

White Fur, Blue Eyes, and Deafness in the Domestic Cat

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THE autosomal dominant gene, *W*, which causes white fur in the cat, also causes blue eyes and deafness in some but not all cats carrying the gene^{9, 48}. The association of white fur, iris hypopigmentation and deafness has been described in other mammals including the mouse, dog, and man⁵².

Because Waardenburg's syndrome, the human analog of this condition, accounts for approximately 5 percent of human profound congenital deafness^{12, 26}, a study of white cats was undertaken in the hope that the cat could be used as a model for genetic, physiologic, histologic, and developmental studies of hearing that could not be performed on man.

The dominantly inherited syndrome that Waardenburg⁵⁷ described in humans includes six signs, three of which—dystopia canthorum, prominent nose root, and hyperplastic medial eyebrows—are difficult to evaluate in the cat. Dystopia canthorum (wide skin folds between nose and eyes with wide set lacrimal puncta) and prominent nose root do not appear to be present on gross observations in the cat (Figure 1). The remaining three signs in humans—heterochromia, nerve deafness, and white forelock—closely parallel the findings in the deaf white heterochromic cat.

The frequency of the hearing defect in white cats

and the relationship of the hearing defect to histological abnormalities of the inner ear have not been studied previously. Neither have the relationships of the eye, ear, and fur components of the phenotype (to each other within individuals as genetic traits) been examined. Little is known about the selective forces that control the frequency of this phenotype and about the number of loci that are involved in its production. The results of studies of these topics are the subject of this report, and are discussed in the context of the broad mammalian occurrence of similar phenotypes, but with particular reference to man.

Literature Review

The early reports on the white cat¹⁶, which have been reviewed by Bamber⁵, were chiefly devoted to erroneous claims about the correspondence between blue eyes and deafness, and to discussion of possible classic recessive albinism in the deaf white cat. Although details of the relationship between blue eyes and deafness in white cats were then unsettled, Bamber⁵ showed conclusively that not all blue-eyed white cats were deaf, nor were all white male cats deaf as had been stated by several authors. Whiting showed that white fur was inherited in cats as an autosomal dominant not related to albinism⁶¹. In a later paper Whiting⁶² presented the hypothesis that the dominant gene *W* may be allelomorphic with a series of genes for white spotting (piebald). Searle⁵² regards the spotting genes as occurring at a separate locus, *S*, in the cat.

Blue eyes have been reported to occur in recessive Burmese dilution (*c^b*) and Siamese dilution (*c^s*) cats⁵². These genes are alleles at the *C* locus, which is considered homologous with albino loci in other animals, although genetic data are not available for the few cases of albino cats reported^{4, 52}. No unusual incidence of deafness has been reported in such blue-eyed cats.

Differential fertility and mortality has not been closely studied in white compared to pigmented cats, nor have differences between cats heterozygous and homozygous at the *W* locus been well defined. Little³⁹ reported that heterozygotes but not homozygotes sometimes have a small pigmented spot between the ears and that blue eyes and deafness

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are rare in heterozygotes. Jones³³ compared the litter size of white and pigmented females sacrificed during pregnancy as a test for a lethal effect among white cats. Since the females were pregnant when obtained by the S.P.C.A. in New York City, and since the majority of males were pigmented, the white fetuses probably were heterozygotes. Litter size in white females was smaller, and the ratio of degenerating to normal fetuses was greater than pigmented females. However, the level of statistical significance was borderline for each effect.

Recent studies of the prevalence of white cats in many areas of the world have demonstrated phenotype frequencies ranging from 0.7 percent in Rochester, New York and 0.9 percent in London⁵¹, to 2.5 percent in New York City^{55, 56} and 7.7 percent in Melbourne, Australia⁴⁴. The last figure is much higher than other world-wide data⁴⁴. Differences may reflect selection of specimens as well as actual population differences. These surveys did not include eye color or hearing studies in white cats.

The first histological studies of inner ears of deaf white cats appear to be those of Alexander¹ and Alexander and Tandler² who described absence of mesodermal pigment in the perilymph cells, bony alterations in the modiolus, and membranous changes in the labyrinth, but no marked change of the spiral ganglion or cochlear nerve. Alexander and Tandler² pointed out the similarity of the changes in affected labyrinths to those found in Scheibe's type of sacculocochlear degeneration in human deaf-mutism. Several other workers have also noted this relationship^{63, 64}. Further detailed studies by Bosher and Hallpike^{9, 10} demonstrated that degeneration of the inner ear structures begins between the fourth and sixth days of postnatal life and may be unilateral.

The absence of the cochlear microphonic in some deaf white cats has been known since the early studies of the electrical response of the cochlea^{17, 30}. Howe³¹ reported on 12 ears of white cats: 5 cats were bilaterally deaf and gave no microphonic while the sixth cat was unilaterally deaf and gave some response at 500 Hz which was interpreted as a pickup from the good ear. This was considered evidence that the microphonic was in fact cochlear in origin since histological studies of these ears showed profound defects of the type seen in Figure 3.

There is only one report of a histological study in a human affected with Waardenburg's syndrome²⁵. The findings coincide with those described above for other animals; namely, absence of the organ of Corti, atrophy of the stria vascularis, and collapse of Reissner's membrane, and were interpreted as being the result of a neural crest defect.

In Waardenburg's syndrome segmental heterochromia of both the iris and choroid of a given eye (sometimes called iris and choroidal bicolor) has been noted in addition to complete lack of uveal pigmentation in a given eye²⁸.

Studies of the syndrome in man have been motivated chiefly by its ability to cause profound deafness in childhood. Waardenburg⁵⁷ found 1.78 per-

cent of deaf mutes in an institution to be secondary to Waardenburg's syndrome. This is undoubtedly an underestimate since his criteria for inclusion were strict. Fraser²⁶ estimated that 2.5 percent of profound childhood deafness is secondary to dominant inheritance with pigmentary anomalies, and 10.0 percent is secondary to dominant inheritance without pigmentary anomalies. Since over 50 percent of patients with Waardenburg's syndrome do not have pigmentary defects, interpolation of the above data produces an estimate of approximately 5 percent of profound childhood deafness due to this syndrome. This is in agreement with the 5 percent incidence of Waardenburg's syndrome found by Brown and Chung¹² at the Clarke School for the Deaf, based on extensive pedigree data.

Several breeds of dog have shown the association of white or piebald coat color and blue iris with deafness^{40, 54, 32, 3}. In dogs there is some variation among different workers and breeds regarding the degree of defect in the spiral ganglion and vestibular labyrinth, but the general picture of sacculocochlear degeneration is like that of the cat. The mode of inheritance in dogs has not been determined and may differ in different breeds with both dominant merle (*M*) and recessive extreme piebald (*s^w*) being involved⁵². A recessively inherited combination of white fur and pigmented iris with deafness and histological abnormality of the inner ear, similar to that reported for the cat, has also been described in the mink⁵⁰.

In rodents both *Mus* and *Peromyscus* have been reported to show deafness associated with pigment reduction⁵². Several different genes have been identified in *Mus* which produced variations of pigment ranging from a white forehead spot to white splotches. These were independent loci and showed several modes of inheritance^{18-20, 41, 42}.

