

Congenital Sensorineural Deafness in the Dalmatian

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Congenital Sensorineural Deafness in the Dalmatian

(Some thoughts on the subject by an interested nonprofessional)

James E. Seltzer, Ph.D.

Deafness and the Genome - CANGEN - 2/28/00

T.. wrote:

"The Dalmatian people, as I understand it, are not accepting of Dr. Strain's conclusions. They have therefore given a grant to the University of Michigan to search for the gene which causes deafness in their breed ..."

Thanks, T., for the information on the DCA/AKC research grants. It seems that the question has become: Since we have a statistical correlation between sw homozygotes, absence of melanocytes in the stria and congenital sensorineural deafness, is there really any need for further research? If the fundamental problem is with the sw allele and modifiers, then the appropriate course of action would seem to be to select against sw (or at least its extreme expression and therefore select for more of Little's "+ modifiers" with consequent increase in patched zones). The answers are not all in as a close reading of Dr. Cattanaach's comments on the migration of melanocyte precursors from the neural crest, their dieback and subsequent re-population reveals. The following (vintage 1997) is also of some interest:

A number of years ago I asked Dr. Strain:

"...Do you believe that the absence of melanocytes in the stria vascularis is the actual CAUSE of sensorineural deafness in Dals, or is this simply an anomaly which is observed in some but not all deaf Dals? In other words, if a Dal is unilaterally deaf, does the stria vascularis in the hearing ear contain melanocytes and the stria vascularis of the deaf ear contain no melanocytes? If the answer is yes, then the genetics of deafness is the genetics of melanocyte development and function, and we need look no further for a gene or combination of genes for deafness per se..."

Dr. Strain responded:

"I believe that the absence of melanocytes is the CAUSE of deafness, but that doesn't turn it into a simple question. There are probably one or more genes that are modifying the expression of the gene(s) responsible for melanocyte migration from the neural crest in the embryo and their differentiation in situ. I don't know anyone who has worked on these modifiers, the tyrosinase gene system, or their mode of inheritance..."

As an aside, I was struck by a vague feeling of unease while reading the article "Asthma, Environment, and the Genome," by Matt Ridley, Natural History, 3/00. Since so many genes "for" asthma are being uncovered in one population that are not related to asthma in another population (or another family or even another sex), some have begun to shrink from the idea that there is actually a

gene “for” anything! That, instead, the expression of attributes or disease is all a matter of “pleiotropy and pluralism.” One is left with the disconcerting feeling that the entire genome is playing some grand symphony and we are trying to understand its beauty and grandeur by isolating a single note and analyzing its mechanics.

Ridley concludes: “We’d better get used to indeterminacy. The more we delve into the genome, the less fatalistic it will seem. Gray indeterminacy, variable causality, and vague predisposition are the hallmarks of the system. The genome is as complicated and indeterminate as ordinary life because it IS ordinary life. This should come as a relief. Simple determinism — whether of the genetic or the environmental kind — is a depressing prospect for those with a fondness for free will.”

Theories on Deafness - CANGEN - 3/3/00

M.. quoting C.: >>I was impressed with Dr Strain’s figures. And if I had a breed, 30% of whom were deaf, I would sure as heck want to review those figures, and try to verify or debunk them. sitting on the banks of de Nile, sure can’t be doing the breed any good.<<

M.: >I’ve been too busy to keep up with the list but I don’t get it. One man with a theory suddenly means those of us concerned with deafness that don’t agree with him are in denile? I must be stupid.<

Jokes aside, M., you are not in de Nile and certainly not stupid, but I’m not sure I understand your specific points of disagreement with Strain’s views on congenital sensorineural deafness.

As I understand your position (correct me if I have misinterpreted), you have found that selection for breeding of dogs that perform well on the BAER test (meaning that their BAER traces show higher synaptic response peaks at lower levels of auditory stimulus than are commonly used) results in fewer progeny that are deaf. This might imply that a deficit, but not total absence of, melanocytes in the stria vascularis could, instead of total deafness, manifest as diminished auditory acuity. The defect would still be potentiated by the expression of the piebald, extreme piebald, or merle genes. If this approximates your position, then I do not believe it is a direct contradiction of Strain’s principal observations. However, I do not believe he has collected data on the density of cochlear melanocytes in dogs that are not deaf but respond only at higher levels of auditory stimuli. To do so would be informative, but obviously not practical since it would require the euthanizing of dogs that can hear.

You will certainly disagree with Strain’s comment: “Deafness may affect one or both ears, but partial hearing loss in an ear does not appear to occur in this disorder.” But I believe this conclusion is based on postmortem evaluation only of deaf puppies that were euthanized and turned over for research.

The OMIM ENTRY 193500 for Waardenburg syndrome does little to resolve this issue:

1. “The work of Boshier and Hallpike (1966) on an animal analog, deaf white cats, suggested that destruction of the inner ear mechanism occurs in the first days of extrauterine life and was correlated with an inability to regulate properly the constitution of the endolymphatic fluid. The cat, like man, may escape deafness in one or both ears. If more of the factors that lead to retention of hearing were known, deafness might be preventable.”

2. "Motohashi et al. (1994) pointed out that melanocytes are a normal component of the inner ear, including the stria vascularis. There are 3 known mutations in the mouse which lead to a deficiency of melanocytes in mast cells: white dominant spotting (W), Steel (Sl), and microphthalmia (mi). All 3 mutants have a thin stria vascularis, without melanocyte-like intermediate cells, and severe impairment of hearing. Thus, the absence of intermediate cells or melanocytes causes severe hearing loss. The absence of melanin has little influence on hearing acuity because albino mice without melanin have no impairment of hearing."

If Dal deafness were homologous to that in white cats, the cochlear degeneration reported in case 1, above, would support the contention of the resultant total deafness, and the etiology of this disorder reported by Strain implies such a similarity. OTOH, if Dal deafness were related to that reported in 2., then "the absence of intermediate cells or melanocytes causes severe hearing loss." This latter statement is more supportive of your position.

I have appended Strain's summary conclusions from his web page. If there are any of these conclusions with which you disagree, I would be very interested in knowing which and why.

***** Extracted from:

http://www.lsu.edu/guests/senate/public_html/recent.htm

SUMMARY/CONCLUSIONS

1. Deafness prevalence in the Dalmatian is approximately twice that seen in other affected breeds where reliable data are available.
2. No deafness prevalence differences by sex or ear were seen.
3. No coat color differences in deafness prevalence within breeds were seen except for the Bull Terrier, where whites had greater deafness than coloreds.
4. Pigmentation traits in Dalmatians were consistent with an association between strong expression of the extreme piebald gene and deafness: dogs with blue irises or missing tapetal pigmentation were more likely to be deaf (piebald suppression of eye pigmentation), while dogs with a patch were less likely to be deaf (failure of piebald to suppress the underlying coat color).
5. The increased prevalence of deafness in dogs with at least one deaf ear among its parents compared to dogs from parents with four good ears supports a hereditary factor in pigment-associated congenital sensorineural deafness, consistent with similar syndromes in humans, cats, mice, mink, and other species.
6. Pigment-associated congenital sensorineural deafness continues to be a significant disorder in dog breeds with the piebald, extreme piebald, and merle genes. Reduction in prevalence can currently only result from selective breeding away from affected animals, including those with unilateral deafness, and animals with a history of high numbers of affected offspring. Hearing registries, such as one recently established by the English Setter Association of America and one proposed by the Dalmatian Club of America, will provide the information base for progress in this area.

