Retinal Disorders in Border Collies

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The retina is the specialized part of the eye that contains the nerve cells that make vision possible. Traditionally, if one compares an eye to a camera then the retina corresponds to the film. This is a useful mental image because one immediately understands that the film cannot work if the camera itself is broken or has the lens cap on; but the camera is totally useless without film in it. A better analogy today would be to compare the eye to a video camera, and the retina to the silicon chips inside that convert light into an electrical signal that can be sent to a video tape recorder or TV monitor. Because the normal eye is transparent, it is possible to look inside with a special instrument called an ophthalmoscope, and see whether the retina is healthy or not.

Retinal diseases destroy its nerve cells, producing either partial or total blindness, in people, dogs, and other animals. In a working dog such as the Border Collie the risk of vision loss, from retinal or any other disease. is particularly threatening. Retinal disease, like diseases elsewhere in the body, can be caused by many agents, including infections, parasites, trauma (that is injury from physical causes), nutrition (diet), and hereditary factors (genes). Also as in diseases affecting other parts of the body, some retinal diseases have known causes, but many others are poorly understood at best. The most important thing that sets retinal disease apart from disease elsewhere in the body is the limited ability of the retina to respond to injury without impairing its own function. Many of the body's defense mechanisms, such as inflammation and other immunity system responses, that are useful in fighting disease elsewhere in the body, can cause irreversible vision loss inside the eye, and specifically in the retina. Even a minor "scar" in the retina for instance can cause a serious problem for vision. For this reason, the body has developed some special techniques to help prevent retinal disease, to limit the amount of scarring possible, and even to convince abnormally functioning retinal cells to commit suicide before they cause further problems. The retina therefore has only a limited number of ways to respond to injury. An unfortunate side effect for ophthalmologists is that many different retinal diseases can look very similar, particularly in the late stages.

Hereditary retinal diseases have a special significance to dog breeders, creating both an unjustified sense of blame and an often illusory hope that these diseases were caused by and could be eliminated by specific breeding practices. Because certain retinal degenerations are clearly hereditary, it is also tempting to assume, in the absence of specific evidence, that other such diseases are too. It is also important to realize that even a disease that is hereditary may have nonhereditary aspects that are important to understand.

There are several well characterized retinal diseases reported in Border Collies, and others that are commonly seen but not as well known or understood. Two of these are reasonably noncontroversial -- Central Progressive Retinal Atrophy, and Collie Eye

Anomaly -- and others are less well described (in Border Collies) and can be very confusing to differentiate. The latter group of diseases includes both acquired retinal diseases (Focal/Multifocal Retinopathy, Sector Retinopathy) and, possibly, Progressive Retinal Atrophy (PRA) which is an inherited retinopathy. Each of these diseases is described below.

CENTRAL PROGRESSIVE RETINAL ATROPHY (CPRA)

CPRA is a disease that primarily affects a special layer of cells, called the retinal pigment epithelium (RPE), that nourish the retinal nerve cells. When the RPE cells become diseased, the retinal nerve cells become impaired, and can die. The changes that take place in a CPRA affected retina are very characteristic, and readily recognized on ophthalmoscopic examination. In the very late stages, however, CPRA can cause the retina to look ophthalmoscopically like a retina that is dead from any other cause.

Prior to the mid 1970's CPRA was widespread in all countries where veterinarians looked at dogs' eyes. The breeds affected included most notably the Labrador Retriever (in all countries including the UK, US and Australia). My colleague, Dr. Gustavo Aguirre, published the first definitive study of the condition (Aguirre GD, Laties A: Pigment Epithelial Dystrophy in the Dog. Exp. Eye Res. 23: 247, 1976). In those years I saw many cases in Australia, particularly in Labrador Retrievers and Corgis. In the late 70's Drs Aguirre, Laties and I developed a small research colony of Shetland Sheepdogs descended from CPRA-affected parents. It was pretty "obvious," then, that CPRA in all these breeds was hereditary, and appeared to be an incompletely dominant trait. Nonetheless, no definitive mode of inheritance was ever firmly established in any of the affected breeds.

In the mid to late 1970's however, something still unexplained occurred, and quite suddenly. In Australia and the USA, CPRA totally disappeared. This was true for all breeds in which the condition had formerly been widespread, in families of dogs with previous high incidence, and in our own research colony. In the UK and Europe on the other hand CPRA persisted, and turned up in several other breeds, particularly the Briard. Since then, CPRA has only rarely been diagnosed in any dog born and bred in this country (USA).

