Clinical observations of the treatment of canine perianal fistulas with topical tacrolimus in 10 dogs

Byron S. Misseghers, Allen G. Binnington, Karol A. Mathews

Abstract — Tacrolimus ointment, a potent immunosuppressive medication, was evaluated for efficacy in the treatment of perianal fistulas in dogs. Ten dogs with perianal fistulas were treated with topical tacrolimus ointment once to twice daily for 16 weeks. Full healing of the fistulas occurred in 50% and was noticeably improved in 90% of dogs.

Résumé — Observations cliniques du traitement de fistules périanales par le tacrolimus en application topique chez 10 chiens. L'efficacité d'une pommade à base de tacrolimus, un puissant immunosuppresseur, a été évaluée dans le traitement des fistules périanales chez le chien. Dix chiens avec fistules périanales ont été traités au tacrolimus en pommade une ou deux fois par jour pendant 16 semaines. Une guérison complète des fistules a été observée chez 50 % des chiens et une amélioration notable chez 90 %.

(Traduit par docteur André Blouin)

Can Vet J 2000;41:623–627

Canine perianal fistulation (PAF) is a well recognized, but poorly understood, disease affecting the perianal skin and deep perianal tissues. The German shepherd breed is uniquely predisposed to this disease, with sporadic occurrences of perianal fistulas being seen in other large- and medium-sized breeds (1–3). The disease is usually progressive and characterized by formation of single or multiple ulcerative perianal skin lesions. As the disease worsens, the extent of the sinus tracts progresses, with up to 360° perianal skin involvement (1) and sinus tracts as deep as 6–7 cm in severely affected cases.

The treatment of PAF has consisted of both medical and surgical intervention; however, it has remained a frustrating disease to manage. This is primarily because of poor response to historical treatment modalities, a high rate of recurrence, and morbidity associated with surgical debridement. Historically, medical therapy has been unsuccessful in resolving the lesions, being only palliative in some cases. In the absence of full knowledge regarding the pathogenesis of PAF, surgical treatment of the ulcerated and sinus-associated tissues has been the treatment of choice.

The observation of clinical similarities between canine PAF and anal fistula formation associated with Crohn's disease in humans recently prompted investigation into immunosuppressive therapy using cyclosporin for the treatment of canine PAF (2,3). Cyclosporin causes immunosuppression by inhibition of T lymphocyte activation and the resultant immunosuppression occurs without cytotoxicity or myelosuppression (4,5). Resolution of PAF occurs in greater than 85% of dogs treated with cyclosporin (2,3), and although the etiopathogenesis of canine PAF still remains unclear, the efficacy of cyclosporin in the treatment of canine PAF lends support to an immune-based etiopathogenesis.

Cyclosporin-mediated immunosuppression has, in the authors' experience, proven to be the treatment of choice for the treatment of PAF. Unfortunately, widespread clinical use of cyclosporin has been limited by the high cost of the medication.

Tacrolimus is a relatively new immunosuppressive drug that has also been used in the prevention of acute and chronic organ rejection following allograft transplantation of solid organs. Although structurally unrelated, both tacrolimus and cyclosporin act similarly by blocking early events in T lymphocyte activation; however, tacrolimus is 10 to 100 times more potent than cyclosporin, with fewer side effects (6).

The purpose for this clinical trial was to develop an affordable medical protocol for the treatment of canine PAF by using a topical tacrolimus ointment, with efficacy and limited side effects, comparable with oral cyclosporin immunotherapy.

Ten dogs, 9 German shepherds and 1 Labrador retriever, with naturally occurring PAF, representing consecutive cases referred to the Ontario Veterinary College Veterinary Teaching Hospital (OVC-VTH), were included in the study (Table 1). Based on the results of Mathews and Sukhiani (2), who noted that perianal

Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1.

Address correspondence to Dr. B.S. Misseghers. Reprints not available.

Dr. Misseghers' current address is 11021 NE 123rd Ln, Apt. C216, Kirkland, Washington 98034 USA.

