Electroretinogram findings and retinal appearance in a confirmed case of ivermectin toxicity in a Lakeland Terrier.

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Purpose:
To describe the electroretinogram findings and retinal appearance in a confirmed case of ivermectin toxicity and discuss their relevance in the diagnosis of this condition.

Case Details:
A 2 year old Female neutered Lakeland Terrier presented with a sudden onset blindness and ataxia of twelve hours duration.

Clinical examination showed ataxia that was more apparent in the hindlimbs, with occasional knuckling whilst walking. Intermittent proprioceptive deficits were also noted. There were no other peripheral neurological deficits. Ophthalmic examination showed absence of menace responses, dazzle reflexes and pupillary light reflexes in both eyes. In both eyes there was persistence of the pupillary membrane arsing from the iris collarette but not attached anywhere else. The pupils were widely dilated and examination of the fundus showed multiple linear and circular areas consistent in appearance with retinal oedema and folds. The optic nerve heads appeared to be grossly normal.

Differential diagnoses for these clinical signs included: inflammatory/infectious disease (toxoplasmosis, crytococcosis, distemper, borreliosis, meningitis and granulomatous meningoencephalitis), lysosomal storage diseases, SARDS and drug induced retinal degeneration/dysfunction

The dog was admitted for supportive fluid therapy, cerebrospinal fluid (CSF) tap, electroretinography and presumptive treatment for toxoplasmosis with clindamycin (22.5mg/kg twice daily).

Blood samples were submitted for *Toxoplasma*, *Neospora*, *Borrelia* and canine distemper virus antibody serology, haematology and biochemistry. Urine was submitted for biochemistry. CSF samples were submitted for bacterial and fungal culture, cytology and protein analysis. There were no significant findings with the blood, urine or CSF samples.

Electroretinogram findings showed reduced amplitude and increased latency.

Further questioning of the owners revealed that the patient could have had access to an ivermectin based equine wormer 7 hours prior to onset of the clinical signs. Based on this CSF and serum samples were submitted for ivermectin assays. Treatment was continued as before.

The patient made a good recovery and 2 days after onset of the clinical signs she was visual in both eyes and had mild hindlimb ataxia. She was discharged without further treatment at this point.

Electroretinography was performed one week later and revealed a comparable latency and amplitude to that seen in a normal eye.

One month later the results of the ivermectin assay were returned. They revealed a positive serum ivermectin level of 1600 µg/kg. CSF levels of ivermectin were <5 µg/kg.

Re-examination 3 months after the onset of clinical signs showed no evidence of vision dysfunction or ataxia. Ophthalmic findings were the very similar in both eyes. There were normal menace responses, dazzle reflexes and pupillary light reflexes. The fundus lesions had altered in appearance leaving areas of tapetal hyper-reflectivity at the site of previous oedema and some retinal folds.

Conclusion:
This is the first documented report of electroretinogram findings in a confirmed case of ivermectin toxicity as far as the authors are aware. Ivermectin toxicity is difficult to diagnose in the absence of an ivermectin assay and the time taken to perform as assay rules it out as a practical diagnostic method.

Further studies of electroretinogram findings in confirmed cases are required before this can be used as a pathognomic diagnostic test but based on this report it would appear to be a useful method in identifying possible cases of ivermectin toxicity.

The retinal appearance in this case has been described in unconfirmed cases of ivermectin toxicity. As yet no suitable explanation for the pathology of these lesions exists.

Plates:

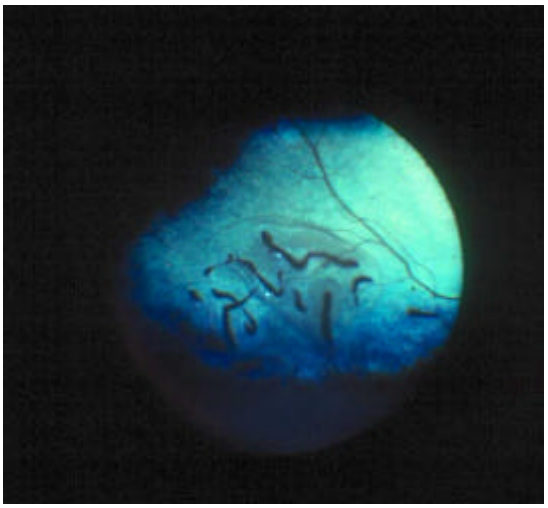

Figure 1: Fundus at presentation

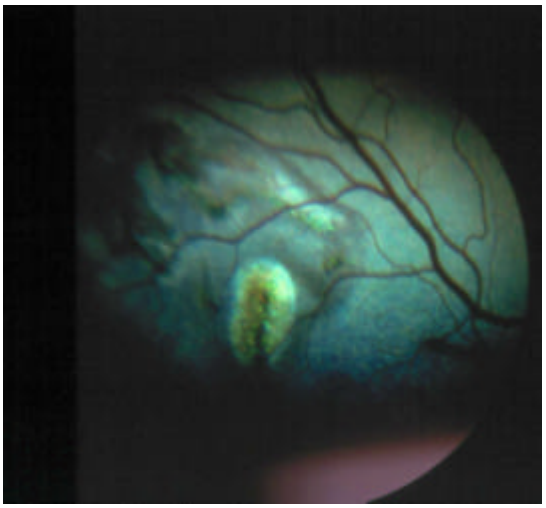

Figure 5: Fundus 3 weeks after presentation.

