

Reduced tear production in three canine endocrinopathies*

OBJECTIVES: Previous reports have suggested that hypothyroid and diabetic patients can be predisposed to keratoconjunctivitis sicca. This study aimed to measure tear production in dogs with diabetes, hypothyroidism and hyperadrenocorticism using the Schirmer tear test and to compare these results with Schirmer tear test values for a group of normal dogs.

METHODS: Schirmer tear tests were performed on 16 dogs with hyperadrenocorticism, 18 with diabetes and 12 with hypothyroidism together with 100 control dogs. Corneal sensitivity was also measured in 12 of the 18 diabetic dogs with a Cochet Bonnet aesthesiometer and compared with age- and breed-matched normal dogs.

RESULTS: Schirmer tear test values in dogs with hypothyroidism, hyperadrenocorticism and diabetes were 12.3 ± 3.2 , 14.0 ± 4.0 and 12.3 ± 5.3 mm/minutes, respectively. Schirmer tear test values were significantly lower than that for the control group (19.6 ± 4.2 mm/minutes) in all dogs with an endocrinopathy. Only in two hypothyroid dogs and three diabetics, this was manifested as profound keratoconjunctivitis sicca with Schirmer tear test value lower than 5 mm/minutes. Diabetic dogs had significantly reduced corneal sensitivity compared with a matched set of control dogs.

CLINICAL SIGNIFICANCE: This study shows a significant reduction in tear production in animals with diabetes mellitus, hypothyroidism and hyperadrenocorticism. Further research is needed to elucidate the mechanisms by which this reduction in tear production occurs. Assessment of tear production should be undertaken in animals diagnosed with these endocrinopathies, as these animals may progress to clinical keratoconjunctivitis sicca.

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INTRODUCTION

Keratoconjunctivitis sicca (KCS) has been reported in individual cases of diabetes mellitus in dogs and human beings as well as in dogs with hypothyroidism and hyperadrenocorticism. In canine diabetes, cataract is the most common ocular lesion (Basher and Roberts 1995) although ocular surface sensory neuropathy has been recently investigated (Good and others

2003). One case of KCS in a diabetic dog has been reported (Barrera and others 1992) although this probably represents merely the tip of an iceberg; a recent publication has reported keratoconjunctival effects of diabetes mellitus including reduced tear production in 15 diabetic dogs (Cullen and others 2005). Recent reports show ocular surface pathology associated with lacrimal insufficiency to be an important ocular complication of both type 1 and type 2 diabetes in human beings (Goebbels 2000, Nepp and others 2000, Dogru and others 2001, Ozdemir and others 2003). In a series of 57 cases of hyperadrenocorticism, 11 dogs had KCS although tear production was not evaluated in all dogs (Lorenz 1982). One report documented the prevalence of hypothyroidism in dogs with KCS, suggesting that up to one-fifth of dogs with hypothyroidism may have KCS (Perruccio 1982). In many human patients with Sjogren's syndrome, the disease affects the lacrimal and salivary glands alone, but in some human patients, lacrimal pathology is part of a wider polyglandular syndrome with extraocular endocrine and exocrine effects (Oxholm 1992). The combination of these reports led us to investigate whether dogs with diabetes mellitus, hyperadrenocorticism and hypothyroidism had reduced tear production.

MATERIALS AND METHODS

Fifty dogs of a wide variety of breeds presented to the Queen's Veterinary School Hospital, University of Cambridge, or to one of five first opinion practices visited in a referral capacity by the primary author (D. L. W.), with a diagnosis of diabetes mellitus, hyperadrenocorticism or hypothyroidism were investigated, together with 100 control dogs again of a variety of breeds from a rehoming charity centre without systemic or ophthalmic disease. All cases fitted the diagnostic criteria for the conditions shown in Table 1. No dogs were under treatment for any ocular disorder at the time of first investigation. A full clinical anamnesis and history was noted for each animal. Animals were examined with direct and indirect ophthalmoscopy