Cattle³⁶⁻³⁸ and horses⁵² have been reported to have pigment variations of fur and iris of similar patterns to those animals with known defects of hearing. We are not aware of studies of their hearing and ear histology.

Materials and Methods

A. The colony

The Foundation stock was 7 male and 14 female mongrel cats with white fur obtained from the Poolesville NIH Animal Quarantine by screening over a one-year period. Most of the original stock displayed one or two blue eyes. The Quarantine obtains cats from vendors who collect the animals primarily from farms in the Pennsylvania, Maryland, Virginia and West Virginia areas closest to Poolesville, Maryland. No selection for/against white cats was made in accepting cats at the Quarantine. Several normally pigmented mongrel cats were introduced into the colony to act as controls for experiments and to maintain normal stock for planned matings.

The cats were housed in air-conditioned, windowless rooms with facilities for both individual

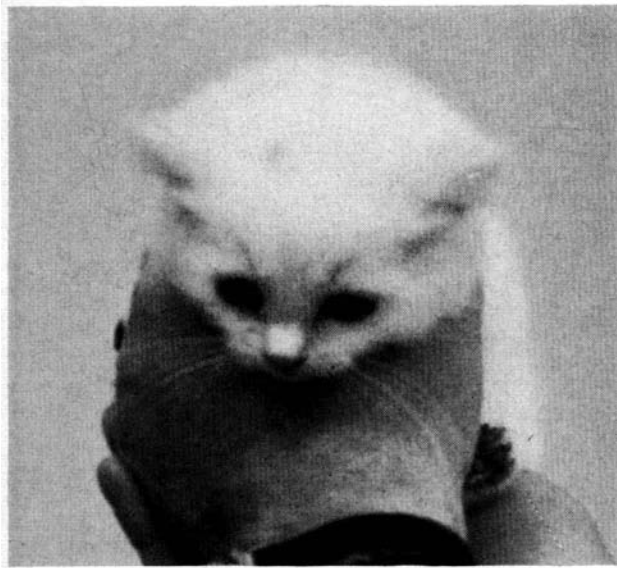


FIGURE 2—A pigmented head spot, as in the kitten above, occasionally occurs in otherwise totally white animals.

cage and herd matings. Facilities for physiological tests were in adjacent rooms. The area was moderately restricted. No new cats were introduced during the last three years and visitors were limited in number. These factors, combined with excellent care provided by a full-time certified animal caretaker resulted in an unusually low death rate from disease in the colony.

B. Description of the phenotype

Fur pigmentation

The coat color pattern of all cats in the colony was examined at intake or weaning and drawn on a schematic diagram from which the area of white was estimated to the nearest 10 percent. This was rechecked at time of sacrifice. Cats were classified as white when less than 10 percent of the body was pigmented. All other animals were classed as pigmented. The majority of adult white cats were totally white. Some retained small pigmented frontal head spots (Figure 2). A source of confusion in classification was the occasional case of high grade spotting where the animal was nearly all white (Figure 1). These usually had pigmentation on tail and/or ears.

Ocular signs and histology

All cats were examined with an ophthalmoscope and the presence or absence of the tapetum was recorded for each eye. The iris color was also recorded as blue or pigmented. In heterochromic cats the relative pupillary size was also noted. Histological preparations of the eye were made in a series of cats with various color and tapetum phenotypes using standard techniques. Small samples of intra-

ocular pressure data for newborn and adult cats of different phenotypes were also collected.

Auditory testing and ear histology

Audiologic studies were of two types, electrophysiological and behavioral. The defect in hearing was most extensively studied by the electrophysiological testing. This technique is based on phase sensitive amplification that can recover regular electrical signals at 70 decibels (db) below noise level¹³. Sounds of known frequency and intensity were presented to one ear and the voltages were detected in skin electrodes that were in phase with the auditory stimulus. This technique has the advantages of 1) rapidity, 2) reproducibility, 3) quantitation of response, 4) unilateral specificity, and 5) acceptability for repeated testing on breeders and young kittens.

Behavioral audiometry was performed on selected cats to classify functional thresholds over a wide frequency range (250 Hz to 60 KHz). The cats were trained to press a central lever to initiate a sound stimulus and to press a left key if they heard it and a right key if not. They were rewarded for correct responses with food on a variable schedule. In effect the cat's responses produced an audiogram comparable to that obtained in humans. The technique has been described by Wakeford *et al.*⁵⁸.

Behavioral audiometry was so time-consuming and expensive that it could be done only on a limited number of animals. It is important to note, however, that the behavioral results on these animals confirmed both qualitatively and quantitatively those of the electrophysiological method described above.

Table I. The relationship of iris color, hearing, and black head spot in white cats

Hearing	Spot on forehead at birth	Iris color			
		Pigm.	Hetero.	Blue	Unk. Total
Normal	Spot	25	12	13	3 53
	No spot	21	16	14	6 57
	Unknown	0	2	0	0 2
	Total	46	30	27	9 112
Unilat.	Spot	2	3	4	0 9
	No spot	3	6	10	0 19
	Unknown	0	0	0	0 0
	Total	5	9	14	0 28
Deaf	Spot	2	2	9	0 13
	No spot	6	7	27	3 43
	Unknown	0	1	0	0 1
	Total	8	10	36	3 57
Unknown	Spot	8	3	6	6 23
	No spot	9	3	14	4 30
	Unknown	1	0	0	3 4
	Total	18	6	20	13 57
Total		77	55	97	25 254

Thus the more easily obtained electrophysiological results were considered reliable markers for classification of hearing.

The histological method for examination of the ear used *in vivo* perfusion with normal saline and then with Heidenhain-Susa solution to prevent autolysis of the inner ear cells²⁴. Serial sections were made and stained with hematoxylin and eosin. Periodic acid Schiff and Wolke's stains were also used on selected sections.

C. Population studies

All cats accepted at the NIH Poolesville Animal Quarantine during a 29-month period were scored for fur and eye color (Table II). Only adult cats that appeared healthy and weighed over 4 pounds were accepted. Survival data during the 30-day quarantine period were kept by the staff. Cats that became severely ill were sacrificed; therefore, lack of survival was a combination of spontaneous death and sacrifice secondary to severe illness. These data are tabulated for white and pigmented cats. (Table III).

Results

A. Fur Color

The phenotypic frequency of white cats accepted for quarantine at Poolesville was 5.7 percent, which was higher than the frequencies of white cats found in most urban areas^{44, 51, 55, 56}. The likelihood that any such white cat was heterozygous was over 98 percent assuming no selection for color and random mating. All fertile white cats introduced into the colony produced pigmented offspring, thus confirming their heterozygosity.