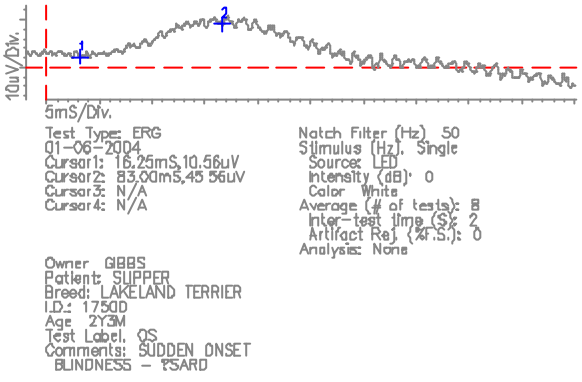

Figure 2: ERG Left eye at presentation

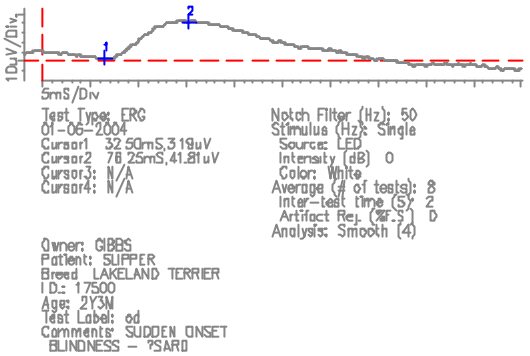

Figure 3: ERG Right eye at presentation

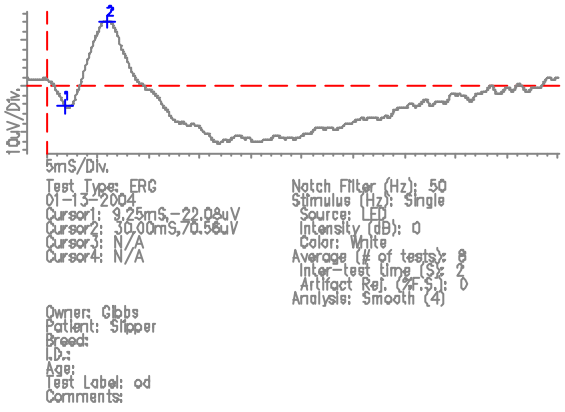

Figure 4: ERG Left eye 3 weeks after presentation

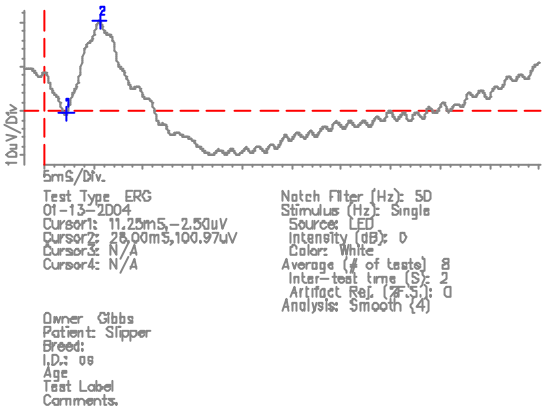

Figure 5: ERG Right 3 weeks after presentation

Case Report:
Presumed immune-mediated pustular keratitis in a Welsh Springer Spaniel

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A four-year-old male neutered Welsh Springer Spaniel was presented to the Animal Health Trust with a chequered history. He had been re-homed six months before having been previously owned by a gamekeeper who was less than attentive. Whilst in the gamekeeper's possession the dog had been presented to the referring veterinary surgeon with bilateral keratoconjunctivitis and perilimbal oedema. Maxitrol ™ (dexamethasone, neomycin, polymixin B, hypromellose; Alcon) and Synulox ™ (amoxycillin-clavulanic acid, Pfizer) were prescribed and the condition had resolved. The condition recurred with neovascularisation and severe oedema in the left eye only. A referral was declined and euthanasia requested five days later when the eye was buphthalmic and uveitic. The eye was enucleated and the patient re-homed. Unfortunately, no histopathology was undertaken on the enucleated globe. Six months after re-homing the remaining eye presented with perilimbal oedema and white corneal deposits and referral was sought.
On presentation there was conjunctival hyperaemia and perilimbal subepithelial pinpoint cream opacities with fine superficial neovascularisation through 360 degrees. On the posterior surface of the third eyelid there was follicular hyperplasia. There were no signs of intraocular inflammation and the remainder of the ocular examination was unremarkable. A conjunctival bacteriology swab revealed a scanty growth of *Pasteurella haemolytica*. Corneal scrapes were unhelpful revealing neutrophils and a few plasma cells and macrophages consistent with a keratoconjunctivitis. Haematology and biochemistry were within normal limits.

A surgical corneal biopsy was taken and revealed an unusual pustular keratitis with focal interface inflammation and separation of the corneal epithelium from the underlying stroma. Plasma cells and degenerate neutrophils with little accompanying stromal necrosis were present focally just below the basal epithelium. No micro-organisms were identified with H&E, Giemsa, PAS and Phloxine Tartrazine stains. An immune-mediated process was suspected.

A mild generalised lymphadenopathy was noted and fine needle aspirate biopsies revealed reactive lymphoidal hyperplasia with no evidence of neoplasia.
Initial treatment with chloramphenicol topically (q2hrs) and carprofen (Rimadyl ™, Pfizer, 4mg/kg) and amoxycillin-clavulanic acid (Synulox ™, Pfizer,12.5mg/kg) orally, whilst awaiting biopsy results, had no effect and the condition continued to worsen. After histology and bacteriology culture results were received the treatment was changed to topical prednisolone acetate (Pred Forte ™, Allergan, six times daily) and ofloxacin (Exocin ™, Allergan, q2hrs) with systemic marbofloxacin (Marbocyl TM, Vetoquinol, 2mg/kg). A dramatic improvement was noted and he was discharged on this medication four days later. Topical prednisolone was tapered off gradually over a six-week period. The patient has been off treatment for six weeks with no recrudescence.

Discussion

Inflammatory material appeared to be focused at the level of the epithelial basement membrane of the cornea. There is some speculation that this may be focusing at the level of the hemidesmosome in a similar manner to that seen in pemphigoid skin disease (e.g. pemphigus vulgaris). No inciting cause could be elucidated in this case and the patient had no skin lesions. From the history it appears that this dog is suffering from a waxing and waning condition that is steroid responsive. However if left untreated during a flare-up the disease is rapidly progressive and globe threatening.
Other immune-mediated corneal diseases include endothelialiitis secondary to canine adenovirus infection ('blue eye') and chronic superficial keratitis (pannus). 'Blue eye' associated with canine adenovirus infection is in part due to direct endothelial cell damage by the virus, but more importantly endothelial destruction occurs secondary to immune complex deposition and activation of complement. The endothelial cell damage results in intense corneal oedema. The pathogenesis of pannus is not fully understood but is characterised by infiltration of the perilimbal anterior corneal stroma by lymphocytes, plasma cells and superficial corneal vascularisation.