Table 1. Demographic and clinical data on 10 dogs with perianal fistulas receiving topical tacrolimus

Case No.	Breed	Age (y)	Sex	Duration of PAF prior to TAC (mo)	Severity of PAF	Treatment schedule	Time to full healing (wk)	Response	Complications	Duration of remission after cessation of therapy
1	German shepherd	6.5	MC	6	moderate	q24h	6	complete	none	TC
2	German shepherd	3	M	18	mild	q24h	12	complete	none	3 mo
3	German shepherd	11	M	5	moderate	q24h	8	complete	pyotraumatic dermatitis	> 8 mo
4	German shepherd	4.5	MC	6	moderate	q24h	12	complete	tooth root abscess	> 7 mo
5	German shepherd	4	F	2	moderate	q12h	NA	partial	none	NA
6	German shepherd	4	M	6	moderate	q12h	NA	partial	none	NA
7	German shepherd	2.5	F	1	moderate	q24h	NA	none	none	NA
8	German shepherd	5	F	1	mild	q12h	NA	partial	none	NA
9	German shepherd	8.5	FS	18	mild	q12h	16	complete	none	4 wk
10	Labrador retriever	8	MC	24	moderate	q12h	12	partial	none	NA

F — female; FS — spayed female; M — male; MC — castrated male; NA — not applicable; TAC — tacrolimus; TC — treatment continued indefinitely

fistulas in untreated dogs were either noticeably worse (7/10) or unchanged (3/10) over a 4-week interval, no nontreatment control group was used in the present study, and all dogs were placed in the treatment group. The owners of all of the dogs provided informed consent prior to treatment. All dogs with clinical evidence of PAF were eligible for inclusion, regardless of the severity or duration of the lesion or previous treatment. The dogs ranged from 2.5 to 11 y of age and consisted of 6 males and 4 females. A complete physical examination, complete blood cell count, and serum biochemical analysis were performed on each patient prior to enrolment into the trial. For each dog, fistulas were graded as mild, moderate, or severe, based on the assessment of surface area involvement, depth of the deepest fistula, and severity of clinical signs.

Following initial assessment, all dogs were given topical immunotherapy, once to twice daily, by using an ointment of 0.1% tacrolimus. The topical medication was formulated as follows: 50 mg of tacrolimus (Prograf; Fujisawa Canada, Markham, Ontario) mixed in 50 g of hydrophilic petrolatum (Aquaphor; Smith & Nephew, Lachine, Quebec) to create a 0.1% tacrolimus ointment. Owners were instructed to gently cleanse the perianal skin with warm water prior to each application. The volume of ointment applied was empirical and was described as a "thin film" of medication over the entire perianal skin.

Follow-up evaluation was obtained by telephone conversation at 2 wk, followed by clinical reevaluation at 4-week intervals until healing, or for at least 16 wk, whichever came first. Response to treatment was assessed as complete, partial, or absent. A complete response was characterized by complete clinical healing of all perianal sinus tracts. A partial response was characterized by greater than 50% reduction in the sinus tract surface area and depth, and the resolution of clinical signs of excessive anal licking, tenesmus, and dyschezia. An absent response was characterized by no change, or worsening, of the perianal fistulas compared with the pretreatment assessment.

Ten dogs were treated with topical tacrolimus for 16 wk. Five dogs showed complete resolution of perianal lesions, 4 dogs showed a partial response (Figures 1 and 2), and 1 dog showed no improvement (Table 1). Four of the 5 dogs showing an incomplete response to topical tacrolimus were sexually intact (3 females, 1 male). Two cases developed complications during treatment with topical tacrolimus (Table 1), both of which resolved with appropriate therapy.