Table II. Fur and eye color of cats accepted at Poolesville Quarantine

Fur color	No.	Phenotypic frequency %	Eye color		
			Pigm.	Hetero.	Blue
Pigmented	8866	94.3	8866		
White	536	5.7	454	56	26
Reduced ratio of eye color in white cats			17	2	1

Table III. Survival of pigmented and white cats at Poolesville Quarantine

	White			Pigmented		
	Lived	Died	% Died	Lived	Died	% Died
7/13/65-6/30/66	107	90	45.7	3126	1674	34.9
7/1/66-6/30/67	163	47	22.4	3237	565	14.9
7/1/67-12/14/67	80	29	26.6	1248	445	26.3
TOTAL	350	166	32.1	7611	2684	26.1

The segregation ratios of all matings involving *W* were compatible with the hypothesis that there was only one locus in our colony at which a dominant gene giving this phenotype occurred (Table IV). Since 21 different heterozygous white cats from the general population of cats initiated the colony, this result suggests that dominant white is usually the result of a mutant allele at a single locus. It must be recognized that the tests for heterogeneity among dominant genes producing the same phenotype were very weak. White animals produced by mating two white parents were backcrossed to pigmented stock to test for the possibility that genes at more than one locus cause the white phenotype as well as to identify heterozygous animals. If more than one locus carried a dominant gene causing white fur, and if our original white animals contained two or more of these different dominant genes, then some of their offspring would be expected to be heterozygous for two loci and thus segregate 1:3 on the backcross to the pigmented stock. There was no evidence for multiple loci since the white cats mated to pigmented ones had offspring that either segregated in a 1:1 ratio as expected for one locus, or had only white offspring suggesting homozygosity.*

With one exception all white cats had at least one white parent. The exception was a white cat (no. 270) born with a head spot that faded and with normal eye pigmentation and hearing. It was the offspring of two spotted animals (no. 007 and no. 512) who each had over 80 percent white fur. Female no. 512 had heterochromia irides, missing tapetum, and unilateral deafness (Figure 1, upper right). These two parents also produced a pigmented, 60 percent white offspring. In other matings of these two animals to solid pigmented cats, each produced several spotted or solid pigmented cats but no white heterochromic or deaf offspring. The result is compatible with a recessive or additive pattern of inheritance but not with a major dominant gene for white fur in these two animals. These data illustrated the phenotypic overlap of the genotype *W*- and other genotypes that result in spotting.

Other examples of heterochromia irides and missing tapetum occurred in no. 328, a 60 percent white spotted offspring derived from a white $\times$ white (no. 011 $\times$ no. 506) cross, and in no. 898, an 80 percent white offspring of a spotted offspring of that cross. Only in these two lines was discordance of the fur and eye phenotypes usually observed. It appeared probable that both no. 011 and no. 506 had two independent genes capable of producing iris and fur depigmentation.

The phenotypic distribution of the area of pigmented fur in nonwhite kittens produced in the

* An appendix, which provides detailed data on the cats studied, is available on request. The appendix includes a description of sire, dam, and offspring with I.D. no., path. no., fur, iris (R/L), hearing (R/L), and sex (of offspring). Address requests to Dr. K. S. Brown, Developmental Genetics Section, Human Genetics Branch, National Institute of Dental Research, NIH, Bethesda, Maryland 20014.

colony (Table V) was quadrimodal with modes at solid pigmentation, 10–40 percent white, 60–70 percent white, and all white. Using the three categories of solid fur pigment, more than 50 percent pigment (low grade white spotting) and some, but less than 50 percent pigment (high grade white spotting), we could examine the segregation of the offspring of classes of parents by their fur pigment. These data (Table VI) include offspring of white cats that were producing nonwhite offspring that segregated for fur spotting.

In evaluating the proportions of white offspring observed, correction must be made for the possible presence of homozygous white parents. This can be done two ways. First, all matings involving white parents who had a probability of less than 1 percent of being heterozygous on the basis of progeny testing can be eliminated and the segregation ratios re-evaluated. Secondly, the recessive trait of pigmented fur can be used to ascertain sibships with two white parents and the simple sib correction then can be used to reestimate the segregation ratio. Both these methods gave results compatible with the simple autosomal dominant model. Complete penetrance is further supported by the failure of pigmented offspring of white cats to produce white offspring except with white mates with the single exception discussed earlier.

The four animals that were possibly homozygous did not appear phenotypically different from those proved heterozygous. However, a preponderance of blue eyes and deafness was noted in these animals. All four were bilaterally blue eyed; three were bilaterally deaf. A much smaller proportion of those proved heterozygous were also blue eyed and deaf.

The strongest candidate for homozygosity produced 8 white and no pigmented kittens when mated to white heterozygous mates, and 10 white and no pigmented offspring when mated to pigmented mates. Therefore, the probability that this animal was a heterozygote was less than 0.00015 and the probability that she was a double heterozygote was less than 0.02. This animal was born with a pigmented spot on the forehead and contradicts the observation³⁹ that pigmented spots between the ears are limited to heterozygotes. Since many

proved heterozygous white cats failed to show the pigmented spot, it had little value in distinguishing genotypes.

B. Iris color and fundus structure

The second sign of the syndrome in cats is lack of uveal tract pigmentation in one or both eyes. The lack of pigmentation in the iris stroma produces a characteristic blue iris that can be distinguished from the pink iris of albinos, which lacks both stromal and posterior epithelial pigment. The absence of pigmentation in the posterior uvea (choroid) results in an extremely interesting condition; namely, absence of the tapetum, which apparently has not been described previously in the cat. The tapetum is the reflective and perhaps fluorescent layer, lying behind the central superior retina of cats, which causes "eyeshine" and is thought to increase the sensitivity of the cat's eye under scotopic (nocturnal) conditions^{21, 59}. Since the tapetum lies behind the retina, any light that it reflects or fluoresces passes through the retinal receptor cells a second time. Figure 5 illustrates the

Table V. The distribution of the area of white fur in kittens born of known parents

% White Area of Body Fur	Number of kittens of recorded parentage born in colony	Code
C = 0	82	Solid = C
0 = 1-9	1	
1 = 10-19	18	
2 = 20-29	11	
3 = 30-39	15	Low grade spotting = L
4 = 40-49	3	
5 = 50-59	5	
6 = 60-69	14	High grade spotting = H
7 = 70-79	6	
8 = 80-89	5	
9 = 90-99	0	
W = 100%	260	White = W

Table VI. The distribution of fur pigment in offspring by parental pigment pattern

Parent phenotype	Solid (C)	Low grade spotting* (L)				High grade spotting (H)				White (W)
		0	1	2	3	4	5	6	7	
C × C	5									
C × L	5				6					
C × H	3				5				10	
C × W	33								3	30
L × L										
L × H						3			7	
L × W	16					16			1	26
H × H									1	1
H × W									3	3
W × W	20					15			5	146
W† × ()										54

* See Table V for explanation of spotting grades

† White animals with only white offspring

Table IV. Observed and expected distributions of fur phenotypes in offspring of pigmented and white cats based on the hypothesis that white fur is an autosomal dominantly inherited trait

Parent fur phenotype	Offspring fur phenotype			
	Pigmented		White	
	Obs.	Exp.	Obs.	Exp.
Pigmented × pigmented	45	46	1	0
Pigmented × white (Ww)*	65	62	59	62
White (Ww) × white (Ww)	40	46.5	146	139.5
White (WW) × white (—)	0	0	54	54

* (Ww) have produced at least one pigmented offspring

differences between tapetal and non-tapetal fundi.

