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Sudden Acquired Retinal Degeneration in the Dog: Clinical and Morphologic Characterization of the "Silent Retina" Syndrome

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Abstract
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This report reviews twenty six cases of SARD examined by the authors at the Veterinary Hospital, University of Pennsylvania (VHUP). The histopathology and ultrastructural morphology of four cases are described.

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SUDDEN ACQUIRED RETINAL DEGENERATION IN THE DOG:

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"Silent Retina" Syndrome

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INTRODUCTION

Adult dogs occasionally become suddenly, totally and permanently blind. If examined soon after the onset of blindness, the dogs show no ophthalmologic evidence of disease sufficient to account for their problem and are usually in otherwise good health. The hallmark of this sudden, acquired retinal degeneration (SARD), that establishes it as a retinopathy, and distinguishes it from neurological disease, is the extinguished electroretinogram. The syndrome has been termed "Silent Retina Syndrome[1]" and "Metabolic Toxic Retinopathy[2]". Although uncommon, SARD has been diagnosed with increased frequency in recent years. Little retinal tissue has, however, become available for histopathologic characterization of the disease.

This report reviews twenty six cases of SARD examined by the authors at the Veterinary Hospital, University of Pennsylvania (VHUP). The histopathology and ultrastructural morphology of four cases are described.

MATERIALS AND METHODS

Between February 1977 and April 1984, 46 dogs, referred to VHUP for evaluation of sudden blindness, showed no ophthalmoscopic evidence of disease sufficient to account for their problem. Fourteen dogs were excluded from this study because consent for electroretinography was not obtained. Also excluded were five dogs with normal ERG's that had neurologic blindness (2 brain tumors, 3 diffuse inflammatory disease). The remaining twenty six dogs with essentially extinguished ERG's form the

study population (Table 1).

All dogs had a general physical, neurologic, and complete ophthalmologic examination. Each dog's visual performance was assessed by its ability to negotiate an obstacle course under photopic (bright) and scotopic (very dim light) situations. Basic hematological and other diagnostic tests performed are summarized in Table 2.

The ERG's were recorded under halothane anesthesia using equipment and procedures previously described[3]. In summary, light flashes of controlled intensity, color, and duration were delivered to the tested eye via a fiber optic cable and through a contact lens equipped with a recording electrode. Responses were displayed on, and photographed from an analog oscilloscope and, in some cases, a digital signal averaging computer. After dark adaptation, responses to scotopically balanced red and blue stimuli and to a strong (20 ms, 4.0 Logfootlamberts) white light stimulus were recorded. Flickering lights were used, in some cases, to differentially stimulate the rod and cone systems.

Full post-mortem examinations were done on three animals (dogs 14, 23, and 24). Seven eyes, removed under general anesthesia, were processed for histopathologic examination (Table 3). Five eyes were fixed by immersion in either glutaraldehyde or glutaraldehyde-paraformaldehyde solution, post-fixed with osmium tetroxide and embedded in epoxy resin for light and electron microscopic examination. Two eyes were fixed in Bouin's solution and embedded in paraffin for routine histopathologic processing.

Follow-up information was obtained by phone consultation or by re-examination of the dog (Table 1).

RESULTS

I. Clinical Findings

The mean and median ages of affected dogs were 9.69 years and 10 years, respectively, with a range of 6 to 14 years (Table 1). Eleven dogs (11/26, 42%) were of mixed breeding; the remaining dogs were of various breeds (Table 1). Seventeen of the affected dogs were female; nine were males (Table 1). Although cases occurred throughout the year (Table 1), there was a clustering in December and January (12/26 cases, 46%). Cases originated equally from urban and rural environments.

Blindness, as perceived by the owners, occurred suddenly ($\leq$ 4 weeks) in all cases. In 13 cases, blindness was estimated to have occurred in less than one week. Three dogs were observed to have lost vision within 24 hours. Four owners reported that they believed night visual acuity was worse initially. Duration of the blindness prior to first examination by us ranged from 1 day to 5 months. Twelve dogs were examined within 4 weeks of onset of blindness (Table 1).

