A Genetic Primer for Breeders

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Expressivity and Penetrance

For a breeder, understanding the inheritance of a trait that is controlled by several genes and influenced by the environment can be a nightmare. Suppose, for example, that you are trying to breed apricot Poodles, but instead of getting only a single shade, your litters always have a variety of shades from pale to dark apricot. You might blame it on variable **expressivity**, which is just a convenient way of saying that you don't know what other genes or environmental factors are also playing a role in determining the color.

One of the "classic" examples of this in dogs is the variable expression of piebald spotting in beagles shown in Little (1957). The dogs all have the same S^p allele, but the colors range from black-and-tan with white feet to predominantly white with a few black spots.

Penetrance is a similar "term-of-convenience" (euphemism). If you are 99+ % certain that Fido carries the allele for six toes (because both his parents and all his sibs have six toes), but Fido has the normal five toes, you blame it on incomplete penetrance, try to look authoritative, and hope that no one asks additional questions. [Actually, it would probably be safer just to say that the trait is not always expressed and avoid possible embarrassment.]

The difference between expressivity and penetrance is that with the former, the trait is expressed to a variable extent, while with the latter it may or may not be expressed even though the genetic makeup (**genotype**) of the animal suggests that it should be.

Sex Linkage

In dogs, as in most animals, sex is determined genetically, but not by a single gene. One of the 39 chromosome pairs is used especially for sex determination. The unusual feature of this system is that the "female-determining" chromosome, called the X chromosome, doesn't even look like the male-determining Y chromosome - though they are still considered a "pair", and are referred to as the **sex chromosomes**. (The other 38 are called **autosomes**.)

As everyone likely already knows, females have two X chromosomes and males one X and one Y. The male normally produces an equal number of sperm with either the X or the Y chromosome. As his mate will only be producing eggs with X chromosomes, an equal number of female (XX) and male (XY) puppies should be produced. Of course chance plays a major role, and litters often don't have a perfect 1:1 ratio.

Mutations undoubtedly occur in genes that control the development and function of the ovaries, testes and other reproductive organs, but few have been described, probably because disruption of the normal reproductive process results in infertility. However, genes are also found on the sex chromosomes that have nothing to do with sex determination. Those found on the X chromosome have no equivalents on the Y chromosome. As a result, males have only one copy of these genes. (As the terms "homozygous" and "heterozygous" apply only when there are two copies, this situation is given a special name: **hemizygous**.)

When mutations occur in these **X-linked** genes, the pattern of transmission of the mutant phenotype differs from that seen for an autosomal gene. If a female carries such a trait, she will not express it (as long as it is recessive), but she will pass the trait to half her sons, and as they receive no X chromosome from their father, it doesn't matter what his genotype is -- half will be affected. Half the daughters will be carriers, but as these are recessive traits, they will not be affected. If the problem does not affect survival and reproduction, an affected male may pass the gene on to his progeny - but only to his daughters, as his sons will get his Y chromosome, and it doesn't have a copy of the gene.

In humans, good examples of sex linkage are red-green color blindness and hemophilia. I have been unable to find an example in the Poodle. Von Willebrands disease, a form of hemophilia, is not equivalent to the human X-linked hemophilia, and follows a normal autosomal pattern of inheritance.

There are also traits that are **sex-influenced**, which means that their expression is influenced by the individual's sex. This does not imply that the gene is sex-linked. A human example is pattern baldness. The gene's expression is influenced by hormonal levels and only one copy of the baldness allele is sufficient to cause baldness in a man, whereas two copies are needed in a woman. In effect, it behaves as a dominant in males and as a recessive in females. Though 1/2 the sons of a female carrier will be affected, a heterozygous male will also pass the trait to 1/2 his sons.

Thus, any trait that appears more frequently in males than females is suspect as either sex-linked or sex-influenced. If it is passed from the father or the mother to 1/2 the sons, it is likely sex-influenced. If it seems to skip a generation and the pattern is grandfather to grandson, it is likely sex-linked.

Determining the Mode of Inheritance

Suppose that you have a litter in which several of the puppies appear to be less healthy than their litter-mates. Suppose that after a few weeks it is readily apparent that they are growing more slowly and appear less energetic. What do you do? Obviously, the first step is take them to your vet for examination.

Without going into details (as this is a hypothetical example), let us suppose that after appropriate tests, he concludes that they have a hole in the septum between the two

sides of the heart that is resulting in a mixing of oxygenated and deoxygenated blood. Quite aside from any considerations about putting down the affected pups, the question remains - what caused the problem? Was it simply a developmental accident, an environmentally-induced condition, or is it genetic? [I have deliberately picked a condition that may arise for any of these reasons.]

As a rule-of-thumb, if only a single pup is affected, the problem has not turned up before in related litters, and the problem does not occur frequently in the breed, it is likely a developmental accident. Nevertheless, given the usual under-reporting of health problems, especially those that may be genetic, a second litter between the same sire and dam might be warranted.

On the other hand, if all, or even the majority of the pups were affected, one might be more inclined to look for something in the environment that could have perturbed the normal developmental process. The majority of genetic abnormalities are recessive and, under normal circumstances, the parents are unlikely to be affected (i.e. homozygous). Therefore, if the problem is a genetic one, it is more likely that the parents will be phenotypically normal carriers (i.e. heterozygous), and the expectation is that 1/4 of the progeny will be affected.

While this is important to keep in mind, obtaining a proportion of affected pups in a litter that is substantially lower or higher than 1/4 is no guarantee that the problem is not genetic. Even the larger breeds only produces litters of about eight, so you would expect only two to be affected. One or three would not be considered unusual, and even getting none is not considered sufficiently improbable to alarm a geneticist. You might well get no affected pups in one litter and four in the next!

Dominant mutations having a significant impact on health will, in most cases, result in death before reproductive age is reached. There are exceptions, such as Huntington's Disease in humans. Any late-onset genetic disease, whether dominant or recessive, represents a potential problem. At least with a dominant you can wait for the progeny to reach an age where the problem would normally have developed, then breed unaffected animals with reasonable assurance that they are not undetected carriers.

