

Effect of omega-3 fatty acids on canine atopic dermatitis

Twenty-nine dogs were included in a double-blinded, placebo-controlled, randomised trial and were orally supplemented for 10 weeks with either flax oil (200 mg/kg/day), eicosapentaenoic acid (50 mg/kg/day) and docosahexaenoic acid (35 mg/kg/day) in a commercial preparation, or mineral oil as a placebo. For each dog, clinical scores were determined based on a scoring system developed prior to the trial. Total omega-6 and omega-3 intake and the ratio of omega-6:omega-3 (omega-6:3) were calculated before and after the trial. The dogs' clinical scores improved in those supplemented with flax oil and the commercial preparation, but not in the placebo group. No correlation was identified between total fatty acid intake or omega-6:3 ratio and clinical scores. Based on the results of this study, the total intake of fatty acids or the omega-6:3 ratio do not seem to be the main factors in determining the clinical response.

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Journal of Small Animal Practice (2004)
45, 293–297

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INTRODUCTION

Canine atopic dermatitis is a common skin disease in small animal practice (Scott and Paradis 1990). It is defined as an inherent predisposition to the development of immunoglobulin (Ig) E antibodies to environmental allergens, resulting in clinical signs following exposure to these allergens (Halliwell and Gorman 1989). Symptomatic treatment modalities for canine atopic dermatitis include glucocorticoids, antihistamines and fatty acid supplementation (Griffin 1993, Mueller 1993, Scott and others 2001). The only specific treatment for atopic dermatitis is allergen-specific immunotherapy wherein allergens identified by intradermal testing or serum testing for allergen-specific IgE are injected subcutaneously. Allergen-specific immunotherapy must usually be pursued for months before an improvement in clinical signs is seen and it is not effective in all patients (Scott and others 1993, Mueller and Bettenay 1996). For these reasons, symptomatic therapies are often explored. Because adverse reactions to glucocorticoid

therapy are common, more attention has been paid recently to treatments that have been associated with fewer adverse effects, such as antihistamines and fatty acid supplementation (Campbell 1993, Paterson 1994).

Essential fatty acids have been used to treat humans with atopic dermatitis (Price 1984, Biagi and others 1988, Fiocchi and others 1994, Paterson 1995, Henz and others 1999) and allergic asthma (Stenius-Aarniala and others 1989, Okamoto and others 2000), and have been shown to modulate the inflammatory response in humans, mice and rats (Higgs 1985, Horii and others 1991, Schafer and Kragealle 1991, Watanabe and others 1994, Terencio and others 1998). Oral fatty acid supplementation has been noted to decrease the inflammation and pruritus associated with canine atopy (Bond and Lloyd 1992b, Scott and others 1992, Logas and Kunkle 1994). These benefits have been related to supplementation with certain omega-6 fatty acids (gamma-linoleic acid [GLA]) (Scarff and Lloyd 1992), combinations of GLA and omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Bond and Lloyd 1992a, Scott and others 1992), variable doses of omega-3 fatty acids (Logas and Kunkle 1994) or omega-3 supplemented whole diets with fixed omega-6:omega-3 (omega-6:3) ratios (Scott and others 1997).

Emphasis has recently been placed on the use of omega-3 fatty acid supplementation at doses higher than the manufacturer's recommendation in the management of canine atopic dermatitis. Combination supplements of EPA and DHA given in the range of 66 mg/kg/day have been noted to clinically benefit pruritic dogs (Logas and Kunkle 1994). The use of flax oil as a source of potentially beneficial omega-3 fatty acids has also been recommended. To the authors' knowledge, there are no published data in the veterinary literature to substantiate claims of efficacy. The purpose of this randomised, double-blinded, placebo-controlled study

was to evaluate the influence of supplementation with flax oil and a commercial product containing EPA and DHA on the clinical signs of atopic dogs.