As a general rule the lack of uveal pigment was an all-or-none phenomenon in any given eye. That is, if the iris was blue the tapetum was missing and the choroid was also devoid of pigment. There were 6 eyes (distributed in 4 cats) among 229 white cats examined with exceptions to this rule. Three of the exceptional eyes had a brown iris without tapetum, 1 had a blue iris with tapetum, and 2 had a partially (segmentally) blue iris with tapetum. The blue eyes of Siamese cats were observed and found to possess tapeta. This was expected since pigment dilution in the Siamese differs from that in white cats⁵².

Direct observations and review of fullface photographs showed conclusively that the pupillary opening was larger in blue eyes than in brown, even when they occurred in the same (heterochromic) cat (Figure 6).

The intraocular pressures of pigmented and blue eyes were the same. Neither kittens nor adult cats showed differences with respect to eye pressure between pigment phenotypes, although the sample tested was small and the variation among individuals was fairly great.

Approximately 50 percent of the eyes of white cats were blue (Table I). A given cat showed a tendency to have either two blue or two brown eyes; only one-fourth were heterochromic (see genetic discussion below and Figure 6).

There was no lateral preference for one eye to be blue in heterochromic cats, nor was the side of the blue eyes of a heterochromic cat correlated with the side of the blue eye of its heterochromic parent(s). The association between the eye colors of parents and offspring is summarized in Tables VII and VIII.

Both mating types showed that the proportion of blue eyes in white offspring was positively correlated with the number of blue eyes in parents. When one parent was pigmented and one was white with two blue eyes, the white offspring had 71 percent blue eyes; if the white parent was heterochromic, 43 percent of the eyes of white offspring were blue; and if the white parent had pigmented eyes, only 33 percent of the eyes of white offspring were blue. These differences were not due to the dose of the *W* gene since all white progeny were heterozygous for *W*.

Table IX. The proportion of blue eyes in white offspring by the number of blue eyes in parents

Two white parents			
No. of blue eyes	Blue eyes in white offspring	Corrected proportion*	Frequency of blue in heterozygote
4	16/20	10/14	.714
3	30/48	18/36	.500
2 (1 × 1)	46/84	20/56	.357
2 (2 × 0)	4/14	4/14	.285
1	25/48	9/32	.281
0	7/14	3/12	.250
One white parent			
No. of blue eyes	Blue eyes in white offspring		Frequency blue
2	50/70		.714
1	29/68		.426
0	10/30		.333

* Subtracting expected proportion of homozygotes ($\frac{1}{3}$)

Table VII. The hearing and iris color of white offspring from one white cat and one pigmented cat by white parental iris color

Eye color of white parent	Offspring hearing status					Offspring iris color				
	Norm.	Unilat.	Deaf	Total scored	Unk.	Pigm.	Hetero.	Blue	Total scored	Unk.
Blue	17	5	5	27	17	8	4	23	35	9
Hetero.	22	3	1	26	10	15	9	10	34	2
Pigment	6	2	1	9	6	8	4	3	15	0
Total	45	10	7	62	33	31	17	36	84	11

Table VIII. The hearing and iris color of white offspring from two white cats by parental iris color

Parental eye color	Offspring hearing status					Offspring iris color				
	Norm.	Unilat.	Deaf	Total scored	Unk.	Pigm.	Hetero.	Blue	Total scored	Unk.
Blue × blue	4	0	5	9	1	0	4	6	10	0
Blue × hetero.	10	2	8	20	4	3	2	14	19	5
Blue × pigm.	3	0	1	4	3	3	4	0	7	0
Hetero. × hetero.	15	5	18	38	7	16	4	22	42	3
Hetero. × pigm.	14	3	10	27	4	8	7	9	24	7
Pigm. × pigm.	2	0	0	2	6	3	1	3	7	1
Total	48	10	42	100	25	33	22	54	109	16

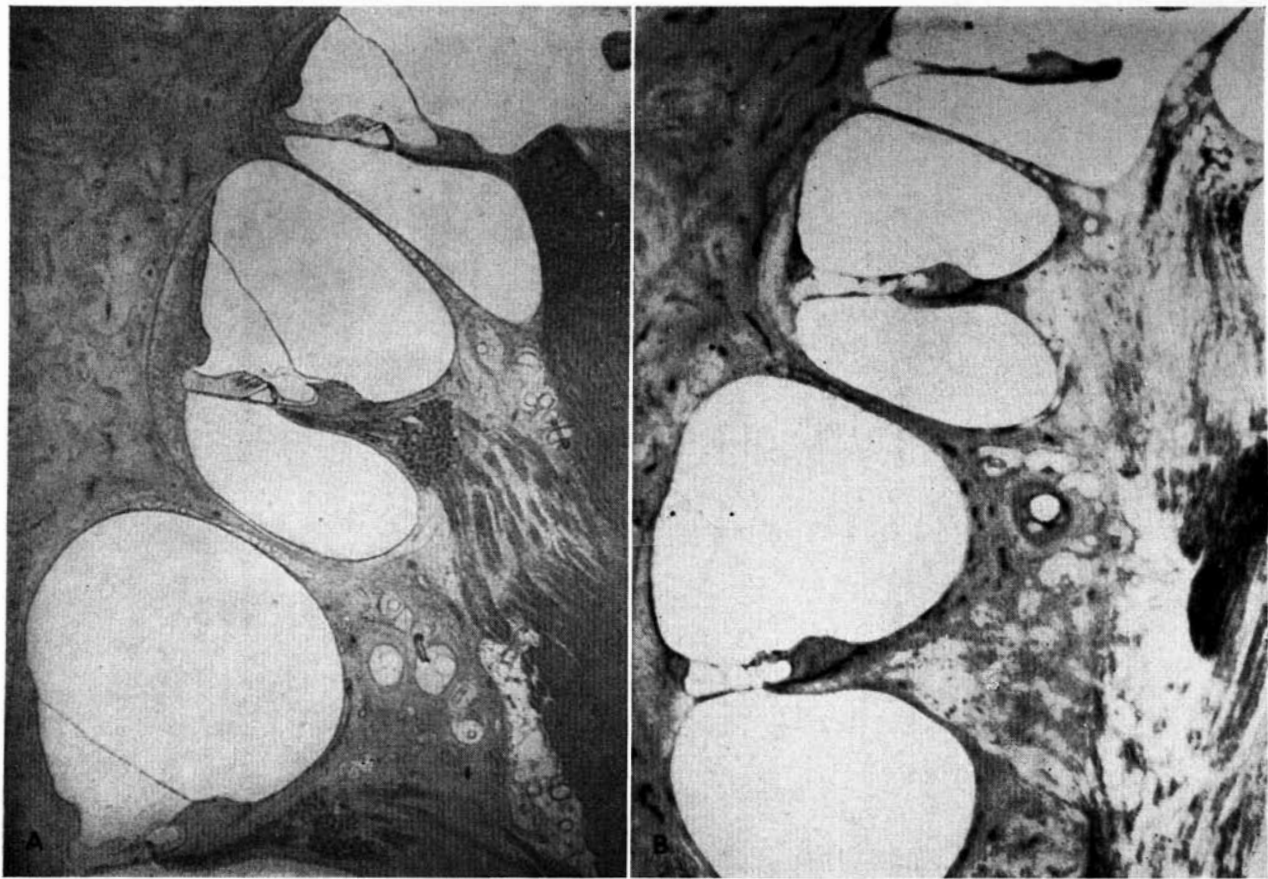


FIGURE 3—A shows normal inner ear histology; B—abnormal ear showing three turns of the cochlea.