Table 1. Inclusion criteria for the endocrinopathies investigated

Disease	Compatible clinical criteria	Diagnostic clinicopathological criteria	Supportive clinicopathological criteria
Hypothyroidism	Lethargy, weight gain, symmetrical alopecia, seborrhoea	T4 less than 20 nmol/l (reference range, 20 to 60 nmol/l) and basal TSH greater than 0.6 ng/ml (reference range, less than 0.41 ng/ml) in the absence of recent drug administration or intercurrent illness	Non-regenerative anaemia, fasting hypercholesterolaemia
HAC	Polyuria-polydipsia, polyphagia, abdominal enlargement with fat redistribution and muscle loss, hepatomegaly, symmetric alopecia, lethargy	ACTH stimulation test with a post-stimulation cortisol of greater than 600 nmol/l or low-dose (0.01 mg/kg) dexamethasone test with either escape from cortisol suppression (>40 nmol/l) at eight hours in pituitary-dependent HAC or no significant suppression as seen in adrenal-dependent HAC and some cases of PDH	Low urinary specific gravity; a stress leucogram; increased ALP, ALT, cholesterol, bilateral adrenomegaly; or an adrenal mass at ultrasound
Diabetes mellitus	Polyuria-polydipsia, polyphagia, weight loss	Blood glucose more than 10 to 12 mmol/l with significant glycosuria	

T4 Thyroxine, TSH Thyroid stimulating hormone, HAC Hyperadrenocorticism, ACTH Adrenocorticotropic hormone, ALT Alanine aminotransferase, PDH Pituitary dependent hyperadrenocorticism

and slit-lamp biomicroscopy. A standard Schirmer tear test (STT) was performed in each eye of patients with endocrinopathies, but to minimise interference with eyes of the dogs in the normal control group, a STT was only performed in the left eye of these dogs. Using one eye of each animal also had the advantage of simplifying statistical evaluation and avoiding the complication arising from possible association between STT results in the two eyes of each animal. Corneal sensitivity (mg/mm²) was measured using a Cochet Bonnet aesthesiometer (Brennan and Bruce 1991) in 12 diabetic dogs and 12 breed-, age- and gender-matched dogs.

Statistical analysis was undertaken comparing the STT values in the left eyes of endocrinopathy patients with that in the left eyes of the control animals using a one-way analysis of variance. Statistical significance was deemed to have been reached at P=0.05.

RESULTS

Sixteen dogs were presented with hyperadrenocorticism, 18 with diabetes mellitus

and 12 with hypothyroidism; inclusion criteria for each of these diseases are shown in Table 1. Details of the animals are presented in Table 2. Mean±standard deviation of STT values for each group are presented in Table 3 together with the P value showing statistical significance of the difference from the control population. The data are presented as box and whiskers plots in Fig 1. In only a limited number of dogs, a time of first diagnosis was available from historical records, but in animals with diabetes mellitus and hypothyroidism, tear production appeared to reduce with increasing duration of disease (Figs 2 and 3). Where sufficient data were available, a trend towards lower STT values with duration was seen, this being significant for diabetic animals (n=6; Spearman correlation r=0.98; P=0.008). No correlation was evident between tear production and blood glucose levels at time of evaluation in the diabetics or between tear production and level of thyroxine in the hypothyroid cases (data not shown). Lower tear production was noted both in treated and untreated animals with diabetes mellitus, hyperadrenocorticism and hypothy-

roidism, and there was no correlation between success or otherwise of treatment and STT values. Corneal sensitivity was lower in diabetic animals than that in age-, breed- and gender-matched normal controls (P<0.0005), as documented in Table 4.

DISCUSSION

This study presents data showing a significant reduction in tear production in dogs with diabetes mellitus, hyperadrenocorticism and hypothyroidism. The study shows that while only a small number of animals with diabetes mellitus (three dogs) and hypothyroidism (two dogs) had frank KCS, a much larger number show a reduction in tear production compared with the normal dogs. From a clinical perspective, this finding might suggest that tear production should be measured in all animals with diabetes mellitus, hyperadrenocorticism or hypothyroidism to ensure that a subclinical tear film disorder is not missed. Early treatment of a dog with subclinical KCS with topical ciclosporin (Optimmune; Schering Plough) is likely to be more successful than treatment when the animal has frank ocular surface disease and a precipitously low STT reading. As yet, we have not had the opportunity to follow the subclinically affected cases noted here in the long term to monitor progression of disease towards a more overt dry eye phenotype and thus it is

Table 2. Clinical details of animals investigated

Disease	Number of animals	New diagnosis untreated (n)	Treated but unstable (n)	Treated and stable (n)	Average age*	Gender, ME:MN:FE:FN
Diabetes mellitus	18	0	13	5	8.6	4:6:2:6
Hypothyroidism	12	2	3	7	8.1	2:3:3:2
Hyperadrenocorticism	16	5	6	5	10.2	2:1:2:5