Pupils were consistently moderately to widely dilated. Pupillary light reflexes were diminished in 23/26 dogs. The fundus was normal ophthalmoscopically in 10 dogs. The remaining cases had, bilaterally, minimal ophthalmologic abnormalities (Table 1). These changes did not appear

sufficient to account for the blindness in any case examined and similar changes are present in many aged animals with normal vision. In retrospect, the fundus appearance corresponded to the time from onset of symptoms to examination (Table 1). Dogs with detectable abnormalities had, generally, been affected longer (mean 78.3 days, range 14 - 150 days) than dogs with no detectable abnormalities (mean 30.6 days, range 1 - 90 days).

Concurrent problems present in the affected dogs are given in Table 1. The most common were obesity and polyuria, polydipsia and/or polyphagia (PU/PD/PP, Table 1 - comments c & d). Ten of the obese and five of the non-obese dogs were reported to have gained weight around the time of visual loss. The nine dogs with PU/PD/PP developed the problem in temporal association with the visual loss and had not received corticosteroids previously. Cases 13 and 17 had received corticosteroids regularly for at least two years but reported no PU/PD/PP. Ten dogs had chronic skin disease. Other abnormalities present in more than 2 cases are listed in Table 1. Recent vaccination administration was not associated with the visual loss in any case. There was no consistent history of exposure to poisons.

Minor hematologic abnormalities were found in 9 cases, Table 2). Thirteen dogs had at least one abnormality reported on serum chemical profiles (Table 2) but few of the abnormalities were consistent. The only assays abnormal

in greater than five dogs were hypercholesterolemia (11 dogs), increased serum alkaline phosphatase (8 dogs), and increased serum aspartate amino transferase (4 dogs). There were no consistent abnormalities found on any other tests performed (Table 2).

Electroretinograms were, in all 26 dogs, not detectable in single (i.e. non-averaged) responses, even to maximal white light stimulation. In 4 of 5 dogs in which responses were summed by signal averaging computer, tiny (<5 uV) negative responses were detectable following bright white light stimuli. The fifth dog had no detectable response even after signal averaging. This dog was tested somewhat later (4 months) from the onset of symptoms than were the other 4 (1 - 3 months).

Eight dogs were lost to follow-up (Table 1). Of the 18 remaining cases, 5 cases were examined at least once, at least 4 months after the initial examination, and all 5 showed typical retinal degeneration which progressed eventually to complete atrophy. Eleven dogs have died from various causes (Table 1). The remaining 7 dogs are reportedly healthy other than their blindness.

Pathology of early disease.

The pathological changes were similar in the different retinal regions of each of the 3 eyes (Eye 1: 3 weeks, Eye 3: 5 weeks, Eye 2: 10 weeks) representing the earliest disease, and were primarily restricted to the photoreceptors themselves. The inner retinal layers (Nerve fibre layer [NFL], Ganglion cell layer [GCL], Inner plexiform layer [IPL] and Inner nuclear layer [INL]), the choroid and the pigment epithelium (PE) were, for the most part, normal.

The most striking abnormality was the total absence of the outer segment layer (OSL). Both rod and cone inner segments were present but none had an outer segment identifiable by light microscopy. Rod inner segments (RIS) were thin (1.2 - 2.0u) at their base. Some appeared short (4.0 - 8.0u) but many were long (15 - 18u) with a very thin (0.5 - 0.75u) middle part and a terminal knob-like expansion (2.5 - 3.0u diameter) in apposition to the PE. Ultrastructurally, some of these knobs had bare ciliary stalks protruding from them and, rarely, a small packet of outer segment discs was nearby.

Cone inner segments (CIS) were prominent. Most were of normal length or slightly elongated (3 - 4u diameter, 13 - 14u long). Some cones had a short (2.0 - 4.0u) stubby inner segment external to the outer limiting membrane (OLM) and an expanded, mitochondria laden, cytoplasmic area internal to the OLM. Some CIS appeared, by light microscopy, to have a thin "wisp" of membranous material associated with them, extending from their tip towards the PE. Ultrastructurally, CIS generally lacked a

ciliary stalk although, rarely, a small packet of outer segment disks was present near, and possibly originating from, a CIS.

The ONL was from 6 to 8 nuclear profiles thick centrally, and approximately 4 thick peripherally, in all quadrants of the 3 eyes. Pyknotic nuclei, found throughout all 3 retinas, made up approximately 0.1% to 0.4% of the ONL and were, almost exclusively, dying rod nuclei.