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Multiple limbal haemangiosarcomas in a Border collie dog: management by lamellar keratectomy/sclerectomy and ^{90}Sr-ß plesiotherapy

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ABSTRACT
An 8 year - old neutered male Border collie dog was presented with a six-week history of left ocular discomfort and a raised red limbal mass. The right eye had been enucleated approximately 12 months previous, following a suspected trauma when the eye became red and painful. The tumour was excised using superficial keratectomy / sclerectomy and the surgery site treated with strontium-90 beta (^{90}Sr-ß) radiation. Histopathological examination of the excisional biopsy specimen revealed interlacing bundles and streams of neoplastic cells within the stroma of the limbus that where forming vascular channels consistent with a diagnosis of haemangiosarcoma (HSA). Two further treatments with ^{90}Sr-ß were applied to the surgical site at weekly intervals. At twenty-six weeks post surgery a second raised red limbal mass became apparent at the medial limbus of the left eye. Surgical excision and adjunctive ^{90}Sr-ß plesiotherapy were performed as described for the initial tumour. Routine histopathological analysis confirmed HSA at this site. At seventy-four weeks following the initial presentation no recurrence of ocular HSA was evident.

INTRODUCTION
Haemangiosarcomas are malignant tumours of vascular origin, which may occur anywhere in the body. Conjunctival tumours of vascular origin reported in dogs include haemangioma, haemangiosarcoma (HSA) (Hargis and others 1978, Mughannam and others 1977, Murphy and others 1989, Peiffer and others 1978)) and angiokeratoma (Buyukmihci and Stannard 1981). Therapy for localised tumours of the conjunctiva or limbus normally involves excisional biopsy and depending on the histological diagnosis some form of adjunctive treatment. In veterinary medicine no studies have documented superior efficacy of one adjunctive treatment over another for conjunctival vascular tumours (Mughannam and others 1977). The prognosis for canine conjunctival HSA is guarded due to the high frequency of local recurrence and the high potential for metastasis (Ward and others 1994).

This case report describes the management of multiple limbal haemangiosarcomas in a Border collie dog by lamellar keratectomy/sclerectomy and ^{90}Sr-ß plesiotherapy

DISCUSSION
Malignant conjunctival tumours of vascular origin are rare in dogs with only two reports concerning conjunctival HSA's being reported in the veterinary literature (Hargis and others 1988, Mughannam and others 1977). Differentiation of haemangiosarcoma from other tumours of vascular origin including haemangioma, lymphangioma and lymphangiosarcoma relies on histopathological examination of tissue specimens. Haemangiomas and lymphangiomas are usually histologically distinct from their malignant counterparts, being composed of attenuated spindle-shaped cells that are organised into around channels or cavernous spaces. The presence of erythrocytes within these channels or spaces helps to differentiate haemangioma from lymphangioma. Depending on their degree of differentiation, haemangiosarcomas and lymphangiosarcomas can be difficult to distinguish by light microscopy alone. Indeed, some are so poorly differentiated that immunohistochemistry is required to identify the neoplastic cell of origin.

The cause of canine conjunctival HSA is not known. Hargis and others (1978) suggested an association between canine conjunctival HSA and increased solar radiation. A causal link between canine cutaneous HSA and solar radiation has also been proposed (Hargis and others 1992). In people an association exists between angiosarcoma and previous radiation therapy or chronic vascular stasis (Prieto and Shea 1999). Although head and neck angiosarcoma occurs most frequently in white patients, minimal evidence exists to suggest a causal link with actinic damage and trauma (Abrahamson and others 2001).

This animal developed two seemingly unrelated HSA's within the ocular surface, developing as discrete lesions at diametrically opposite limbal positions. The presence of circumferential vascular

networks within the perilimbal sclera including the intrascleral venous plexus and the arterial circle formed by branches of the anterior ciliary arteries could have allowed a "skip" metastasis (Van Burskirk 1979, Sharpnack and others 1984). Alternatively the multiple HSA's may have occurred independently within the conjunctiva OS. Conjunctival haemangioma occurring bilaterally and synchronously has been described in the literature (Murphy 1989). There are two main theories as to why multiple HSA could arise in the same tissue. 'Field carcinogenesis', initially expounded by Slaughter and others (1953), suggests that exposure of one type of tissue to carcinogens may lead to the independent development of synchronous non-related tumours at different sites within that tissue. The concept of 'field carcinogenesis' has yet to be explored in relation to haemangiosarcoma. Multiple tumours are also described in humans having a germline mutation in genes important for the regulation of cell cycle and are often found bilaterally.

Therapy for tumours of the ocular surface in dogs normally involves an initial excisional biopsy which depending on the histological diagnosis may be curative. For malignant tumors and those extending beyond the biopsy field adjunctive treatment may be required. Adjuvant treatment of canine cutaneous HSA with combined chemotherapy or radiotherapy is recommended due to the high frequency of local recurrence and the high potential for metastasis (Ward and others 1994). Treatment reported for canine conjunctival HSA have included surgical excision and enucleation (Hargis and others 1988) and excision either alone or in conjunction with cryoablation, Nd: YAG photocoagulation or ^{90}Sr-ß plesiotherapy (Mughannam and others 1997). Due to the limited number of cases reported in these studies no information regarding the relative efficacy of the various treatments can be made.

Strontium – 90ß plesiotherapy therapy is suitable only for superficial ophthalmic lesions due to the limited tissue penetration of beta particles. Approximately 85 – 90 % of the emitted radiation dose is absorbed in the first 3 mm of tissue (Friedell and others 1950). Surgical debulking of tumours with a depth greater than 2 mm is therefore required to ensure adequate tumour irradiation. The dose of radiation required for tumour control is determined by a number of factors, including the radiosensitivity and size of the tumour and the tolerance of the surrounding tissues (Theon 1998). The radiation dosages, and optimal radiation delivery protocols for conjunctival tumours in domestic species have not been established.

The use of ^{90}Sr-ß plesiotherapy in veterinary medicine has been reported in the treatment of equine corneal and conjunctival SCC (Owen and Barnett 1983, King and others 1991, Rebhun 1998), and equine perilimbal angiosarcoma (Hacker and others 1986). For equine conjunctival and corneoscleral tumours a prescribed (minimal) tumour dose of 75 – 100 Gy per site (surface dose 200-250 Gy) is recommended, with the total surface dose not exceeding 500 Gy which may permanently damage the corneal endothelium (Theon 1998 & Rebhun 1998). Of the six cases of canine conjunctival HSA described by Mughannam and others (1997), one patient was treated with surgical excision and adjunctive ^{90}Sr-ß plesiotherapy on three occasions before the globe was finally enucleated. Potential reasons for radiation therapy failing to control a tumour include low inherent tumour radiosensitivity, excessive tumour volume and insufficient radiation dose. The dose of radiation delivered in this case was not specified. In the present case a total surface radiation dose of 123 Gy was delivered in three fractions over a 2-week period to both tumour sites. No recurrence of HSA at either tumour site had occurred at seventy-four weeks following initial presentation.

