated.

TABLE 12 - MAIN CAUSES OF RECURRING PYODERMA

Anatomical faults - Folds, excessive humidity **Pre-existing dermatoses** - Ectoparasitoses, keratinization problems, allergic dermatitis - Endocrinopathies	**Iatrogen causes** - Glucorticoid therapy - Irritating topical therapy - Unadapted or too brief antibiotic therapy **Immunodeficiency**

> Diagnosis

The diagnosis of dietary hypersensitivity is based on the elimination of other causes of pruritus (especially infections and parasites) and the beginning of an elimination diet.

It is tempting to measure specific dietary allergen IgE dosages to identify a dietary allergy or to eliminate some foods from the diet. At this time, such an approach is totally unjustified. The few studies that have been published show that allergy tests lack reliability in this capacity *(Jeffers et al, 1991; Kunkle & Horner, 1992; Hillier, 1994; Ermel et al, 1997; Mueller & Tsohalis, 1998; Jackson & Hammerberg, 2002; Foster et al, 2003; Jackson et al, 2003; Wilhelm & Favrot, 2005)*.

This approach is justified only in the case of an immediate pure allergy, as in human medicine. In humans, the positive result of measurement of specific IgE for peanuts, eggs or cow's milk is an excellent predictor in a patient presented with anaphylactic reactions. For the evaluation of atopic dermatitis, the value of these tests is as poor as it is in canine medicine *(Sampson, 2004)*.

> Practicalities of elimination diets

The principle of an elimination diet is based on the administration of a diet containing proteins that the animal has never previously ingested. It is vital that an elimination diet be rigorously followed. The compliance with such a diet is its main limitation.

TABLE 13 - EXAMPLE OF INGREDIENTS THAT CAN BE USED AS PROTEIN AND CARBOHYDRATE SOURCES IN A HOMEMADE DIET

Proteins	Carbohydrates
Venison	Rice
White fish	Corn
Duck	Tapioca (manioc)
Chicken	Potatoes
Lamb	Sweet potatoes
Rabbit	Bananas

• *Monitoring of dietary habits*

An elimination diet must be prescribed only after a highly detailed investigation and with the clear consent of the owner. The diet preparation phase conditions the subsequent implementation.

It is not easy to keep a log of the food ingested by the dog, because the dietary sources are highly varied. The questionnaire during the consultation should focus on describing the food itself and identifying all the extras and potential hidden sources of food consumption. If necessary, the owner must be asked to keep a log of all the food consumed over a two-week period. The diet supplements and medication that may contain protein palatability factors (e.g. liver) must also be taken into account.

• *Choice of food*

Protein sources

The ideal is to use sources of proteins and carbohydrates that the dog has never previously ingested. That is why venison, duck, rabbit and white fish are the most often used ingre-

dients (tuna, which is high in histamine, should be avoided). Protein hydrolysates with a low molecular weight to ensure low immunogenicity and high digestibility can be used whatever the source. (The available hydrolysates are generally extracted from poultry or soy proteins.)

Homemade preparations

Homemade preparations must be based on a limited number of sources of protein and carbohydrate **(Table 13)**. The significance of homemade preparations is connected with the control of raw ingredients. Dogs that are used to preparations of this type often find them more palatable than dry commercial foods.

The use of homemade diets is limited by the practicability of such a preparation, especially for large dogs. They are increasingly rare for companion dogs because even for a period of one or two months the preparation of the homemade diet can prove very difficult.

The imbalance of these diets can be easily compensated if the diet has to be followed for more than two months or if the dog is a puppy. However, the supplementary constraints imposed on owners may become limiting factors in the good observance of the diet **(Tables 14-15)**.

Commercial foods

There are a great number of commercial foods labeled "hypoallergenic" or "for allergic dermatitis". Three categories can be distinguished.

- Foods with proteins that **mostly** come from selected sources: they cannot be considered acceptable for an elimination diet as the protein sources are highly diverse.
- Foods with proteins that **exclusively** come from selected sources: these are more acceptable. This is the only category that has been subjected to controlled studies and the results are sometimes disappointing *(Vroom, 1994; Leistra et al, 2001; Leistra & Willemse, 2002)*.

Table 14 - Theoretical pros and cons of commercial and home-made foods

Homemade diets	Commercial Foods
Pros	
Involvement of the owner	Practicality
No additives	Nutritional balance
Control of protein sources	
Great diversity of protein sources	Digestibility (hydrolysates)
Effectiveness	Low allergenicity (hydrolysates)
Palatability	Palatability
Cons	
Difficult preparation	No control over protein sources
Often too high a protein content	Possible presence of additives
Necessity of balancing the ration for a puppy	Great diversity of foods available

The use of protein hydrolysates raises many questions in both human and veterinary medicine. Only the studies of cohorts in human medicine come close to answering any of them.

- Is a highly hydrolyzed food more effective than a traditionally hydrolyzed food? This has not been shown in either veterinary or human medicine *(Osborne & Sinn, 2003)*.
- Is a hydrolysate more effective than a homemade diet for dogs? There are no studies that demonstrate an advantage for any one type of food.
- Is it worthwhile using a hydrolyzed food on a patient at risk after the appearance of symptoms? This has been shown only in infants when they cannot be breastfed *(Osborne & Sinn, 2003)*.

- Foods formulated on the basis of **protein hydrolysates** are in principle less allergenic than non-hydrolyzed preparations. The purpose of the hydrolysate is to fractionate the proteins into small peptides of low molecular weight. So in practice these hydrolysate-based diets are the most suited to a commercial elimination diet *(Biourge et al, 2004; Loeffler et al, 2004)*.

Hydrolysis reduces the molecular weight and intrinsic antigenicity of the food, and also renders it more digestible. These two properties act in synergy to offer less stimulation of the gastrointestinal immune system.