For a dominant mutation that is rare, most crosses will be between a heterozygous affected individual (*Aa*) and a normal one (*aa*). The expectation is that 1/2 the progeny will be *Aa*. Should both parents be *Aa*, 1/4 will be *aa* (normal) and 3/4 either *Aa* or *AA*. Sometimes the *AA* progeny will be affected more severely, or even die before birth.

Doing the necessary crosses to establish the mode of inheritance can be an expensive and time-consuming task, to which is added the thankless prospect of prospect of putting down sick puppies and finding pet homes for the remainder. Consequently, test matings are seldom done on a scale sufficient to produce numbers that can be subjected to statistical analysis. [One notable exception is the monumental study by Bourns on Dayblindness in Alaskan Malamutes.]

One alternative is restrospective analysis of the pedigrees of affected animals. As one generally needs a number of related animals occurring over several generations, the problem will likely already have become fairly common. The accuracy of such analyses is directly affected by the number of relatives for which data exists - a strong argument for the open exchange of information between owners, breeders, veterinarians and researchers.

Inbreeding

Inbreeding is the practice of breeding two animals that are related (i.e. have one or more common ancestors). The degree of inbreeding may be assigned a value between 0 and 1, called the inbreeding coefficient, where 0 indicates that the animals have no common ancestors. Inbreeding produces animals that acquire the same allele from both parents as a result of their common ancestry. Thus, it increases number of genes that are homozygous. However, it does not discriminate between good alleles and bad, and therefore is just as likely to make genes homozygous for bad alleles as for good ones.

Line breeding is a form of inbreeding practiced by some breeders -- often by ones trying to maintain a recessive color -- where a son (or less commonly a daughter) is bred to a female relative generally less closely related than a first cousin.

Inbreeding occurs in most pure-bred domestic animals as the result of several common practices. One is that some breeders own a small number of animals and breed only within their own group. A second is that many breeders have the idea that outstanding animals can be produced by inbreeding -- by doubling up on the good alleles while somehow avoiding the bad. Even if you were to point out to someone that this is a gamble, they might respond that they are simply helping natural selection.

If we lived in a world where all the genes followed the simple rule that there may only be good alleles, which are dominant, and bad alleles, which are recessive, then inbreeding could be an effective tool for improving a breed providing the latter were rare (see, however, genetic load) .

Unfortunately, geneticists discovered, fairly early in the game, that there are also alleles that could be described as fair or poor. (They are generally ones that retain a portion of their normal function.) Suppose we have a "mutant" allele that has lost only 1/4 of its normal function. In many cases, this would not even have a noticeable effect. If you made an individual homozygous for this allele, you would not even be aware that you had done so. Now consider that the same fate may befall a number of genes during an inbreeding program. Eventually, you will have an individual that is considerably less fit than one carrying the normal alleles for all (or even most of) these genes. There is no magic formula for regaining what you have lost. You must start again.

[Sometimes mutant alleles result in an even more dramatic loss of function, but remain undiscovered under normal conditions. See, for example, the story of vWD in Dobermans.]

About the only animals that are routinely inbred to a high level are laboratory mice and rats. There, the breeders start breeding many lines simultaneously in the expectation that the majority will die out or will suffer significant **inbreeding depression**, which generally means that they are smaller, produce fewer offspring, are more susceptible to disease, and have a shorter average lifespan. Dogs are no different. If you can start with enough lines, a few may make it through the "genetic bottleneck" with acceptable fitness. However, dog breeders generally don't have the resources to start several dozen or more lines simultaneously.

If that is not sufficient to discourage you, then consider the following. During the past 25 years, geneticists have been going out and measuring genetic diversity in natural

populations directly by looking at the DNA or proteins, rather than at the phenotype. The have found that many individuals that cannot easily be distinguished by their phenotypic appearance nevertheless have considerable differences in their genotype. This came as a considerable surprise, as the expectation was that even those alleles that only reduce function marginally should, over time, be selected against in the real world.

This discovery led to the theory of "neutral isoalleles" and the concept that heterozygosity might actually be a good thing -- of itself. Neutral isoalleles produce proteins that are different, but function equally well under normal conditions. In combination, they may function even better. Consider the analogy of a soccer match in which each team is allowed two goalies. One team has identical twins who are good at covering the center, the other fraternal twins, one of whom is better at covering the right and the other the left. All else being equal, which team is going to win?

This is not a universally accepted theory, but today one is hard pressed to find a conservation or zoo biologist, concerned with preserving an endangered species, who would not list maintaining maximum genetic diversity as one of his/her primary goals. They equate inbreeding depression with loss of heterozygosity.

Beyond the conventional close-relative inbreeding there is another type of breeding that has much the same effect -- that is the over-use of a recognized champion. Many, in fact, believe they are doing a "good thing", as they will be increasing the frequency of occurrence of the genes that made him/her a champion. What they may not realize is that they are increasing the frequency of all genes carried by this animal, whether they be good, bad or innocuous -- and that champions, like any other animal, carry a number of undesirable recessive alleles that are masked by wild-type alleles. The result is that almost all the breed carry a little bit of Jake Hugelberg, and any undesirable trait carried by Jake will no longer be rare. Finding a safe, unrelated mate becomes an exercise in futility.

Notes

- The term **wild-type** literally means the most common type found in the wild. In a Samoyed, it would be white. In a poodle, it would be black. Though we usually equate "wild-type" with "normal", and a white Samoyed is certainly normal for the breed, Samoyeds nevertheless have a genetic deficiency in pigmentation.
- Actually, we should not be saying that the allele functions abnormally. The allele carries the wrong information. The consequence of that information being used results in an abnormal functioning of some process.
- **Agouti** is a sort of mottled brown color not seen in poodles. Geneticists try to be consistent in their naming of genes and don't use different symbols for different breeds, or even different species, providing the genes are known to have the same action.
- Inbreeding calculations do not account for the possibility that an allele will become homozygous by "chance", though this too can be calculated if the frequency at which an allele occurs in the whole population is known. Most basic Genetics texts explain how. (See, for example, Willis, pp. 293-295 - "**The Hardy-Weinberg Law**")

References

Little, C.C. "The Inheritance of Coat Color in Dogs", Howell, New York, 1957.