Because of this dramatic change in incidence, and because Dr Ron Riis has demonstrated that you can create a CPRA-like condition in dogs that are made extremely vitamin E deficient (Riis RC; Sheffy BE; Loew E; Kern TJ; Smith JS. Vitamin E Deficiency Retinopathy in Dogs. *American Journal of Veterinary Research*. 1981; 42(1): 74-86), most ophthalmologists realized that CPRA was not simply an hereditary disease, but had a major (unidentified) environmental component, that most of us guess has something to do with diet, and probably with vitamin E metabolism.

Therefore Dr Aguirre, and I, in collaboration with Dr Peter Bedford, imported half a

litter of Briards bred in England from CPRA affected parents. The balance of the litter was reared in England under Dr Bedford's supervision. The pups reared in England all developed CPRA, but none of those reared in the US did (regardless of vitamin E content of diet).

In more recent years CPRA now appears to be disappearing or has disappeared from the UK and the rest of Europe, just as it did from Australia and the US in the mid-late 1970s. Several colleagues from England (eg: Paul Evans, Peter Bedford, pers comm 1996) have noted that CPRA in UK Border Collies has not been seen for 8 years in their CERF equivalent eye exams, and appears to be a disappearing phenomenon. It is irresistibly tempting to conclude that this is related to the change from "home-formulated" dog foods to strictly commercial diets, as this change took place in Australia and the US in the mid-late 1970s, and has only happened as a widespread phenomenon in Europe in more recent years.

So the good news about CPRA is that it is dying out, and it seems to be preventable by diet or some other environmental factor. The bad news is that we do not know what the preventive factor is.

COLLIE EYE ANOMALY (CEA)

CEA is a defect in formation of the eye. Several aspects of the disease are recognized, but the crucial lesion (observed defect) is a pale patch seen ophthalmoscopically at the back of the eye. This lesion is called choroidal hypoplasia (CH), and is a local defect in formation of the blood vessels and adjacent tissues underlying the retina. All dogs affected by CEA have choroidal hypoplasia, by definition. More severely affected dogs may have pits (colobomas) affecting the retina and adjacent tissues. In the most severely affected eyes retinal detachments and haemorrhages may occur, producing blindness. The disease is known to occur in Australian Shepherds, Border Collies, Rough and Smooth Collies, Shetland Sheepdogs, and other breeds.

Editor's Note: The remainder of the CEA section of this paper is of historical interest only, thanks to the discovery by Dr. Acland and colleagues of the primary causative mutation for CEA, and their subsequent development of a DNA test to identify CEA affecteds, carriers and clear dogs. For current information about the disease and its detection, please see these articles by Dr. Acland:

Collie Eye Anomaly Genetics, http://www.optigen.com/opt9_gregmess.html

Collie Eye Anomaly/Choroidal Hypoplasia (CEA),
http://www.optigen.com/opt9_test_cea_ch.html

PROGRESSIVE RETINAL ATROPHY (PRA)

Progressive retinal atrophy, or PRA as it is frequently termed, is a long recognized, hereditary, blinding disorder. The first modern description of this problem was in Gordon Setters in Europe, in the early years of the twentieth century, but since then PRA has been recognized in most purebred dogs.

PRA is a genetic disease of the retina. This tissue, located inside the back of the eye, contains specialized cells called photoreceptors that absorb the light focused on them by the eye's lens, and converts that light, through a series of chemical reactions into electrical nerve signals. The nerve signals from the retina are passed by the optic nerve to the brain where they are perceived as vision. The retinal photoreceptors are specialized into rods, for vision in dim light (night vision), and cones for vision in bright light (day and color vision). PRA usually affects the rods initially, and then cones in later stages of the disease. In human families the diseases equivalent to PRA (in dogs) are termed retinitis pigmentosa.

In all canine breeds PRA has certain common features. Early in the disease, affected dogs are nightblind, lacking the ability to adjust their vision to dim light; later their daytime vision also fails. As their vision deteriorates, affected dogs will adapt to their handicap as long as their environment remains constant, and they are not faced with situations requiring excellent vision. At the same time the pupils of their eyes become increasingly dilated, causing a noticeable "shine" to their eyes; and the lens of their eyes may become cloudy, or opaque, resulting in a cataract.