The major advantage of hypoallergenic commercial foods is their ease of use. This however, does not mean that the owner should neglect the constraints of such a diet. The prescription of a commercial diet goes hand in hand with a warning against the possibilities of food consumption over and above the base diet.

• *Concomitant treatments*

Antibacterial and systemic steroid therapy may be required when an elimination diet is initiated. The prescription of flavored medication must be avoided. If the medication must be administered by mouth with a food, any potential source of protein must be avoided, such as butter, cheese, ice cream, and meat. Honey is preferred.

The effectiveness of the diet is interpreted six weeks after the end of the course of medication.

• *Special cases*

Multi-pet households

If more than one animal lives in the household, access to the other animals' bowls must be avoided or all animals must be given the elimination diet.

TABLE 15 - EXAMPLES OF POSSIBLE FOOD INTAKE OVER AND ABOVE THE DOG'S REGULAR FOOD INTAKE

Possible food sources	Special occasions
Toys	Breakfast
Leather bone	Appetizers
Trash	End of meal
Toothpaste	TV snacks
Flavored medication	
Treats used in the administration of medication	
Vitamin or trace element supplements	
Food given by well-intentioned neighbors	
Other animal's food	
Leftovers	
Dog or cat feces (in the home or outside)	

Puppies
Balancing a homemade ration for a growing animal requires special consideration (see the examples for homemade rations at the end).

Aging dogs
In older dogs, the fairly short length of the elimination diet should not pose any problems in the case of a commercial food or a balanced homemade ration **(see the examples for homemade rations at the end)**. On the other hand, the use of standard foods may be problematical: for example, meat as lean as venison may lead to weight loss. It is also important not to abruptly change the dog's habits.

Difficult dogs
For difficult dogs, two or three days may be needed to obtain normal consumption of the food. While feeding should begin with a palatable supplement, after four weeks a supplement of a different nature must be selected and used for the following four weeks (e.g. beef gravy, then fish).

Associated diseases
In cases with an associated disease, it is preferable to use a hydrolysate-based commercial food and to closely monitor the concurrent disease (e.g. serum fructosamine concentrations after 15 days of the diet in a diabetic dog).

- ***Monitoring the diet***

Compliance with the diet can be difficult, and information and motivational visits are often necessary. Every member of the family must be informed of forbidden foods that could affect the interpretation of the trial (**Table 15**).

Regular appointments are needed to monitor compliance with the diet. This will allow the potential secondary effects of the elimination diet to be identified, which are refusal to eat or digestive problems. A two-day fast is tolerated. In the case of failure, a new diet must be initiated. To limit the appearance of digestive problems, a period of gradual dietary transition from the previous diet of at least four days is recommended.

Depending on the food, weight gain or weight loss may ensue. Owners must be informed so that they can monitor the dog's weight and body condition score and adjust the quantities given when necessary.

- ***Length of the diet***

There is consensus on the duration of 6-8 weeks to 10-12 weeks at most. Continuing the diet after this period will be useless if no improvement has been observed.

- ***Interpretation of the results***

The appreciation of clinical improvement is simple when it is spectacular, but more difficult when it is partial. Photographs and lesional scores **(simplified CADESI: Table16)** or pruritus scores **(Table 17)** may prove highly useful.

More is needed if the food is to be identified as the cause of the genesis of pruritic dermatitis than the observation of a significant improvement. A certain number of dogs do not have any recurrence when they ingest the initial food again. As a consequence, a provocative test must be conducted in order to correctly interpret the effects of an elimination diet.


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If a puppy has to follow an elimination diet it is important to ensure that the diet is properly formulated for the special needs of growth.

- *Provocation*

There are two options: either the previous diet is given or a new protein source is introduced every one or two weeks. The latter option will identify the foods responsible for the hypersensitivity.

3 - Nutritional therapy in dermatology

► Dull coat, xerosis

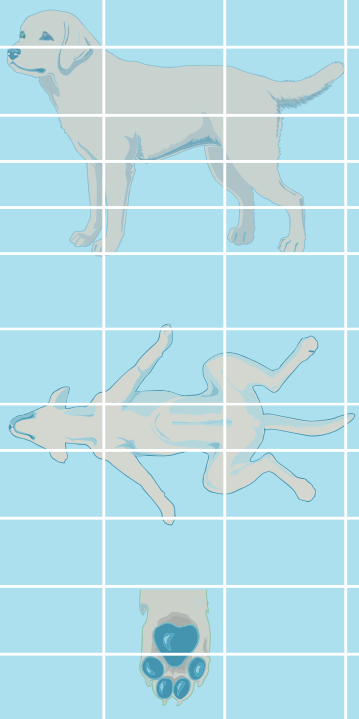
The coat's sheen is connected to the composition of sebum, a natural wax secreted by the sebaceous glands and stored in the hair follicles. Sebum also has the role of preventing the felting of the hairs by eliminating the relief of the hair scale. Sebum makes the keratin in the hair more elastic and more flexible. The lipids in the composition of the sebum are species and breed speci-

TABLE 16 - EXAMPLE OF PRURITUS SCORES

Score	Description
0	Absence of pruritus
1	Discrete pruritus, not spontaneously described by the owner, less than one hour per day
2	Moderate pruritus, spontaneously described by the owner, one to three hours per day
3	Significant pruritus, three to six hours per day
4	Very significant pruritus, permanent, observed in consultation, sleeping problems

TABLE 17 - SIMPLIFIED CADESI*

Clinical signs:		Erythema	Lichenification	Excoriations	Spontaneous Alopecia	Total
Region of the body						
Face	Periocular region Perilabial region					
Ears	Left internal surface Right internal surface					
Neck	Ventral surface					
Armpit	Left					
	Right					
Inguinal region	Left					
	Right					
Abdomen	-					
Forelimbs	Left (fold of the elbow) Right (fold of the elbow)					
Fore feet	Left Right					
Hind legs	Left: fold of the hock Right: fold of the hock					
Hind feet	Left Right					



* *Atopic Dermatitis Extent and Severity Index "(CADESI) adapted from the SCORing Atopic Dermatitis (SCORAD)".*

fic *(Dunstan et al, 2000)*, but the production and the quality of the sebum is also influenced by the food. Some essential nutrients given in higher quantities than the strict recommended minimal quantities produce a significant improvement in the appearance of the dog's coat. This is notably so with PUFA from vegetable sources (omega 6) and zinc. A combined zinc/linoleic acid supplement improves the coat's brilliance and reduces scale *(Marsh et al, 2000)*.