Willis, M.B. "Genetics of the Dog", Whitherby, London, 1989.

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Genetics

The Dog Center

Diversity and the Purebred Dog
(The Poodle and the Chocolate Cake)

John Armstrong

The Nature of Diversity

Think of genes as recipes. They carry the instructions for the various components that go into making up an organism. Each recipe specifies a particular component, and different individuals may carry different versions of the same recipe. (In the jargon of genetics, we say that they carry different alleles of a particular gene.) Individuals within a population often carry similar or identical recipes, for example, chocolate cake for a Poodle, lemon cake for a Beagle, and white cake for a Samoyed. A different canine species might be represented by a fruit cake. When you consider animals that are quite different, such as frogs and chickens, you will generally find "homologous" recipes, say for pies or puddings. Thus, there is more diversity among mammals than among carnivores, more among the carnivores than among the Canidae, and more among the Canidae than among the wolf group.

An organism carries a collection of recipes, and the collection defines the organism. The great diversity in the possible collections of recipes is the reason for the great diversity in the animal and plant kingdoms. The more closely related two individuals are, the greater the similarity in their collections. The number of combinations is huge, and during evolution, the recipe collection was undoubtedly reshuffled many times. The combinations that worked well survived and multiplied. Those that did not work quickly died out. In theory, one may make a meal of Champagne with tacos and Yorkshire pudding, but they don't really belong together. As time passed, exchange of recipes became difficult between animals that differed substantially in their physical and behavioural characteristics. Different groups, therefore, became constrained to work with only a subset of the total possible collection of recipes.

One definition of a species is that members of two different species bred to each other cannot produce a fertile hybrid. However, a more modern definition is that two species are geographically, physiologically, or behaviourally isolated such that they do not normally produce hybrids. Additionally, they should have features that differ sufficiently to allow them to be distinguished from each other. The domestic dog, wolf, coyote, and jackal can all mate with each others (barring size constraints) to produce viable and fertile hybrids. Yet, they have been considered different species (within the genus Canis) because they normally live in different places,

behave differently, and can usually be told apart. (Though there has been a recent move to change *Canis familiaris* to a subspecies of *Canis lupus*.) However, a jackal will not mate with a dog unless they have been raised together from pups (presumably due to a learned behavioural difference). Furthermore, no Canis species can produce a hybrid with a fox. This is not because the kinds of genetic recipes are greatly different, but because foxes do not share the same number of chromosomes. (In other words, their recipes are filed under a different, incompatible system – somewhat akin to filing one under DOS and the other on a Mac.)

Genetic recipes may get modified when they are passed on. Many of the modifications will make no noticeable difference, or only a very subtle one. Some may improve the recipe and others will not. If we are making a chocolate cake and a critical ingredient is forgotten, or the cake is baked too long or at the wrong temperature, we end up with a disaster. (If we don't understand what has gone wrong, we will likely throw out the recipe and look for a new one.) We may even make deliberate modifications in an attempt to get a more memorable cake. Among the "chocolate cake" population, there will be a variety – or diversity – of recipes and, therefore, of cakes.

This, I would say, is a "good" thing. Do we always want the **same** chocolate cake? Surely we will tire of it, and even if we don't, we lose the pleasure of anticipation. If, for some unforseen reason, everyone suddenly loses their taste for **THE** chocolate cake, it will surely go extinct. *To have the potential for evolution and adaptation, we must risk the possibility of the bad.* That is the "cost."

In a large, naturally breeding population, we will end up with a number of versions (alleles), some so slightly different that we will never notice, some perceptibly different (but still functional), and some that just don't work at all. However, if we remove the diversity we lose the potential for evolution and for surviving unexpected change. To have the potential for evolution and adaptation, we must risk the possibility of the bad. Geneticists call that cost **genetic load**. (This "bad" group persists because every individual carries two copies of every recipe, and often having just one "good" copy is enough for normal function.) In most populations, every individual carries a portion of the load – three to five bad recipes out of several thousand. The load is so well distributed that if two individuals compare their recipe collections they will generally not have two copies of the same bad recipe.

Loss of Diversity

Suppose we start a new population with only six or eight founders. (A number of breeds have started with that few.) We will get rid of hundreds of bad recipes, but the remaining dozen or two will be encountered much more frequently. Furthermore, if there are several good or excellent recipes, the chance of dropping one of these from the collection grows greater as the number of founders diminishes, and the risk of losing one remains high as long as the effective population size remains low. Working with small numbers will inevitably decrease the diversity, simply because individuals do not pass on their recipes equally to the next generation and some recipes are accidentally lost. This has the superficially desirable result of giving a more reproducible phenotype, but at the expense of an

overall reduction in quality, health, and longevity.

If breeders had the ability to recognize each individual recipe and choose only those that were excellent, breeds could be produced with a small number of individuals that lacked genetic problems. However, what we see (the phenotype) is the product of all the recipes and, for the most part, we cannot distinguish the individual recipes. Moreover, we do not have the option of selecting recipes individually. When we select an animal for breeding, we are forced to accept a complete set. Even in those few cases where we now have a DNA test for a bad recipe (allele), we do not possess the ability to correct or selectively discarded it. We are therefore forced to work around it, or to discard the whole collection, with the attendant risk of discarding something excellent along with it.

The common practice of almost everyone rushing to breed to the currently-popular male show champion is probably the most significant factor reducing whatever diversity remains. Consider your own breed (the situation for most breeds is similar). Can you find one or more males that appear in most pedigrees? Almost everyone decides they like the recipes of (*insert name*) – or at least the ones they can see readily – and abandons other recipes with little thought to the eventual consequences. In a few generations, almost everyone has a substantial number of his recipes, though not necessarily his exceptional ones, and many excellent alternatives are very hard to find.

How precious is the individual that comes along with some of the missing recipes and relatively few of the "popular" collection? Do we hesitate because there are also a few bad recipes in this alternate collection? Are we now so accustomed to dealing with the more-popular collection that we have lost the vision of the "memorable" chocolate cake?