MATERIALS AND METHODS

Approval for the study was obtained from the Animal Care and Use Committee of Colorado State University. Dogs with non-seasonal atopic dermatitis were included in the study. Atopic dermatitis was diagnosed by history, clinical examination and exclusion of differential diagnoses such as food adverse reactions or scabies with appropriate tests or treatments as described elsewhere (Mueller 1993, Scott and others 1993, 2001). Offending allergens were identified with an intradermal test.

Dogs were fed the same recorded type and amount of diet for eight weeks prior to and during fatty acid supplementation. The total amounts of omega-3 and omega-6 fatty acids received before and during the trial were calculated for each dog using the manufacturer's information outlining the fatty acid content of the used commercial diet and adding the fatty acid content of the administered supplement.

Each dog was assigned to one of three groups of 10 dogs using a table of random numbers and simple randomisation. The groups were treated, at a dose of at least one capsule per 5 kg of bodyweight, with a commercial fatty acid supplement (3V Caps; DVM Pharmaceuticals), flax oil capsules containing 570 mg of α -linolenic acid and 170 mg of linoleic acid per capsule, or a placebo containing mineral oil. Thus the dose range for each animal varied from 50 to 85 mg of EPA/kg and 35 to 55 mg of DHA/kg every 24 hours for the dogs receiving the commercial fatty acid supplement, and from 200 to 335 mg/kg of flax oil every 24 hours for the second group. Neither owner nor clinician was aware of the nature of the supplementation. Supplements were given for 10 weeks. Owners and clinicians completed evaluation forms immediately

before and after the fatty acid therapy.

Owner clinical scores were obtained by adding the scores for pruritus, skin lesions and medication. Pruritus was scored on a continuous visual analogue scale of 0 to 30, 0 being no pruritus, 30 being intense pruritus noted at all times. Each observed skin lesion (erythema, papule or crust) was counted separately and graded as: mild, 1.5 points; moderate, 3 points; and severe, 4.5 points. No concurrent medication was scored as 0 points, topical therapy as 5 points and antihistamines as 10 points. Frequent antibiotic therapy (more than 21 days during the 10-week study) scored 20 points, while less frequent antibiotic administration during this period scored 10 points. The score for glucocorticoids was determined by the dose. A calculated daily average dose of 1 mg/kg or more scored 40 points, between 0.5 mg/kg and 1 mg/kg daily scored 30 points, between 0.2 mg/kg and 0.5 mg/kg daily scored 20 points and less than 0.2 mg/kg daily scored 10 points. The overall maximum score for an animal was 117.5 points.

Clinician clinical scores were obtained similarly, but pruritus scored 0 when absent, 10 points when mild (scratching was not seen in the waiting or examination room, but could be induced), 20 points when moderate (scratching, licking or rubbing could be observed in the examination or waiting room, but ceased during the examination) and 30 points when severe (scratching, rubbing or licking occurred during the examination).

The mean total number of positive intradermal reactions was determined for each group and compared with a Kruskal-Wallis test. Total dietary omega-3 and omega-6 fatty acid intakes before and after supplementation were calculated by adding dietary intake and supplementary fatty acid content together. The total fatty acid intake of the three groups was compared with a Kruskal-Wallis test. Subjective evaluations of pruritus, performed by continuous scale plotting, were quantitated and the scale distances were evaluated as continuous data for normality of distri-

bution by the Kolmogorov-Smirnov test. Normally distributed data were compared over time by one-way analysis of variance (ANOVA). Group means were compared by a Kruskal-Wallis test, and clinician and owner scores within groups by a Wilcoxon matched pair test. A Pearson's test was used to evaluate correlations between intake of omega-3 and omega-6 fatty acids or omega-6:3 ratio and clinician scores. The correlation between clinician and owner scores was also examined with a Pearson's test. A P value of less than 0.05 was considered significant.

In addition to statistical evaluation, the dietary intake of fatty acids and the omega-6:3 ratio of the dogs responding fully to therapy were compared with a corresponding number of dogs in the same groups not responding at all to detect possible differences that could not be identified with the statistical evaluation, due to the large standard deviation of most values within groups.