The sensitivity of PUFA sources to oxidation demands close monitoring of their resistance to oxidation, and increased quantities of vitamin E in the food.

► Excessive shedding

Shedding experienced by dog owners as excessive may be physiological, whether it is continuous or seasonal. The intensity of this shedding depends on many factors including the genetic potential, the hormonal balances, the photoperiod and nutrition.

When excessive shedding leads to a veterinary consultation, an attempt must be made to identify the potential causes of anomalies in the pilary cycle:
- endocrinopathy
- unadapted environment
- relative deficiency of PUFA, biotin, tyrosine, tryptophan, cystine, vitamin E, vitamin A, choline or folic acid.

Many nutrients are used to stimulate hair growth, including biotin *(Fromageot & Zaghroun, 1990)* and paprika. The addition of paprika (*Capsicum tetragonum*) to the food increases the intensity of hair coloration and stimulates the hair growth, particularly during shedding *(Greer, 1981)*.

However, no studies have yet proved that shedding in a dog on a balanced diet can be controlled by nutritional or pharmacological measures.


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Figure 20 *- Abundant scaling, showing major xerosis in an atopic Labrador.*

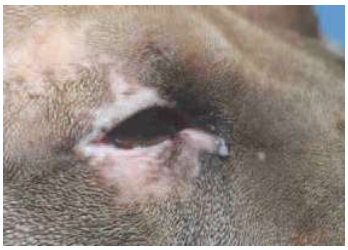
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Figure 21 *- Depigmented vitiligo lesions in a Shar Pei.*

► Black coat with red reflex

It is possible to prevent the reddening of the coat of dogs with black coats by enriching the diet with tyrosine. The response time varies according to the hair cycle. If the majority of hairs are in the telogen phase they are replaced more quickly. The hairs that redden during shedding remain red even after supplementation of aromatic amino acids.

► Vitiligo

Vitiligo is characterized by depigmented lesions preferentially in the mucocutaneous junctions **(Figure 21)**. Depigmentation is due to the absence of melanocytes. The causes of vitiligo are highly varied and few effective treatments have been identified at this time. In humans, L-phenylalanine is regularly used *(Antoniou & Katsambas, 1992; Camacho & Mazuecos, 2002)* and has produced good results in dogs *(Guaguère, personal communication)*.

► Skin wound healing

Nutritionists have studied the nutrients that improve the healing of wounds, so as to be in a position to propose nutritional supplements in the pre- and post-surgery period. Human medicine has a great number of enteral preparations in liquid form. The sought-after properties are stimulation of re-epithelialization and stimulation of the immune system to limit infection. They could potentially be used in adult dogs, but the protein concentration is insufficient for puppies.

Dogs suffering from a **protein** deficiency (e.g. during a fast due to hospitalization) have delayed wound healing. It is essential to safeguard nitrogen balance to facilitate tissue regeneration, paying particular attention to glutamine and arginine contents in the food. The production of nitric acid from arginine stimulates the expression of the endothelial vascular growth factor.

Zinc deficiency is associated with delayed wound healing. Zinc is essential to cell replication and proliferation.

Iron and vitamin C are involved in hydroxylation of proline, a major amino acid in the structure of collagen. Iron deficiency affects the quality of the scar tissue.

Omega 3 fatty acids have a positive effect on the inflammatory reaction at the site of wound healing. A vitamin E supplement helps protect PUFA's from oxidation.

The positive role of curcumin, aloe vera and bromelaine has been shown in the wound healing process *(Fray et al, 2004)*.

Ideally, these nutrients should be administered 8 weeks before surgery. This period is needed for the PUFA to act effectively in the skin. The treatment must be continued for at least four weeks after surgery, depending on the required length of wound healing.

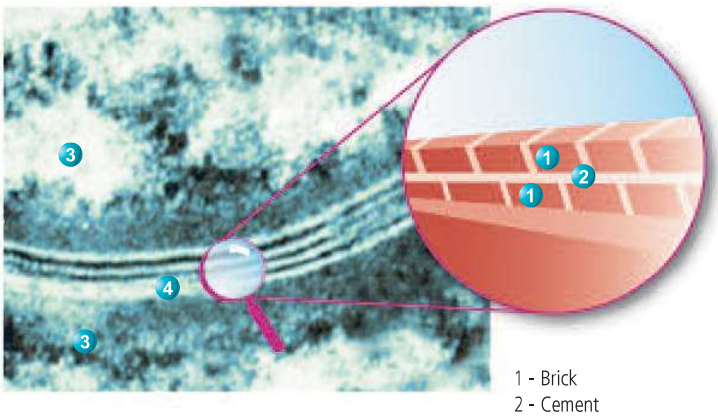
► Atopic dermatitis

Canine atopic dermatitis, like human atopic dermatitis, is a multifactorial disease in which nutrition can be used at three levels.

- Re-establishment of the skin barrier function

Atopic dogs have problems with function of the skin barrier, especially defects in the intercellular cement formed by the ceramides **(Figure 22)** *(Inman et al, 2001)*. This allows water loss, increased transcutaneous penetration by antigens and increased adherence of staphylococci to the surface of the corneocytes.