Population Genetics and the Breeder

What is often called **Mendelian** genetics deals with the outcome of specific crosses. **Population genetics** deals with the distribution of alleles in a population and the effects of mutation, selection, inbreeding, etc., on this distribution. As a breeder, you are a practicing geneticist. A knowledge of both Mendelian genetics and population genetics is critical, not only to your own success, but also to the survival of your breed.

Because many early geneticists believed that there were only two possible alternatives for a gene – "good" alleles that functioned normally and "bad" alleles that didn't – they expected to find little genetic variability in a population. The majority of individuals were expected to be homozygous for the good allele for most genes.

But with the advent of modern biochemical and molecular tools, geneticists studying populations found far more variability (diversity) than they had expected. There are a number of possible reasons for this, and even the experts are not in total agreement on the most likely reason(s). However, geneticists have also discovered that populations lacking genetic diversity often have significant problems and are at greater risk from disease and other changes in their environment. The conclusion is that genetic diversity is desirable for the health and

long-term survival of a population.

Are purebreds dogs genetically diverse? Some may regard that as a contradiction in terms. The very concept of creating a breed with characteristics that are distinctly different from other breeds implies a certain limitation on diversity. Nevertheless, within the standards for a breed, diversity should still be possible for genes that do not affect the essential characteristics that distinguish one breed from another. If, in order to maintain breed identity, one has to compromise on genes that relate to general structural soundness, good health, intelligence, and temperament, perhaps this breed should not exist. However, as long as these essentials are not compromised, I see no reason why one cannot have different breeds with different appearances and different talents.

For those genes that establish breed identity, there will be markedly less variability within a breed than within *Canis familiaris* as a whole. The tricky bit is restricting variability for those genes that make a breed distinctive without sacrificing the variability/diversity that is necessary for good health and long-term survival of the breed. In many cases, this has not been achieved, and we are now paying the price in terms of high incidence of specific genetic diseases and increased susceptibility to other diseases, reduced litter sizes, reduced lifespan, inability to conceive naturally, etc.

Why has this happened, and do we have to accept it as an inevitable consequence of creating a breed? I don't think we do.

The principal reasons for limited genetic diversity are:

1. Many breeds have been established with too few founders or ones that are already too closely related.
2. The registries (stud books) are closed for most breeds; therefore you cannot introduce diversity from outside the existing population.
3. Most selective breeding practices have the effect of reducing the diversity further. In addition, the wrong things are often selected for.
4. Even if the founders were sufficiently diverse genetically, almost no one knows how their genetic contributions are distributed among the present day population. Consequently, breeding is done without regard to conserving these contributions, which may be of value to the general health and survival of the breed.

A role for the breed clubs

Each breed needs a database with all the breedable animals recorded with all their ancestors back to the founders. This would most appropriately be the task of the breed club. Are any actually doing this (outside some of the rare breeds)?

Such a database would enable breeders to identify which individuals are most likely to carry the genes from each founder. At the level of the individual breeder, it would enable him/her to make intelligent, informed choices when selecting mates. Measures might also be considered to re-balance the breed, in

order to ensure that the remaining diversity is more evenly distributed and that, therefore, there is less risk of loss.

References

Hartl, D.L. A Primer of Population Genetics, Sinauer, Sunderland, MA, 1988.

Notes

A population is regarded as genetically diverse if a substantial proportion of the genes are polymorphic. A polymorphic gene is one for which the most common allele has a frequency of less than 0.95 (95%). Mammals are about 15% polymorphic.

A gene that is not "polymorphic" is called "monomorphic", but this does not imply only one allele. Most monomorphic genes have rare alleles, generally occurring at frequencies below 0.005.

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III. The Nature of Genetic Disease

by John Armstrong

Many people label any problem that appears to be inherited a "genetic disease." However, though there are legitimate genetic diseases, there are also a variety of problems that have an inherited component but are of a fundamentally different nature. Dealing effectively with any genetic problem requires an understanding of the relationship between the genes (genotype) and the phenotype. In many cases this is lacking. In this article, I would like to describe some of the differences, in order to give breeders and owners a better understanding of what they are dealing with.

Inborn Errors of Metabolism: The true "genetic diseases"

The first clearly-described relationship between genotype and metabolic deficiencies is credited to Sir Archibald Garrod, an English physician. In 1901, he showed that the inherited disease alkaptonuria results from an inability to metabolize certain amino acids, leading to the accumulation of homogentisic acid. Some of this compound accumulates in skin and cartilage (the latter leading to arthritis). The rest is excreted in the urine, turning it black. Garrod suggested that the metabolic block was caused by an enzyme deficiency, though this was not confirmed until the enzyme (homogentisic acid oxidase) was characterized in 1958.

Since Garrod's time, many other inherited metabolic diseases have been discovered. Some can be managed by careful attention to diet; others cannot. A particularly nasty example is Tay-Sachs disease, which involves an enzyme important in lipid metabolism. Individuals homozygous for a deficiency in this enzyme accumulate a compound called a ganglioside in the nervous system. They appear normal at birth, but progressively lose motor function and die around three years of age. There is no treatment.

Most of these conditions involve mutations that lead to the production of a nonfunctional enzyme, or one that is totally absent. In heterozygotes, the single good copy of the gene is generally able to produce sufficient enzyme to handle the normal workload. However, in a few cases, carriers as well as affected individuals have to be careful about their diet or may exhibit less severe phenotypic effects.

Example of inherited metabolic diseases in dogs include phosphofructokinase deficiency in Cocker and Springer Spaniels, and pyruvate kinase deficiency in Basenjis.

Not all mutations involve metabolic pathways. Some involve proteins that have structural roles in cells and tissues. Others involve regulatory genes that control the correct sequence of events during development. These may lead to such problems as septal defects in the heart or the failure of the embryonic kidney to develop into the adult form. Nevertheless, all can legitimately be considered genetic diseases, as there is a direct one-to-one relationship between a single mutated gene and a particular problem.

Conformational Diseases: The result of unnatural selection

Problems such as bloat (gastric dilatation-volvulus, or GDV) and hip dysplasia clearly have a genetic component, but also an environmental component and, perhaps, a behavioral one, as well (which also may be determined partially by the genes).