The success of radiotherapy must not only consider disease control but also the incidence of unacceptable normal tissue toxicity, in particular with regard to severe late radiation-induced side effects. Late radiation induced side effects occur in highly differentiated tissues, which may show signs of toxicity up to many years following exposure (Steel 2002, LaRue and Gillette 2001). The incidence and nature of late radiation induced complications following ^{90}Sr-ß plesiotherapy in dogs has not been reported. Late radiation induced complications reported in people include conjunctival telangiectasis, thinned avascular conjunctiva, corneal scarring, neovascularisation and ulceration, scleral ulceration, perforation and pseudomonal endophthalmitis, symblepharon and cataract (Tarr and Constable 1980). Radiation doses of 5-10 Gy may result in cataract formation (Griffiths and Short 1994). This is particularly significant when treating perilimbal tumours due to the close proximity to the radiosensitive equatorial region of the lens. In the present case persistent asymptomatic cystic changes at the treatment site covered by thinned avascular conjunctiva were apparent at sixty-two weeks. Long term monitoring will be necessary to establish if more severe signs of radiation toxicity develop at this site.

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Chronic Ocular Lesions in Tawny Owls (*Strix aluco*) After Vehicular Trauma

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Introduction A large number of raptors are presented to rehabilitation centres following vehicular trauma and in a substantial proportion of these ocular trauma is an important part of the post-trauma sequelae. The immediate findings in the majority of these eyes involve signs of adnexal injury, blunt corneal trauma and intraocular haemorrhage. Here the long-term sequelae of such high-speed vehicular impacts are investigated in fifty tawny owls with such ocular injuries.

Materials and methods Fifty tawny owls (*Strix aluco*) in long-term captivity in two rehabilitation centres after being retrieved as road-side casualties, were examined by direct and indirect ophthalmoscopy and slit lamp biomicroscopy. Tawny owls were chosen as a study group because of the sizeable population of this species submitted to rehabilitation centres after vehicular trauma, the ease of examination of this species without causing undue stress and because their pupils are more dilated in low ambient light than those of, for example barn owls, thus facilitating fundoscopy. Ophthalmoscopic details were noted and recorded photographically with a Kowa RC2 fundus camera. A medified Schirmer tear test after Korbel was performed and applanation tonometry with a Tonopen XL tonometer was used to determine intraocular pressure. Given the similarity between some retinal lesions observed in these owls and the posterior segment pathology in human toxoplasmosis (Roberts and McLeod 1999, Williams and others 2001), Toxoplasma serology was carried out on all birds examined to determine whether there was an association between retinal lesions and toxoplasma seropositivity. Association between retinal lesions and seropositivity was assessed by use of a 2x2 contingency table and the chi-squared test with statistical significance deemed to have been reached at $p=0.05$.

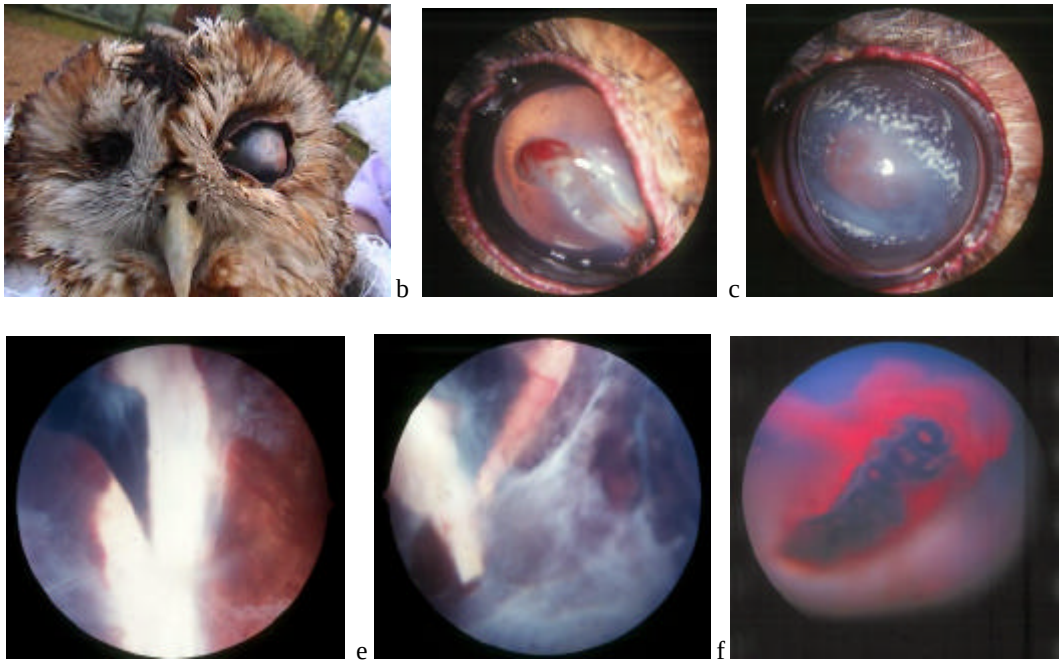
Results: Ophthalmic findings are detailed in table 1 and illustrated in figures a-f. The ocular lesions could be categorised into a relatively small number of pathological changes, namely adnexal and corneal fibrosis and scarring (figs a, b and c), persistent corneal erosion (figs a, b), iridal- and cyclo-dialysis, cataract, retinal detachment with pre-retinal fibrosis (figs d and e), retinal and choroidal rupture with fibrosis (fig d), and finally phthysis bulbi or clinical anophthalmos (fig a). In one case, a bird in captivity for 11 months, fresh peripectenal posterior segment haemorrhage was observed on two occasions (fig f). Mean and standard deviation of intraocular pressure are shown in table 2 for eyes with differing ocular pathology. Eyes with intraocular inflammatory lesions showed a significantly lower intraocular pressure than normal eyes and those with iridodialysis or cyclodialysis showed a higher intraocular pressure. Mean and standard deviation of Schirmer tear tests are shown in table 3 for eyes with differing ocular pathology. While no group showed a statistically significant difference in measure of tear production from normal eyes, birds with corneal ulcerative pathology and to a lesser extent with adnexal pathology, showed a trend toward higher tear levels. Numbers of Toxoplasma seropositive and seronegative owls with and without scarring retinal lesions are given in the 2x2 contingency table in table 4. There was no association between retinal lesions and Toxoplasma seropositivity ($p=0.73$).