PRA is recognized, and defined, by predictable consistencies in the expression of disease. In all affected dogs, both eyes are affected equally. Furthermore, in each affected breed, the pattern of disease expression is highly consistent and recognizable as a function of age. These consistencies are the hallmarks that define PRA, and distinguish it from other retinal diseases. In the absence of these consistencies, it is not appropriate to term a retinal disease PRA.

The big difference in PRA among breeds is in the age of onset and the rate of progression of the disease. Certain breeds, notably including the Collie, the Irish Setter, the Norwegian Elkhound and the Miniature Schnauzer, have early onset forms. In these breeds the disease results from abnormal or arrested development of the photoreceptors -- the visual cells in their retina, and affects pups very early in life. In other breeds, including the Miniature Poodle, the English and American Cocker Spaniel, and the Labrador Retriever, PRA is much later in onset. Affected dogs in these breeds appear normal when young, but develop PRA as adults.

Diagnosis of PRA is normally made by ophthalmoscopic examination. This is undertaken using an instrument called an indirect ophthalmoscope, and requires dilatation of the dog's pupil by application of eyedrops. Broadly speaking all forms of PRA have the same sequence of ophthalmoscopic changes: increased reflectivity

(shininess) of the fundus (the inside of the back of the eye, overlain by the retina); reduction in the diameter and branching pattern of the retina's blood vessels; and shrinking of the optic nerve head (the nerve connecting the retina to the brain). These changes occur in all forms of PRA, but at different times in the different breed-specific forms. Usually by the time the affected dog has these changes there is already significant evidence of loss of vision.

Confirmation of the diagnosis can be undertaken by electroretinography. This is an electrical measurement of retinal function somewhat similar to an electrocardiographic test of heart function, but with two differences: the electroretinogram (ERG) can only be recorded as a response to a flash of light (ie: it is not a free running signal like the EKG); and accurate recording of the ERG requires that the dog be anesthetized. In all dogs showing clinical evidence of PRA, the ERG is severely diminished or extinguished.

The ERG can also be used for early diagnosis of specific forms of PRA, that is, to detect PRA-affected dogs before they demonstrate clinical evidence of disease. This requires very carefully controlled ERG recording conditions, and a well-defined understanding of the age of onset and rate of change of ERG dysfunction in the specific form of PRA under consideration.

Our laboratory has been actively involved in PRA research for over 20 years and research is currently making rapid progress in the development of DNA tests for PRA in the various affected breeds. At the end of this article I have appended some tables, historical summary, and publications relevant to the history of research on this condition. I have also appended a report summarizing current progress in our research directed towards identification of the genes involved in PRA, and to development of DNA based diagnostic tests.

Inheritance of PRA.

With one exception, PRA in all breeds so far studied is an autosomal recessive disorder. That means that to be affected a pup has to receive one copy of the defective gene from both parents. Thus both parents of an affected pup must be either carriers or affected themselves. Similarly, because affected dogs have two copies of the defective gene, all their progeny will be at least carriers.

Three of the early onset forms of PRA -- rcd1 in Irish setters, rcd2 in collies, and erd in Norwegian Elkhounds -- are known to represent different, nonallelic, gene mutations. In contrast, several of the late onset forms of PRA (those present in the Miniature Poodle, the English and American Cocker Spaniel, and the Labrador Retriever) are known to be mutations in the same, as yet unidentified, gene.

The Siberian Husky is the only known breed, so far, in which PRA is not autosomally inherited. In these dogs PRA is X-linked. In X-linked inheritance, the gene determining

the phenotype is on the X-chromosome, the chromosome that determines gender (sex). Females have two X-chromosomes (XX) and males have one X-Chromosome and one Y-Chromosome (XY). Thus if 2 alleles (X1, X2) exist for an X-Linked gene, males can only be hemizygous (X1Y) for allele 1, or hemizygous (X2Y) for allele 2 but females can be either homozygous (X1X1) for allele 1, homozygous (X2X2) for allele 2, or heterozygous (X1X2).

An example of X-linked inheritance that many people are familiar with is the inheritance of certain coat colors in cats. The gene for Orange is X-linked in cats, with two alleles (alternative genes): XO for orange and X+ for black. So male cats can only be either orange (XO/Y) or black (X+/Y). Female cats can also be either orange (XO/XO) or black (X+/X+) if homozygous for that allele, but in addition can be tortoiseshell if heterozygous (XO/X+), having one of each allele.