FIGURE 22 - STRUCTURE OF AN INTERCELLULAR JUNCTION



1 - Brick
2 - Cement
3 - Skin cell
4 - Ceramides (skin lipids)

As cement holds together the bricks in a wall, the ceramides are responsible for the cohesion of the skin cells.

- Reduction in inflammation

By using nutrients acting on the inflammatory (long-chain omega 3 polyunsaturated fatty acids: EPA and DHA) or immune response (probiotics) *(Baillon et al, 2004)*.

- Prevention or control of dietary hypersensitivities

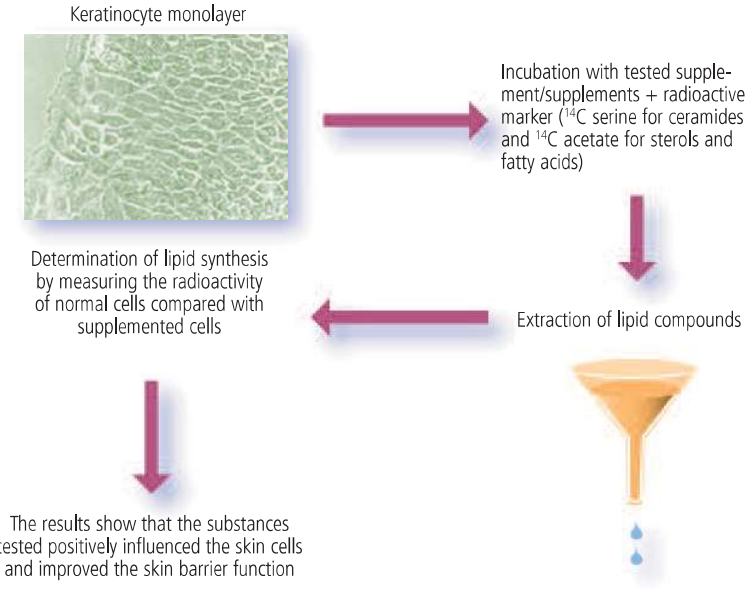
Due to highly digestible and/or hypoallergenic foods.

> Reinforcement of the skin barrier function

In vitro studies (keratinocytes cultures) conducted by the Waltham Research Centre have shown that some nutrients (in particular: nicotinamide, pantothenic acid, histidine, inositol and choline) improve the structure and the function of the skin. Others (pyridoxine and proline) stimulate the synthesis of ceramides **(Figure 23)** *(Watson et al, 2003)*.

In vivo studies have confirmed this approach. After nine weeks of supplementation with a supplement composed of nicotinamide, pantothenic acid, histidine, inositol and choline, the cutaneous water loss was significantly reduced in atopic dogs. The reduction in water loss and so xerosis can have a positive effect of reducing allergen penetration, and also limit bacterial and fungal colonization, which may cause the development of atopic dermatitis.

FIGURE 23 - MEASURING THE SYNTHESIS OF SKIN LIPIDS
(From Watson, 2003)



> Polyunsaturated fatty acids (PUFA)

In the case of pruriginous dermatitis caused by an allergy, omega 3 and omega 6 PUFA may be used to limit skin inflammation, restore the integrity of the hydrolipidic film and limit the transcutaneous penetration of allergens and bacterial and fungal infections. Various studies show that the use of supplements high in PUFA reduces skin inflammation, but does not have any obvious effect on pruritus. They also reduce the dose of long-term corticosteroid therapy when this is necessary *(Saevik et al, 2004)*. The efficacy of such a therapeutic approach in the case of canine atopic dermatitis is more significant in the early stages of the disease *(Abba et al, 2005)*.

In human medicine the preventive use of PUFA is envisaged in the mothers of atopic children. A mother's food is high in omega 3 and omega 6 PUFA and impacts the immune response of breastfed children, favoring a Th1-type response *(Das, 2004)*. Such an approach has not been used in dogs, but it could be tried in dogs of high-risk breeds, like the Shar-Peï and the West Highland White Terrier.

> Curcumin

The addition of curcumin can also benefit dogs suffering from atopic dermatitis, through mechanisms that are focused on the immune response (inhibition of mast cell activation, inhibition of lipoxygenase and cyclooxygenase synthesis, immunoglobulins, etc) *(Cuendet & Pezzuto, 2000)*.

The presence of borage oil in food provides interesting results in various allergic manifestations *(Quoc & Pascaud, 1996)*. Borage oil is frequently used in human dietetics and cosmetology and is the only oil that contains more than 20% gamma linolenic acid (GLA).

The efficacy of borage oil is improved when it is used in association with fish oils, which have high EPA and DHA contents *(Sture & Lloyd, 1995)*.

These very long-chain omega 3 fatty acids act in the same way as gamma linolenic acid, albeit through different metabolic processes. They inhibit the synthesis of arachidonic acid and its derivatives, which are responsible for inflammatory manifestations.

► Keratoseborrheic states

TABLE 18 - DOSES OF RETINOIDS IN DOGS

Retinods	Dose	Daily intake
Vitamin A (retinol)	1000 IU/kg/day	1
Acitretin	1-2 mg/kg/day	1
Isotretinoin	1-2 mg/kg/day	1

> Primary keratinization disorders

Many primary keratinization disorders justify the use of PUFA or retinoids. Retinoids control the proliferation of keratinocytes by reducing the synthesis of sebum and the inflammatory reaction (inhibition of the expression of chemokines). They are much more effective than vitamin A and produce fewer secondary effects. Their use however, is not without risk and they must be part of a prescription in which the owner is informed and monitoring is provided **(Table 18)**.

• *Vitamin A responsive dermatoses*

Vitamin A regulates the growth of epidermal cells and the production of sebum. It helps combat seborrhea and the pellicles that often form after a pruritic episode. It acts in synergy with zinc and sulfated amino acids.