Strain may also have reached other conclusions, but these are the only ones I could find listed on his most recent web page.

Ethical Question - SHOWDALS - 3/15/00

*****Part 1*****

L.. wrote:

”...The reasons given for the policy include an increased risk of being hit by a car, as a result of the deafness, and an increased tendency to bite, because the dogs are so easily startled. You check the Dalmatian Club’s Web site to substantiate the claims of increased injuries and biting problems but find no data to support the claims. You routinely euthanize dogs on humane grounds, but this situation is somewhat different. How should you proceed?”

L.., you have opened a subject that has no easy answers, evokes strong opinions, and is certainly divisive. I have no solution to all the many issues that have been raised on both the pro- and con-euthanasia sides. I have observed, however, that many arguments are transparently fraudulent, and, in positing these as an official DCA position, diminish the stature and credibility of our club. Because the decision to euthanize has such an overwhelming emotional content, it is not surprising that we are prone to seek consolation by embracing platitudes.

Having spent the better part of a lifetime in scientific research - studying, interrogating, experimenting, hypothesizing and then throwing it all away and starting over when the expected results do not fit the data - my innate nature rebels against the simple answers, distortions, rejection of data that do not fit preconceptions, and outright prevarications that have characterized this subject.

Increased risk of being hit by a car:

I have known several Dalmatians that were struck by cars and killed - none were deaf. I have never known any Dals that could be considered street-wise in the sense of that stalwart subculture of canines that adapt and survive in the streets and alleys of metropolitan areas. The Dals that I have known have always expected that pedestrians, bicycles, and motor vehicles were obliged to yield the right-of-way to the Dal - a presumed position of dominance in the hierarchy that does not bode well for survival on the street, but irrespective of the hearing status of the Dalmatian.

Once, while hiking with several of my Dals off-lead in the woods, two of them decided to take off in the direction of the road. I yelled - they were both bilateral normal hearing - but the spirit of rebellious adventure carried them on and I could merely follow. When I heard the beeping of a horn, I became even more worried. When I finally reached the road, I found both Dals sitting in the road directly in front of a stopped school bus, totally oblivious to the impatience of the bus driver.

Increased tendency to bite: Let’s face it, some Dals have a nasty disposition. This might be an atavistic attribute that traces its hereditary roots to the days when Dals were supposed to be tough and aggressive to fulfill their function as guard dogs. I had been involved in the fancy for many years

before I met some really vicious Dals. But as I became more involved with my all-breed club's training programs in both puppy kindergarten and obedience, I found more than one Dalmatian enrolled in these courses that demonstrated a keen dislike for both humans and canines and quickly became anathema to the class and the scourge of the instructor. These Dals could hear, they simply paid no heed, nor did they require provocation to charge full speed with bared teeth. As most of you are aware, several years ago an effort by a regional Dalmatian club to collect and evaluate statistics on the relative incidence of behavioral problems in deaf vs. hearing Dals revealed no significant difference. Yet, to my knowledge, this study has still not been published.

(Deaf) dogs are so easily startled:

Yes, more easily startled because of their lack of auditory cues, but anyone that approaches a dog without providing some notice of his approach invites a startle response from the dog. There is more than a little folk wisdom in the adage: "Let sleeping dogs lie." All dogs, particularly the geriatric members, can be provoked into a startle response with untoward consequences, especially for young children.

*****Part 2*****

At one time there had been a lot of blather about brain anomalies in deaf Dals among the fancy, which, in addition to their deafness, was thought to make them unsuitable as pets. However, Dr. George M. Strain, published in the British Veterinary Journal early in 1995.

"It has been shown that the auditory cortex of deaf Dalmatians is grossly reduced in size (Ferrara & Halnan, 1983) leading the authors to the suggestion that the origin of deafness in the breed was central rather than peripheral. Although not reported, it is likely that other CNS structures in the auditory pathway were also smaller than in hearing animals. However, it is well known from classical studies that kittens whose eyelids were sealed after birth failed to develop normal CNS visual structures, demonstrating that normal sensory input is necessary for the full maintenance of these structures. As a result, the findings in the Dalmatian are undoubtedly a reflection of the same pathology. These CNS changes in deaf dogs have been used to justify euthanasia on the basis of having an "abnormal" brain, but neurologically the brain function of deaf animals is normal except for the loss of auditory function."

This concern for abnormal CNS patterns is somewhat paradoxical since many of these same fanciers do not hesitate to mutilate their dogs by trimming the vibrissae (whiskers) to present a "smoother appearance" in the show ring. While congenitally deaf Dal puppies are condemned to early euthanasia because of their hearing disability and the purported brain abnormalities, the fancy's show mentality nonetheless justifies the destruction of a major sensory organ with concomitant loss of tactile neuronal pathways. It is known that in marine mammals the vibrissae are especially important. Their vibrissae are sensitive up to 100 Hz signals which means they provide some auditory (vibrational) reception in the infrasonic region.

I did a web search for information on vibrissae, tactile sensory attributes, and neuronal paths. The best reference I found is: <http://www.neurobio.pitt.edu/barrels/intro.htm>

The figure on that web page "shows a remarkable correspondence between the pattern of the

mystacial vibrissae (whiskers) on the face of a mouse and the spatial organization of neuron clusters in its contralateral cerebral cortex. Because of their characteristic three-dimensional shape, Woolsey and Van der Loos called these neuronal structures 'barrels'. [The] figure presents the authors' 'one barrel-one vibrissa' hypothesis which proposed the now firmly established one-to-one relationship between individual whiskers and their corresponding cortical barrels."

The report continues: "Woolsey's and Van der Loos' 'one barrel-one vibrissa' hypothesis was quickly confirmed. Influenced by classical neuroembryological experimentation, Van der Loos and Woolsey (1973) ablated selected whisker follicles in newborn mice and observed, in the mature animal, an absence of cortical barrels corresponding precisely to the damaged vibrissae." This statement relating to experiments on mice tends to corroborate John's comment regarding degeneration of certain brain tracts in dogs when vibrissae are cut.

Yet the evidence condemning this type of mutilation is even stronger. Of all mammalian species, humans are virtually alone in being deprived of vibrissae and the corresponding sensory inputs. The work of Woolsey and Van der Loos reveals a spatial mapping and one-to-one correspondence between the vibrissae and the tactile sensations as mapped onto the brain. The closest analog to this that I am aware of is the patterned correspondence of images in the visual field and corresponding excitation of the visual cortex. Thus it would appear that vibrissae stimulation can provide an alternative (distinct from and somewhat coarser than visual images) mapping of external reality in a spatial 3-dimensional context.