Tacrolimus is a macrolide immunosuppressant that exerts most of its inhibitory effects on T lymphocyte activation by blocking the production of, and responsiveness to, interleukin-2 (IL-2), as well as other cytokines, such as TNF-α, IL-4, and IL-5 (7). It also suppresses the expression of IL-2 and IL-7 receptors and inhibits the generation of cytotoxic T cells and T cell-dependent B cell activation (7). As a result, tacrolimus and other similar medications (cyclosporin) can produce immunosuppression without cytotoxicity or myelosuppression. Both tacrolimus and cyclosporin have been used most extensively in the management of solid organ transplantation in humans.

In addition to the extensive data in the human literature demonstrating the unique immunosuppressive effects of cyclosporin and tacrolimus for the prevention of acute and chronic organ allograft rejection, these agents have also been investigated for the treatment of

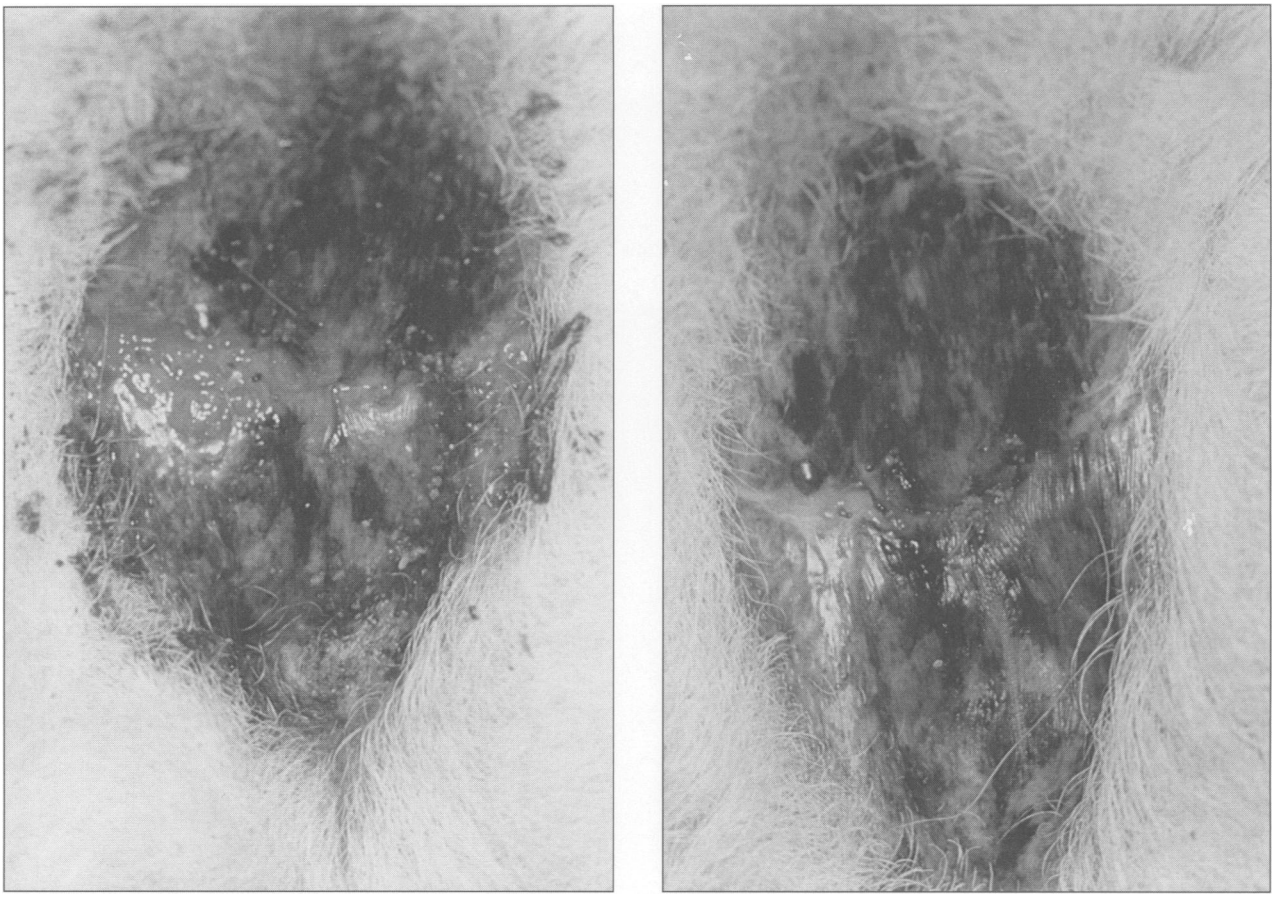

Figure 1. Appearance of case 3 before treatment (left) and after 8 wk of topical tacrolimus treatment (right).