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Figure 24 *- Attached scaling lesions in a Cocker Spaniel presenting with vitamin A responsive dermatosis.*

Vitamin A responsive dermatosis is a rare and much discussed keratinization disorder described only in the Cocker Spaniel. It is clinically characterized by dull hair and thick, foul-smelling scaling **(Figure 24)**. The diagnosis is based on histopathology that reveals major follicular orthokeratotic hyperkeratosis. Vitamin A supplementation (1000 IU/kg/day) leads to a recovery, although the response is fairly slow. In case of failure or partial remission, retinoids may be used.

• *Ichthyoses*

Ichthyoses are genetic keratinization problems. Patients present with thick scaling around the pads and over the body from a very early age **(Figure 25)**. Predisposed breeds include Cavalier King Charles Spaniels, Cocker Spaniels, Retrievers, Soft Coated Wheaten Terriers, West Highland White Terriers, Jack Russell Terriers and Rottweilers. Histopathology helps identify the diagnosis. Treatment is based on the combined use of keratolytic shampoos and PUFA or synthesized retinoids **(Table 18)**.

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Figure 25 *- Perinipple ichthyosis lesions in a Cavalier King Charles.*

• *Idiopathic seborrheas*

The primary seborrheas will appear at a very early age in some predisposed breeds (particularly American Cocker Spaniels). This is a genetic anomaly caused by the accelerated regeneration of the epidermis. The lesions are generalized (oily scaling), sometimes with major localized thickening (on the ventral surface of the neck or in the fold of the elbow, for instance). The diagnosis is based on the elimination of all causes of seborrhea and skin biopsies.

Treatment includes an anti-infection treatment, localized care (clipping and keratolytic shampoos) and synthetic retinoids. They are administered every day for 3-5 months. If control is satisfactory, intake is reduced to once every two or three days.

> Zinc responsive dermatosis

Several zinc salts are available for the treatment of zinc responsive dermatoses **(Table 7)**. The very cheap zinc sulfate can be poorly tolerated (vomiting) and must be administered with meals. Zinc gluconate is generally better tolerated *(Guaguère & Bensignor, 2002)*. Zinc methionine is probably the best absorbed, but it is available only in a preparation in which it is associated with vitamin A and it is expensive. The length of treatment varies from three to eight weeks depending on the animal and must often be life long.

- *Secondary seborrheas*

Many keratinization disorders may be accompanied by inflammatory dermatoses caused by an allergen or a parasite. They do not justify retinoid treatment. The treatment of the associated infection or the primary cause will control it. Some authors consider that the nutritional requirements are greater during the keratoseborrheic state and that it is accordingly necessary to provide an appropriate diet, enriched with PUFA, vitamin E, zinc and trace elements.

► Granulomatous sebaceous adenitis

Granulomatous sebaceous adenitis is a genetic disease characterized by destruction of the sebaceous glands, which gradually disappear, causing keratinization disorders in the hair follicle with alopecia and the formation of hair flanges. The lesions appear gradually and can be localized in any region of the body **(Figures 26 A & B)**.

All breeds can contract this disease, but there are some clear breed predispositions: Akita Inus, Poodles, Samoyeds and Lhassa Apsos. The diagnosis is based on the examination of multiple biopsies that confirm the destruction of the sebaceous glands. The treatment requires localized care (keratin modulation shampooing) and general treatments: essential fatty acids, corticotherapy, cyclosporine, synthetic retinoids **(Table 19)**. The prognosis is always guarded. Given the potential secondary effects (retinoids, corticoids) or the cost (cyclosporin A) of alternative therapeutics, the administration of PUFA must be attempted first, in association with keratin modulating shampoo.

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Figure 26A *- Granulomatous sebaceous adenitis in an Akita Inu: irregular alopecia over the whole trunk, associated with a keratoborrheic state.*

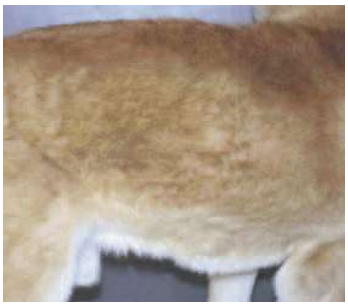

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Figure 26B *- Same dog as in Figure 26A, after two months' treatment with polyunsaturated fatty acids and keratin modulating shampoo.*

► Various immune dermatoses

Vitamin E, due to its antioxidant action, and PUFA are commonly used on their own or as an adjuvant for immune mediated dermatoses.

Vitamin E (400-800 IU BID) is used as an adjuvant for lupus *(Scott et al, 2001)* and dermatomyositis *(Hargis & Mundell, 1992)*. Used on its own, it is only effective in a very limited number of cases.

PUFA are used for their anti-inflammatory or immunomodulating action in the treatment of lupoid onychodystrophies with excellent results in one in three cases *(Mueller et al, 2003)*.

► Recurring bacterial infections

Nutrition can play an essential role in controlling recurring infections by helping to reestablish the skin barrier (skin barrier-type nutrients, PUFA) or by helping to control allergic inflammation (PUFA, hypoallergenic foods).

► Prophylactic nutrition

In canine dermatology, nutritional interventions continue to be almost exclusively devoted to therapeutic functions. In human dermatology however, especially allergic dermatology, nutrition is used preventively **(Table 19)**.

TABLE 19 - EXAMPLES OF NUTRITIONAL RECOMMENDATIONS FOR LIMITING THE RISK OF FOOD ALLERGIES IN CHILDREN
(Sampson, 2004)

- Breastfeeding for three to six months
- Use of hydrolysates if breastfeeding is not possible
- Avoidance of peanuts and seafood during pregnancy and breastfeeding
- Avoidance of high-risk foods (peanuts, hazelnuts, seafood) before three years of age

Such an approach could be interesting, the more difficult problem is the identification of individuals at risk. This is problematical in humans *(Osborn & Sinn, 2003)*, but is much easier in dogs, as certain breeds and lines are predisposed to nutritional or immune dermatoses *(Scott et al, 2001)*.