Discussion: This case series documents the long-term injuries seen in Tawny owls after presumed vehicular trauma. As such it is a biased population, only being birds sustaining injuries insufficient to lead to death, yet severe enough to prevent early release. It does not thus claim to be a full investigation of post traumatic ocular disease in the raptor but nevertheless seeks to document the chronic ocular injuries seen in these birds. Interestingly the range of lesions seen n these birds correlates reasonably closely with those seen in the human eye after high speed blunt trauma; persistent corneal erosion, cataract, iridodialysis and retinal or choroidal rupture being seen in man also. The long-term consequences of severe ocular injury raise several issues regarding the husbandry of injured raptors; should one eyed birds be released back into the wild? Should blind or severely visually impaired birds be kept in captivity if release is not possible? The one conclusion possible from this study is that every raptor should be given a full ophthalmic examination before release.

Chronic Ocular Lesions in Tawny Owls (*Strix aluco*) After Vehicular Trauma

DL Williams

Plates and Tables



a. Unilateral post-traumatic clinical anophthalmos with severe contrateral corneal scarring and buphthalmos.
b. Persistent corneal erosion with peri-ulcerative epithelial fibrosis
c. Central chronic corneal oedema with paracentral corneal lipid deposition
d. A peripectinal chororioretinal rupture with fibrosis
e. Post-detachment retinal fibrosis
f. Persistent haemorrhage from a traumatised pecten

	adnexal fibrosis and scarring	persistent corneal ulceration	corneal scarring with lipid keratopathy	iridal or cyclodialysis with glaucoma	cataract	pre-retinal fibrotic membranes	retinal or choroidal scarring or rupture	phthysis bulbi or clinical anophthalmos
No. birds examined (%)	16 (32)	20 (40)	14 (28)	4 (8)	32 (64)	28 (56)	34 (68)	4 (8)
number of eyes examined	10	12	7	2	22	32	20	2

Table 1 Ocular lesions observed in the birds examined

	normal eyes	eyes with adnexal lesions without intraocular disease	corneal lesions without intraocular disease	anterior segment inflammatory pathology	irido- or cyclo-dialysis	lens pathology alone	posterior segment pathology alone
intraocular pressure (mmHg)	15.6±3.4	14.2 ±3.6	18.2±5.4	7.4±4.6	35.4±12.2	12.2±3.8	13.6±4.8
significance of difference from normal	-	p=0.11	p=0.082	p=0.042	p=0.034	p=0.13	p=0.75

Table 2 Intraocular pressure in groups of birds with different ocular pathology

	normal eyes	eyes with adnexal lesions without intraocular disease	corneal lesions without intraocular disease	anterior segment inflammatory pathology	irido- or cyclo-dialysis	lens pathology alone	posterior segment pathology alone
Schirmer tear test (mm/min)	3.2±0.4	3.8 ±0.5	4.2±1.3	3.4±0.8	2.9±0.6	3.2±0.8	3.6±0.7
significance of difference from normal	-	p=0.12	p=0.09	p=0.17	p=0.24	p=0.16	p=0.18

Table 3 Modified Schirmer tear test in groups of birds with different ocular pathology

	toxoplasma serology negative	toxoplasma serology positive	total
observed			
normal retina	20	18	38
retinal scarring	7	5	12
total	27	23	50
expected			
normal retina	20.52	17.48	38
retinal scarring	6.48	5.52	12
total	27	23	p=0.73

Table 4 2x2 contingency table for retinal lesions and toxoplasma seropositivity

Tumours of the optic disc in a cynomolgus monkey (*Macaca fascicularis*)

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Two white, apparently proliferative and progressive, lesions were observed affecting the optic disc of one eye of a young cynomolgus monkey (*Macaca fascicularis*). The clinical progression and histopathological diagnosis will be discussed.

We have found few reports of naturally occurring proliferative optic disc lesions in primates, despite the common use of some species in the toxicological assessment of potential new medicines and the importance placed on ophthalmic assessments during such toxicological studies. Suzuki et al. (1985) reported the results of examination of the ocular fundi of 1,151 cynomolgus monkeys ranging in age from newborn to 19 years. Twenty three optic disc abnormalities were found (3 cases of micropapilla, 4 of ectasia and 16 of myelination of the retinal nerve fibres); no proliferative optic disc lesions were reported. Rubin (1975) reported observations during the routine ophthalmoscopic examination of 3,650 young rhesus monkeys (*Macaca mulatta*); no proliferative lesions affecting the optic disc were seen (Rubin LF, personal communication). Bellhorn et al. (1972) reported a haemangioma of the optic nerve head in a rhesus monkey; Munger et al. (2002) describe bilateral neuroepithelial choristomas of the optic discs in a 6-year-old cynomolgus monkey.

The animal was a male captive-bred cynomolgus monkey of Mauritian origin, 21 months of age when the lesion was first observed, kept under standard laboratory conditions in a group of four to six male animals of similar age. It was one of 32 animals that were the subjects of a 15 week oral administration toxicology investigation of a potential new medicine under development for use in man. On the basis of previous short term studies, the dose of the investigational drug administered to this animal was anticipated to result in little or no toxicity. Care and use of the animal were in accordance with the provisions of the Animals (Scientific Procedures) Act, 1986.

Ophthalmoscopy was performed shortly before the study start and during the twelfth study week. The animal was sedated with ketamine (Vetalar, Pfizer Ltd.; approximately 10 mg/kg intramuscularly) and mydriatic applied topically (tropicamide 0.5%, Mydriacyl, Alcon Laboratories (UK) Ltd.).

The lesion reported here was first observed during ophthalmic examination prior to the commencement of the study. During routine health examination the examining veterinarian observed a single white mass at the edge of the optic disc of the left eye. No abnormalities were noted in the anterior segment, lens or anterior vitreous. The remainder of the optic disc and retina appeared normal. The right eye was unremarkable.

Twelve weeks later indirect ophthalmoscopy was repeated by one of the authors (GJH). Two irregular white nodular or verrucose proliferative lesions were seen attached to the optic disc. Both lesions clearly appeared to be elevated, extending into the vitreous, and obscuring underlying retinal blood vessels. The larger lesion was slightly smaller than the optic disc, and overlaid the disc margin ventromedially. The smaller lesion was about one sixth of the size of the larger and overlaid the dorsomedial margin of the disc. The two lesions appeared not to be attached to each other. The remainder of the optic disc and retina appeared normal. No abnormalities were noted in the anterior segment, lens or anterior vitreous. The right eye was again unremarkable.