numerous dermatoses in humans, including atopic dermatitis and psoriasis. Cyclosporin is efficacious in the treatment of many inflammatory skin diseases in humans when taken orally, but not as a topical treatment, unless systemic levels of cyclosporin are achieved (8). In comparison, studies have indicated that topical tacrolimus is effective in the treatment of dermatoses without achieving systemic immunosuppressive levels (8,9). It has been shown that tacrolimus permeates human skin better than does cyclosporin (8); several unique factors regarding tacrolimus may explain this difference. First, tacrolimus has a smaller molecular weight (MW 822 Da) compared with cyclosporin (MW 1202 Da), which may allow for easier permeation. Second, although both cyclosporin and tacrolimus are highly lipophilic, cyclosporin is more lipophilic than is tacrolimus and this relatively higher lipophilicity may slow its permeation from the lipid-rich stratum corneum to the hydrated lower epidermis (8). A final significant advantage is tacrolimus' greater biological activity, being 10 to 100 times more potent than cyclosporin in blocking T cell activation (6–8).

When considering the treatment of canine perianal fistulas, topical therapy has several potential advantages for immunosuppression over oral administration. For the most part, the disease is local, so systemic immunosuppression may not be indicated, or even desirable. Experimentally, local immunosuppression can be achieved by using topical tacrolimus without producing detectable levels of tacrolimus in whole blood (9). This is significant, since the majority of side effects related to cyclosporin and tacrolimus are dose dependent, with higher systemic concentrations resulting in higher frequencies of complications. In addition, higher local drug concentrations may possibly be achieved by using a topical route of administration, resulting in faster rates of resolution and, possibly, more complete resolution. Lastly, the overall cost of medication is substantially reduced through the use of less medication at lower concentrations. All of these advantages are noteworthy when considering the treatment of perianal fistulas, which may require long-term, if not indefinite, treatment to control the disease.

In humans, side effects associated with the use of tacrolimus parallel those seen with cyclosporin and most of the serious side effects appear to be dose-dependent (7). Surprisingly, even though tacrolimus is 10 to 100 times more potent than cyclosporin, tacrolimus and cyclosporin have similar frequencies of major side effects in humans, most notably nephrotoxicity (6). Other minor side effects commonly associated with cyclosporin, such as hypertrichosis and gingival hyperplasia (both observed in canine patients on cyclosporin), are less common with tacrolimus (10). No clinical side effects were noted in any of the dogs treated with tacrolimus ointment. This may be a result of the small number of animals treated by this route, but more than likely reflects the dose-dependent nature of tacrolimus toxicity. The 0.1% tacrolimus