A similar but less significant relationship was seen in the proportion of blue eyes in the offspring of two white parents. These data became more like those of the matings with one white parent when the expected proportion of homozygotes (WW) ($\frac{1}{4}$) was subtracted from the bilateral blue-eyed white offspring (Table IX). The corrected data show that when one parent had two pigmented eyes about one-fourth of the eyes of white offspring were blue regardless of the phenotype of the other parent. When both parents had at least one blue eye there was a relationship between the proportion of blue eyes in the parents and the proportion in the offspring very similar to that seen in the offspring of one white and one pigmented parent.

It appeared that a parent with pigmented fur contributed a similar genetic potential for blue eyes to that of a second white furred parent. This suggested that the genes controlling blue eyes were independent of those for white fur but were able to express themselves only in the presence of the white gene.

There was no simple segregation pattern for blue eyes in white offspring. The blue eye tended to be

bilateral, and heterochromia in the parents did not predispose to heterochromia in offspring. The genes controlling the expression of blue eyes appeared to be recessive since blue eyes in both parents of a white by white mating gave at least one blue eye in every offspring. However, they may be additive with a threshold. At least there appeared to be considerable overlap in expression of genotypes.

C. Hearing and inner ear history

Among 162 white cats born in the colony 69 were profoundly deaf in one or both ears. Only one of 60 pigmented cats tested was deaf and that was no. 512, a unilaterally deaf high grade spotted adult described earlier because she produced a totally white normal-hearing offspring when mated to a normal-hearing spotted male. Among 30 pigmented cats with temporal bones examined histologically, none had the pattern of degeneration seen in the deaf white cat. The only other histological ear abnormality seen was middle ear infection.

The histological findings of the normal cat ear are not described in detail. Figure 3 shows normal and abnormal microscopic anatomy of the cat ear. The

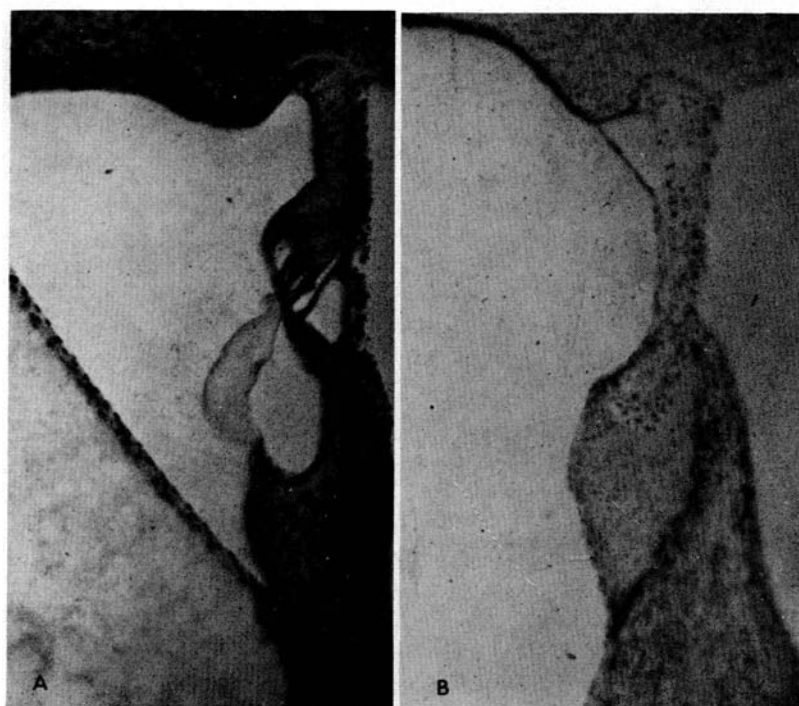


FIGURE 4—History of the organ of Corti. *A*—normal; *B*—abnormal.

histological criteria for diagnosing the inherited deformity were 1) collapse of Reissner's membrane, 2) atrophy of the hair cells and balling up of the tectorial membrane (i.e., atrophy or dysgenesis of the organ of Corti), 3) hyalinization of the stria vascularis, and 4) degeneration or absence of the oticonia and collapse of the saccular macula. Various degrees of severity of the above occur; for example,

the organ of Corti may be normal in some areas and affected in others. Figure 4 demonstrated changes 1 through 3 above.

There was a significant difference in the proportion of deaf white kittens depending on whether one or both parents were white (Tables VII and VIII). Only 7 of 62 white kittens with one white parent were bilaterally deaf, while 42 of 100 kittens

Table X. The hearing and iris color of white offspring from one white and one pigmented cat classified by white parental hearing status

Hearing status of white parent	Offspring hearing status					Offspring iris color				
	Norm.	Unilat.	Deaf	Total scored	Unk.	Pigm.	Hetero.	Blue	Total scored	Unk.
Deaf	15	7	6	28	17	8	6	25	39	6
Unilateral	14	2	0	16	8	9	8	3	20	4
Normal	16	1	1	18	8	14	3	8	25	1
Total	45	10	7	62	33	31	17	36	84	11

Table XI. The hearing and iris color of white offspring from two white cats classified by parental hearing status

Parental hearing status	Offspring hearing status					Offspring iris color				
	Norm.	Unilat.	Deaf	Total scored	Unk.	Pigm.	Hetero.	Blue	Total scored	Unk.
Deaf × deaf	3	0	4	7	0	0	4	3	7	0
Deaf × unilat.	15	2	11	28	5	5	7	14	26	7
Deaf × norm.	10	1	4	15	3	7	4	6	17	1
Unilat. × unilat.	6	2	4	12	1	4	0	8	12	1
Unilat. × norm.	5	3	7	15	3	4	1	12	17	1
Norm. × norm.	9	2	12	23	13	13	6	11	30	6
Total	48	10	42	100	25	33	22	54	109	16