ME Male entire, MN Male neutered, FE Female entire, FN Female neutered
*years/months

Disease	Mean STT (mm/minutes)	Standard deviation	P value showing significance of difference from control	Number of animals with STT value less than 10 mm/minutes
Control population	19.6	4.2	—	1
Diabetes mellitus	12.3	5.2	0.001	5
Hypothyroidism	14.3	3.1	0.001	2
Hyperadrenocorticism	13.6	4.1	0.0009	5

STT Schirmer tear test

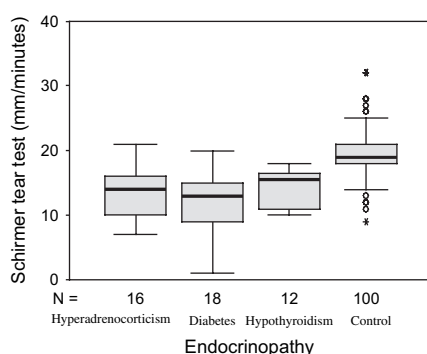


FIG 1. Tear production in normal control dogs and dogs with hyperadrenocorticism, diabetes mellitus and hypothyroidism

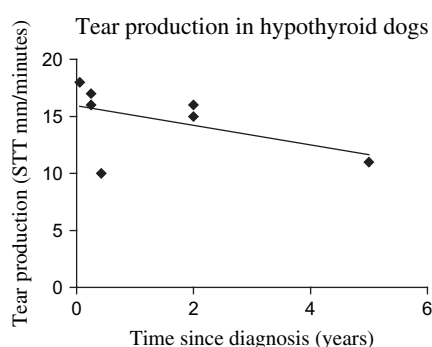


FIG 3. Inverse correlation between STT value and time since diagnosis of hypothyroidism in dogs where adequate accurate case history was available. STT Schirmer tear test

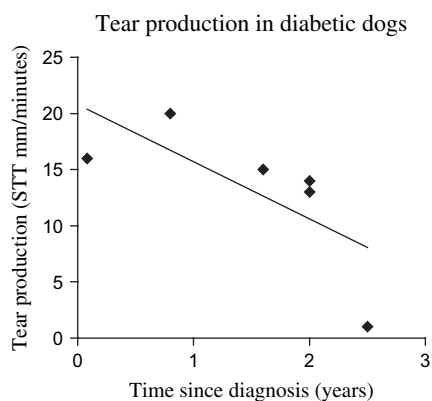


FIG 2. Inverse correlation between STT value and time since diagnosis of diabetes mellitus in dogs where adequate accurate case history was available. STT Schirmer tear test

	Diabetic dogs	Matched control non-diabetic dogs
	0.96	3.2
	0.96	2.4
	1.08	1.84
	0.96	1.84
	1.16	6.64
	1.16	2.4
	0.96	3.2
	1.16	3.2
	0.96	1.84
	1.16	4.6
	1.4	4.6
	1.08	1.16
Mean	1.083333	3.076667
Standard deviation	0.134795	1.553924

These values are significant with a paired t test at P<0.0005

impossible to be sure what proportion of dogs with a reduced tear production but no overt clinical signs will progress to full-blown KCS. Nevertheless, in a limited number of cases the time of first diagnosis of disease was clearly evident from historical records, and for those animals, inverse correlation of STT value and duration of disease was evident. Tear production was not correlated with success of treatment in these animals. Neither did we find a correlation of STT value with severity of

signs or clinical pathology data such as circulating glucose levels in diabetes or thyroxine levels in hypothyroidism.

An important confounding factor in this study could have been that the dogs investigated were of breeds predisposed to KCS. In fact rather the opposite was the case; no West Highland white terriers were involved, and only three cavalier King Charles spaniels and two English

cocker spaniels were involved. All the other dogs in the study were of breeds not considered as being predisposed to KCS (Kaswan and others 1998).