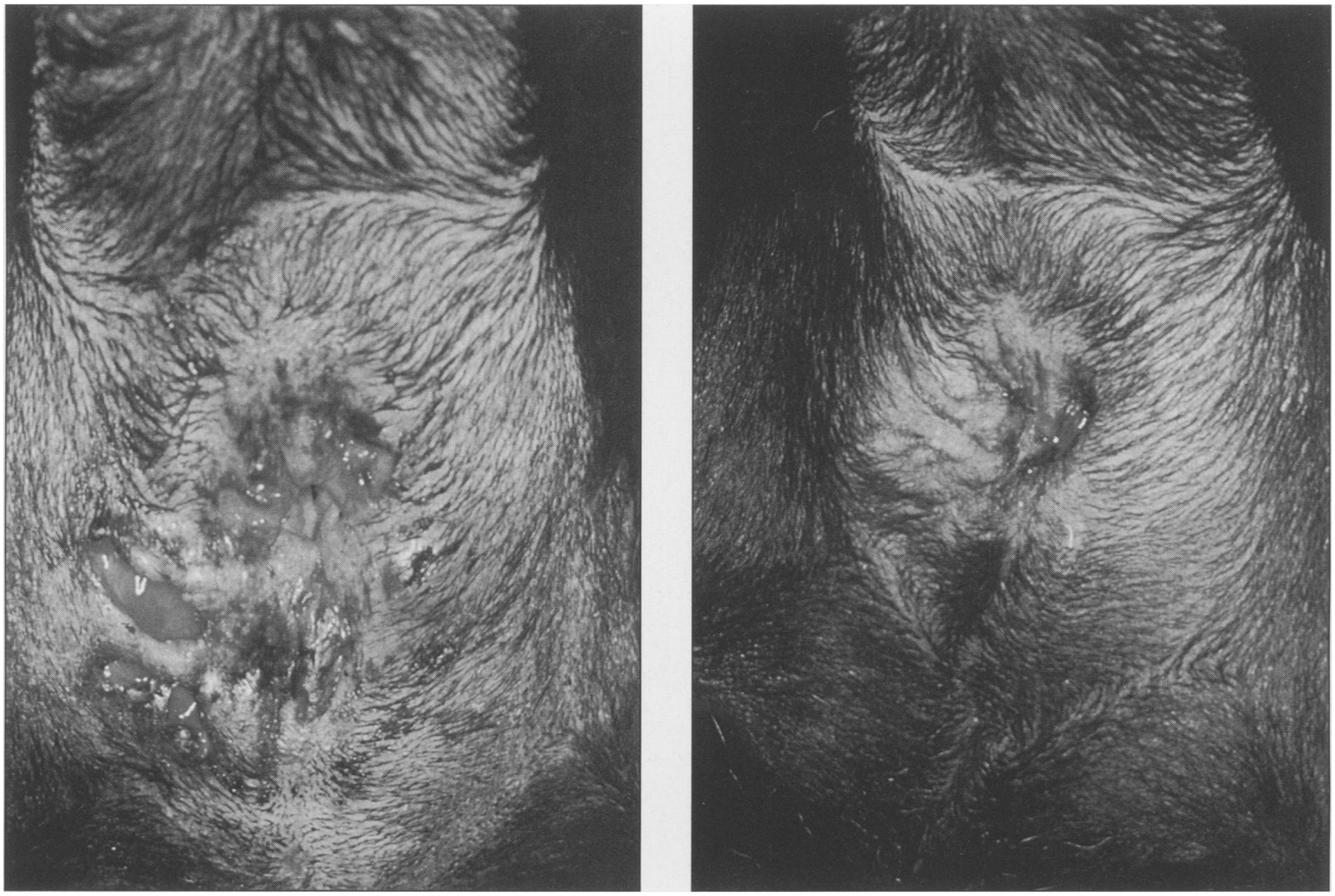

Figure 2. Appearance of case 10 before treatment (left) and after 12 wk of topical tacrolimus treatment (right).

ointment that was used represents a minute fraction of the oral dose of cyclosporin that would have been used to obtain the same clinical results.

A 0.1% ointment was selected for this trial based on preliminary work on the use of tacrolimus ointment for psoriasis and atopic dermatitis in humans. An ointment concentration of 0.3% in humans resulted in noticeable tacrolimus blood levels (10–15 ng/mL) in a number of patients, sufficient to result in systemic immunosuppression (Fujisawa Pharmaceutical, personal communication). Tacrolimus blood levels were not assessed in this trial. Similar work assessing topical immunosuppression of skin grafts in mice showed clinically undetectable blood levels of tacrolimus (less than 0.5 ng/mL) when a 0.3% ointment was used (9).