The damning aspect of this is that we, being ourselves singularly deprived of the rich mental stimulation of vibrissae tactile sensations, value it so little that we casually deprive our dogs of these attributes. One can only imagine that were we all born without eyes, we might be equally likely to blind our dogs for cosmetic purposes having no understanding of what we were taking from them.

*****Part 3*****

L.. continued:

"I would like to invite your responses to this scenario and your feelings on this issue to help me compile a response for our journal. Beyond the reasons given above I am concerned with the potential for abuse of the deaf dog when it fails to respond (due to inability of the trainer/owner). A deaf dog has special needs and requires a skilled trainer. I think that it's hard enough to find good homes for a lively, intelligent breed like the Dalmatian without adding a handicap like deafness. I don't feel that euthanasia is cruel, inhumane or immoral and have always been a proponent for "quality of life vs. quantity". As long as healthy puppies and dogs of any breed are being euthanized simply for lack of an available home, I don't see the need to "save" dogs with a handicap that could provide potential for abuse and a poor quality life."

This gets to the crux of the matter. It points to the core of our priorities, and, some would argue, to the maturity of our ethical standards. Finding a good home for a Dal puppy is no easy task. It gets harder if the puppy is apparently imperfect in some recognizable way: is patched, has parti-colored eyes — or is unilaterally or bilaterally deaf. There was a time when "bucketing" an entire litter of puppies of poor quality was an acceptable and expected route for the practiced breeder. The hardness of our purebreds is said to have grown out of this unforgiving culling where only the fittest

survived and propagated. Many will find this argument inadequate.

Unbiased surveys and a multitude of news reports have shown that deaf puppies can be successfully integrated into a caring family and not be subjected to abuse. The real difficulty in placing a deaf Dal puppy is the need for the breeder to allocate sufficient time to find a suitable home and to continue to provide support for the owners and assistance with the training as the puppy matures. This means that the breeder must balance the time spent in the further pursuit of show wins against that needed to ensure the proper placement and care for deaf Dal puppies that were produced by his own breeding program.

One does not breed every Dal — only the select few are deemed worthy of passing on their genes to the future. In the same manner, one does not breed deaf dogs, so the issue of propagation and consequent increase in the rate of deafness is moot.

The real issues are a lot tougher and involve the circumscription of our own individual responsibilities. We may not be able to assist, or feel responsible for the plight of all the hungry children in Somalia — this does not in any way limit our responsibilities with respect to our own children. In much the same manner, we may not feel directly responsible for the plight of puppies in shelters that are doomed to extinction — yet, our personal responsibilities toward puppies that we have produced is not thereby diminished.

The questions are tough and the answers are not any easier; I certainly don't have any. It would seem that each one is obliged to do his own soul searching. My dispute, if I have any at all, is with the people who try to make this a simple, cut-and-dried issue — especially those that claim to be the oracle for the “ethical” position or those that fabricate or falsify data to promote their views.

*****an afterthought*****

Ethical standards that counsel club members to humanely euthanize all bilaterally deaf puppies produced by the member's brood bitch or sired by the member's stud dog seem to me to be in the same vein as the mother who tells her reluctant 5-year old to eat his broccoli and to “think of all the starving children in the world who would be happy to have it.” This might work with a 5-year old. However, should she use this approach with her 10-year old, she would probably get the response: “If I eat my broccoli, will there be any fewer starving children?” We might do well to emulate the 10-year old and ask whether the breeder who euthanizes a deaf Dal puppy rather than allocating his time and resources to find a suitable home will then utilize his time and resources to alleviate the problem of finding homes for all the unwanted Dal puppies that are waiting in the animal shelters.

Dalmatian Spots and Chaos - CANGEN - 3/30/00

Mary is 99 years young, a resident at a nursing home that I visit with one of my Dalmatian therapy dogs every week. When I approach Mary's wheelchair with my Dal, Mary invariably asks, “What's the dog's name?” I answer, “Her name is Punky, and she was named after the little girl, Punky Brewster, on TV.” Mary will then ask, “Did you count the spots?” I say “No, but if you want to help

to count them, I can start at the tail and you can start at the nose, and when we get to the middle we will know how many spots Punky has.” Mary responds with some degree of exasperation, “You can count them yourself! You’re just too lazy!”

Relevant to predictability I found a short commentary by Prof. Richard Lewontin, “Computing the Organism,” in *Natural History*, 4/00. Lewontin disputes a statement by an unnamed, eminent molecular biologist who claimed “that if he had the complete sequence of an organism’s DNA and a large enough computer, he could ‘compute’ the organism.” Lewontin cites the variational characteristics of several cloned *Achillea* plants that were caused by the sequence of environments in which they developed. He states: “Moreover, recent animal cloning experiments have repeatedly shown striking variations among individuals with the same DNA. Although this has apparently surprised the cloners, it should not have.”

Another example refers to the bristles, sensory hairs, on fruit flies. He notes that genetically identical flies will, on average, have the same number of bristles on each side, but “one fly may have nine on the right and five on the left; another, six on the right and eight on the left.” And asks: “What is the source of this fluctuating asymmetry?” The flies have the same genes, “and it seems ridiculous to say that the developmental environment — temperature, humidity, oxygen concentration — was different on the right and left sides of an insect that is two millimeters long and one millimeter wide and that developed its bristles while adhering to the inside of a glass vessel in a laboratory.”

Most striking are Lewontin’s statements: “The variations are instead caused by developmental noise — random events at the molecular level. So, an organism is not computed from its genes, or even from the information in the genes plus the sequence of its environments. Computation is a metaphor, and like any metaphor, it catches some aspects of the truth but leads us astray if we take it too seriously.”

It would seem from the recent discussions on this list that the tyrosine to melanin sequence can be attributed to specific sets of genes that each play a role in the process. Different or mutant alleles at any stage and the final phenotypic outcome is altered. But presumably this modified chain of events would still produce a predictable result if we only had precise information concerning the relevant set of alleles.

Dr. Bruce Cattanach has discussed the initial migration of melanocyte precursors from the neural crest, the dieback before birth, and the subsequent repopulation to produce the final appearance of the adult animal. He noted that there can be considerable right-left asymmetry in the various piebald patterns. One can only speculate on the ultimate predictability (or lack thereof) of the final “tide mark” pattern and/or the locations and sizes of the spots attributable to the ticking gene. Even with complete knowledge of the animals DNA, random events seem to control the details.

1. How robust are the processes that govern embryological development, i.e., how subject to minor, unpredictable variations? The relevant processes involve interactions at the molecular level, not merely the sequential activation of a clockwork mechanism but a vastly more complicated train of events.

2. When the genome has been sequenced, specific alleles have been mapped, and their functional attributes identified, how much closer will we be to predicting the fine details of the phenotype?

3. Does chaos theory play a role in defining the resultant phenotype? That is, can the very small influences be neglected, e.g., a few base pair replacements, or do these blow up to have arbitrarily large effects; in other words, is it likely that there is a “butterfly effect” involved in the totality of genomic interactions? If so, will geneticists (and dog breeders) be limited to the prediction (in)accuracy of the meteorologists when it to the fine details (which seem to be governing factors determining whether a Dal will be born deaf or with normal hearing)?