Bloat is not a "genetic disease" in the same sense as the metabolic and other disorders described above, and it seems unlikely that a single gene is responsible for bloat. One might better compare a bloat attack to a bad case of indigestion in a human. Some people are more prone to such attacks than others, and there may well be an

inherited component, but other factors also come into play. Research into bloat suggests that diet, behavior, and conformation may all play a role.

Leaving aside the question of the role of genetics in behavior, the results suggest that the incidence of bloat increases with the size of the dog and the depth-to-width ratio of the chest cavity. This is a conformational problem, not a genetic disease. Certainly, the overall conformation is, ultimately, determined by the genes, but not by a single gene. There are probably dozens or hundreds of genes that go into determining the shape and size of the head, trunk, and limbs. Wherever there is genetic variability, one can select for larger, smaller, narrower, wider, etc. If the fancy as a whole decides that a taller, narrower dog looks more "refined," more of that description will be kept for breeding purposes, and the population will be shifted toward a more bloat-prone conformation.

When it comes to the question of correcting this problem, the solution, in theory, is simple. We stop breeding for a bloat-prone conformation and select for a slightly smaller dog with a chest cavity that is not so deep or narrow. Some may regard this as a retrogressive step, but we have to decide which we want to sacrifice.

I do not rule out the possibility that two dogs of identical conformation may have one or more genes that lead to one being more bloat-prone than the other. If we could identify these genes, we might be able to reduce the incidence of GDV somewhat while retaining some of the desired "refinement."

While it may be argued that there is nothing wrong with a tall, narrow dog aside from the greater risk for bloat, selecting for a conformation that is not **functionally** sound is a recipe for disaster. Wild canids do not move awkwardly. Any that did would be eliminated by natural selection. After thousands of years of evolution, the musculoskeletal system of the average wolf has found a combination that works efficiently. Because there is diversity in the gene pool, there is always the possibility of a chance combination of genes that produces an individual that can move more quickly and efficiently. There is also the possibility that a less efficient combination may arise, but it is not likely to be favored.

In the artificial world of the show dog, one can insulate an individual from natural selection and favor a conformational extreme, because the breeder or the public thinks it looks more attractive or just different. Two such extreme dogs, bred together, may lead to something even more extreme and more popular. However, the changes in one component must be accompanied by changes in others, or the result, from a structural standpoint, may impose stresses that the components are not designed for. The result will be components easily damaged or deformed while the puppy is still growing.

In such a case, one may not be dealing with genes that are "bad" and make a nonfunctional or defective product, just with a bad combination of genes. But if, during this "unnatural selection," the genes necessary to make a good combination have been discarded, where does this leave the breed?

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All in the Family (Part 4)

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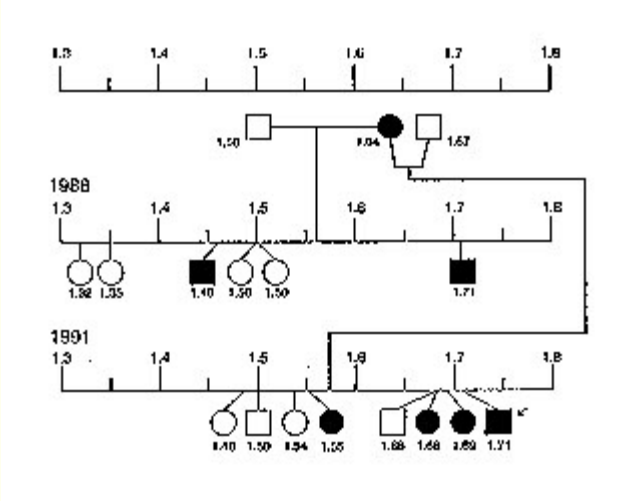
We continue to follow a family of Irish Setters in which several dogs have already bloated. This family study is another attempt to better understand genetic influences on bloat, which can cluster within certain families (familial bloat) or occur in unrelated animals (sporadic bloat). Geneticist Dr. Robert Schaible and Irish Setter breeder Jan Ziech collaborated with the Purdue Bloat Research Team in this study.

Measurement data and bloat histories were collected for all but 1 of 15 surviving pups in 2 litters, whelped in 1988 and 1991, respectively, that had the same dam but different sires. The parents' measurements and bloat histories were obtained. The pedigree was plotted on a scale of chest depth/width ratios. The ratios in this family are spread across a wide range of values for Irish Setters enrolled in the ongoing prospective study.



Pedigree of parents and pups in 2 Irish Setter litters, with chest depth/width ratio for each dog. Circles indicate females, squares indicate males. Solid symbols indicate dogs that have bloated. (Modified from Schaible et al.)

The pattern suggested that incomplete dominance of a major gene is the mode of inheritance of chest depth/width ratio. The data support the hypothesis that dogs with a deeper chest relative to width are at greater risk of developing bloat than dogs of the same breed with smaller chest depth/width ratios. The pattern for this family will not be complete, however, until all dogs have been followed throughout their lifetime. Breeders who want to do a similar family study can call Dr. Schaible at 812-876-9884.

Reference: RH Schaible et al. *J Am Animal Hosp Assoc* 33:379-383, 1997

The Value of Population Genetics to the Breeder

by John Armstrong

As a breeder, you are a practicing geneticist. To breed effectively you need to know something about genetic principles. (Would you sit down to a bridge game expecting to win without any knowledge of the rules?)

What is often called "Mendelian genetics" deals with the outcome of specific crosses. Population genetics deals with the distribution of alleles in a population and the effects of mutation, selection, inbreeding, etc. on this distribution. A knowledge of both is critical not only to your own success, but also to the survival of your breed.

Once-upon-a-time, many geneticists believed that there were only two alternatives for a gene - "good" alleles that functioned normally and "bad" alleles that didn't. If things were this simple, then the task of the geneticist-breeder would be simplified to one of identifying the bad alleles and trying to eliminate them from the population. Such a simplistic model could be modified to allow for different "good" alleles, but it should not matter whether you have one or another. These early geneticists expected to find little genetic variability in a population. The majority of individuals were expected to be homozygous for the good allele for most genes.