What this means in the context of X-Linked PRA in Siberian Huskies, is that this PRA gene is on the X-chromosome; and there are 2 alleles -Xpra, the mutated disease gene, and X+ the allele present in normal dogs. Thus the normal male Husky has the genotype X+/Y, and the affected male has the genotype Xpra/Y. Similarly a normal female Husky is X+/X+; an affected female Husky is Xpra/Xpra; and the carrier female Husky is Xpra/X+. Note that only females can be carriers of X-Linked PRA, males must be either affected or normal. All mothers of affected males are carriers, and so are all daughters of affected males.

Another feature of X-linked inheritance is a process called "lyonization" or random X inactivation. The principal is that all female mammalian cells only express genes present on one of their two X-chromosomes, but which one of the two X-chromosomes is active, and which one is inactive, varies randomly among individual cells. This means that if a female is heterozygous for an X-linked gene, then she is a mosaic of cells expressing the two different alleles.

In the example of the tortoise shell cat heterozygous for the orange gene (XO|X+) they are tortoiseshell because some hairs are black, and some hairs are orange. So you can look at a tortoise shell cat and *see* what X-chromosome each hair cell is using.

The same principal applies to X-linked disease genes. If a female is a carrier for an X-linked disease, then some of her cells (half, on average) express the normal gene and the balance express the disease gene. Depending on the mechanism of disease, the female carrier might exhibit a partial disease state. This is particularly likely if the mutation is directly toxic to the cell expressing the disease gene. This is seen in some females heterozygous for the husky XLPRA gene: they show a patchy pattern of lowgrade degeneration in their retina, and a modest level of reduction in their ERG amplitudes.

PRA in Border Collies

From the CERF figures for 1991 thru 1995, all cases of PRA diagnosed in Border Collies (29) have been in males, and the overwhelming proportion of PRA-suspicious cases have also been in males.

This, obviously, suggests that PRA in BCs may be either an X-linked or a sex-limited disease. If X-linked, then it is likely to represent either a totally new canine PRA locus (there are at least 3 RP loci, and several other retinal disease/dysfunction loci, on the human X), or an allele of the husky XLPRA mutation. I think it is pretty unlikely, although possible, that the husky mutation and a putative BC mutation would have arisen in a common ancestor.

The CERF statistics aroused my interest, because of the possibility of this being another X-linked PRA, and I have therefore examined a fairly large number of these dogs, as well as "random" BCs that had had no prior exams.

To this date (with one exception), all of the Border Collies previously diagnosed as "affected" or "suspicious" of PRA that I have seen personally, and all the exam forms I have reviewed from dogs that I have not had the chance to examine personally have lesions that are **incompatible** with a Dx of PRA. These dogs all have had one or the other of two conditions (an acquired focal/multifocal retinopathy and an acquired sector retinopathy) that are described later in this article. Both of these diseases are not well understood, and are at least controversial as to their cause, but they are definitely **not PRA.** I am also convinced that neither is a simply heritable disorder. One thing that needs to be borne in mind with these acquired lesions, is that once a certain threshold of insult has taken place, the canine retina appears to progress to generalized retinal degeneration spontaneously. Thus the late stages of both these disease processes can resemble PRA, but a careful exam should allow recognition of the actual disease pathogenesis.

I only know of one Border Collie, that I have personally examined, with fundus lesions that I regard as compatible with a diagnosis of true PRA. This dog is a male, and developed lesions characteristic of true PRA by 2 years of age. I know of 1 or 2 more dogs that reportedly have lesions that resemble the first dog's, and developed at a similar age. This age of onset, and the fundus appearance, are similar to those of Siberian Huskies affected with XLPRA, so X-linked PRA may be present in the Border Collie. However, until **proven** otherwise, one should **not** regard it as established yet that PRA exists in the Border Collie. I would love to be proven wrong, and would appreciate hearing from anyone who has information on any case of PRA in a Border Collie.

If PRA does exist in Border Collies, then it is important to require that it be very definitely and carefully distinguished from the acquired lesions that certainly are present in BCs, and are clearly being confused in at least some cases with true PRA.

The **minimum** evidence required to establish that PRA exists in a breed is documentation that multiple affected dogs have been diagnosed with a consistent

disease phenotype, and that there exists between these affected dogs a pedigree relationship that supports a recognizable pattern of inheritance. This situation definitely has **not** been established, yet, for the Border Collie.