RESULTS

Thirty dogs were included in the study. All dogs had positive intradermal tests; the mean number of positive reactions was nine in the placebo group (range three to 18) and 10 in both the group treated with a commercial product and the flax oil group (ranges four to 19 and four to 22, respectively). There was no significant difference in positive reactions between groups using a Kruskal-Wallis test ($P=0.87$).

Supplementation was discontinued for one dog in the placebo group when it developed diarrhoea. Twenty-nine dogs completed the study. Of these 29 dogs, 13 dogs had been on antihistamines with incomplete response prior to the study. In all dogs these antihistamines were continued at the same dose until the end of the study. Similarly, 13 dogs received weekly shampoo therapy at the beginning of the study and this continued unchanged throughout the study. In one dog,

Table 1. Total dietary intake of omega-3 and omega-6 fatty acids and standard deviation in dogs supplemented with placebo, flax oil or commercial EPA/DHA capsules (mean $\pm$ standard deviation)

	Omega-3 fatty acids (mg/kg bodyweight)	Omega-6 fatty acids (mg/kg bodyweight)
Placebo	84 $\pm$ 73	509 $\pm$ 196
Flax oil	327 $\pm$ 437	468 $\pm$ 199
Commercial capsules	141 $\pm$ 67	426 $\pm$ 174

EPA Eicosapentaenoic acid, DHA Docosahexaenoic acid

shampoo therapy was added during the study. None of these shampoos contained fatty acids.

Three dogs were on glucocorticoid maintenance therapy prior to inclusion, with unsatisfactory results. In all three dogs, the dose was less than 0.2 mg/kg/day and was continued throughout the study. In one of these dogs, the dose could be decreased further, but due to the low initial dose the score assigned was unchanged. Two of the dogs improved by 25 per cent in pruritus scores. One of these dogs was on placebo, the other on commercial supplement. The last dog was on commercial supplement without any improvement.

Antibiotics were administered in seven dogs prior to the study. Six dogs were on antibiotics at the end of the study. Four dogs had developed a pyoderma during the study. Two dogs received antibiotics as pulse maintenance therapy prior to inclusion and throughout the study.

The daily dietary intakes of omega-3 and omega-6 fatty acids were calculated by adding the fatty acid content of the consumed diet and the supplement (Table 1). The dietary intake of omega-3 and omega-6 fatty acids was not different between the three groups at the beginning of the trial ($P=0.546$ and $P=0.489$, respectively). The dietary intake of omega-3 fatty acids more than doubled with supplementation in the group receiving the commercial capsules (to 141 $\pm$ 67 mg/kg, $P=0.0001$) and quadrupled in the flax oil group (to 327 $\pm$ 436 mg/kg, $P=0.0011$). The omega-6 intake increased by an average of 17 per cent in the flax oil group (to 548 $\pm$ 218 mg/kg, $P=0.579$).

There were no significant differences between groups at the beginning of the trial for clinical scores determined by clinicians ($P=0.623$) or owners ($P=0.612$) (Table 2). Clinical scores for dogs receiving flax oil and commercial EPA/DHA supplements improved significantly during the 10 weeks of supplementation compared with the control group ($P=0.008$, $P=0.01$ and $P=0.297$, respectively) (Table 2). The mean scores of dogs receiving the commercial EPA/DHA supplement and the flax oil capsules at the end of the study were lower than those of dogs receiving placebo. However, the difference was not significant for owner or clinician scores.

Improvement of more than 50 per cent was seen in the owner scores of two dogs and the clinician score of one dog in the placebo group and in both scores of four dogs in the group receiving flax oil capsules. Five of the dogs receiving commercial EPA/DHA capsules improved by more than 50 per cent according to clinicians and four of these improved based on owner scores. Complete clinical remission with no other treatment but the supplementation was seen in two dogs receiving commercial EPA/DHA capsules and one dog given flax oil capsules. In two of these dogs, supplementation was discontinued and clinical signs recurred. Dogs improved again when supplementation was resumed. In the third dog, supplementation was administered continuously after the study and no recurrence occurred during a 12-month follow-up period.