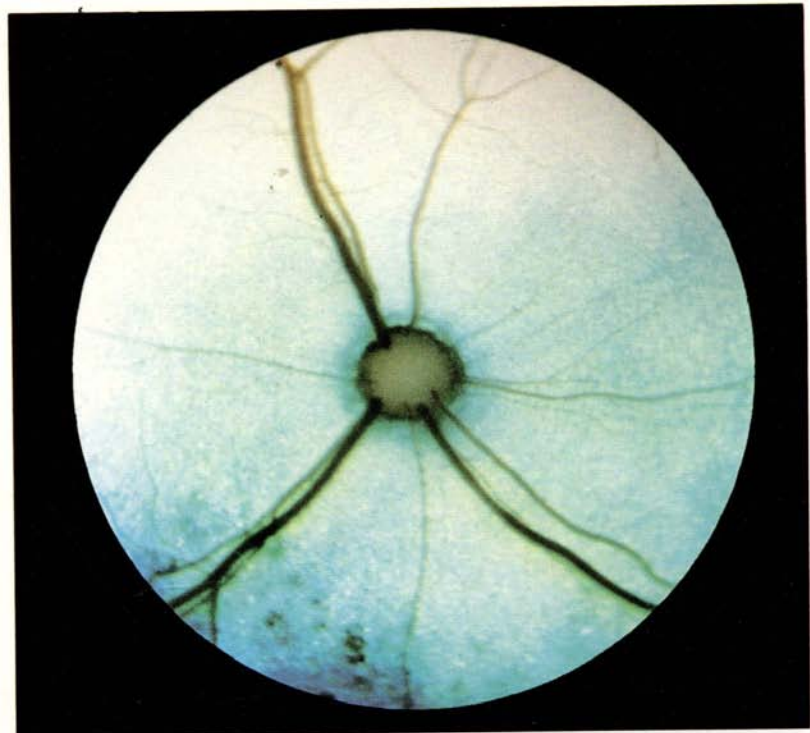
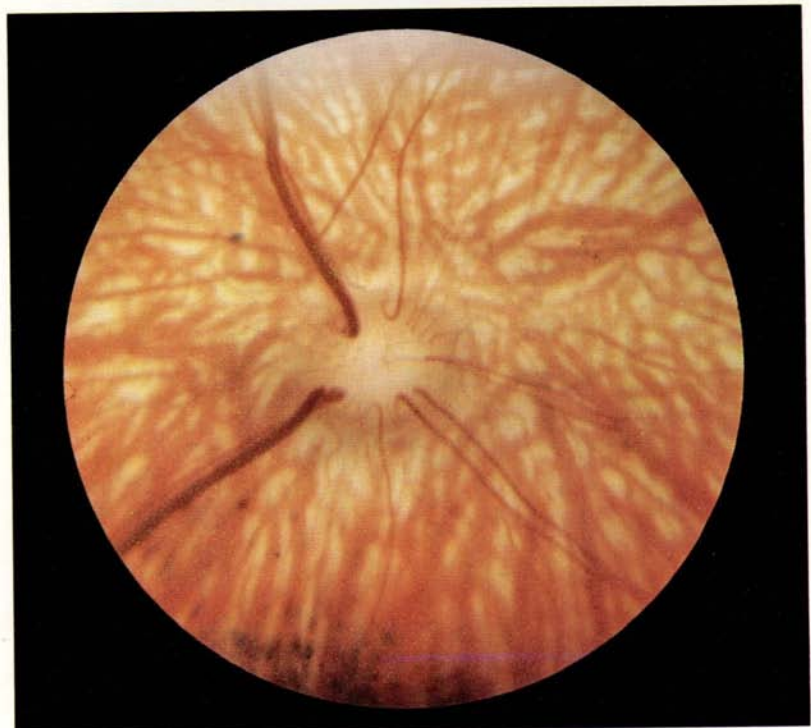


FIGURE 5—The top photograph shows a normal cat eye with tapetum, retinal arteries and veins, and reflection from tapetum behind the retina. The eye in the bottom photograph lacks the tapetum, which reveals choroidal as well as retinal vessels, and prevents the normal reflection from that membrane.



with two white parents were bilaterally deaf. Considering both unilateral and bilateral deafness, 17 of 62 offspring with one white parent were defective while 52 of 100 white offspring of two white parents were defective in one or both ears.

The white offspring of one white parent were all heterozygous for *W* and about one-fourth of them had abnormal hearing. If this proportion occurred

among the heterozygous white offspring of 2 white parents, the $\frac{2}{3}$, (the proportion expected to be white heterozygotes) $\times 100$, (the number of animals) $\times \frac{1}{4}$ were expected to show hearing loss, or about 18. Since the white by white matings were mostly between cats heterozygous for *W*, about $\frac{1}{3}$ of the white offspring were expected to be homozygous for *W* or 33 animals. Thus, the expected



FIGURE 6—Three cats with unilateral blue eyes and absence of tapetum, showing larger pupil aperture on the side of the missing tapetum. The animal with the black patch of fur is no. 512, see text.

total is 33 plus 18, or 51.

Fifty-two of the white offspring were observed to have abnormal hearing. This seemed compatible with the hypothesis that all WW cats had hearing abnormality in one or both ears. As mentioned above the four homozygotes demonstrated by progeny test all had hearing abnormality. It is possible,

however, that an occasional homozygous normal-hearing cat may occur.

In Tables X and XI the distribution of the offspring phenotypes in relation to parent hearing status is presented. There was no clear association between parental hearing status and white offspring hearing within the white by pigmented or white by white mating types. This suggests that other genes did not interact with W in the production of deafness as they did in the case of blue eyes.

There was no correlation between the proportion of deaf offspring and parental eye color either in offspring of one white parent or two white parents (Tables VII and VIII). However, there was some tendency for deaf parents to have a higher proportion of offspring with blue eyes. This was most noticeable in the offspring of matings of white by pigmented cats (Table X), but was also present in matings with two white parents (Table XI).

There were nine cats in the colony that were unilateral for both blue iris and deafness. No relationship was present between the side of deafness and the side of blue iris. The observed frequency of unilateral expression of eye and ear defect was not different from the product of the expectations of unilaterality for each condition alone. This suggests that these two parts of the syndrome are independent of each other in expression.

D. Relationship between eye color, hearing, and head spot

Despite the absence of correlation in laterality, pooled data revealed an association between the number of blue eyes and number of deaf ears within individual white cats (Table I). Bilaterally blue-eyed cats were more frequently deaf than were heterochromic white cats, which in turn were more frequently deaf than bilaterally brown-eyed cats. An analysis of the relationship of blue eyes and deafness to the presence of a head pigment spot is presented in Table XII. The deaf white cats were significantly more often blue eyed, and less often had head spots than did hearing cats. White cats with a head spot were less often blue eyed or heterochromic than were those without a head spot.

Since the black spot disappeared in many cases it was necessary to have matings of cats known from birth to get data on the inheritance of the head spot in white animals. Table XIII shows the distribution of the occurrence of head spotting in white kittens classified by the head spotting present in their parents. Unfortunately, the numbers were small and were complicated by the lack of sufficient progeny testing of some white parents. However, it is possible to suggest from the data that the head spot was inherited, that the mode of inheritance was complex—rather like that of blue eyes—and that it may be more frequent in cats heterozygous for W than in those homozygous for the white gene.

E. Comparison of general cat population and colony

The fur and eye color of cats accepted at the NIH

Animal Quarantine at Poolesville, Maryland, are presented in Table II. The criterion for classification as a white cat was less than 10 percent pigmented fur. However, nearly all of the white cats actually fell into the class of pure white or white with a small pigmented patch on the forehead. Eighty-five percent of white cats at Poolesville had bilaterally pigmented eyes. However, of the white kittens born in the colony, only 33 percent had bilaterally pigmented eyes (Tables IV and V).