The good news for PRA, if it exists in Border Collies, is that a gene test may become possible for this disease. The best hope would be for it to be the same gene as in the Siberian Husky, because there is very active research going on at the moment, in our laboratory, to identify the gene in the Husky. The only way to tell if this is true, is to identify those Border Collies that have the most certainly diagnosed PRA, and collect DNA from them and their close relatives for testing as soon as the Husky XPLPRA test becomes available. *[Editor's Note: Since this was written, a test for XPLPRA in the Siberian Husky has been developed.]*

Even in the absence of a gene test, however, there could be relative good news if PRA does exist in BCs. If the disease is X-linked, then rational breeding strategies can be designed to control reduce or eliminate the disease, without destroying valuable breeding lines. For example, a male dog affected with an X-linked disease only passes his "bad" gene on to his daughters, **never** to his sons. Furthermore, his daughters, although receiving his "bad" gene will not be affected unless they get a second "bad" gene from their mother. So even an affected male could be used if he was otherwise desirable.

FOCAL/MULTIFOCAL ACQUIRED RETINOPATHY (FMAR)

This disease is probably the most frequently seen retinal lesion in Border Collies. It is also very widespread in other athletic dogs such as racing and performance sighthounds, working herding dogs, and sledding huskies. Most ophthalmologists recognize the lesions, but there is a great variability in opinion and favored diagnoses for the disease, common descriptive labels being "distemper scars", "worm scars" or multifocal retinopathy. Frequently it is either ignored or dismissed as an acquired inflammatory retinopathy on CERF exams, though it often does get reported as PRA or suspicious of PRA, and ends up being included as such in CERF statistics. A similar disease has been reported in multiple publications in different breeds, and these probably all represent a single entity. Claims for inheritance have been put forward, but there is no solid evidence, and the frequently familial occurrence of the disease more likely reflects shared environmental effects.

The basic pathogenesis of this disease involves microhemorrhages of the traversing capillaries of the choroid. The resulting jet lesion into the vitreous resolves within a few days usually leaving, in the tapetal fundus, a characteristic bull's-eye lesion- a central blackish scar with a hyperreflective rim. In the nontapetal fundus the primary lesion is less noticeable and is a concentrically hyper and hypopigmented geographic "scar." Focal vitreal degeneration/ liquefaction, and vitreal membranes in the inferior quadrant are not uncommon, though sometimes subtle. Affected dogs can have one or more such lesions, and the lesions can accumulate over several years. The pathology is a focal nongranulomatous retinitis and vitritis in early cases, followed by a more

widespread nongranulomatous and degenerative retinopathy in longstanding progressive cases. The pathology of this disease argues very strongly against an inherited cause, and makes it clear that whatever this disease is, **it is not PRA.**

There is a great range in the age of onset, rate of accumulation, and rate of progression of these lesions. Characteristically there is a large excess of cases in males over females, and the lesions are usually asymmetrical between the two eyes. Affected dogs are often the best performing/hardest working dogs in the pack, or kennel, at least until they become visually impaired. A certain percentage of affected dogs develop a generalized retinopathy that is sometimes ophthalmoscopically indistinguishable, at least eventually, from typical PRA.

The bad news about this disease is that it is alarmingly common, and we have no idea how to control, prevent or treat it. As it is not hereditary, or at least is not simply heritable, there is no foreseeable likelihood of being able to eradicate it by genetic testing and rational breeding strategies. Furthermore, as it appears to be frequently mistaken for PRA, it confounds attempts to estimate the prevalence and inheritance of true PRA, and makes it harder to approach genetic control of true PRA in Border Collies.

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SECTOR ACQUIRED RETINOPATHY (SAR)

This retinopathy looks ophthalmoscopically most like an unusual dysplasia, but it is acquired rather than developmental, is seen almost exclusively in dogs working cattle and is, I suspect, secondary to trauma. The lesion always occurs as a triangular area (apex at or towards the optic nerve head) of retinal thinning and disorganization in an otherwise normal retina. I have seen such "triangulr" lesions occupying almost 50% of the retina, but this is the exception not the rule. As with FMAR, whatever this disease is, it is not PRA. One thing that needs to be borne in mind with these acquired lesions, is that once a certain threshold of insult has taken place, the canine retina appears to progress to generalized retinal degeneration spontaneously. Thus the late stages of acquired disease processes can resemble PRA but a careful exam should allow recognition of the actual disease pathogenesis.