There was generally a good correlation between owner and clinician scores, between overall owner scores (the sum of

their pruritus, clinical and medication scores) and owner pruritus scores, and overall clinician scores and clinician pruritus scores ($P=0.001$, $r^2=0.754$). Owner and clinician scores differed by more than 20 per cent for judging improvement in seven of the 29 dogs completing the study. Owner scores revealed a better improvement in two dogs; clinician scores revealed a better improvement in five dogs.

There was no correlation between clinician score and omega-3 fatty acid intake ($P=0.19$), omega-6 fatty acid intake ($P=0.84$) or omega-6:3 ratio ($P=0.18$). Comparing the dogs in remission on therapy with the corresponding dogs not improving at all, there were no obvious differences in the dietary intake of omega-3 or omega-6 fatty acids or the omega-6:3 ratio, or in the clinical scores at the start of supplementation.

DISCUSSION

Pruritus scores, overall clinician scores and overall owner scores associated extremely well for all groups before and after fatty acid supplementation. This suggests that the scoring system was valid and that the degree of pruritus is generally a good indicator of the severity of atopic dermatitis in dogs.

Supplementation with essential fatty acids has been reported as a successful alternative to glucocorticoid therapy in the treatment of pruritic dermatoses in dogs (Bond and Lloyd 1992b, Logas and Kunkle 1994) and cats (Harvey 1991, 1993, Logas and Kunkle 1993). Proposed mech-

Table 2. Clinical scores reported by owners and clinicians before and after treatment with placebo, flax oil or a commercial product (mean $\pm$ standard deviation)

	Placebo	Flax oil	Commercial capsules
Pretreatment clinician scores	29.0 $\pm$ 10.0	25.2 $\pm$ 12.2	31 $\pm$ 14.5
Post-treatment clinician scores	23.5 $\pm$ 7.9 ($P=0.297$)	18.1 $\pm$ 13.0 ($P=0.008$)	15.4 $\pm$ 11.1 ($P=0.01$)
(P value)*			
Pretreatment owner scores	36.8 $\pm$ 11	29.7 $\pm$ 13.2	29.9 $\pm$ 15.6
Post-treatment owner scores	30.2 $\pm$ 14 ($P=0.313$)	20.5 $\pm$ 12.5 ($P=0.004$)	17.3 $\pm$ 11.2 ($P=0.02$)
(P value)*			

*P values obtained by comparing clinical scores of clinicians/owners before and after treatment with a Wilcoxon matched pairs test

anisms of action include modulation of eicosanoid production, inhibition of cellular activation and an increase in the epidermal barrier function. Eicosapentaenoic acid (omega-3) and dihomogammalinoleic acid ([DHGLA], omega-6) both compete with arachidonic acid ([AA], omega-6) as a substrate for cyclo-oxygenase and 5-lipoxygenase, which converts these fatty acids to prostaglandins (PGs) and leukotrienes (LTs), respectively (Wright 1991). Pro-inflammatory PGs such as PGE₂ and PGF_{2α} and LTs such as LTB₄ are derived from AA. Eicosanoids derived from DHGLA and EPA have less inflammatory or anti-inflammatory action (Miller and others 1991, Gallai and others 1995). Increases in anti-inflammatory eicosanoids and concurrent decreases in their pro-inflammatory counterparts presumably decrease cutaneous inflammation. Decreased concentrations of cutaneous LTB₄ and decreased production of LTB₄ by activated neutrophils have been reported in dogs after receiving diets with lower omega-6:3 ratios and diets higher in omega-3 fatty acids, respectively (Vaughn and others 1994, Byrne and others 2000).

A number of clinical studies have been published evaluating fatty acid supplementation for the treatment of canine atopic dermatitis. However, to the authors' knowledge, none have quantified the total fatty acid intake by calculating the sum of dietary intake and supplementation. In this study, intake of omega-3 and omega-6 fatty acids, as well as their ratios, varied enormously before the trial due to variable dietary intake (240 to 942 mg/kg omega-6, 20 to 260 mg/kg omega-3 fatty acids and 0.84:1 to 20:1 omega-6:3 ratio) and during the trial due to the combination of dietary intake and supplementation (Table 1).