> Hypoallergenic and highly digestible foods

Hypoallergenic and highly digestible foods are used in dermatology for therapeutic purposes. In human medicine these foods are mainly used in the prevention of food allergies in high-risk children, or even breastfeeding mothers. Hydrolysates are used for high-risk children that cannot be breastfed to significantly reduce the risk that clinical manifestations of atopy will develop *(Osborn & Sinn, 2003)*. Such an approach could be useful in canine medicine, but it must undergo controlled clinical studies.

> Probiotics

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In high-risk breeds, with respect to dermatology it would be useful to try to prevent hypersensitivity phenomena by modifying the mother's food during gestation, as occurs in human medicine.

In humans, there is a correlation between the use of antibiotics in infancy or in the mother during the perinatal period and the development of atopic dermatitis. Conversely, random double-blind studies show that the administration of probiotics to mothers at risk limits the occurrence of manifestations of atopic dermatitis (extrinsic form) in children *(Flohr et al, 2005)*.

In dogs, the addition of probiotics in the food presents technical problems *(Weese & Arroyo,2003)*. It is however possible to include them in a dry food and to observe their effect on immune response *(Baillon et al, 2004)*. If the goals of feeding such a food are aimed at the gastrointestinal tract, preventive or curative use in atopic dogs could also be practical.

> Polyunsaturated fatty acids

Recurring bacterial infections are most often caused by allergic dermatopathies (dietary hypersensitivity, atopic dermatitis) or non-specific skin defense problems. In both cases PUFA supplementation or a skin barrier cocktail may limit the risks of a relapse. It is essential however that the causes of recurring pyodermititis be identified before diagnosing an idiopathic recurring pyodermititis **(Table 12)**.

PUFA supplementation in human mothers during pregnancy and lactation helps limit the dietary hypersensitivity phenomena in children *(Korotkova et al, 2004)*. Such an approach could be useful in bitches of high-risks breeds like Shar-Peis or West Highland White Terriers.

Conclusion

Food plays a fundamental role in cutaneous homeostasis and in the treatment of many inflammatory dermatoses. The study of the diet is therefore an integral part of the dermatological history. The correction of dietary imbalances (with respect to zinc and essential fatty acids in particular) is a necessary factor in good dermatological therapy.

It is important to challenge ideas that impede the management of chronic pruriginous dermatitis on a daily basis. These include the harmfulness of food based on their origin, the value of IgE doses of dietary allergens, the absence of flea infestation opportunities and the harmfulness of short-term corticosteroid therapy.

The treatment of keratinization disorders or allergenic dermatites involves the use of nutrients that reinforce the skin barrier function, or even play an anti-inflammatory role. The future is open to the possible use of food for prophylactic purposes (probiotics, essential fatty acids, etc) in animals at risks of skin disease.

Frequently asked questions – Influence of food on dermatology

Q	A
Which nutritional deficiencies are most commonly implicated in dermatology?	The nutrients involved in skin diseases that are caused by deficiencies are zinc and essential fatty acids.
How can a zinc deficiency be identified?	It can be tempting to measure the zinc level in the blood or in the hair, but these methods are unsatisfactory. The diagnosis is based histopathology of the skin lesions (parakeratotic hyperkeratosis) and the response to supplementation or correction of the diet.
What should you do when a Siberian Husky showing signs of zinc responsive dermatosis does not respond to the administration of zinc?	First the zinc salt should be changed, for example, prescribe zinc gluconate or zinc methionine instead of zinc sulfate. The prescription of a low dose of corticosteroids (prednisolone: 0.2 mg/kg/day) generally leads to a very significant improvement in zinc absorption and the control of dermatosis.
Which foods are the most likely to cause allergenic reactions?	The data provided in the literature do not permit the identification of sources of more allergenic proteins. The knowledge of the very nature of allergens may permit definition of the high-risk foods in the near future.
Is white meat less allergenic than red meat?	This belief is incorrect. The color of the meat does not have any influence on its potential allergenic or hypoallergenic character. Indeed, the origin and the color of the meat are not implicated in the studies on the etiopathogenesis of food intolerances in dogs. On the other hand, the risk increases with the quantity of meat ingested. A very red meat like venison is very widely and successfully used as a basis for elimination diets.
Can atopic dermatitis be controlled simply with PUFA supplementation?	Yes, but if the response is unsatisfactory after two months of treatment other therapeutics should be used.
Can dietary imbalance create an immune deficiency?	Only serious protein or fatty acid deficiencies can cause an immune deficiency. This has been observed only in cases of debilitating diseases or serious chronic digestive problems.

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EXAMPLES OF NOVEL PROTEIN

Example 1

COMPOSITION
(1000 g diet)

Venison, back ..... 475 g
Potato, cooked, with skin ..... 500 g
Rapeseed oil ..... 25 g

Add a well-balanced mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 27% dry matter and 73% water		
	% dry matter	g/1000 kcal
Protein	43	102
Fat	16	37
Available carbohydrate	29	68
Fiber	3	7

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1140 kcal/1000 g of diet prepared (4250 kcal/1000 g DM)			
Dog's weight (kg)**	Daily amount (g)*	Dog's weight (kg)**	Daily amount (g)*
2	190	45	1980
4	320	50	2140
6	440	55	2300
10	640	60	2460
15	870	65	2610
20	1080	70	2760
25	1270	75	2910
30	1460	80	3050
35	1640	85	3190
40	1810	90	3330

Key Points

- **Control raw ingredients used**
  - Use of a single source of highly digestible proteins, against which the dog is not sensitized (i.e. has not previously consumed)
  - Use of a single source of extremely digestible carbohydrate

- **Palatability** to facilitate the strict observation of the diet

* *The rationing is offered in accordance with the dog's healthy weight. In case of obesity, the rationing must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
** *The quantities can be adapted as the dog's weight develops, but no other ingredients must be incorporated into the ration and no supplements must be given.*