German Deafness Study - SHOWDALS - 10/9/01

Thanks, S..., for posting Dr. Cattanach’s response to the German deafness study. I was afraid cranking up the Dal deafness issue once again might turn into a monologue rather than the discourse desired.

I need to organize my thoughts on this subject and can think of no better way than to put them in writing and expose them to the scrutiny of this forum — though this list focus is SHOW, I do not know anyone who shows and does not breed, either actively or prospectively; hence, the subject matter of congenital sensorineural deafness is certainly pertinent.

First, let us look at the principal players:

1. As most are already aware Dr. Cattanach is a respected professional geneticist in the UK whose principal contributions have been in the field of mouse genetics. He has also selectively cross-bred a boxer bitch to a Pembroke Corgi to produce a strain of bob-tailed Boxers.

Cattanach has once more reiterated his primary thesis: “...Coming back to the starting point, it would take a different mechanism altogether to get this form of deafness WITHOUT the sw [extreme piebald] allele. ... I think the bottom line is that if breeders want to reduce the risks of deafness they should select against excessive white markings (in any breed and with any spotting gene), especially in head regions. There are really no surprises or contradictions anywhere.”

The logic behind this position is predicated on the following (“DALMATIAN DILEMMA - white coat colour and deafness,” Dr. Bruce Cattanach):

”Apart from external factors, many different genes are known to cause deafness in both laboratory mice (Steel 1995) and dogs (Strain 1996), this attributable to specific types of abnormalities within the inner ear. The type associated with white coat colour is described as sensorineuronal. It has been shown in mice that the presence of pigment cells is essential for normal development of the inner ear where they normally colonize the stria vascularis.

”In their absence, as is also well documented in the dog, the stria degenerates and as this provides the energy supply to the cochlea, damage to this structure occurs and the sensory hair cells necessary for hearing die. Clearly the effect is variable as BAER testing has demonstrated that one, both, or neither ear may be affected. Pigment cells are invariably absent from the stria of deaf mice which

have a white coat colour attributable to pigment cell deficiency.

”The relationship of deafness with white coat colour and blue eyes is therefore clear. In all cases the lack of pigment cells is responsible. The fewer the number and the more limited pigment cell spread, the greater the proportion of the coat lacking these cells and appearing white. Similarly, there is also the greater the risk of one or both eyes being unpigmented to give the blue appearance. And, most importantly for this report, there is also the greater risk of pigment cells being absent from the stria of one or both ears to result in unilateral or bilateral deafness. On the basis of these findings there is no need to postulate specific single or multiple genes for deafness or blue eyes in pigment cell deficient white dogs. All the effects can be attributed to the s gene.”

Based on these premises, Cattnach observes: ”It should be clear from the above that white coat, blue eyes and deafness are intrinsically linked. All have the common basis of absence of pigment cells. It should also be clear from the findings described that each type of effect can be modified by selective breeding. ... Selection for hearing (whether by BAER testing or DNA approaches), or against blue eyes (Greibrokk 1994), may be expected to increase the incidence of dogs with the pigmented patches. But, the presence of patches does not accord with the breed Standard. There is therefore breeder selection against patches, and this means unwitting reverse selection for deafness.

”To expect that selection against deafness will lead to the production of hearing dogs without patches is asking a lot. It means that in some way it is possible to increase the numbers and/or migration of the pigment cells such that there is an increased chance of them specifically reaching the stria of the inner ear but not regions of the skin and coat. Amazing things have been achieved in dogs by selective breeding but this would represent the hardest of all. It is rather like expecting to be able to breed si or sp dogs with a long white sock on one foreleg but full pigmentation on the other. Variations between extent of white on the legs does occur but generally the amounts tend to be similar. To change this by selection must be virtually impossible.”

Hence, if I may be so bold, summarizing Dr. Cattnach’s positions on sensorineural deafness: a. We know the etiology (lack of melanocytes in the stria vascularis). b. We know the cause (white-coat phenotype resulting from the sw extreme piebald gene and its various modifiers). c. We know how to select against it (selectively breed toward more patches and against blue eyes). d. Identifying specific genetic loci (e.g., canine genes homologous to the human Waardenburg’s syndrome, MITF gene) that are functionally related to this type of deafness is unlikely to reverse the premise of c., above.

(Continuing)

I previously listed the players as I know them. They can be sorted according to where they stand with respect to two opposing points of view on this subject:

1. The “Pogo” answer — “We have met the enemy, and he is us!” The Dal Breed Standard disqualifies patched Dals from conformation competition, and therefore effectively from the Dal breeding pool. Yet, selecting for lower incidence of patches is equivalent to selecting for a higher incidence of deafness — one cannot select against patches and against deafness simultaneously.

2. The “Deafness gene” answer — Continuing to examine the Dalmatian genome, especially the

DNA territory associated with melanocyte anomalies (if we are patient, persistent, and spend enough money on research) will uncover the errant nucleotides so that a DNA test can be developed. Thereafter, DNA testing of prospective mating pairs will soon eliminate congenital sensorineural deafness as a Dal problem.

Sorting the list of players:

"Pogo"



Bruce Cattanach

George Strain

Vilma Yuzbasiyan-Gurkan

Keith Murphy



Juraschko (German investigator)

"Deafness Gene"

We need to examine the strength and weakness of the arguments posited by these investigators.
(Continuing)

I need to introduce a couple of topics to help answer some of the private email questions I have received so far.

First, what is the importance of results from our own breeding experiences that seem to run counter to the statistics published by Dr. Strain and others? Strain gives the results for patches as:

"Dalmatians with a patch had significantly less deafness (8.46% uni/1.99% deaf, N=402) than those without (23.36% uni/8.43% deaf, N=4,152) ($p < 0.001$)."

We can see that Dr. Strain tested 402 patched Dals and 4,152 unpatched Dals. You will observe that the deafness incidences for both unis and deafs were much less for the patched Dals than the unpatched Dals. But were there really enough Dals in the set to make a valid judgement? This is where the ($p < 0.001$) comes in. It means that you can expect this large a difference in results when you randomly pick a set of 402 Dals simply on the basis of the "luck of the draw" less than one time in a thousand. This is so unlikely that the result is labeled "significant" and we conclude that patched Dals are indeed less likely to be deaf than unpatched Dals.

Well, suppose you have a litter of 6 Dal pups, and the 5 unpatched pups are normal but the one patched pup is deaf. Does this result overturn Strain's conclusions? No, your sample size of 6 pups is simply too small to draw any inferences, and you can actually expect just such a result on the rare occasion.

Second, when is a gene not a gene? Answer: when it was "discovered" or "named" before sequenc-

ing the genome. Most of the canine genetics books (especially those related to coat color) discuss genes in the classic manner of, for example, Clarence Little, “The Inheritance of Coat Color in Dogs.” We continue to use the names and symbols for these classic genes as though they represented actual sequences of DNA — in most cases, they do not.

Little, Hutt, Robinson, Burns & Fraser, Willis, etc. all discuss the spotting or S series of alleles (with S as the most dominant full-color allele, running through si, sp, to sw as the most recessive extreme-white piebald). We treat these symbols as though they represent variants of nucleotide sequences at some fixed location on a canine chromosome, but, to the best of my knowledge, no one has yet mapped such a sequence in dogs and the evidence for their existence derives strictly from breeding experiments.