However, there was no correlation between omega-3 intake, omega-6 intake or omega-6:3 ratio and pruritus scores, clinician scores or owner scores before and after the trial. This suggests that the effective dose depends on more than the total intake or ratio of essential fatty acids. As of

yet unidentified individual idiosyncratic factors may be relevant for individual responses. Fatty acids can influence the immune system by acting as second messengers, regulators of signal transducing molecules or transcription factors (Hwang 2000). They have been reported to suppress interleukin-2 (IL-2) production and mononuclear cell proliferation (Endres and others 1993). To what degree direct effects of fatty acids on immune function are responsible for the clinical effects of omega-3 supplementation in the atopic dog is unknown.

In this study, the response to flax oil supplementation was less pronounced than supplementation with a commercial product containing EPA and DHA. Flax oil contains predominantly α-linolenic acid which is desaturated and elongated in various steps to EPA, a substrate competing with AA for cyclo-oxygenase and lipoxygenase to be processed to less inflammatory eicosanoids. Final concentrations of EPA attained are therefore potentially widely variable, depending on the capabilities of the individual to process the α-linolenic acid as outlined above. To the authors' knowledge, there are no data quantifying this conversion in the dog to date. In contrast, commercial EPA/DHA capsules contain predominantly EPA, which should be immediately available for competitive metabolism with AA. Based on the results in this study, it is difficult to determine the preferred fatty acid (α-linolenic acid versus EPA and DHA) for supplementation in dogs with atopic dermatitis, due to the small number of dogs in each group.

In this study, approximately half of the 10 dogs in each treatment group improved by more than 50 per cent. Complete remission was achieved in 10 to 20 per cent of dogs. However, although the only significant improvement in scores with treatment was seen in dogs treated with the commercial product containing EPA and DHA, there was no significant difference between treatment groups and the placebo group (in which one dog improved by

more than 50 per cent) at the end of the study. Neither total intake of omega-3 or omega-6 fatty acids nor their ratio was correlated to clinical improvement. Further studies with larger numbers of animals are needed to explore these findings further and to examine the benefit of supplements containing predominantly omega-6 fatty acids for the treatment of canine atopic dermatitis.

Acknowledgements

This study was financially supported by a grant from the Shipley Foundation. The placebo capsules and the commercial fatty acid supplements were kindly donated by DVM Pharmaceuticals, Miami, FL, USA.

References

- BIAGI, P. L., BORDONI, A., MASI, M., RICCI, G., FANELLI, C., PARTIZI, A. & CECCOLINI, E. (1988) A long-term study on the use of evening primrose oil (Efamol) in atopic children. *Drugs under Experimental and Clinical Research* **14**, 285-290
- BOND, R. & LLOYD, D. H. (1992a) A double-blind comparison of olive oil and a combination of evening primrose oil and fish oil in the management of canine atopy. *Veterinary Record* **131**, 558-560
- BOND, R. & LLOYD, D. H. (1992b) Randomized single-blind comparison of an evening primrose oil and fish oil combination and concentrates of these oils in the management of canine atopy. *Veterinary Dermatology* **3**, 215-219
- BYRNE, K. P., CAMPBELL, K. L., DAVIS, C. A., SCHAEFFER, D. J. & TROUT, H. F. (2000) The effects of dietary n-3 vs n-6 fatty acids on ex-vivo LTB₄ generation by canine neutrophils. *Veterinary Dermatology* **11**, 123-131
- CAMPBELL, K. L. (1993) Clinical use of fatty acid supplementations in dogs. *Veterinary Dermatology* **4**, 167-173
- ENDRES, S., MEYDANI, S. N., GHORBANI, R., SCHINDLER, R. & DINARELLO, C. A. (1993) Dietary supplementation with n-3 fatty acids suppresses interleukin-2 production and mononuclear cell proliferation. *Journal of Leukocyte Biology* **54**, 599-603
- FIOCCHI, A., SALA, M., SIGNORONI, P., BANDERALI, G., AGOSTONI, C. & RIVA, E. (1994) The efficacy and safety of gamma-linolenic acid in the treatment of infantile atopic dermatitis. *Journal of International Medical Research* **22**, 24-32
- GALLAI, V., SARCHIELLI, P., TREQUATRINI, A., FRANCESCHINI, M., FLORIDI, A., FIRENZE, C., ALBERTI, A., DIBENEDETTO, D. & STRAGLIOTTO, E. (1995) Cytokine secretion and eicosanoid production in the peripheral blood mononuclear cells of multiple sclerosis patients undergoing dietary supplementation with n-3 polyunsaturated fatty acids. *Journal of Neuroimmunology* **56**, 143-153
- GRIFFIN, C. E. (1993) Canine atopic disease. In: *Current Veterinary Dermatology*. Eds C. E. Griffin, K. W. Kwochka and J. M. Macdonald. Mosby, St. Louis. pp 99-120
- HALLIWELL, R. E. W. & GORMAN, N. (1989) Atopic disease. In: *Veterinary Clinical Immunology*. Eds R. E. W. Halliwell and N. Gorman. W. B. Saunders, Philadelphia. pp 232-252