The interphotoreceptor matrix (IPM), extending from the OLM to the PE between the elongated rod inner segments, was abnormally prominent. Microscopically it was unusually dark with a patchy, granular to blotchy pattern. Ultrastructurally the IPM held clusters of irregularly shaped, membrane bound vesicular profiles containing a mixture of osmiophilic amorphous materials of varying densities. A few of these vesicles were very closely associated with inner segment plasma membranes, particularly those of RIS, as if recently extruded, but most lay free in the IPM. They appeared similar to the vesicular profiles seen in progressive rod-cone degeneration in miniature poodles but were far more extensive both in total volume and number.

Macrophages were numerous (5 - 15 per ten 40X high power fields [10HPF]) in the IPM. Their nucleus was large and irregularly shaped and had a prominent nucleolus and peripherally condensed chromatin. Their cytoplasm contained many variously sized phagosomes and phagolysosomes in various states of degradation. The largest of these packets were often as large as the nucleus itself and appeared to contain the most recently

ingested material. When sectioned through their central soma or nucleus these cells were up to 15u long and 5 to 10u wide. By high power light microscopy or by electron microscopy many smaller profiles containing phagolysosomes but no nucleus were recognizable. These smaller profiles, presumably, represent pseudopodal extensions of the macrophages, radiating through the IPM.

The PE was normal except for the presence of many lipofuscin granules (residual bodies) in many cells. These granules were most prominent in the 5 week retina (eye 3) and in the nonpigmented PE of the tapetal region. They were seen at all levels of the cell, but especially basally, and made up as much as one third to one half of the PE cytoplasmic volume. No fresh phagosomes or phagolysosomes were observed in the PE. PE apical villi did not extend into the IPM between the inner segments but were folded back to lie loosely parallel to the PE apical cell surface. Vesicular profiles were present, singly or in small clusters, loosely trapped among and even touching the PE villi.

The Muller cell villi, or fibre baskets, which normally project through the OLM into the IPM between the photoreceptor inner segments, were abnormal. At 3 weeks they were contorted and lacked their normal radiating erect appearance. By 5 weeks they were almost totally absent.

The OPL, in all 3 eyes, was thin and indistinct by light microscopy--more so peripherally than centrally and at 10 weeks than at 3 and 5 weeks. Ultrastructurally, fewer rod synaptic profiles than normal were seen and cone synaptic profiles were

small and radially flattened. A few synapses were obviously degenerate.

The INL was normal at 3 and 5 weeks but at 10 weeks there were a very few pyknotic nuclei that may have been either Muller cell or bipolar cell nuclei; they did not appear to be nuclei of either horizontal or amacrine cells.

Pathology of advanced degeneration.

(Eye 4: 27 weeks, Eyes 6 and 7: 52 weeks).

The PE held no phagosomes or phagolysosomes. Lipofuscin residual bodies were present in non pigmented PE cells, except where the retina was severely atrophic, but were not as prominent as in the 5 week retina (eye 3) . As in earlier disease the PE villi lay flat against the cell's apex. In areas of severe inner retinal degeneration the PE cells were flat and straplike, less than half their normal plumpness.

The inner segments of both rods and cones were severely diminished in size and number. RIS were 4 to 8u long at 27 weeks but almost totally absent at 52. CIS appeared to have degenerated more slowly. AT 27 weeks they were 2 to 5u long and pyramidal. At 52 weeks they were approximately 2u long and, although not numerous, they considerably outnumbered the RIS's.

Where there were RIS's present (most areas of the 27 week and patches of the 52 week retina) the IPM was similar in appearance to that in early disease, and proportionate in amount to the volume of RIS. Where RIS were scant or missing entirely

there was very little IPM, and very few vesicular profiles, even where (diminutive) CIS were present.

There were many more nucleated cells in the IPM at 27 weeks than in earlier disease. Although most of these were macrophages, as seen in early disease, many appeared to be displaced photoreceptors. Macrophages were most frequent centrally, but only occurred where RIS's persisted and the IPM was prominent. In these areas there as many as 35 per 10HPF. Displaced photoreceptor nuclei were most frequent in the mid-peripheral retina, in a transitional zone between, centrally, the best preserved retina and, peripherally, the most degenerate region. Fewer nuclei were seen in the IPM at 52 weeks (approximately 5 per 10HPF), but more of them appeared to be photoreceptors. The pattern of distribution of macrophages and displaced photoreceptors was similar to that at 27 weeks. Most of the displaced photoreceptor nuclei resembled rods rather than cones.