When we do a search for the “piebald” gene on OMIM <http://www.ncbi.nlm.nih.gov/Omim/searchomim.html> we get a list of genes such as:

PIEBALD TRAIT; PBT ENDOTHELIN RECEPTOR, TYPE B; EDNRB WAARDENBURG SYNDROME, TYPE I; WS1 etc.

These notations represent actual DNA sequences. For example, the EDNRB gene occurs in all mammalian species, and in the mouse this sequence consists of 1958 base pairs located on the mouse chromosome 14. If you are so inclined you can even look at the genetic code by going to: http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query_old?uid=6681268&form=6&db=n&Dopt=g to view all 1958 base pairs. If you want to locate the same (homologous) gene in the human, look at the human chromosome number 13. If you would like to take a close-up look at this DNA sequence on human chromosome 13, go to: <http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/maps.cgi?ORG=hum&CHR=13&maps=loc-r,morbid.gene&R1=on&query=EDNRB&VERBOSE=ON&ZOOM=3> (all on one line) and zoom in as close as you want.

The problem is that you will not be able to find the S-series genes or the sw extreme piebald gene anywhere. The S gene might or might not be a specific DNA sequence on a dog chromosome (and it could, in fact, be the canine homolog of EDNRB, (or KIT, or EDN1, or PAX3, etc) but at this time we simply do not know).

So when we want to follow the trail for a genetic defect found in a Dal (or canine of any breed) we try to relate that defect to a similar one found in other animals or in humans: <http://www.vet.cornell.edu/publicresources/newsletter/spring98/canine.htm> ”This group of geneticists is interested in the potential of the canine species to shed light on the inheritance of human diseases and other traits. ’In many cases, the dog is the only naturally occurring homolog for a human disease of interest,’ explains Ostrander [Elaine Ostrander, PhD at the Fred Hutchinson Center]. ‘To date, characterization of genes and genetic defects in dogs has relied on knowledge of homologous human genes. The availability of a canine genetic map will make it possible to reverse the direction of this information flow.’”

It would be great if canine geneticists knew where on a canine chromosome to look for the S-series (especially to identify the sw allele) and also the so-called “modifiers” that Little, Cattanaach and others refer to so that it would be possible to track down the relationships between the Dal white

coat, patches, and deafness, but, to my knowledge, sequencing of the canine genome is not there yet.

(Continuing)

I wrote: “We need to examine the strength and weakness of the arguments posited by these investigators.”

When ordering the key players, I placed Dr. Bruce Cattnach squarely on the “Pogo” end of this issue. So I will start there. Bruce’s position is elegant in its simplicity and uncompromising in its remedy. He clearly defines the fundamentals of the problem and carries these to their logical conclusions — quotes are from his report: <http://www.shoal.net.au/~ndcdalmatian/cattnach.html>

1. congenital sensorineural deafness is caused by the absence of stria melanocytes, whose presence or postnatal development is suppressed by the piebald or merle genes — “In their absence, as is also well documented in the dog, the stria degenerates and as this provides the energy supply to the cochlea, damage to this structure occurs and the sensory hair cells necessary for hearing die.”

2. “...The relationship of deafness with white coat colour and blue eyes is therefore clear. In all cases the lack of pigment cells is responsible. The fewer the number and the more limited pigment cell spread, the greater the proportion of the coat lacking these cells and appearing white. Similarly, there is also the greater the risk of one or both eyes being unpigmented to give the blue appearance. And, most importantly for this report, there is also the greater risk of pigment cells being absent from the stria of one or both ears to result in unilateral or bilateral deafness. On the basis of these findings there is no need to postulate specific single or multiple genes for deafness or blue eyes in pigment cell deficient white dogs. All the effects can be attributed to the s gene.”

3. “The association of blue eyes with deafness in white dogs has been recognized since the first reported case in 1896 (Rawitz, in Hayes 1981). ...It may be seen that the risks of both bilateral and unilateral deafness in blue eyed dogs are about 2 - 3 times higher than in brown eyed dogs, and even the presence of one blue eye signals almost the same high level of risk.”

4. “Just as selection against blue eyes has been found to reduce the incidence of deafness, it may be expected that selection for patches would have the same effect.”

5. In another correspondence (CANGEN, 7 Nov 2000) relating to deafness in Boston terriers, Bruce wrote: “At the other end of the scale, the poor Dalmatian breeder is stuck. The Dalmatian Standard specifies a white dog (with spots). Blues eyes may readily be discarded, but this and any form of selection for more pigment cells (such as will be produced even with BAER) will result in the detested patching. So, there is little scope for improvement. They are seeking an effect which will specifically enhance pigment cell numbers reaching the inner ear but they don’t want this effect elsewhere. The expectations of success are I think pitifully low, and the cost even of the attempt will be astronomically high.”

Dr. Cattnach recognizes the usefulness of BAER testing and the feasibility of collecting/collating all the information we can about the breed’s deafness. However, he expects selecting on the basis of BAER results will produce identical results to those achieved by selecting against blue eyes and for

more pigment: “As a consequence BAER is an expensive way of selecting for essentially the same end result (more pigment cells) as the other assessments (eyes, patching). So while [he] would not discount BAER [he] would expect much faster progress with eye/patching selection.”

He feels “very deeply on the subject of s-locus based deafness in dogs [and expresses] tremendous sympathy with breeders in dealing with this difficult subject.”

I love consistency in laying out an argument, and Bruce Cattanach has certainly given us that. Yet, we should ask if there are any weaknesses in his presentation — as I see it, we might be able to uncover a few.

(Continuing)

Nothing I can think of is likely to totally overturn Cattanach’s principal thesis: “...there is no need to postulate specific single or multiple genes for deafness or blue eyes in pigment cell deficient white dogs. All the effects can be attributed to the s gene.”

Yet, to the best of my knowledge, geneticists still haven’t mapped the “s gene” and even Clarence Little (who introduced the idea for this gene, ca 1920) discussed “modifying factors.” (see Little, “The Inheritance of Coat Color in Dogs,” 1984, p74)

Little: “At each level of white spotting or pigment distribution characteristic of each of the alleles at this locus, various genetic factors independent of the main gene are operative. These cause the extent of pigmented or white areas to fluctuate...”

Little also observed: “...an appreciable amount of variation in the extent of body-surface pigmentation is usually nongenetic in nature..” “Wright found that unanalyzable and unpredictable individual variation still remained. This he attributed to an ‘unanalyzable residue’ of causative factors, and there we must, at present, leave the matter in dogs as well as rodents.”

So the probability that the pigment cells (melanocytes) during their multiplication and migrations manage or fail to reach the developing ears of the embryo is determined by

a. potentially controllable genetic factors and b. uncontrollable random factors.

Hence, a tension exists between the possible gains achievable by breeder selection and the unrelenting capriciousness of the crap shoot.