- HARVEY, R. G. (1991) Management of feline miliary dermatitis by supplementing the diet with essential fatty acids. *Veterinary Record* **128**, 326-329
- HARVEY, R. G. (1993) Effects of varying proportions of evening primrose oil and fish oil on cats with crusting dermatosis ('miliary dermatitis'). *Veterinary Record* **133**, 208-211
- HENZ, B. M., JABLONSKA, S., VAN DE KERKHOFF, P. C., STINGL, G., BLASZCZYK, M., VANDERVALK, P. G., VEENHUIZEN, R., MUGGLI, R. & RAEDERSTORFF, D. (1999) Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *British Journal of Dermatology* **140**, 685-688
- HIGGS, G. A. (1985) The effects of dietary intake of essential fatty acids on prostaglandin and leukotriene synthesis. Proceedings of the Nutrition Society **44**, 181-187
- HORII, T., SATOUCHI, K., KOBAYASHI, Y., SAITO, K., WATANABE, S., YOSHIDA, Y. & OKUYAMA, H. (1991) Effect of dietary alpha-linolenate on platelet-activating factor production in rat peritoneal polymorphonuclear leukocytes. *Journal of Immunology* **147**, 1607-1613
- HWANG, D. (2000) Fatty acids and immune responses – a new perspective in searching for clues to mechanism. *Annual Reviews of Nutrition* **20**, 431-456
- LOGAS, D. & KUNKLE, G. A. (1994) Double-blinded crossover study with marine oil supplementation containing high-dose eicosapentaenoic acid for the treatment of canine pruritic skin disease. *Veterinary Dermatology* **5**, 99-104
- LOGAS, D. B. & KUNKLE, G. A. (1993) Double-blinded study examining the effects of evening primrose oil on feline pruritic dermatitis. *Veterinary Dermatology* **4**, 181-184
- MILLER, C. C., TANG, W., ZIBOH, V. A. & FLETCHER, M. P. (1991) Dietary supplementation with ethyl ester concentrates of fish oil (n-3) and borage oil (n-6) polyunsaturated fatty acids induces epidermal generation of local putative anti-inflammatory metabolites. *Journal of Investigative Dermatology* **96**, 98-103
- MUELLER, R. S. (1993) Diagnosis and management of canine atopic disease. *Australian Veterinary Practitioner* **23**, 20-27
- MUELLER, R. S. & BETTENAY, S. V. (1996) Long-term immunotherapy of 146 dogs with atopic dermatitis – a retrospective study. *Australian Veterinary Practitioner* **26**, 128-132
- OKAMOTO, M., MITSUNOBU, F., ASHIDA, K., MIFUNE, T., HOSAKI, Y., TSUGENO, H., HARADA, S. & TANIZAKI, Y. (2000) Effects of dietary supplementation with n-3 fatty acids compared with n-6 fatty acids on bronchial asthma. *Internal Medicine* **39**, 107-111
- PATERSON, S. (1994) Use of antihistamines to control pruritus in atopic dogs. *Journal of Small Animal Practice* **35**, 415-419
- PATERSON, S. (1995) Additive benefits of EFAs in dogs with atopic dermatitis after partial response to antihistamine therapy. *Journal of Small Animal Practice* **36**, 389-394
- PRICE, M. L. (1984) The role of diet in the management of atopic eczema. *Human Nutrition. Applied Nutrition* **38**, 409-415