After recovery from sedation and subsequently, the monkey appeared visually unimpaired. It interacted with cage mates normally and moved around its environment without difficulty. Menace responses and pupillary light reflexes in both eyes were normal. Eight days later the animal was re-examined by indirect ophthalmoscopy and fundus photography was performed. On this occasion the lesions appeared slightly larger in area, the lesion edges were less distinct and were difficult to bring into focus.

At the end of the study period the animal was humanely sacrificed and a full macroscopic post-mortem examination was performed; no gross pathological lesions were observed. The

left eye was removed whole and preserved in Davidson's solution prior to paraffin wax embedding. The lesions were step sectioned in the sagittal plane at levels approximately 50 µm apart and stained with haematoxylin and eosin (H&E). Subsequently immunohistochemical techniques were used to establish the likely cell line of origin of the tumours.

The histopathological results and diagnosis will be discussed.

Acknowledgement

The authors thank Mr AJH Basford MRCVS for the fundus photography and the Histology Department of Covance Laboratories Ltd., Harrogate for processing the histological sections.

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Cataract Surgery in the horse – practicalities and pitfalls

This lecture will talk about case selection, preoperative medications, instrumentation, intraoperative complications, but mostly about postoperative complications. These include, but are not limited to, uveitis, corneal edema, glaucoma, corneal ulcers, and the worst, endophthalmitis. Not to mention pneumonia, salmonellosis, and cecal impaction.

Building an image of the orbit

This lecture will begin with a look at the anatomy of the orbit, using diagrams, drawings, and actual sections of the head. The differences between microphthalmia, phthisis bulbi, and enophthalmos will be discussed. A list of differential diagnoses for exophthalmos will be given, and a plan for working up a case of exophthalmos will be discussed, including the use of ultrasonography and CT.

Ocular conditions we could import to the UK from Texas

This lecture will be my chance to talk about all the systemic diseases that we see in Texas, that you are lucky not to see in the UK. These include anterior uveitis and chorioretinitis caused by systemic fungal disease, rickettsial disease, and parasites.

Haemangiosarcoma Involving the Third Eyelid in the Horse: Two Case Reports

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Haemangiosarcoma (HAS) would appear to be a highly aggressive malignant tumour reported in a number of species, most frequently the dog (Hargis et al 1978, Murphy et al 1989) but also the cat (Multari et al, 2002), the horse (Leapis et al 2004. Hacker et al 1986 ,Hargis and Mcelwain 1984, Bolton et al 1990, Southwood et al 2000) and the cow (Sutton and Lenman, 1982, Zachary et al 1981). In the horse the most likely presentations are cutaneous, {Baker and Leyland (1975)} or ocular or multicentric (Jubb et al 1993).

Vascular tumors that involve the eye would appear to arise from conjunctiva either at the lateral or medial canthus, sometimes arising as discrete masses. The prognosis for ocular haemangiosarcoma is poor with spread to the globe, orbit, local lymph nodes, and facial muscle. A clinical feature of many of these cases was a serosanguineous discharge from the eye and nose.

A recent review of disseminated HSA indicated that they occurred in mature middle aged horses, with no sex predilection. The respiratory and musculoskeletal systems were over represented (Southwood et al, 2000).

Two cases of ocular haemangiosarcoma in the horse will be described. One was a 15 year old Irish Draught grey mare and the other a 22 year old Chestnut gelding. The clinical presentation in both cases was similar with extensive conjunctival involvement and a serosanguineous discharge.

A diagnosis was obtained on histopathology.

The clinical presentation, the histopathology and the outcome will be described.

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Ligneous Conjunctivitis in a Doberman

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A six year-old female-neutered Doberman presented with a three and a half year history of intermittent bilateral purulent conjunctivitis which had proven unresponsive to topical antibacterials or steroids.

Ophthalmic examination revealed a tenacious mucopurulent discharge, ulcerative conjunctivitis with raised greyish /white plaques, and low Schirmer Tear Test readings bilaterally. The dog was in good bodily condition but the owner reported recent inappetence. Ulceration of the buccal mucosa and tongue was noted.

Differential diagnosis for the ocular lesions alone include, infectious or immune mediated conjunctivitis, conjunctival neoplasia, and keratoconjunctivitis sicca. Taking into account the oral lesions, further differentials were multisystemic ligneous conjunctivitis, bullous pemphigoid, pemphigus vulgaris, pemphigus erythematosus, erythema multiforme, epitheliotropic lymphoma or other neoplastic disease. Work-up involved conjunctival swabs, routine haematology and biochemistry, urinalysis, ultrasonography of globes and abdomen, conjunctival and oral biopsies, FNA of submandibular lymph nodes, and chest and abdominal radiographs.

Significant results were as follows: bacteriology yielded a scanty growth of E.coli, slightly raised blood urea and creatinine, occasional red and white blood cells and some bacteria in the urine. Ultrasound examination of the abdomen revealed a small nodule in the bladder suspected to be a polyp or early neoplasia. Histopathology of conjunctival and oral biopsies showed ‘marked chronic ulcerative conjunctivitis and stomatitis with adherent hyaline debris’ This pathology was consistent with the presumptive diagnosis of ligneous conjunctivitis.

Ligneous conjunctivitis is a rare condition of unknown cause to which the Doberman appears predisposed (Ramsey et al, 1996). It is characterised by a bilateral pseudomembranous conjunctivitis. The palpebral, bulbar and nictitans conjunctiva can all be affected. The disease is frequently multisystemic with similar changes seen in the oral, urinary or upper respiratory tract. A clinically and histopathologically similar condition exists in humans. It is rare, principally affecting infants and children, with females > males in a 60:40 ratio (Hidayat and Riddle, 1987). The most common site for lesions in humans is the upper palpebral conjunctiva. Corneal involvement (not normally a feature of canine disease) is seen in 26-30% of cases, and this can lead to blindness through scarring. As in dogs other mucous membranes are frequently affected; the upper respiratory tract, urinary tract, kidney, vagina, fallopian tubes and peritoneum have all reportedly been affected. Secondary infections are common. In humans, ligneous conjunctivitis is thought to be inherited in an autosomal recessive mode (Bateman at al, 1986). It is believed to be associated with Type 1 plasminogen deficiency, and there is some evidence for a mutation in the plasminogen gene (Schuster et al, 1999)

Rare cases in humans have been reported to resolve spontaneously, but usually treatment is required. Surgical removal of pseudomembranes, topical hyaluronidase or alpha-chymotrypsin, corticosteroids, cyclosporin, and more recently topical or i/v plasminogen (Schott et al, 1998) have all been reported as treatments for the human disease. Putative treatments include liver transplant, for children with life threatening respiratory complications, and gene therapy.
In veterinary patients treatment tends to be directed towards immune modulation: topical and systemic corticosteroids, topical cyclosporin have all been used with little success. Topical antibiotics, chemical cautery with copper sulphate, and surgical removal of pseudomembranes have also been reported. As in humans, the latter appears to act as a

potent stimulus for regrowth. Ramsey (1996) reports one case of remission using azathioprine.