Though geneticists have mapped out the general outline for the pathways that carry the pigment cells from the part of the embryo known as the neural crest to the developing inner ear, they have made little headway in discovering the genes that control this process. I find some hope in this relatively unexplored territory. So long as we cannot rule out the possibility of a deterministic genetic control, we have reason to continue the search for that “bad” gene that is not quite doing its job during the early stages of inner ear development.

I can think of several unanswered questions that have a bearing on Cattanach’s thesis:

1. There are other completely white sw-sw breeds (such as Samoyeds) that have a very low incidence of sensorineural deafness. But Sammies might actually be “patched” with the patches showing up as cream or biscuit colored areas due to the chinchilla and other dilution genes.

2. The intensity of spotting (controlled by the ticking, T, gene and modifiers) has not shown any correlation with the incidence of deafness. I once thought this was due to the time-phasing of T vs. sw control, but this was just a conjecture on my part.

3. Eye color might only be partially controlled by the piebald, sw, gene. In humans there are at least two genes known to influence eye color: bey (brown/blue eyes now called EYCL3 found on human chromosome 15) and gey (green/blue eyes now called EYCL1 found on human chromosome 19). The interaction of these (and other genes as well) results in many possible shades of eye color. It is interesting to note that true albinism (which is rare in dogs) results in pink eyes totally devoid of pigment, but albinos do not have a deafness problem. To understand the eye-color/deafness relationship requires that we discover whether the color of the iris is caused by lack of pigment cells (definitely a worry) or lack of pigment produced by the cells that are present (may be OK) — and this might vary from dog to dog.

I sometimes surrender to the same precept that Cattanach has embraced: if you live on a wind-swept, tropical island where typhoons are frequent, you should not express surprise when your straw hut occasionally blows away — if you breed dogs that are mostly white, you should not be surprised when there are not enough pigment cells to get to the places they are needed. The Butterfly Principle trumps scientists every time.

(Continuing)

R.. wrote: ”...you can breed for either no deaf or no patches but not both.” T.. wrote: ”How do you breed for no patches? Do you mean avoiding the use of patched puppies in breeding programmes?” S.. wrote: ”...most of the well-used stud dogs that produced really good hearing numbers have produced a fair number of patches. Seems to be an appropriate trade off to most people who are trying to avoid the possibility of deafness...”

This exchange is an excellent lead to the subjects of breeding selection, heritability, and the role of chance. I can only scratch the surface so if you want to read more I suggest a good text such as “Genetics of the Dog,” by Malcolm B. Willis.

Selection -

In general, most breeders will use the word selection to mean that individual dogs are evaluated for the traits (patches, deafness, temperament, etc.) that they are interested in and the best are chosen to be parents. If they want to select for more than one trait at a time, and this the general rule, they will prioritize these traits and pick the best according to their own assessment of which traits are most important. The emphasis is on the individual dog, and geneticists call this method ”Individual Selection.”

There are other methods of selecting the breeding parents:

Family selection - whole families are selected or rejected as units. With respect to dogs, this could mean only breeding within, or refusing to breed to certain breedlines.

Sib selection - selection of a breeding parent based on the evaluation of its brothers and sisters.

Progeny testing - selection of a breeding parent based on the evaluation of the pups it has produced.

There are many ways to select the parents depending on the nature of the traits (recessive, dominant, polygenic). The success of a selection method is measured by the rate of improvement of the pups that are produced in the succeeding generations, and the key to this is heritability.

Heritability -

Again, this subject is difficult to explain without a lot of technical background, so I will knowingly oversimplify. In the Dal breed, a trait that has a continuous variation, such as the height at the withers, is partly controlled by several genes and partly controlled by environmental influences such as nutrition.

A simple definition, which will suffice for our purposes, is: Heritability is that part of the total variation of some trait that is under control of the genes. Heritability is a number that ranges from zero to one.

The importance of heritability is its use in selecting the parents. If we find that all of the pups we are producing are too small, and we want to breed to increase the average height, then selection of the parents for this trait can only work if the heritability of height is fairly large, say 0.5 or larger (if it is not, then we should look to nutrition or some other factor as the source of the problem).

But patches and deafness do not vary continuously such as height at the withers. A Dal either IS or IS NOT patched, though the size may vary (IS or IS NOT deaf, though one or both ears could be affected). Nonetheless, these conditions are probably polygenic (controlled by more than one gene), and geneticists have estimated their heritabilities. The rationale is that there is probably some threshold level (like 24" at the withers for conformation DQ), that trips the balance between the normal and the defective.

The problem of selecting Dal parents to minimize deafness gets a little more complicated, so hang in there!

When selecting Dal parents with the objective of reducing the incidence of deafness:

Dr. Bruce Cattanaach recommends - 1. Do not breed deafs or unis 2. Do not breed blue-eyed Dals 3. Accept "limited" patching

Dr. George Strain recommends - 1. Do not breed deafs or unis 2. Do not breed blue-eyed Dals

The correlation of white coat/blue eyes and deafness was already reported in 1896 (Rawitz), and has been widely publicized to Dalmatian breeders for at least ten years. However, the incidence of deafness statistics do not show improvement.

In August, 1998, Dr. Strain reported: “Out of 5,009 Dalmatians that I have hearing tested (BAER),
Bilaterally hearing: 3,510 (70.1%) Unilaterally deaf: 1,100 (22.0%) Bilaterally deaf: 399 (8.0%)

Strain said, “Unfortunately, these percentages do not appear to be improving at any discernable rate...”

Dr. Thomas Famula, UC Davis, in an interview with Denise Powell (Spotter, Summer 2000) stated: “But when I look at the data collected here at Davis over the past 10 years there has not been much change in the genetic merit of deafness in Dalmatians.”

Famula estimates heritability of deafness in Dals at 0.21 which he calls “moderate” - a value that suggests selection can be successful, but it will take time. Famula cautions on the use of blue-eyed dogs for breeding as well as those known to be carriers for blue eyes, not because such selection is a perfect indicator for the likelihood of producing deaf pups but because such dogs are “suspect.” I could find nothing in Denise’s interview regarding Famula’s opinion on patches.

So much for the “expert” opinion, but how then is one to set up an individual breeding program?

A model program could be constructed based on the premises: 1. a DNA test for a “deafness” gene is not likely to be discovered; 2. the Dal Standard is not changed to accept patches in conformation; 3. blue eyes in Dals are caused by the strong expression of the sw gene (i.e., not by some other innocuous gene(s) unrelated to sensorineural deafness).

It is assumed that the selection pool consists of Dals that satisfy the Breed Standard and are outstanding representatives of the breed.

Select for breeding those parents that:

1. Are bi-lateral hearing
2. Are not blue-eyed

To increase the intensity of the selection process and, thereby, decrease the risk of producing deaf pups, add the following:

3. Bi-lateral hearing grandparents, siblings, and progeny
4. Higher than average incidence of patches in collateral (aunts, uncles, siblings), though not direct (parents, grandparents) relatives
5. No blue-eyed direct or collateral relatives

Of course, if the Dal Standard were changed to accept patches, or blue-eyed Dals were found to segregate into two classes (those that are related to a higher rate of deafness and those that are not), these selection rules would need to be modified.