It is unclear what mechanism or mechanisms associate these endocrinopathies with reduced tear production. A reduction in corneal sensation is known to occur as part of diabetic neuropathy in human beings (Rosenberg and others 2000) and the dog (Good and others 2003), and this reduces tear production, in effect giving the effect of a Schirmer II tear test rather than a Schirmer I. In retrospect, all animals should have been subjected to Cochet Bonnet aesthesiometric determination of corneal sensation. The failure to include this test in the ophthalmic examination of all animals renders it difficult to correlate tear production with corneal sensitivity in all cases, although the finding of reduced corneal sensitivity in diabetic dogs here confirms previous research in the area (Cullen and others 2005). Axonal neuropathy is reported in human patients with hypothyroidism (Khedr and others 2000) but reduced corneal sensation has not been documented. We are currently investigating corneal aesthesiometry in dogs with diabetes, hyperadrenocorticism and hypothyroidism to advance the investigations presented here.

A possible mechanism linking diabetes and tear production is related to the importance of insulin in lacrimal gland signalling (Rocha and others 2000). It may be the case that lower circulating insulin levels have a negative effect on neurological stimulation of lacrimal function, but as yet we have no evidence that this is the case.

An autoimmune mechanism links reduced lacrimal function and diabetes in the non-obese diabetic (NOD) mouse (Moore and others 1996, van Blokland and Versnel 2002, Cha and others 2002). A lacrimal autoantibody has been detected in NOD mice but not in a control population and may be the link between the lacrimal exocrinopathy and the pancreatic endocrinopathy (Esch and others 2002). Other abnormalities in lacrimal and pancreatic islet apoptosis (Kong and others 1998, Silva and others 2003) and dendritic cell function (van Blokland and others 2000) link autoimmune destruction

in different organs in both the NOD and MRL/lpr mouse models of lacrimal gland dysfunction. These changes are not merely documented in experimental models; similar findings have been seen in human patients with Sjogren's syndrome (Oxholm 1992). Autoantibodies directed against thyroid antigens have been detected in patients with Sjogren syndrome (Ruggeri and others 2002), and in patients with primary biliary cirrhosis, the finding of antithyroid autoantibodies was highly correlated with lacrimal deficiency (Crowe and others 1980).

Human patients with simple hypothyroidism have not been reported to have lacrimal insufficiency although, as noted above, Perruccio (1982) documented a correlation between canine hypothyroidism and KCS. Dogs with experimentally induced hypothyroidism did not show changes in tear production (Miller and Panciera 1994), but the duration of that study was probably insufficient to show the chronic changes that effect lacrimal parameters. Investigation of ocular abnormalities in hypothyroidism in human beings is complicated by the ocular lesions in Grave's ophthalmopathy. While the exophthalmopathy and ocular surface defects noted in thyroid eye disease are normally seen in hyperthyroid patients, they can be associated with hypothyroidism (Kho and others 2000), and so attempting to correlate reduced tear production with thyroid status in human beings is difficult not to say impossible. Antilacrimal autoantibodies have been detected in patients with Grave's ophthalmopathy (Kiljanski and others 1996), and some researchers consider the condition an ocular and thyroidal manifestation of wider autoimmune disease.

Ironically, reports of polyglandular disease, a set of wider autoimmune endocrinopathies, seen in human beings (Obermayer-Straub and others 2000, Schatz and Winter 2002, Manns and others 2003, Shimomura and others 2003), in experimental animal models (Ikegami 2002) and also reported in the dog (Kooistra and others 1995) rarely include mention of lacrimal insufficiency, although as Tabbara and Vera-Cristo (2000) note, "activated lymphocytes in patients with autoimmune diseases appear to have selective homing into the lacrimal

and salivary glands leading to tissue damage". Whether such a pathogenesis could account for the reduced tear production in cases presented here is unclear. Further research is necessary to unravel the pathogenesis of this link between endocrine pathology and lacrimal function.

What is clear from this study, however, is that lacrimal function should be tested in all animals with diabetes mellitus, hypothyroidism or hyperadrenocorticism to determine whether subclinical or, indeed, clinical KCS is present and whether treatment with topical ciclosporin and/or tear replacement would be advisable.