In the case described here, topical and systemic cyclosporin therapy (Optimmune, Schering Plough; Atopica, Novartis) failed to produce any improvement in clinical signs within 4 weeks, in fact the oral lesions deteriorated and the dog became increasingly inappetent. A switch to azathioprine produced a dramatic improvement in ocular signs within two weeks. However the oral lesions persisted. Eight weeks after the initial diagnosis the dog was anorexic, depressed and lethargic. Blood biochemistry at this stage indicated multi-organ failure and the owner decided upon euthanasia. Unfortunately the offer of a post mortem examination was declined.

Given the similarity between the human and canine forms of ligneous conjunctivitis it seems likely that the aetiology is comparable. The breed predisposition of Dobermans to the condition would suggest a possible genetic component. A 5ml blood sample in EDTA from the case described was submitted to the Genetics Department at the Animal Health Trust and it is hoped that it may be useful in future research. However, these cases are extremely uncommon and we would urge anyone who has a Doberman with histologically- confirmed lesions to submit a sample.

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An Introduction of Exotic Animal Ophthalmology

Nick Millichamp

Exotic species are not uncommonly affected with ocular disease. Although in general the conditions seem mirror those in domestic animals there are disorders which are unique in exotics. This reflects anatomical and physiological differences and the effects of captive husbandry, nutritional practices and the effects of epizootics of infectious diseases specific to particular groups of animal. Although it is possible to recognize patterns of ocular disease in certain species the pathogenesis of many of these conditions is still often poorly understood.

The approach to diagnosis and treatment is identical to that followed in domestic animals although the problems of restraint for ophthalmic examination and repeated treatment present significant challenges and the need to come up with innovative approaches to treatment.

This introduction will present some of the more frequently encountered ocular disorders in exotic species which may be encountered in the private or zoo environment.

Letter from Texas

Nick Millichamp

Our perspective of life in academia and private specialty practice in the US will be illustrated based on our our experiences in Texas during the last twenty years. When we started work at Texas A&M University in 1985 the balance between academic ophthalmologists and specialists in private practice was quite even. That situation has undergone considerable change in favor of the private specialty practice much as is now occurring in the UK.

In this presentation I highlight some of the facets of life in Texas as well as the changing face of academia and development of private specialty practice in this large and diverse state.

Ophthalmic Telemedicine Anyone?

Nick Millichamp

As we enter the wired and wireless twenty first century it is perhaps only to be expected that we seek to find ways to incorporate telecommunications technology in all areas of medicine.

Use of telecommunications for medical consultation is hardly a new field having been used as early as the 1960s. Progress in telemedicine has however been rather slow and marked by peaks of activity followed by troughs. Indeed in the early years outside of certain limited and specialized fields (notably the military and space program) telemedicine appeared rather like a technology seeking an application in medicine rather than the other way around. Recently there has been a resurgence of interest, sparked in part by the possibilities suggested by the growth of the internet.

In human ophthalmology there have been some attempts to develop telemedicine applications for particular diseases and now there is growing interest in developing standards for some of these entities.

In veterinary ophthalmology, as in veterinary medicine in general the progress and interest in telemedicine has been very limited largely due to limited funding opportunities. Additionally, ophthalmology presents some unique challenges not present in other medical fields such as psychiatric or dermatologic telemedicine. Obstacles to ophthalmic telemedicine will inevitably be overcome in ensuing years. Positioning ourselves as veterinary ophthalmologists to take advantage of the new technologies will be of benefit to both our patients and clients.

Lecture outline Mr Richard Newsom

Consultant Southampton Eye Unit

17 May 2005

What's New in AMD

- **Epidemiology / Classification**
- **Treatments**
- PDT
- **TAP / VIP / VPDT**
- TTT
- Anecortave
- Macugen
- Anti-VEGF aptomer
- **Developing Treatments**
- Combination treatments
- Macular rotations
- Pneumatic displacement
- Subretinal surgery
- **Treatment plans**

Age related maculopathy (ARM)

- **Hard Drusen**

Age related macular degeneration (AMD)

Wet AMD

Classification of CNV

- **Classic with no occult**
- **Occult**
  - Fibro-vascular PED
  - Late leak of undetermined source
- **Mixed CNV**
  - Predominantly Classic
    - **50-99% Classic CNV**
  - Minimally Classic
    - **1-49% Classic**

Other angiographic features

- **Tears / rips**
- **Fading CNV**
- **Feeder vessels**
- **Loculated fluid**
- **Disciform**
- **Subretinal / vitreous hemorrhage**

Treatments

- **Photodynamic therapy (PDT) with Verteporfin**
- **Chemical structure**

PDT Laser

Laser controls

Clinical example PDT

PDT + 2 months

PDT + 6 months

PDT + 9m

Problems with PDT

TAP-2 24m results

Arch Ophth 119:2001,198-207

- **Whole group**
  - PDT 47%> 15 letter lost (402)
  - Control 62%>15 letters lost (207)
- **Predominantly classic**
  - PDT 41% > 15 letters lost (n=94)
  - Control 69% > 15 letters lost (n=26)
- **Classic and no occult**
  - PDT 30% > 15 letters lost (n=65)
  - Control 71% > 15 letters lost (n=14)

VIP Verteporfin in photodynamic therapy. Report 2

Am J Ophth 2001;131:541-560

- **Whole group**
  - PDT 54%> 15 letter lost (225)
  - Control 67%>15 letters lost (114)
- **Occult and no classic**
  - PDT 55% > 15 letters lost (n=166)
  - Control 68% > 15 letters lost (n=63)
- **4.9 Treatments**
- **Loss to 34 letters, CS, progression of lesion, size etc…**
- **Smaller lesions worse acuity did best**

Effect of lesion size, visual acuity in TAP studies

Am J Ophthalmol 2003 136: 407-18

- **Assess effect of baseline size, VA, lesion composition on outcome**
- **Baseline**
  - Predom classic 3.4 DA
  - Min classic 4.7 DA
  - Occult and no classic 4.3 DA