HOME-PREPARED ELIMINATION DIETS

Example 2

COMPOSITION
(1000 g diet)

Duck ..... 500 g
Rice, cooked ..... 480 g
Cellulose ..... 10 g
Rapeseed oil ..... 10 g

Add a well-balanced mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1325 kcal/1000 g of diet prepared (4480 kcal/1000 g DM)			
Dog's weight (kg)**	Daily amount (g)*	Dog's weight(kg)**	Daily amount (g)*
2	170	45	1700
4	280	50	1840
6	380	55	1980
10	550	60	2120
15	750	65	2250
20	930	70	2370
25	1100	75	2500
30	1260	80	2620
35	1410	85	2750
40	1560	90	2870

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	g/1000 kcal
Protein	37	82
Fat	14	31
Available carbohydrate	43	95
Fiber	4	9

Contra-indications

For a puppy a commercial low-allergenic diet is preferable until the end of the growth phase

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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The beauty of the coat obviously depends on the genetic data selected by the breeders, but these natural qualities are only realized if the food provides the nutrients essential to growth and regeneration.

Key Points
to remember:

The role of nutrition in preventing and treating skin diseases in dogs

Objective #1: strengthening the effectiveness of the skin barrier

The Waltham Research Center has screened 27 substances that are likely to have a beneficial effect on skin barrier function. The selection criteria were based on limiting water loss through the epidermis and the synthesis of skin lipids.

Four group B vitamins and one amino acid acting synergistically were identified (*Watson et al, 2006*). Group B vitamins are water soluble and are not stored in the body. In general, a balanced diet and synthesis by the intestinal bacteria guarantee sufficient intake, although intake can become marginal in situations of major water loss or antibiotic treatment.

- **Niacin** (or nicotinamide) is synthesized from tryptophan. It is essential for cellular respiration. With deficiency, pruriginous dermatitis of the abdomen and the hind limbs occurs in dogs (termed pellagra in human medicine).

- **Pantothenic acid** is involved as a coenzyme in many metabolic pathways, including those of fatty acids.

- **Choline and inositol** work together in the formation of cell membranes. Combined with phosphorus, choline forms phospholipids.

- **Histidine** is essential to the growth and maturation of the epidermal cells (keratinocytes).

Administration of these nutrients has a beneficial effect after approximately two months, due to the time needed for the epidermal cellular differentiation process.

Objective #2: controlling inflammation with essential fatty acids

Some fatty acids are termed essential because the organism is incapable of synthesizing them. In the case of deficiency, the skin undergoes major desquamation with alterations in the skin barrier function.

The essential fatty acids have a dual action: they rebalance the composition of the superficial lipid film to limit skin drying phenomena *(Fray et al, 2004)* and they decrease the synthesis of inflammation mediators. The anti-inflammatory properties of long-chain omega 3 fatty acids (EPA/DHA) are widely used in human and veterinary dermatology *(Byrne et al, 2000)*.

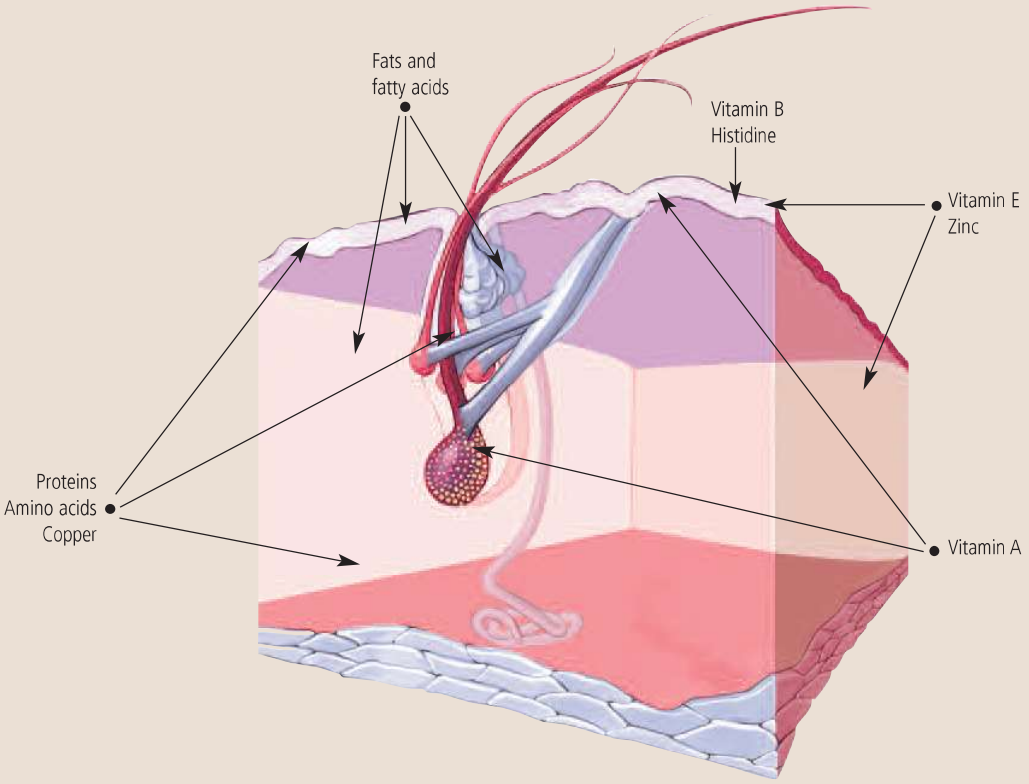
Objective #3: ensuring the vitamin intake meets the major requirements of the coat

Vitamin A regulates the growth of epidermal cells and the production of sebum. It helps combat seborrhea and the dandruff that often forms after pruritus. It acts synergistically with zinc and sulfated amino acids.