As noted before, the proportion of pigmented eyes was the same whether one or both parents were white. Thus the proportion of blue-eyed and heterochromic white cats in the colony may represent the proportion at birth of blue eyes among white cats in nature. Some bias was introduced because only 20 percent of the white cats selected as breeders were bilaterally brown-eyed. Twelve of the 17 basic stock were heterochromic. However, even the bilaterally brown-eyed cats produced less than 55 percent brown-eyed, white kittens. Thus, the observed adult frequency of brown eyes in white cats in the NIH Quarantine appeared to differ from that at birth.

Survival of white and pigmented cats at the NIH Quarantine is documented in Table II. There was a significant difference in mortality between white and pigmented cats. The average viability of white relative to pigmented was about 0.92 during the 30-day quarantine period. The mortality experience

in the breeding colony showed no significant difference between pigmented and white cats for two reasons: 1) most animals were sacrificed at an early age for testing, and 2) the mortality rate had been very low (5–15 percent) for both pigmented and white cats in the colony. As noted earlier, conditions in the colony were designed to protect the animals and therefore provided an inadequate test of differential survival ability.

Although survival data of significance could not be obtained from the breeding and testing colony, it was possible to collect reliable data on litter size. No significant differences in litter size were observed between white and pigmented animals for various

Table XIV. Litter size in pigmented and white animals in the colony

Mating type	Number of litters	Total offspring	Average litter size
A. White ♂ × white ♀	51	180	3.53
B. Pigm. ♂ × white ♀	33	112	3.59
C. White ♂ × pigm. ♀	18	53	2.94
D. Pigm. ♂ × pigm. ♀	12	45	3.83
Combinations			
A + B White ♀ total	84	292	3.48
C + D Pigm. ♀ total	30	99	3.30
A + C White ♂ total	69	233	3.37
B + D Pigm. ♂ total	45	158	3.51

Table XII. Analysis of relationships of hearing, iris color, and head spot in white cats

Hearing	Iris color				Total	Head spot by hearing		
	Pigm.	Hetero.	Blue	Unk.		Spot	No spot	Unk.
Normal	46	30	27	9	112	53	57	2
Unilat.	5	9	14	0	28	9	19	0
Deaf	8	10	36	3	57	13	43	1
Unk.	18	6	20	13	57	23	30	4
Total	77	55	97	25	254			
Head spot by iris color						Chi-square test:		
Spot	37	20	32	9		Hearing vs. iris color:		
No spot	39	32	65	13		$\chi^2 = 28.3, P < 0.001$		
Unk.	1	3	0	3		Head spot vs. hearing:		
						$\chi^2 = 10.3, 0.01 > P > 0.001$		
						Head spot vs. iris color:		
						$\chi^2 = 4.4, 0.2 > P > 0.1$		

Table XIII. The presence of head spot in white cats (spot) or generalized fur pigment (pigm.) classified by mating type of their parents for head spot or generalized fur pigment

Parents type	No. matings	Offspring fur			Average litter size
		Spot	No spot	Pigm.	
Spot × pigm.	5	4	5	17	5.20
No spot × pigm.	8	5	10	11	3.25
Spot × spot	4	5	5	2	3.00
Spot × no spot	6	3	8	6	2.8
No spot × no spot	2	1	4	0	2.5

mating combinations (Table XIV). The data were contrary to that expected if there was a significant intrauterine lethal effect of the *W* gene. There did appear to be a suggestion of a relation between presence of head spot in a parent and litter size (Table XIII) but the numbers were not large enough for statistical testing.

Sex ratios and fur color ratios of offspring for each mating type were also studied in the colony. These ratios did not deviate significantly from expected ratios and did not show any pattern suggesting sex linkage or differential loss of white fetuses.

Discussion

Our results strongly support the conclusions reached by earlier workers that the white fur with blue eyes and hearing loss is usually due to an autosomal dominant gene. The distinction between genes at one or more than one locus cannot be made from our data, but the weight of evidence is in favor of only one locus. The *W* gene appeared to be allelic with a series of alleles controlling spotting and some of these alleles did result in a full white phenotype and in blue iris and deafness of the same type as in the white cat.

The relationship between *W* and the genes of the allelic series causing varying degrees of piebald spotting was somewhat clarified by our data. In 12 backcross matings of white cats to solid pigmented (62 kittens) we never observed segregation of white and two different classes of piebald in one litter. The offspring showing pigmented fur were all within one class. Since the solid parent could not contribute piebald genes we concluded that there was only one gene at the piebald locus free to vary in the white parent. Thus, the dominant white was an allele at the locus for piebald spotting. Similarly, for matings of two white heterozygotes, their pigmented offspring were almost always of one class although three exceptional individuals of adjacent degrees of piebald were observed who differed in degree from their pigmented siblings. These exceptions among 40 pigmented kittens may represent errors in classification or phenotypic overlap.

The segregation of the offspring supported the conclusion of Whiting⁶² that white is an extreme of piebald and top dominant of an allelic series. There was a tetramodal distribution of pigmentation and there appeared to be four alleles of increasing dominance *w*, *W*¹, *W*², and *W*³ for solid color, low degree of piebald, high degree of piebald, and total white. We have observed that the phenotypic classes overlap and that the high degree piebald could have white fur, blue eyes and be deaf (no. 512, no. 270). The genes reducing pigment areas most were dominant over those reducing pigment less, and genes giving all white were the most dominant.

Since it is clear that a high degree of piebald is associated with pleiotropic effects on eye and ear, it seems appropriate to distinguish it from white spotting without pleiotropic effects (*S*) as characterized by Searle⁶². The actual distinction of these two phenotypes may depend on background geno-

type and not on the major gene in question. As there is no evidence for anemia in these animals these alleles are probably not homologs of the dominant spotting and anemia (*S1* and *W*) in mice, or the fox, which also differ in that they show lethality in homozygotes.

The homology of the high degree of piebald allele and Waardenburg syndrome in man is strengthened by the presence of premature graying in affected members of both species. This is illustrated by Figure 1 (upper and lower right), which shows the change in intensity of the pigmented areas in one cat over a one-year period.

The eye pigmentation and ear defects differed in relation to the major pigment change in the fur. The (*WW*) homozygote had bilateral blue eyes. The expression of blue eyes in the heterozygote (*Ww*) appeared to be controlled by other genes that were present with similar frequency in white and pigmented cats. The average penetrance of blue iris was about .25 in heterozygotes regardless of the rest of the genome, but was increased by the presence of other genes that did not show any simple segregation among offspring and appeared to act in an additive manner.

The ear defect was about 43 percent penetrant and had a dosage relationship to *W* so that *W* acted as an incomplete dominant with very high penetrance in the homozygote and about 27 percent penetrance in the heterozygote. Hearing status did not appear to be affected by other genes.

The pigment spot on the head of a white cat had a significant relationship to its hearing status. The data did not permit genetic analysis of the inheritance of head spot as a part of the dominant white phenotype and distinguished from other body spotting. Results suggested that both the dosage of *W* and other components of the genome were related to the expression of head spotting. Analysis was not a simple matter since three of the four progeny-tested *WW* homozygotes had head spots.