With the advent of modern biochemical and molecular tools, geneticists studying populations found far more variability (diversity) than they had expected. There are a number of possible reasons for this, and even the experts are not in total agreement on the most likely reason(s). However, geneticists have also discovered that populations lacking genetic diversity often have significant problems and are at greater risk from disease and other changes in their environment. The conclusion is that genetic diversity is desirable for the health and long-term survival of a population.

Are purebreds dogs genetically diverse? Some may regard that as a contradiction in terms. The very concept of creating a breed with characteristics that are distinctly different from other breeds implies a certain limitation on diversity. Nevertheless, within the standards for a breed, diversity should still be possible for genes that do not affect the essential characteristics that distinguish one breed from another. If, in order to maintain breed identity, one has to compromise on genes that relate to general structural soundness, good health, intelligence and temperament, perhaps this breed should not exist. However, as long as these essentials are not compromised, I see no reason why one cannot have different breeds with different appearances and different talents. For those genes that establish breed identity, there will be markedly less variability within a breed than within ***Canis familiaris*** as a whole.

The tricky bit is restricting variability for those genes that make a breed distinctive without sacrificing the variability/diversity that is necessary for good health and long-

term survival of the breed. In many cases, this has not been achieved, and we are now paying the price in terms of high incidence of specific genetic diseases and increased susceptibility to other diseases, reduced litter sizes, reduced lifespan, inability to conceive naturally, etc.

Why has this happened - or do we have to accept it as an inevitable consequence of creating a breed? I don't think we do.

The principal reasons for limited genetic diversity are:

1. Many breeds have been established with too few founders or ones that are already too closely related.
2. The registries are closed for almost all breeds. Therefore you cannot introduce diversity from outside the existing population.
3. Most selective breeding practices have the effect of reducing the diversity further. In addition, the wrong things are often selected for.
4. Even if the founders were sufficiently diverse genetically, almost no one knows how their genetic contributions are distributed among the present day population. Consequently, breeding is done without regard to conserving these contributions which may be of value to the general health and survival of the breed.

Each breed needs a database with all the breedable animals recorded and all their ancestors back to the founders. This would most appropriately be the task of the breed club. Are any actually doing this? (All the large databases I know about are maintained by individuals with an interest in genealogy.)

Such a database would enable breeders to identify which individuals are most likely to carry the genes from each founder. In practical terms, measures might then be considered to rebalance the breed in order to ensure that the remaining diversity is more evenly distributed end that, therefore, there is less risk of loss.

At the level of the individual breeder, it would enable him/her to make intelligent, informed choices when selecting mates.

A Lesson from the Poodles

As a poodle owner my interests naturally started with the poodle. With the assistance of several others, we are building a Standard Poodle database. The goal is to be able to trace any current SP back to the imports into North America (most of which were in the 1930s) and beyond that where possible. For a breed such as the poodle, which is not of modern origin, establishing all the original founders is impossible. However, as these imports came from a variety of countries, they would appear to represent reasonable diversity.

Though our work is far from complete, I am able to give a breeder a profile of their dog. Armed with this information, a breeder may then be able to avoid inadvertently breeding to a "cousin" (with the attendant risks of doubling up on undesirable recessive traits). There are no guarantees. Until DNA tests are developed for the most common problems, this is often the best we can offer.

You might think that the situation I have described would suggest that there is reasonable diversity in the SP population. This, unfortunately, is not the case. Over-use

of popular males from the same line during the past forty years has come close to wiping out the other lines and the majority of the population owe far too much of their heritage to a small number of ancestors. The same potential exists for degrading the gene pool in any breed.

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DOGBREEDING SCHEMES

I. Basic Concepts

by John Armstrong

Introduction

Most of you are undoubtedly aware that color and certain diseases such as progressive retinal atrophy (PRA) are inherited that is, passed down from one or both the parents. However, you may wonder how a trait that does not appear in the dam's pedigree can suddenly turn up in a litter out of Ch. Jacob Hugelsberg. Is it inherited or just an accident? Surely, Jake has been used so often that someone would have noticed if the problem came from him.

Just how much of a role does genetics play in health, general conformation and temperament? Probably, you would like to know exactly what traits are inherited; but, once someone starts talking about "partial dominance" or "expressivity," you get glassy-eyed. The objective of this guide is to explain some of the basics of inheritance and how to use these concepts to breed healthier dogs — hopefully without losing you in complex technical jargon.

What Traits (or Characteristics) Are Inherited?

The answer is "almost all," from temperament to size and coloring, as well as genetic diseases like progressive retinal atrophy (PRA). Infectious diseases are not inherited, though the susceptibility to them may be, to a greater or lesser extent.

The occurrence of any particular characteristic depends on two factors: genetics and the environment. "Genetics" refers to the encoded information (instructions) controlling all biological processes that are carried within the cells of all living organisms. These encoded instructions are responsible not only for maintaining the continuity of a species (or breed), but also for many of the differences between individuals within a species or breed.

The environment also contributes to the differences between individuals. The relative contribution of

genetics and environment is not the same for every trait. Some traits, such as color, are influenced very little by the environment. For others, such as temperament, the effect of the environment is much greater. Geneticists use the term heritability to indicate the proportion of the total possible variability in a trait that is genetic. However, when genetic differences are not the main source of variability, the heritability of a trait may be difficult to establish and may not be the same for different breeds. Therefore, I cannot tell you that the heritability of size, for example, is 70% (or whatever it may be).

Before moving on to a more detailed discussion of genetics, I would like to take a brief look at what is meant by "environment," in the present context. For a puppy, the first environment it encounters is that of the mother's womb. Is the mother well nourished, healthy, and free from stress? How old is she? Is this her first litter? How big is the litter? Once the puppy is born, it experiences a new environment, where it has to compete for food and attention. Litter size is still a factor. How much food does the puppy get? How much attention does it get from the mother, the breeder, and the eventual owner? Does it have a safe and healthy environment? Does it have other dogs to associate with? The answers to these questions define, in part, the puppy's environment.

Genes...