- SCARFF, D. H. & LLOYD, D. H. (1992) Double blind, placebo-controlled, crossover study of evening primrose oil in the treatment of canine atopy. *Veterinary Record* **131**, 97-99
- SCHAFER, L. & KRAGALLE, K. (1991) Supplementation with evening primrose oil in atopic dermatitis: effect on fatty acids in neutrophils and epidermis. *Lipids* **26**, 557-560
- SCOTT, D. W., MILLER, W. H. & GRIFFIN, C. E. (2001) Canine atopic disease. In: *Small Animal Dermatology*. W. B. Saunders, Philadelphia. pp 574-601
- SCOTT, D. W., MILLER, W. H., DECKER, G. A. & WELLINGTON, J. R. (1992) Comparison of the clinical efficacy of two commercial fatty acid supplements (EfaVet and DVM Derm Caps), evening primrose oil, and cold water marine fish oil in the management of allergic pruritus in dogs: a double-blinded study. *Cornell Veterinarian* **82**, 319-329
- SCOTT, D. W., MILLER, W. H., REINHART, G. A., MOHAMMED, H. O. & BAGLADI, M. S. (1997) Effect of an omega 3/omega 6 fatty acid-containing commercial lamb and rice diet on pruritus in atopic dogs: results of a single-blinded study. *Canadian Journal of Veterinary Research* **61**, 145-153
- SCOTT, D. W. & PARADIS, M. (1990) A survey of canine and feline skin disorders seen in a university practice: small animal clinic, University of Montreal, St Hyacinthe, Quebec (1987-1988). *Canadian Veterinary Journal* **31**, 830-835
- SCOTT, K. V., WHITE, S. D. & ROSYCHUK, R. A. W. (1993) A retrospective study of hyposensitization in atopic dogs in a flea-scarce environment. In: *Advances in Veterinary Dermatology*. Eds P. J. Ihrke, I. S. Mason and S. D. White. Pergamon Press, New York. pp 79-87
- STENIUS-AARNIALA, B., ARO, A., HAKULINEN, A., AHOLA, I., SEPPALA, E. & VAPAATALO, H. (1989) Evening primrose oil and fish oil are ineffective as supplementary treatment of bronchial asthma. *Annals of Allergy* **62**, 534-537
- TERENCIO, M. C., FERRANDIZ, M. L., POSADAS, I., ROIG, E., DE ROSA, S., DE GIULIO, A., PAYA, M. & ALCARAZ, M. J. (1998) Suppression of leukotriene B4 and tumour necrosis factor alpha release in acute inflammatory responses by novel prenylated hydroquinone derivatives. *Naunyn Schmiedeberg's Archives of Pharmacology* **357**, 565-572
- VAUGHN, D. M., REINHART, G. A., SWAIM, F. S., LAUTEN, S. D., GARNER, C. A., BOUDREAX, M. K., SPANO, J. S., HOFFMAN, C. E. & CONNER, B. (1994) Evaluation of effects of dietary n-6 to n-3 fatty acid ratios on leukotriene B synthesis in dog skin and neutrophils. *Veterinary Dermatology* **5**, 163-173
- WATANABE, S., SAKAI, N., YASUI, Y., KIMURA, Y., KOBAYASHI, T., MIZUTANI, T. & OKUYAMA, H. (1994) A high alpha-linolenate diet suppresses antigen-induced immunoglobulin E response and anaphylactic shock in mice. *Journal of Nutrition* **124**, 1566-1573
- WRIGHT, S. (1991) Essential fatty acids and the skin. *British Journal of Dermatology* **125**, 503-515