The ONL was reduced to 3 to 4 cells thick centrally and 1 to 2 cells peripherally at 27 weeks. At 52 weeks only one cell layer remained for most of the ONL. At 27 weeks 1% to 2% of the remaining ONL nuclei were pyknotic and at 52 weeks 20% were, overall, and as many as 50% were pyknotic in small areas. Most pyknotic nuclei appeared to be rod nuclei. At 52 weeks, however, a few of them were , for the first time, clearly identifiable as dying cone nuclei.

The OPL was either thin (centrally) or undetectable (peripherally) at both 27 and 52 weeks. A few vestigial synaptic structures were occasionally seen ultrastructurally in the

rounded up cytoplasm of the few remaining photoreceptors.

Pyknotic INL nuclei were also more common than in early disease, particularly in the 52 week eyes. These were not evenly distributed throughout the INL but tended to occur in clusters of 2 to 10 nuclei. Overall they accounted for approximately 5% of the INL nuclei but locally for as many as 30%. They were not directly identifiable as either bipolar or Muller cell nuclei but did not appear to be horizontal or amacrine cells. In regions where the INL was markedly reduced in thickness (ie: peripherally) the missing cell type was predominantly the bipolar; Muller cells were relatively better preserved. Presumably, therefore, the pyknotic INL nuclei are mostly those of bipolar cells.

The tapetal region of one retina (eye 7, 52 weeks) was relatively less degenerate than elsewhere. This eye was fixed for routine histopathology and was not examined ultrastructurally. The ONL was 4 to 5 cells thick and inner segments appeared to be better preserved. Macrophages were more frequent in the IPM of this region than elsewhere in the same retina. The OPL was thicker and there was less evidence of INL degeneration. Nontapetal regions of this retina were similar to the retina of the fellow eye (eye 6).

DISCUSSION

The typical SARD-affected dog presents a consistent clinical appearance. A mature adult dog, often of mixed breeding but if purebred then of almost any breed, in good health and condition or moderately obese, has recently and suddenly become blind. A pupillary light reflex deficit is apparent but the retina appears normal ophthalmoscopically. Until recently, the first problem suspected would have been optic neuritis. The ERG, however, establishes that it is a retinopathy.

Despite a variety of diagnostic tests no consistent pattern of other abnormalities has yet emerged in these dogs. Some dogs do appear to have a subclinical hepatopathy and some a subclinical to subacute hyperadrenalcorticism. Neither problem develops to significant clinical disease and many SARD-affected dogs do not exhibit evidence of either one.

A clinical history of sudden blindness in an animal merits careful, even sceptical, appraisal. When dogs go blind slowly (from, for instance, progressive retinal degenerations) they often compensate for their diminished vision by behavioural adaptations and, as long as they stay in a constant environment, may disguise their blindness from their owners completely. A sudden change in the environment will cause confusion, decompensation and apparent sudden blindness. Evidence of long standing progressive ocular disease will convince the ophthalmologist and careful recollection of the dog's behaviour will usually convince the owner of the gradual nature of the disease. It has been our experience that most owners of dogs

affected with SARD, however, remain sure of the rapidity with which their pet became blind.

Sudden bilateral blindness can result from several ocular and neurologic diseases. Ocular causes include acute inflammation, retinal detachment, intraocular hemmorrhage and retrobulbar optic neuritis (papillitis). In the absence of obvious ocular disease a neurologic problem is often suspected.

Defective afferrent pupillary light reflexes indicate a lesion between the lateral geniculate body and the retina (more central lesions should not affect these reflexes). Diseases affecting the intraorbital optic nerve, for instance, may cause blindness as the sole clinical sign. Affected animals will have defective pupils and a normal fundus. The critical diagnostic test is electroretinography. A diagnosis of peripheral neurologic blindness cannot be supported without demonstration of a normal electroretinogram. Conversely, an extinguished electroretinogram is necessary to establish a diagnosis of SARD.