The gene is often called the basic unit of inheritance. A gene carries the information for a single step in a biological process; but most biological processes — even the ones that may appear to be simple — are made up of more than one step. Thus, one should not get the idea that a trait is determined by a single gene, but rather that the general rule is that many genes control a single trait. A good example is color. In some breeds, such as the Poodle and the Borzoi, there are a great variety of colors, so it should come as no surprise that this is the result of the action of a variety of genes. There are not only genes for making the different colored pigments, but also genes which control the distribution of the pigments, both within the individual hairs and over the entire body. (Other breeds may come in only one color. They have the same genes, but only a single allele of each.)

All animals have thousands of genes, but they do not float around loose in the cells. To make cell division and reproduction more manageable, genes are physically connected to other genes to form chromosomes. Most "higher" animals have two sets of chromosomes: one set from the mother and the other set from the father. So that the number of sets does not keep increasing from one generation to the next, sperm and eggs get only one set each. However, the mechanisms that assure this are not able to tell which chromosomes came from the mother and which from the father. Therefore, the set that is passed on in a particular egg or sperm is a mixed set. The number of possibilities depends on the number of chromosomes. Since dogs have 39 chromosomes in a set, the number of possible combinations is well over one billion! Therefore, the possibility of getting two litter-mates that have exactly the same combination of chromosomes is extremely remote. (Incidentally, wolves also have 39 chromosomes in a set and can breed with domestic dogs. Foxes, however, have only 19 chromosomes and cannot.)

One of the 39 chromosomes carries genes that determine sex. In mammals, the chromosomes carrying the "female" genes is designated X and the one carrying the "male" genes is designated Y. An animal with

two X chromosomes will be a female, while one with an X and a Y will be a male. (One with two Ys will be in serious trouble!) Genes other than those determining sex are also located on these chromosomes and are said to be sex-linked.

...and Alleles

Most genes carry out their functions correctly, but some are altered by exposure to radiation (natural or man-made), certain chemicals, or even by accident when a cell divides. A gene may be thought of as a small program. There are many possible places in the program where an error (mutation) might be introduced. Many of these will have the same effect: the program will not function. Others may modify the action of the program. Some may appear not to affect the program at all. Since the latter produce no observable effect, we need not worry about them. All, however, regardless of their effect, change the information carried in the program, so that, strictly speaking, each is a different version of that program. In genetics we call each version an allele. Technically, different versions, even if they produce the same effect, are different alleles; but we generally only worry about the ones that produce different effects, and we simply treat those that produce the same effect as though they were the same.

Though there are potentially a large number of alleles for each gene, by far the most common are those that prevent function entirely. Therefore, for many genes we only find the normal allele, often called the wild-type, and "no-function" (null) alleles. For some genes, we also get alleles that function partially or abnormally. However, no matter how many alleles there are in a population, an individual can carry only two — one from the sire and one from the dam. When the two alleles are the same, the individual is said to be *homozygous* for that gene. When the alleles are different, it is *heterozygous*.

Naming Genes

There are rules for naming genes — unfortunately, not all geneticists use the same system. The one I will use here is common, but not universal.

A gene is named for the first mutant allele discovered. For example, in the fruit fly (Drosophila), which normally has dark reddish-brown eyes, a mutant with white eyes was discovered many years ago.

Consequently, the particular gene in which this mutation occurred is called "white" and given the symbol *w*. The mutant allele is designated *w* (notice that it is italicized), and the wild-type allele is designated w^+. Another mutation, discovered later, has light yellowish-brown eyes and is called "eosin." However, it is also an allele of the same gene and is, therefore, not given a different letter designation. Instead, it is designated w^e. (This system reserves capital letter designations for dominant mutant alleles.)

The alternative system that you will more likely encounter is very similar, except we don't use a + sign to designate the wild-type allele. This can introduce an element of confusion. For example, gray coat color is not considered the normal (wild-type) color in Poodles. However, as it is dominant, it is given the symbol *G*, while the wild-type allele is *g*.

The naming of genes can also be eccentric. The dilute gene results in a lightening of the basic color and, appropriately, is designated *D*. A second gene has a similar effect, and is called *C* (for color). However, the best known mutant allele of this gene is the one that results in albinos, so the gene really should be called *A* — but this designation had already been used for agouti.

Dominance

If, for a particular gene, the two alleles carried by an individual are not the same, will one predominate? Because mutant alleles often result in a loss of function (null alleles), an individual carrying only one such allele will generally also have a normal (wild-type) allele for the same gene, and that single normal copy will often be sufficient to maintain normal function. As an analogy, let us imagine that we are building a brick wall, but that one of our two usual suppliers is on strike. As long as the remaining supplier can supply us with enough bricks, we can still build our wall. Geneticists call this phenomenon, where one gene can still provide the normal function usually met by two, dominance. The normal allele is said to be dominant over the abnormal allele. (The other way of saying this is that the abnormal allele is recessive to the normal one.)

When someone speaks of a genetic abnormality being "carried" by an individual or line, they mean that a mutant gene is there, but it is recessive. Unless we have some sophisticated test for the gene itself, we cannot tell just by looking at the carrier that it is any different from an individual with two normal copies of the gene. Unfortunately, lacking such a test, the carrier will go undetected and inevitably pass the mutant allele to some of its progeny. Every individual, be it man, mouse or dog, carries a few such dark secrets in its genetic closet. However, we all have thousands of different genes for many different functions, and as long as these abnormalities are rare, the probability that two unrelated individuals carrying the same abnormality will meet (and mate) is low.

Sometimes individuals with only a single normal allele will have an "intermediate" phenotype. (For example, in Basenjis carrying one allele for pyruvate kinase deficiency, the average life-span of a red blood cell is 12 days, intermediate between the normal average of 16 days and the average 6.5 days in a dog with two abnormal alleles. Though often termed partial dominance, in this case it would be preferable to say there is no dominance.

To carry our brick wall analogy a bit further, what if the single supply of bricks is not sufficient? We will end up with a wall that is lower (or shorter). Will this matter? It depends on what we're trying to do with the "wall" and, possibly, on non-genetic factors. The result may not be the same even for two individuals that have built the same wall. (A low wall may keep out a small flood, but not a deluge!) If there is the possibility that an individual carrying only one copy of an abnormal allele will show an abnormal phenotype, that allele should be regarded as dominant. Its failure to always do so is covered by the term penetrance.