Full healing of perianal fistulas occurred in 5 of the 10 cases treated in this uncontrolled clinical trial. At the concentration of tacrolimus used for this trial, it is apparent that topical tacrolimus is inferior to oral cyclosporin, which has a success rate of greater than 85% after 16 wk of therapy, but it still compares favorably with other forms of medical treatment (11) and without the morbidity of surgical treatment. An interesting association was noted in that 4 of the 5 incomplete responders to topical tacrolimus were sexually intact. Previous reports indicate that the frequency of perianal fistulation is higher in sexually intact dogs (1,12,13), and the size of the sinus tracts, as well as the severity of inflammation and clinical signs, is increased during estrus in bitches. This may, in part, account for the less than full response in this trial. Neutering is routinely recommended, in conjunction with immunotherapy (local or systemic), based on these observations. An additional point of interest was noted with regards to the frequency of administration of the tacrolimus ointment. Of the 5 complete responders, 4 were treated only once daily and 1 was treated twice daily. Of the 5 incomplete responders, 1 was treated once daily and 4 were treated twice daily. The impression is that more frequent administration of the medication did not result in a better outcome. In fact, the opposite appears true, in that more frequent administration was associated with a poorer (incomplete) response. Although, due to the small sample size, this association is not statistically significant, once daily administration is still recommended initially. The rationale for this result is not known.

Recurrence of disease is a common problem following cessation of immunosuppressive treatment for immune-mediated diseases, such as immune-mediated anemia and thrombocytopenia and immune-mediated polyarthritis, especially if treatment is discontinued prematurely. Although an immune-mediated basis for canine PAF has not been established, the risk of recurrence of PAF following cessation of treatment is also problematic. It is recommended, therefore, that treatment with tacrolimus be continued for at least 4 wk beyond clinical healing.

Fifty grams of 0.1% ointment typically lasted between 4 to 7 mo, depending on frequency of administration. The average cost for the ointment (assuming 4 mo of

medication) was $53.13/mo. In comparison, current costs for oral cyclosporin (at 3 mg/kg, q12h, for a 30 kg dog) are at least $376.20/mo. This represents a savings of 85.9%.

In conclusion, the results of this study indicate that local treatment with topical tacrolimus can be considered as an alternative to systemic cyclosporin immunosuppression for the treatment of mild to moderate canine perianal fistulation, or following cyclosporin-mediated healing to reduce the risk of long-term recurrence. Although topical tacrolimus cannot be considered as effective as systemic cyclosporin, a substantial cost savings associated with topical therapy was noted. Improved success in sinus tract healing may also occur with the use of higher tacrolimus concentrations or different delivery vehicles. CVJ

References

1. Killingsworth CR, Walshaw R, Dunstan RW, Rosser Jr EJ. Bacterial population and histologic changes in dogs with perianal fistula. Am J Vet Res 1988;49:1736–1741.
2. Mathews KA, Sukhiani HR. Randomized controlled trial of cyclosporine for treatment of perianal fistulas in dogs. J Am Vet Med Assoc 1997;211:1249–1253.
3. Mathews KA, Ayres SA, Tano CA, Riley SM, Sukhiani HR, Adams C. Cyclosporin treatment of perianal fistulas in dogs. Can Vet J 1997;38:39–41.
4. Bennett WM, Norman DJ. Action and toxicity of cyclosporine. Annu Rev Med 1986;37:215–224.
5. Zenke G, Baumann G, Wenger R, et al. Molecular mechanisms of immunosuppression by cyclosporins. Ann NY Acad Sci 1993; 685:330–335.
6. Wiederrecht G, Lam E, Hung S, Martin M, Sigal N. The mechanism of action of FK-506 and cyclosporin A. Ann N Y Acad Sci 1993;696:9–19.
7. Spencer CM, Goa KL, Gillis JC. Tacrolimus. An update of its pharmacology and clinical efficacy in the management of organ transplantation. Drugs 1997;54:925–975.
8. Lauerma AI, Surber C, Maibach HI. Absorption of topical tacrolimus (FK506) in vitro through human skin: Comparison with cyclosporin A. Skin Pharmacol 1997;10:230–234.
9. Yuzawa K, Taniguchi H, Seino K, Otsuka M, Fukao K. Topical immunosuppression in skin grafting with FK 506 ointment. Transplant Proc 1996;28:1387–1389.
10. Mihatsch MJ, Kyo M, Morozumi K, Yamaguchi Y, Nickeleit V, Ryffel B. The side effects of cyclosporine-A and tacrolimus. Clin Nephrol 1998;49:356–363.
11. Harkin KR, Walshaw R, Mullaney TP. Association of perianal fistula and colitis in the German Shepherd Dog: Response to high-dose prednisone and dietary therapy. J Am Anim Hosp Assoc 1996;32:515–520.
12. van Ee, Rene T. Perianal fistulas. In: Bojrab MJ, ed. Disease Mechanisms in Small Animal Surgery. 2nd ed. Philadelphia: Lea & Febiger, 1993:285–286.
13. Hedlund, CS. Perianal Fistulae. In: Fossum TW, ed. Small Animal Surgery. St. Louis: Mosby-Year Book, 1997:356–360.