The individual breeder will need to tailor the rules to meet his/her own needs, but the guidance from those who have collected the statistics and done the research is available. As S. observed, this type of breeding selection will increase the number of patches. This must be balanced, but it is not intrinsically different than breeding to a height standard that penalizes for being too short or too tall.

(Continuing)

D.. wrote: "Obviously, we need more data on BLUE-EYED dogs that produce well. ...breeders who claim to have good hearing statistics in lines with lots of blue eyes to participate in the ongoing research on the link between eye color and deafness." "As several people have pointed out already, PATCHED puppies do not always have bilateral hearing." [emphasis mine]

Our own breeding results are always interesting, and, if they seem to overturn the statistics, they can get a lot of attention. Many of us have a personal aversion to numbers and statistics, but if we take the time to carefully review what they tell us, we can better understand the meaning of our results. We can find the accumulated statistics for over 5000 BAER test results at Dr. Strain's web page.

I would like to summarize these in a table, which I hope does not get too complicated. I give the category and Strain's results for the percent bi-deaf; then I give the percent of the litters of ten pups each that we should expect to produce ALL hearing pups (normals and unis, combined). I could also tabulate combining unis with deafs, but this table should get the point across without getting too cluttered.

<u>Category</u>	<u>% Deaf</u>	<u>% Litters</u>
Blue-eyed pups	18.24%	13.4%
Uni-parent	11.3%	30.2%
Unpatched pups	8.43%	41.4%
Brown-eyed pups	6.67%	50.2%
Bi-Bi parents	5.91%	54.4%
Patched pups	1.99%	81.8%

By way of example, the first category is blue-eyes (which means we are considering litters of ten pups, all of which are blue-eyed — I am forced to use this category since we have no tabulated hearing stats on the pups produced by blue-eyed parents). Even in this category we should expect to find a litter of this size, none bi-deaf, every 7th or 8th litter.

At the opposite end of the table is the all-patched puppies. In this case we can expect to find that for litters of 10 patched puppies, all the pups will generally be hearing (either normal or uni). However, in this category about one litter in 5 can be expected to have at least one patched, totally deaf puppy.

I did this little exercise not to overwhelm with numbers, but simply to demonstrate that the results we often see in our own breeding experiences do not preempt Strain's data. On the contrary, the exceptionally good or exceptionally bad result should occur some of the time.

BTW, for those who asked (and those who wanted to ask), the “Butterfly Effect” or “Butterfly Principle” is a term some mathematicians apply to the unpredictable — those events that we think we should be able to understand and control but cannot because they are just too complicated. Some phenomena are known to be extremely sensitive to the fine details (e.g., implantation location in the uterus of the fertilized ovum and its effect on the migration of melanocytes from the neural crest to the stria). This is sometimes referred to as the butterfly effect - “A butterfly flapping its wings in South America can affect the weather in Central Park.”

Sorry, I missed Dr. Strain’s complete list of recommendations to Dal breeders. I thought he had recommended not eliminating patches (same as Cattanach), but when I went looking for this in writing, I could not find it. I finally rediscovered it on his web pages. (from G. Strain, Oct ‘97 Lecture Series): <http://www.lsu.edu/deafness/deaftalk/deaftalk.htm>

[Strain] recommends the following:

1. Don’t breed unilaterally deaf animals.
2. Do not repeat breedings that produced many deaf.
3. Avoid breeding to lines that have produced many deaf.
4. Do not eliminate patched dogs.
5. Do not breed blue-eyed dogs.
6. Make breeding decisions thinking about what is best for the breed, not what might be best for your kennel.

Responding to M.’s comments, I found that Strain reported the following statistics for various combinations of eye colors and deafness — (not my data, not my analysis - all credit to Dr. Strain): <http://www.lsu.edu/deafness/deaftalk/deaftalk.htm> (Strain’s Slide 25)

Color of one eye/Color of other eye

1. Brown/Brown	deaf: 7%	uni: 21%	normal: 73%
2. Brown/Blue	deaf: 18%	uni: 33%	normal: 49%
3. Blue/Blue	deaf: 17%	uni: 33%	normal: 50%

Perhaps someone who has heard his lectures can confirm this, but I believe that Dr. Strain classified a dog as blue-eyed if any part of the iris in either eye was blue. If you look at his picture of the deaf liver Dal bitch, Demi Azure, (slide 6), you will see that “... half of the left iris is blue because the piebald gene suppressed pigmentation there, and pigment is missing from the back of the retina - this shows up as red from the blood vessels that are no longer covered by pigmentation.” According to her pedigree, (slide 17), “...born from two accidentally bred uni parents, she was one of only two affected in a litter of 8.” Demi Azure was twice bred experimentally to a deaf male, Bubba, producing 9 deafs out of 16 total pups.

Dr. Strain's data gives us the incidence of deafness in blue-eyed dogs and compares this with deafness in brown-eyed dogs. This is interesting but not the entire story.

The information on blue eyes and production of deafness that IMO a breeder really needs is:

1. What is the incidence of deafness in litters produced by mating two blue-eyed parents?
2. What is the incidence of deafness produced in litters produced by mating a blue-eyed parent with a brown-eyed parent?

We cannot get this information from Strain's database; I asked him several years ago about this but he did not collect this information. However, we can try to get this in a roundabout way by answering the following — and I ask that those with data on this respond either privately or to the list:

1. If you breed two blue-eyed Dals, what fraction of the pups are blue-eyed, how many brown-eyed, how many with one blue and one brown eye?
2. If you breed a blue-eyed Dal with a brown-eyed Dal, what are the results?

We used to think that blue eyes were a simple recessive characteristic and made jokes about the brown-eyed child with two blue-eyed parents — we now know that it is not that simple, but exactly how does this work in Dals?

(Continuing)

I took a few minutes to check back through nearly 20 years of the "Spotter," looking for articles on Dal deafness. It should come as no surprise that the controversy over blue eyes and deafness was just as lively two decades ago as it is today.

Patti Strand wrote an article in '87 postulating two genetically distinct types of blue eyes. She wrote: "The washed-out, whitish eye which is also called the "china-blue" eye, is the one associated with the gene for deafness... The other sort of blue eye which apparently exists in our breed is phenotypically different from the china-blue eye. It has a darker outer rim and appears to have rays emanating from the pupil outward. Overall, it looks somewhat three-dimensional when compared with the china-blue type. This eye... appears to be unrelated to the gene for deafness."

In '90, Dr. Strain wrote: "We found that there were statistically significant differences among the sites [Baton Rouge, Arizona, Northern California] ... for left and right iris pigment (blue eyes)... This suggests that different populations exist, and the associations between [blue eyes] and deafness may only be valid for the region in which the association existed." —1,031 Dals tested.

However, moving forward to an article by Strain in '94: "One pigment marker that had previously appeared to be associated with deafness was the presence of a blue iris, but some questions were raised by us at that time since there appeared to be regional differences (Baton Rouge vs Arizona vs Northern California) on whether the association was significant. With data now [1994] available on many more dogs there is no longer any question that the relationship exists." — 4,284 Dals tested.