References

- BARRERA, R., MANE, R. C., RODRIGES, J. F. & JIMENEZ, A. (1992) Keratoconjunctivitis sicca and diabetes mellitus in the dog. *Journal of the American Animal Hospital Association* **20**, 1967-1968
- BASHER, A. W. & ROBERTS, S. M. (1995) Ocular manifestations of diabetes mellitus: diabetic cataracts in dogs. *Veterinary Clinics of North America: Small Animal Practice* **25**, 661-676
- VAN BLOKLAND, S. C., VAN HELDEN-MEEUWSEN, C. G., WIERENGA-WOLF, A. F., DREXHAGE, H. A., HOOLKAAS, H., VAN DE MERWE, J. P. & VERSNEL, M. A. (2000) Two different types of sialoadenitis in the NOD and MRL/lpr mouse models for Sjogren's syndrome: a differential role for dendritic cells in the initiation of sialoadenitis? *Laboratory Investigation* **80**, 575-585
- VAN BLOKLAND, S. C. & VERSNEL, M. A. (2002) Pathogenesis of Sjogren's syndrome: characteristics of different mouse models for autoimmune exocrinopathy. *Clinical Immunology* **103**, 111-124
- BRENNAN, N. A. & BRUCE, A. S. (1991) Aesthesiometry as an indicator of corneal health. *Optometry and Visual Science* **68**, 699-702
- CHA, S., PECK, A. B. & HUMPHREYS-BEHER, M. G. (2002) Progress in understanding autoimmune exocrinopathy using the non-obese diabetic mouse: an update. *Critical Reviews in Oral Biology and Medicine* **13**, 5-16
- CROWE, J. P., CHRISTENSEN, E., BUTLER, J., WHEELER, P., DONIACH, D., KEENAN, J. & WILLIAMS, R. (1980) Primary biliary cirrhosis: the prevalence of hypothyroidism and its relationship to thyroid autoantibodies and sicca syndrome. *Gastroenterology* **78**, 1437-1441
- CULLEN, C. L., IHLE, S. L., WEBB, A. A. & MCCARVILLE, C. (2005) Keratoconjunctival effects of diabetes mellitus in the dog. *Veterinary Ophthalmology* **8**, 215-224
- DOGRU, M., KATAKAMI, C. & INOUE, M. (2001) Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. *Ophthalmology* **108**, 586-592
- ESCH, T. R., POVEROMO, J. D., AIKINS, M. C. & LEVANOS, V. A. (2002) A novel lacrimal gland autoantigen in the NOD mouse model of Sjogren's syndrome. *Scandinavian Journal of Immunology* **55**, 304-310
- GOEBBELS, M. (2000) Tear secretion and tear film function in insulin dependent diabetics. *British Journal of Ophthalmology* **84**, 19-21
- GOOD, K. L., MAGGS, D. J., HOLLINGSWORTH, S. R., SCAGLIOTTI, R. H. & NELSON, R. W. (2003) Corneal sensitivity in dogs with diabetes mellitus. *American Journal of Veterinary Research* **64**, 7-11
- IKEGAMI, H. (2002) Animal models of autoimmune polyglandular syndrome. *Endocrinology and Metabolic Clinics of North America* **31**, 431-439
- KASWAN, R., PAPPAS, C. Jr, WALL, K. & HIRSH, S. G. (1998) Survey of canine tear deficiency in veterinary practice. *Advances in Experimental Medicine and Biology* **438**, 931-939
- KHEDR, E. M., EL TOONY, L. F., TARKHAN, M. N. & ABDELLA, G. (2000) Peripheral and central nervous system alterations in hypothyroidism: electrophysiological findings. *Neuropsychobiology* **41**, 88-94
- KHOO, D. H., ENG, P. H., HO, S. C., TAI, E. S., MORGENHALER, N. G., SEAH, L. L., FONG, K. S., CHEE, S. P., CHOO, C. T. & AW, S. E. (2000) Graves' ophthalmopathy in the absence of elevated free thyroxine and triiodothyronine levels: prevalence, natural history, and thyrotropin receptor antibody levels. *Thyroid* **10**, 1093-1100
- KILJANSKI, J., NEBES, V. & WALL, J. R. (1996) Significance of tissue specific and tissue non specific autoimmune reactions of Graves' disease. *Clinical and Experimental Rheumatology* **15** (Suppl), S69-S76
- KONG, L., ROBINSON, C. P., PECK, A. B., VELA-ROCH, N., SAKATA, K. M., DANG, H., TALAL, N. & HUMPHREYS-BEHER, M. G. (1998) Inappropriate apoptosis of salivary and lacrimal gland epithelium of immunodeficient NOD-scid mice. *Clinical and Experimental Rheumatology* **16**, 675-681