- **Smaller < 4.0 DA min classic and occult had similar VA outcome as predom classic**
- **Size was a greater predictor than composition or visual acuity**

VIP 3 – PDT in pathologic myopia

Ophthalmology 2003:110:1315-20

- **Multi-center randomised trial of sub-foveal, classic CNV <5400, VA>20/200**
- **Whole group**
  - PDT 36%> 15 letter lost (81)
  - Control 51%>15 letters lost (36)
  - **P=0.11**
- **Improvement 5 letters**
  - PDT 40%
  - Control 5%
  - **P=0.05**

PDT idopathic CNV

Rogers et al Ophthalmology 2002 109 1499-505
- **Case selected trial**
- **19 patients, followed for 12 m**
- **Results**

NICE and PDT
Guidance
Qualys?
NHS implications
- **5000-7500 cases per year**
- **Around 10-15 / 100,000**
- **Cost per patient £ 5250 / year**
  - Total £39,375,000
  - Allocated £4,000,000
- **= DOH math**
- **Local commissioning underway**

V-PDT Cohort Study
- **All angiograms (1.1 & 1.2) will be submitted**
  - <90% submission
  - <80% convergence rate
- **Data collected on database**
  - Vision, CS, refraction, angiogram lesion type and position, treatment, etc.
- **Problems**
  - No control group, no data……
  - No money from PCT…
  - Confusion of patients over PDT status…

Trans-pupillary thermotherapy (TTT)

- **Low power**
- **Large spot 0.8mm - 3 mm (x2)**
- **Long pulse (1 min)**
- **Lower intralesional temperature rise**
- **(4-9°C vs 20-50°C) for threshold coagulation**
- **Confined thermal damage**

Mechanism of action

- **Heat shock protein (HSP) hyperexpression**
- **HSP maintain cellular functions following stress**
- **Expressed in response to:**
  - Heat, free radicals and inflammation
- **Endothelial cell apoptosis**
- **Riechael and Meinster 2001**

Classic CNV

Occult - fibrovascular PED
Occult - fibrovascular PED

Visual outcome: occult CNV

Follow up	**28.4m**
Visual change LogMAR lines	**-1.4 8**
Loss of 15 letters	**40.0%**
No of treatments	**2.9**

Transpupillary thermotherpay of predominantly occult choroidal neovascularization in age related macular degeneration with 12 month follow up. Peep Algvere Acta Ophthalmo Scand 2003;81:110-117

- **113 patients**
- **Occult and no classic**
  - TTT 36.7% > 15 letters lost
  - PDT 51% > 15 letters lost (12m)
  - VIP Control 55% > 15 letters lost (12m)
- **Minimally classic**
  - TTT 38.5% > 15 letters lost

Summary

- **TTT effectively stabilizes visual loss in:**
  - 70% of patients with classic CNV
  - 70-90% of occult CNV
- **Achieved with 2.2-2.9 treatments**
- **29m follow up shows good medium term stability**

Intravitreal triamcinalone acetonide in exudative age-related macular degeneration Danis RP, Ciulla TA Retina 2000;20:244-50

- **27 eyes compared to matched controls**
- **VA better in treated group**
- **Fluorescein angiography was better**
- **IOP raised in 25% of patients**
- **Controlled with monotherapy**

Anti-angiogenic thearpy

- **Triamcinalone**
- **Anecortave acetate**
- **Macugen**
- **Lucentis**

- ? Combinations with PDT

Anecortave acetate as monotherapy for the treatment of subfoveal neovascularization in age related macular degeneration: 12 month clinical outcomes

The Anecortave acetate clinical study group Ophthalmology 2003 110:2372-2383

Genentech's / Novartis Lucentis

- **ruFab V2 (ranibizumab) Ab fragment**
- **Phase Ib/II AMD study**
- **64 AMD followed for 98 days.**
- **Treated every 4 weeks with Lucentis (n = 53)**
  - or with usual care of observation,
  - or photodynamic therapy (n = 11).
- **40 patients 6 m**
  - 97.5% (n=39) had stable or better, of which
  - 45% (n=18) improved >15 ETDRS letters.

Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovasculaisation secondary to age related macular degeneration. **Eye Tech study group Ophthalmology 2003;110 979-86**

- **Macugen – blocks VEGF decreasing neovasculaization and permeability**
- **Injected every 6 weeks**
- **Phase II trial, 21 patients, intravitreal injection**
- **3month FU**
- **87.5% stable or improved VA**
- **25% 3+ line gain**
- **60 % 3+ line gain with PDT added**

Combinted PDT and intravitreal triamcinalone acetonide for choroidal neovascularisation Spaide R Ophthalmology 2003;110:1517-25

- **26 Eyes with 3-6 month FU**
- **13 Eyes PDT then IVTA**
  - 33% 15+ letter improvement
  - Mean 2.4 line improvement
  - 15.4% re-treatment at 6m
- **13 eyes prior PDT**
  - 9% 15+ letter improvement
  - Mean 0.1 line improvement

Pneumatic displacement

- **Uses**
  - Displaces potentially toxic blood
  - Improves visual acuity
  - Enables fluorescein angiography
- **Method**
  - 50mcg TPA with 0.3ml SF6
  - 4mm behind limbus
  - Diamox / Iopodine
  - Posture
  - **Face up 24 hours, face down 72 hours**

Sub-retinal surgery

- **In type II CNV**
  - Histoplasmosis
  - Laser scars
  - PIC / MIC
- **In type II CNV**
  - Peri-papillary CNV only
  - PE is removed

75 Yrs, CF in left

Macular rotation

- **Indications**
- **Second eye**
- **Recent visual loss to 6/36 or worse**
- **Retinal detachment / vitreous haemorrhage**

Ocuvite Preservision contains

Vitamin A	**beta-carotene 14,320 IU**	**286%**
Vitamin C	**ascorbic acid 226 mg**	**376%**
Vitamin E	**200 IU**	**666%**
Zinc	**zinc oxide 34.8** mg**	**232%**
Copper	**cupric oxide 0.8 mg**	**40%**

AREADS Trial

- **Ten year trial Ocuvite Preservision**
  - 4,757 Patients 50-80yrs
  - **Randomised to Zinc / Antioxidents / Combination**
  - Reduces incidence of visual loss in 28% of patients with contra lateral disease
  - Side effects, allergy, GIT, Skin
  - Smoking contraindicated

Treatment algorithm 2004

Treatment Algorithm

Peri-papillary CNV