Clinically, electroretinographically and morphologically the time course of SARD appears to involve an initial, very rapid loss of the functional and structural integrity of photoreceptor outer segments, followed by a slow degeneration of the rest of the retina. The initial phase certainly occurs over less than 3 weeks, is probably much faster, and may be effectively instantaneous. The main evidence for this conclusion is the overwhelming similarity of affected retinas, by all the above methods of assessment, during the first 3 months from the onset

of blindness.

Whatever happens to the outer segments appears to affect rods and cones equally and all retinal regions simultaneously. This is in distinct contrast to most of the hereditary retinal degenerations, where rods and cones, and different retinal regions, are apparently affected differentially. As in many retinal diseases SARD-affected photoreceptors seem unable to survive for long once their outer segments are destroyed and their death is followed by that of the inner retinal cells. Cones degenerate more slowly than rods and rods, themselves, degenerate more slowly in regions where cones persist. This is true of other degenerative retinal diseases as well, and is observed morphologically as a regional variation in degeneration, with peripheral regions degenerating faster than central.

We have few clues to the cause of this syndrome. The variety of breeds and proportion of mixed bred dogs affected argue against an hereditary cause as, to a lesser extent, do the age and rapidity of onset. An unspecified toxic or metabolic cause has been postulated by several workers, but there is no direct evidence to support this speculation. The results of clinical pathology testing, though far from consistent, suggest that disturbed adrenal cortical function may play a role in the syndrome, but whether that is causal, responsive, or incidental is far from clear.

TABLE 1 - Summary of cases

CASE NUMBER	AGE (yrs)	BREED	SEX*	MONTH OF ONSET	RAPIDITY OF ONSET	DURATION TO EXAM	FUNDUS APPEARANCE#	FOLLOW-UP COMMENTS@	OTHER COMMENTS**
1	9	Dachshund	FS	January	1-3 wks	3 wks	Normal	1	a, c, d, e, f
2	11	Miniature Poodle	M	October	1-3 days	4 mos	Abnormal$_1$	2	b, c, d, e, k
3	14	Mixed	M	June	1-3 days	6 wks	Abnormal$_1$	3	b, c, d, g
4	11	Mixed	FS	January	2-3 wks	3 mos	Abnormal$_{1,2}$	4	c, h
5	7	Mixed	M	July	1 day	2 wks	Normal	5	c, i,
6	8	Golden Retriever	M	August	1 day	1 wk	Normal	1	c, j
7	9	Labrador Retriever	FS	December	2-3 wks	3 mos	Abnormal$_{1,2}$	6 (2 yrs)	c, e, h, j,
8	14	Mixed	FS	January	2 wks	1 mo	Abnormal$_2$	7	d, f, g, i, l
9	13	Mixed	F	December	<1 wk	2 mos	Normal	5, 8	c, d, i, k
10	10	Mixed	FS	January	<1 wk	3 mos	Abnormal$_{1,2}$	1	
11	11	Mixed	M	June	3 days	2 wks	Abnormal$_2$	1	c, d, e
12	12	Collie	FS	September	<4 wks	3 wks	Normal	9	c, g, j, l
13	7	Yorkshire Terrier	FS	August	3-4 wks	3 mos	Abnormal$_2$	5,6 (2 yrs)	b
14	9	Beagle	FS	November	1 day	1 day	Normal	5, 10	f, l, m
15	13	Mixed	FS	December	1-3 wks	2 mos	Abnormal$_{1,2}$	11	c, m
16	8	Mixed	FS	January	2-3 wks	2 mos	Abnormal$_2$	6 (1 yr)	c, d, n, o
17	10	Australian Terrier	FS	April	<1 wk	3 wks	Normal	6 (8 mos)	b, c, e,

18	7	Mixed	FS	March	<1 wk	5 mos	Abnormal$_{1,2}$	6 (8 mos)	c, e
19	10	Dachshund	FS	January	1-3 wks	4 mos	Abnormal$_{1,2}$	1	e, f
20	10	Toy Poodle	FS	March	<4 wks	3 mos	Normal	1	
21	6	Miniature Schnauzer	M	June	<1 wk	1 mo	Normal	1	a
22	10	Australian Terrier	FS	July	1 mo	3 mos	Abnormal$_2$	1	e, f, h
23	7	Golden Retriever	M	December	2 wks	1 mo	Normal	5, 12	d
24	9	Miniature Poodle	FS	November	<1 wk	3 wks	Abnormal$_1$	13	e, f, i
25	10	Mixed	M	January	1 mo	1 mo	Abnormal$_1$	6 (4 mos)	b, c, d, e, h,
26	7	Scottie	M	December	<1 wk	4 mos	Abnormal$_{1,2}$	6 (5 mos)	c, e, k, n, o

*Sex: M=male; MC=castrated male; F=female; FS=female spayed.