- KOOISTRA, H. S., RIJNBEEK, A. & VAN DEN INGH, T. S. (1995) Polyglandular deficiency syndrome in a boxer dog: thyroid hormone and glucocorticoid deficiency. *Veterinary Quarterly* **17**, 59-63
- LORENZ, M. (1982) Diagnosis and medical management of canine Cushing's syndrome: a study of 57 consecutive cases. *Journal of the American Animal Hospital Association* **18**, 707-716
- MANN, M. P., STRASSBURG, C. P. & LANKISCH, T. (2003) Autoimmune polyglandular syndrome type 1. *Experimental and Clinical Endocrinology and Diabetes* **111**, 298
- MILLER, P. E. & PANCIERA, D. L. (1994) Effects of experimentally induced hypothyroidism on the eye and ocular adnexa of dogs. *American Journal of Veterinary Research* **55**, 692-697
- MOORE, P. A., BOUNOUS, D. I., KASWAN, R. L. & HUMPHREYS-BEHER, M. G. (1996) Histologic examination of the NOD-mouse lacrimal glands, a potential model for idiopathic autoimmune dacryoadenitis in Sjogren's syndrome. *Laboratory Animal Science* **46**, 125-128
- NEPP, J., ABELA, C., POLZER, I., DERBOLAV, A., & WEDRICH, A. (2000) Is there a correlation between the severity of diabetic retinopathy and keratoconjunctivitis sicca? *Cornea* **19**, 487-491
- OBERMAYER-STRAUB, P., STRASSBURG, C. P. & MANN, M. P. (2000) Autoimmune polyglandular syndrome type 1. *Clinical Reviews of Allergy and Immunology* **18**, 167-183
- OXHOLM, P. (1992) Primary Sjogren's syndrome - clinical and laboratory markers of disease activity. *Seminars in Arthritis and Rheumatism* **22**, 114-126
- OZDEMIR, M., BUYUKBESE, M. A., CETINKAYA, A. & OZDEMIR, G. (2003) Risk factors for ocular surface disorders in patients with diabetes mellitus. *Diabetes Research and Clinical Practice* **59**, 195-199
- PERRUCCIO, C. (1982) Incidence of hypothyroidism in dogs affected by keratoconjunctivitis sicca. Proceedings of the American College of Veterinary Ophthalmologists. Las Vegas, NV, USA. pp 47-48
- ROCHA, E. M., DE M LIMA, M. H., CARVALHO, C. R., SAAD, M. J. & VELLOSO, L. A. (2000) Characterization of the insulin-signalling pathway in lacrimal and salivary glands of rats. *Current Eye Research* **21**, 833-842
- ROSENBERG, M. E., TERVO, T. M., IMMONEN, I. J., MULLER, L. J., GRONHAGEN-RISKA, C. & VESALUOMA, M. H. (2000) Corneal structure and sensitivity in type 1 diabetes mellitus. *Investigative Ophthalmology and Visual Science* **41**, 2915-2921
- RUGGERI, R. M., GALLETTI, M., MANDOLFINO, M. G., ARAGONA, P., BARTOLONE, S., GIORGIANNI, G., ALESCI, D., TRIMARCHI, F. & BENVENGA, S. (2002) Thyroid

- hormone autoantibodies in primary Sjogren syndrome and rheumatoid arthritis are more prevalent than in autoimmune thyroid disease, becoming progressively more frequent in these diseases. *Journal of Endocrinological Investigation* **25**, 447-454
- SCHATZ, D. A. & WINTER, W. E. (2002) Autoimmune polyglandular syndrome. II: Clinical syndrome and treatment. *Endocrinology and Metabolic Clinics of North America* **31**, 339-352
- SHIMOMURA, H., NAKASE, Y., FURUTA, H., NISHI, M., NAKAO, T., HANABUSA, T., SASAKI, H., OKAMOTO, K., FURUKAWA, F. & NANJO, K. (2003) A rare case of autoimmune polyglandular syndrome type 3. *Diabetes Research and Clinical Practice* **61**, 103-108
- SILVA, D. G., SOCHA, L., CHARLTON, B., COWDEN, W. & PETROVSKY, N. (2003) Autoimmune diabetes in the NOD mouse: an essential role of Fas-FasL signalling in beta cell apoptosis. *Annals of the New York Academy of Science* **1005**, 161-165
- TABBARA, K. F. & VERA-CRISTO, C. (2000) Sjogren syndrome. *Current Opinion in Ophthalmology* **11**, 449-454