The sensitivity of polyunsaturated fatty acids to oxidation requires close monitoring of their resistance to oxidation and an increase in the quantities of vitamin E in the food.

Biotin (vitamin H) is essential to skin integrity. Biotin deficiency can lead to mild or severe hair loss.

ACTION OF NUTRIENTS IN THE SKIN



Many nutrients are essential to the complex organ that is the hair and skin. This figure only briefly summarizes the many essential elements that permit normal skin function.

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Focus on:

BORAGE OIL

Borage (*Borago officinalis*) is a plant from Asia that is also grown in North Africa and various European countries, including the UK, Germany, France and the Netherlands. The oil is obtained by pressing the grains.

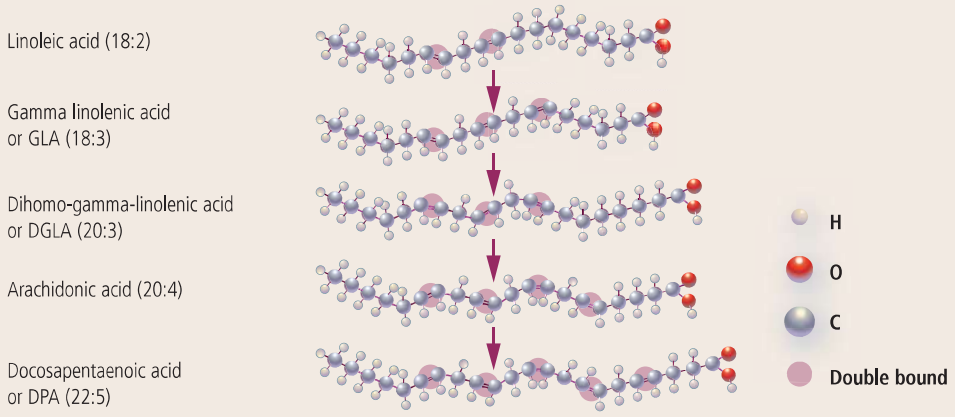
Borage oil is characterized by large quantities of fatty acids, especially those of the omega 6 family such as gamma linolenic acid or GLA. Most vegetable oils have high linoleic acid content, but the only oils that provide significant quantities of GLA are: borage oil, evening primrose oil and blackcurrant seed oil. Of course, borage oil contains the highest GLA content.

The diagram below illustrates the successive transformations linoleic acid goes through to produce the whole omega 6 fatty acid family. Each step in the transformation is characterized by the facilitation of a specific enzyme.

COMPARISON OF GLA CONTENTS FOR VARIOUS VEGETABLE OILS

Vegetable sources	Linoleic acid %	Gamma-linolenic acid %
Borage	35-40	20-25
Blackcurrant seeds	45-50	15-20
Evening primrose	70-80	8-12
Soy	50-55	-
Olive	8-10	-

STEPS IN THE SYNTHESIS OF POLYUNSATURED FATTY ACIDS OF THE OMEGA 6 SERIES

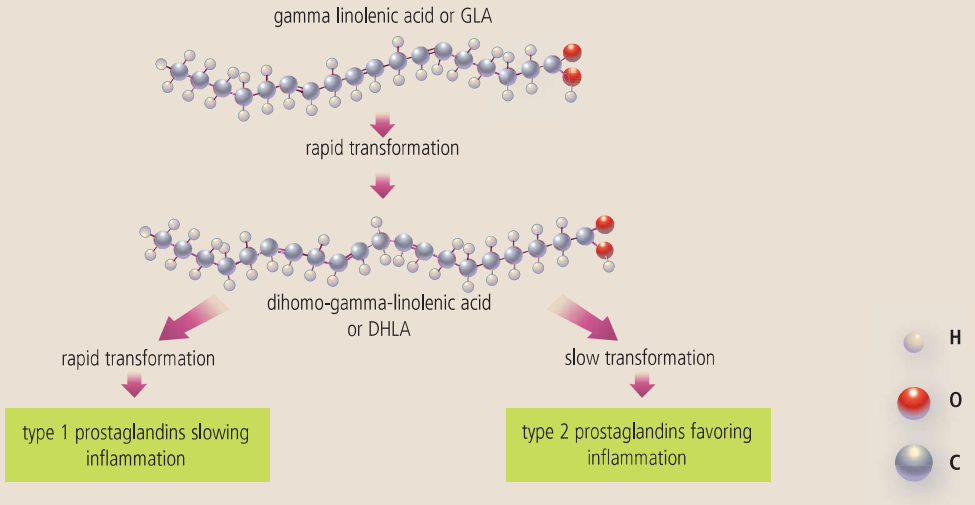


The addition of GLA to the diet favors the incorporation of GLA into tissues including the liver, red blood cells, and the vessel walls. The efficacy of this supplementation in the cell membranes is much clearer than that obtained from the transformation of linolenic acid. The dietary intake of GLA therefore prevents the risk of deficiency in animals at highest risk such as aging dogs or dogs suffering from enzyme deficiencies.

Borage oil has potential for the treatment of all inflammatory problems. The best studies into the beneficial effects of borage oil have been in dermatology. GLA supplementation favors an increase in the production of hormones with well known anti-inflammatory effects (type 1 prostaglandins). This production is at the expense of the synthesis of type 2 prostaglandins, which have a pro-inflammatory effect.

Decreasing the transformation of arachidonic acid limits the negative effects of its derivatives, type 2 prostaglandins and the excessive inflammatory phenomena associated with them.

ORIGIN OF THE BALANCE BETWEEN TYPE 1 & 2 PROSTAGLANDINS



The positive effects are significant in dogs presented with an inherited predisposition. The results are also promising with respect to problems with excessive sebum production by the skin (seborrhea).

Borage oil is also used in cosmetology where it is incorporated into products aimed at regenerating the flexibility and elasticity of the skin. It is indicated when the skin is dry.

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