The absence of head spot in cats appeared to be similar in relationship to *W* as did the white hair spot to Waardenburg's syndrome of man^{15, 67} in which fewer pigmentation defects were correlated with a lower incidence of deafness. In general, lesser pigment was associated with higher frequency of hearing defect. This was probably a reflection of the common mechanism involved in the development of both components of the syndrome.

The defects found in the cat, in man and in several other animals exhibiting this syndrome all appear to be related to maldevelopment of structures derived from the early embryonic neural crest^{6, 19, 22, 23, 25, 29, 45, 47}. Various mechanisms (e.g., failure of neural crest migration, improper interaction with other cell lines, etc.) have been proposed, but the evidence is not conclusive^{8, 41, 42, 46, 53, 60}. It is interesting that some of the cats in question exhibited coat patterns similar to those which have been shown to be secondary to neural crest clone effects in allopheic mice⁴⁸.

The specific defect in the inner ear is probably in the efferent component of the eighth nerve and the

spiral efferent intraganglionic fibers that synapse on the hair cells of the organ of Corti. There are apparently no efferent nerve endings in the organ of Corti of the deaf dalmation dog³ and nerve endings are also missing in the deaf shaker-1 mouse^{34, 35}.

The efferent cochlear pathway acts to suppress the auditory action potential²⁷. In the mouse the efferent nerve endings arrive at the hair cell on the tenth postpartum day and this is associated with the appearance of hearing function³⁴, suggesting that these efferent fibers play an essential role in cochlear function.

There is evidence that the efferent cochlear pathway contains postganglionic neurons (parasympathetic)⁴⁹. Such postganglionic neurons in other parts of the body, such as the paraspinal ganglia, are of neural crest origin⁶⁰. In fact some of the piebald mouse mutants have megacolon with reduction of the myenteric ganglion⁷. If the efferent intraganglionic spiral fibers of the cochlea are indeed postganglionic it makes their neural crest origin probable and explains that association of the ear defect and the defects of pigmentation.

These efferent intraganglionic spiral fibers should be distinguished from the afferent fibers that constitute the bulk of the spiral ganglion, which are of placodal origin^{14, 65}. The afferent ganglia are only rarely involved in pigment defect associated deafness. It is not necessary to suppose that the ganglion as a whole is of neural crest derivation, as proposed by Deol¹⁸⁻²⁰.

A defect of neural crest cell migration, or a defect of neural crest cell interaction with the several structures involved in the syndrome, would explain the correlation of deafness with blue eyes and lack of forehead pigmentation, since whatever predisposes to improper function of neural crest cells in one region might be expected to produce similar effects in other regions as well.

Extending this reasoning one might consider other tissues that are derived from neural crest as possible sites of additional defects in the cat. These tissues and expected clinical abnormalities have been described for the human by Brown and Podasin¹¹. Dental aplasia, urinary incontinence, and fecal incontinence were not observed in the white cat. We did, however, observe a decreased blood vessel tone and prolonged bleeding when white cats were given intravenous injections as compared to pigmented cats in our colony. The function of spinal ganglia and the chromaffin system and the anatomy of the meninges have not yet been investigated. Negative findings would not be unexpected, however, since Brown and Podasin were describing a syndrome clearly distinct from Waardenburg's in the human. Moreover, the functions of these spinal neural crest derivatives have not been described as defective in Waardenburg's syndrome.

The comparison of the cat population and colony phenotypic frequencies provided evidence that selection was taking place both among cats affected by the syndrome and between such cats and the "normal" variety. First, population surveys revealed

phenotypic frequencies of white cats ranging from 0.7 to 7.7 percent (see above and Moffatt⁴⁴ and Todd⁵⁵). All of these values were too high to be maintained by mutation at a single locus in the face of the demonstrated negative survival value of white cats at the NIH Quarantine. Secondly, the ratio of eye colors of white cats accepted at the NIH Quarantine was highly biased towards bilaterally pigmented in spite of the evident ability of heterochromic and blue-eyed cats to reproduce their kind and survive within the breeding colony.

Several mechanisms could be proposed to explain the above findings. First, there may be positive selection for white cats by man. This would be a form of frequency dependent positive survival value for white cats at the frequencies observed above. Second, although the lack of tapetum in blue-eyed cats did not seem to explain strong negative selection against the syndrome, particularly in heterochromic cats, the demonstrated association of blue eyes and deafness may be a potent force, which explains the marked deficit of blue-eyed and heterochromic cats in the Poolesville sample compared to the breeding colony. Finally, the syndrome probably involves other physiological defects affecting survival that have not yet been detected, since even brown-eyed white cats did not survive as well as pigmented cats at the NIH Quarantine.

In contrast to the findings of Jones³³ described above there was no decreased litter size of white females in our colony. His comparison was primarily between pigmented and white females mated to pigmented males. Jones' interpretation implied reduced survival of the heterozygote. The difference may be due to a more severe environment affecting the animals Jones studied, similar to the data from Poolesville.

Although some homozygous cats of both sexes proved to be fertile, we attempted to breed several white animals without success. This was not true of any pigmented cats. Among white animals produced by matings of known white heterozygotes, the theoretical expectation was that $\frac{2}{3}$ were heterozygous and $\frac{1}{3}$ were (*WW*) homozygous. The reproductive behavior observed in the colony supported this expectation in that 11 of 16 white cats that had white parents and had been tested were heterozygous. There were an additional eight white cats that had had two or more years of mature exposure to possible mating partners of proven fertility without reproduction. This suggested that some proportion of white cats of both sexes were sterile, but that this was not more likely in homozygous *WW* than in heterozygous *Ww* animals.

There were thus several mechanisms for selection operating on *W*, sterility of some white animals and selection against white animals with blue eyes and deafness after birth. The decreased ability of the white animal to resist disease appeared to be a possible major selection factor.

In the face of these selection pressures there was question as to what maintained the white phenotype. Obviously, in a domestic animal the desires of man

are a significant factor. This is well documented by the cat fanciers who value heterochromia and white fur. It did not seem that mutation at a single locus could maintain *W* in the observed frequency. However, if there were several independent loci with genes controlling the development of neural crest the cumulative mutation rate might balance the observed selection. The failure to detect evidence for more than one locus in the offspring of 21 independent white cats from the wild animals that were white suggested that human selection was the major factor in maintaining this gene.

Summary

The phenotypic characteristics of a syndrome in cats causing white fur, blue eyes, and deafness are described. Its relationship to syndromes in other species, especially man, is reviewed. The syndrome results from a dominant autosomal gene *W* that is fully dominant with complete penetrance in the production of white fur, with incomplete penetrance of deafness, and incompletely dominant in the production of blue iris. Blue iris is also conditioned by other genes that produce high degrees of white spotting that are allelic to *W* and by other independent genes. The basic common path of action of the *W* gene appears to be on the development of structures derived from neural crest.

Strong natural selection was observed against the *W* gene. It appears to be maintained through human selection in the face of reduced disease resistance and semisterility, as well as deafness and reduced vision in low light conditions.

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