#Fundus Appearance: Abnormal$_1$ = slightly decreased caliber vessels; Abnormal$_2$ = slight peripheral retinal degeneration (grayness, granularity, increases tapetal reflection, and/or ridged appearance).

@Follow-up comments: (1) Lost to follow up; (2) Euthanasia 2 years after presentation (unable to walk for 6 mos); (3) Euthanasia at presentation; (4) Died with renal disease 3 yrs after presentation; (5) Follow-up examination showed progressive retinal degeneration; (6) Doing well other than blindness (time since first exam to phone report); (7) Euthanasia 12 mos later (personality change, ataxia); (8) Euthanasia 14 mos later (multiple problems); (9) Euthanasia 10 mos later (no reason given); (10) Presented for euthanasia 1 yr later (cystitis); (11) Euthanasia 3 mos later (kidney disease); (12) Presented for euthanasia and post-mortem 7 mos later (personality change); (13) Donated for further evaluation.

**Other comments (historical and/or physical examination results present in >2 cases): (a) Diet changed prior to blindness; (b) On medications chronically (including diethylcarbamazine, steroids, thyroid supplement, etc); (c) overweight; (d) polyuria, polydipsia and/or polyphagia not associated with steroid administration; (e) seborrhea; (f) dental disease; (g) poor hearing and/or smell; (h) possible nyctalopia initially; (i) mitral insufficiency; (j) recent gastroenteritis; (l) on corticosteroids subsequent to blindness; (l) otitis externa; (m) chronic degenerative joint disease; (n) hepatomegaly; (o) pendulous abdomen.

TABLE 2 - SUMMARY OF DIAGNOSTIC TESTS

TEST	DOGS TESTED	RESULTS	
		No. Normal	No. Abnormal
Complete blood count	25	16	9
erum creatinine	25	25	0
Serum chemical profile*	2, 5, 7, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19, 22, 23, 24, 25, 26	5	13
erum amylase, lipase	1, 5, 7, 8, 9	4	1
Urinalysis	1, 5, 6, 7, 8, 9, 10, 14, 16, 23, 24, 25	8	4
Urine amino acids	5, 14, 18, 24, 26	5	0
lood lead levels	7, 8, 9, 14	4	0
Cerebrospinal tap/ analysis	5, 14, 24, 26	4	0
Adrenal gland function tests#	14, 16, 19, 24, 25, 26	3	3
hyroid function tests	13, 14, 16, 17, 24, 25	4	2
luorescein angiography	14, 24	2	0

*Tests included blood urea nitrogen, phosphorus, glucose, total protein, albumin, globulin, calcium, serum glutamic-pyruvic transaminase, alkaline phosphatase, total bilirubin, sodium, potassium, and cholesterol.

#Tests includes baseline cortisols, adrenocorticotrophic hormone response and low and high dose dexamethasone supression tests (0.015 an mg/kg dexamethasone IM, respectively)

TABLE 3 - HISTOPATHOLOGIC DATA SUMMARY

EYE NUMBER	DOG NUMBER	EYE	ESTIMATED TIME FROM ONSET BLINDNESS TO ENUCLEATION (weeks)	FIXATION PROCESS
1	24	OD	3	1
2		OS	10	1
3	3	O?	5	1
4	23	OS	27	1
5		OD	27	2
6	14	OS	52	1
7		OD	52	2

1 = aldehyde/osmium/plastic
2 = Bouins/paraffin

Addendum to SARD ACVO 1984

Note that the printed transactions had some problems in compilation, and the references for the SARD paper by Acland *et al*. were left out .

I am not sure anymore what reference 1 was (and this was the source of the term "Silent Retina") - possibly something from Lonnie Rubin? or another presentation by Sam Vainisi?

Reference 2 was:

2. Vainisi SJ, Schmidt GM, West CS, *et al*. (1983) Metabolic toxic retinopathy preliminary report. Trans Am Coll Vet Ophthalmol 14, 76-81