CLASSIFICATION OF DIFFERENT FORMS OF PR

Breed	Disease name	gene symbol
Early Onset Forms of PRA		
I. Autosomal Recessive		
Irish Setter	Rod Cone Dysplasia 1	rcd1
Collie (Rough & Smooth)	Rod Cone Dysplasia 2	rcd2
Norwegian Elkhound	Rod Dysplasia	rd
Norwegian Elkhound	Early Retinal Degeneration	erd
Miniature Schnauzer	Photoreceptor Degeneration	pd
Late Onset Forms of PRA		
I. Autosomal Recessive		
Miniature Poodle	Progressive Rod Cone Degeneration	prcd
English Cocker Spaniel	Progressive Rod Cone Degeneration	prcd
American Cocker Spaniel	Progressive Rod Cone Degeneration	prcd
Labrador Retriever	Progressive Rod Cone Degeneration	prcd
Portuguese Water Dog	Progressive Rod Cone Degeneration	prcd
Tibetan Terrier	"Progressive retinal atrophy"	rdi
II. X-Linked		
Siberian Husky	X-Linked Progressive Retinal Atrophy	XLPRA
III. Undefined		
Australian Cattle Dog		
Belgian Malinois		
Dachshund (MLH)		
Dachshund (SWH)		
English Mastiff		
English Setter		
Novia Scotia Duck Tolling Retriever		
Rottweiler		
Tibetan Spaniel		
& numerous other breeds		

A BRIEF AND PARTIAL TIMELINE OF RESEARCH IN PRA

1911 First description of PRA, in Gordon Setters (Magnusson)
1938-55 PRA recognized in Irish Setters (UK: Rasbridge, Hodgman, Parry, Lucas)
1962-65 PRA in Miniature Poodles (UK: Barnett)
1975 First definition of the rod & cone disease in different forms of PRA (Aguirre, 1976).
1975- Characterization of breed-specific single gene diseases:

Irish Setter Rod-Cone Dysplasia 1 (Aguirre et al, 1975; 1978; 1982)
Collie Rod-Cone Dysplasia 2 (Wolf et al, 1978)
Norwegian Elkhound Rod Dysplasia (Aguirre et al, 1971; Aguirre, 1978)
Miniature Poodle Progressive Rod Cone Degeneration (Aguirre et al, 1975; 1982)
Norwegian Elkhound Early Retinal Degeneration (Acland & Aguirre, 1983)
Tibetan Terrier PRA (Millichamp et al, 1988)
Miniature Schnauzer Photoreceptor Dysplasia (Parshall et al, 1991)
Siberian Husky X-Linked PRA (Acland et al, 1994)

1978 Definition of biochemical defect in rcd1 (Aguirre et al).
1982 Definition of biochemical defect in rcd2 (Woodford et al).
1986 Recognition by Breeders & Dolly Trauner of CERF that only male Siberia Huskies get PRA
1987 Recognition of nonallelism of rcd1, rcd2 & erd (Acland & Aguirre)
1988 Discovery that prcd in Miniature Poodles, English and American Cocker Spaniels and Labrador retrievers represents mutations at the same locus (Aguirre & Acland)
1991 Recognition of PDEB mRNA defect in rcd1 (Farber et al)
1993 Gene mutation in rcd1 reported (Suber et al)
1993-4 DNA tests for rcd1 (UK: Clements et al; USA: Ray et al)
1994 Publication of first study of XLPRA, establishing that Husky PRA is X-linked
1995 Exclusion of Opsin, PDEB and rds/peripherin as candidate genes for prcd and erd.

PRA: CLINICAL SIGNS & AGE OF ONSET

	Early Onset Forms	**Late Onset Forms**
Vision Problems		
Night Blindness	from birth	1 to 5years
Total Blindness	1 to 5 years	3 to >5 years
Electroretinogram		
Rod dysfunction	from birth	<6months to >3years
Cone dysfunction	from birth to 2 years	from <6 months to >5 years
Fundus (Eye Exam)		
Early Disease	from 8wks -12 months	from 1 to >3years
Mid-Stage PRA	from 6 months to 2 years	from 2 to >5 years
Late-Stage PRA	from 1 to > 2 years	from 3 to >5 years

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