Strain '96: "Dalmatians with blue irises had significantly more deafness (32.62% uni/ 18.24% deaf, N=466) than those with brown irises (20.99% uni/6.67% deaf, N=3,912) ($p < 0.001$); no differences were seen between dogs with one (N=339) or two (N=125) blue eyes. Insufficient numbers of blue-eyed dogs were seen in other breeds for analysis. — 4,596 Dals tested."

Another set of results from Holliday, et al: "Association of blue eyes with deafness in Dalmatians," (J. Vet. Intern. Med. 6:166-174 (1992) Brown/Brown 5.6% deaf, 18.8% uni, 75.5% normal Brown/Blue 15.8% deaf, 39.5% uni, 44.7% normal Blue/Blue 22.2% deaf, 33.3% uni, 44.4% normal — 902 Dals tested

J.. (Jan 1997) posted to this list information from the report, "Hereditary Deafness in the Dalmatian: Relationship to Eye & Coat Color," T. Greibrokk, Journal of the American Animal Hospital Assoc.,30:170-176 (1994). This was a study of dalmatian puppies whelped in Norway 1979-1991 - a total of 1843 puppies. The Norwegian study found "...more blue-eyed pups and fewer patches occur in litters with deaf pups." The report concluded, "In populations which contain less genetic diversity, particularly in regions where blue-eyed as well as unilateral deaf dogs have been utilized substantially in breeding, the most effective means for reducing the deafness rate is to identify and stop breeding unilateral deaf dogs as well as blue-eyed dogs."

We can track the evolution of the idea that blue-eyes and deafness might be related only for some regional populations of blue-eyed Dals and only for certain types of blue eyes to the more widespread recognition that such a relationship exists in general and is world wide.

This all finally leads up to the question of whether we should accept these data and therefore stop breeding blue-eyed Dals — with the idea that blue-eyed Dals are more likely to produce blue-eyed pups. Strain's data includes about 5,000 Dals total and nearly 500 of these were blue-eyed. Since there are about 5,000 Dals AKC registered each year (excluding the years of the "101 Dalmatians" breeding frenzy), Strain's sample is about equal to a full-year of registered Dals. From a statistician's point of view, this should be a sufficient data set to draw some valid conclusions.

Even large data samples can be biased and lead to erroneous conclusions, but we need to scratch to find bias in the Dal BAER screening. I can think of only a few possibilities:

1. respondent effect — could it be that many of the blue-eyed Dals that have normal hearing are not being BAER tested, possibly because of unavailability of testing facilities in some regions where blue-eyed Dals with normal hearing are more prevalent?
2. induced bias — are breeders testing full litters or are they excluding pets, and, if so, are some blue-eyed Dals not tested because they are considered pet quality?
3. judgement bias — does every BAER test facility use the same criteria for classifying eyes. Are Dals with part-blue eyes classified as blue-eyed by every test station? Are some testers only classifying the "china-blue" eye as blue and the darker blue eye as brown?

IMO, the sample population of BAER tested Dals has become so large, and by now includes so many geographic areas, that bias alone and errors due to chance are not likely to invalidate the results and overturn Cattanch's and Strain's breeding recommendations. On the contrary, the correlation of

blue-eyes and increased deafness, first recognized in 1896, has continued to get further confirmation with every updated report.

Deafness and White Ears - SHOWDALS - 2/4/02

S.. wrote: "He [Robert Cole] says this about one of the dogs who shows a whole white ear - he says "my understanding is the lack of spotting on the ear is a strong indication of probable deafness in the Dalmatian."

I know of no reported statistical evidence that supports Cole's thesis (which is not to say that he is wrong, but it would be nice to know on what data he bases this conclusion).

Dr. George Strain wrote: "The lightness or heaviness of the spotting is thus controlled by the ticking gene and not the extreme piebald gene, and it is not a factor in the prevalence of deafness. (Strain GM, Kearney MT, Gignac IJ, et al: Brainstem auditory evoked potential assessment of congenital deafness in Dalmatians: associations with phenotypic markers. J Vet Internal Med 6:175, 1992).

With only minor exceptions, most Dals are born totally white. The most frequent exceptions are on the nose leather, eye trim, and at the front of the ear where it attaches to the head (ear pip).

To understand what is going on during the development of color markings I rely on Dr. Bruce Cattanach's explanation: "Studies in laboratory mice have shown that the pigment cells derive from the neural crest of the fetus. Prior to birth, they migrate from this tissue and colonize pairs of specific sites on each side of the head and the backline of the body. Three pairs of sites exist on the head. One site lies close to the eye, another lies close to the ear, and a third lies at the occiput, the latter no doubt being the basis of the Blenheim spot of Cavalier King Charles Spaniels. Various estimates suggest that there are about six sites along each side of the body, with a possible larger number along the tail (Schaible 1969; Mintz and Russell 1967; Cattanach 1974). At each site one or a very few pigment cells (maybe up to three, Lyon 1970) proliferate to give clones of cells which migrate outwards so that they join up with each other, but they also spread down each side of the head and body so that they may meet up on the underside."

Cattanach notes that the piebald genes (especially the sw gene homozygous in Dals) interfere with the survival of the pigment cells: "it seems likely that pigment cell migration initially covers the whole of the body. There is then a period (before birth) in which most pigment cells in the potentially white areas fail to survive. Then proliferation and migration restarts (after birth)..." He continues: "...with the extreme sw, most of the coat is white with only the occasional pigmented patch seen in regions close to the original sites, notably those around the eyes and ears."

If I read this correctly and draw reasonable inferences, I conclude that the ear pips which are common to virtually all Dals at birth are residues of surviving pigment cells from the initial migration from the neural crest. It would seem reasonable that such markings at birth should also correlate statistically with the survival of pigment cells in the cochlear stria which are essential to normal hearing and which probably derive from the same pair of sites referred to by Cattanach above.

A number of years ago (I am not sure I can resurrect the old correspondence) Cattanach and I exchanged ideas on the lack of correlation between spotting density, especially on the head and ears, with the rate of deafness in Dals. As noted above, Strain's results do not support any connection.

Cattanach expressed some surprise at Strain's result. I conjectured that the developmental timing of pigment cell repopulating induced by the T (ticking) gene was too delayed to prevent the degenerative effects that were already taking place in the stria vascularis, but there is no evidence to support this.

Does anyone know if microscopic evaluation of pigment cells taken from a patch can be distinguished from pigment cells taken from a spot? The quality and depth of the color of the hair is visually obvious, but I believe that is most likely a consequence of melanocyte density in the hair follicle and the size and density of the pigment granules in the hair shaft. If the melanocytes from patch and spot are functionally identical, then I would expect the degree of expression of the T gene to have some impact on the incidence of deafness.

If a pigment cell from a patch is the same as a pigment cell from a spot then the etiology of congenital sensorineural deafness points to a likely correlation between density of spotting, especially in the vicinity of the ear and more so as an extension of the original ear pip, and rate of deafness (which would support Cole's thesis), but Strain's statistics do NOT support it - so, as far as I know, that is where it rests at this time.

---- compiled 2/15/02 *JES*