BOOK REVIEW

COMPTE RENDU DE LIVRE

Colmery BH, DeForge DH. ***An Atlas of Veterinary Dental Radiology.*** Iowa State University Press, Ames, 2000, 320 pp, ISBN 0-8138-2997-6. US$114.95.

Believe it or not, this is the second veterinary dental radiology book to appear on the market in the last 2 years. So far, it is the only dental discipline to receive such attention, and it exemplifies the importance of radiology in veterinary dentistry. Oral radiography is one of the most important and common procedures performed while doing veterinary, or human, dentistry. As such, anyone engaged in its practice needs to interpret correctly the radiographs that illustrate the pathology happening below the gum and inside the tooth.

This volume bears the fruits of the cooperation of nearly half the specialists in veterinary dentistry. As befits an atlas, it contains over 500 radiographs, as well as computerized tomography scans, photos, tables, and diagrams. Each radiograph is accompanied by a short, well-structured text, describing the view, identifying the important points, and explaining the diagnostic meaning of the pathology described. All radiographs are printed on glossy paper and are of high quality. Normal anatomy, pedodontics, endodontics, restoratives, orthodontics, oral neoplasia, and trauma are covered for both dogs and cats. Moreover, separate chapters are dedicated to film problems, zoo animals, and rodents and rabbits. An extensive glossary has been added to facilitate the understanding of all that new dental language. The chapter on Normal Anatomy is very important, as it serves as a base for recognizing signs of disease. The chapter on Pedodontics shows the difference between deciduous and succedaneous teeth; it also demonstrates what a busy place the jaws are when both dentitions are in. The chapter on Endodontics covers the variations in endodontic techniques and the many pitfalls one encounters when performing root canal treatments. The chapter on Oral Neoplasia points out the changes neoplastic processes exert on the various tissues of the oral cavity, while that on Trauma shows how slight the signs of oral fractures may be and details ways of repairing some of the breaks one sees in practice. The chapter on Film Problems reviews the many ways there are of rendering a radiograph useless, or even totally confusing. The last 2 chapters give one a glimpse that dentistry is not limited to dogs and cats but is spreading quickly to the majority of the earth fauna, just as dental disease has done.

This volume has little room for improvement, but perhaps the second edition could expand on temporomandibular joint views and positioning techniques, as well as showing a few more postoperative views following trauma and oral neoplastic surgeries.

A tremendous amount of expertise went into the creation of this book, and it will quickly become a mandatory purchase for any serious student of the art of veterinary dentistry. It can be used not only to compare with one's own radiographs, or to study the radiographic image of certain disease processes, but also to show clients what a pathosis or a treatment procedure look like.

Reviewed by ***Loïc Legendre, DVM, FAVD, Dipl. AVDC, Dipl. EVDC,*** *Northwest Veterinary Dental Services Ltd., 4037 Sunset Boulevard, North Vancouver, British Columbia V7R 3Y7.*