A third possibility is that one of the suppliers sends us substandard bricks. Not realizing this, we go ahead and build the wall anyway, but it falls down. We might say that the defective bricks are dominant.

Advances in the understanding of several dominant genetic diseases in man suggest that this is a reasonable analogy. Dominant mutations usually affect proteins that are components of larger macromolecular complexes. These mutations lead to altered proteins that do not interact properly with

other components, leading to malfunction of the entire complex. However, some dominant mutations undoubtedly produce their effects in other, poorly-understood ways.

Dominant mutations may persist in populations if the problems they cause are subtle, not always expressed (see below), or occur later in life, after an affected individual has reproduced.

Expressivity and Penetrance

For a breeder, understanding the inheritance of a trait that is controlled by several genes and influenced by the environment can be a nightmare. Suppose, for example, that you are trying to breed apricot Poodles, but instead of getting only a single shade, your litters always have a variety of shades from pale to dark apricot. You might blame it on variable expressivity, which is just a convenient way of saying that you don't know what other genes or environmental factors are also playing a role in determining the color.

One of the classic examples of this in dogs is the variable expression of piebald spotting in beagles shown in Little (1957). The dogs all have the same Sp allele, but the colors range from black-and-tan with white feet to predominantly white with a few black spots.

Penetrance is a similar term-of-convenience (euphemism). If you are 99+ % certain that Fido carries the allele for six toes (because both his parents and all his sibs have six toes), but Fido has the normal five toes, you blame it on incomplete penetrance, try to look authoritative, and hope that no one asks additional questions. [Actually, it would probably be safer just to say that the trait is not always expressed and avoid possible embarrassment.]

The difference between expressivity and penetrance is that with the former, the trait is expressed to a variable extent, while with the latter it may or may not be expressed even though the genetic makeup (genotype) of the animal suggests that it should be.

Sex Linkage

In dogs, as in most animals, sex is determined genetically, but not by a single gene. One of the 39 chromosome pairs is used especially for sex determination. The unusual feature of this system is that the female-determining chromosome, called the X chromosome, doesn't even look like the male-determining Y chromosome — though they are still considered a "pair" and are referred to as the sex chromosomes. (The other 38 are called autosomes.) As everyone likely already knows, females have two X chromosomes and males one X and one Y. The male normally produces an equal number of sperm carrying either the X or the Y chromosome. As his mate will be producing eggs carrying only X chromosomes, an equal number of female (XX) and male (XY) puppies should be produced. Of course, chance plays a major role and litters often don't have a perfect 1:1 ratio.
Mutations undoubtedly occur in genes that control the development and function of the ovaries, testes, and other reproductive organs, but few have been described, probably because disruption of the normal reproductive process results in infertility. However, there are also genes found on the sex chromosomes that have nothing to do with sex determination. Those found on the X chromosome have no equivalents on the Y chromosome. As a result, males have only one copy of these genes. (Since the terms "homozygous" and "heterozygous" apply only when there are two copies, this situation is given a special name: hemizygous.)

When mutations occur in these X-linked genes, the pattern of transmission of the mutant phenotype differs from that seen for an autosomal gene. If a female carries such a trait, she will not express it (as long as it is recessive), but she will pass the trait to half her sons, and as they receive no X chromosome from their father, it doesn't matter what his genotype is — half will be affected. Half the daughters will be carriers, but as these are recessive traits, these carrier daughters will not be affected. If the problem does not affect survival and reproduction, an affected male may pass the gene on to his progeny — but only to his daughters, as his sons will get his Y chromosome, which doesn't have a copy of the gene.

In humans, good examples of sex linkage are red-green color blindness and hemophilia. I have been unable to find an example in the dog. Von Willebrands disease (vWD), a form of hemophilia, is not equivalent to the human X-linked hemophilia and follows a normal autosomal pattern of inheritance

equivalent to the human X-linked hemophilia and follows a normal autosomal pattern of inheritance.

There are also traits that are **sex-influenced**, which means that their expression is influenced by the individual's sex. This does not imply that the gene is sex-linked. A human example is pattern baldness. The gene's expression is influenced by hormonal levels and only one copy of the baldness allele is sufficient to cause baldness in a man, whereas two copies are needed in a woman. In effect, it behaves as a dominant in males and as a recessive in females. Though half the sons of a female carrier will be affected, a heterozygous male will also pass the trait to half his sons.

Thus, any trait that appears more frequently in males than females is suspect as either sex-linked or sex-influenced. If it is passed from the father or the mother to half the sons, it is likely sex-influenced. If it seems to skip a generation and the pattern is grandfather to grandson, it is likely sex-linked.

Determining the Mode of Inheritance

Suppose that you have a litter in which several of the puppies appear to be less healthy than their litter-mates. Suppose that after a few weeks it is readily apparent that they are growing more slowly and appear less energetic. What do you do? Obviously, the first step is take them to your vet for examination.

Without going into details (as this is a hypothetical example), let us suppose that, after appropriate tests, he concludes that they have a hole in the septum between the two sides of the heart that is resulting in a mixing of oxygenated and de-oxygenated blood. Quite aside from any considerations about putting down the affected pups, the question remains: what caused the problem? Was it simply a developmental accident, an environmentally-induced condition, or is it genetic? [I have deliberately picked a condition

that may arise for any of these reasons.]

As a rule-of-thumb, if only a single pup is affected, the problem has not turned up before in related litters, and the problem does not occur frequently in the breed, it is likely a developmental accident. Nevertheless, given the usual under-reporting of health problems, especially those that may be genetic, a second litter between the same sire and dam might be warranted.

On the other hand, if all — or even the majority — of the pups were affected, one might be more inclined to look for something in the environment that could have perturbed the normal developmental process. The majority of genetic abnormalities are recessive and, under normal circumstances, the parents are unlikely to be affected (i.e., homozygous). Therefore, if the problem is a genetic one, it is more likely that the parents will be phenotypically normal carriers (i.e., heterozygous), and the expectation is that one-quarter of the progeny will be affected.

While this is important to keep in mind, obtaining a proportion of affected pups in a litter that is substantially lower or higher than one-quarter is no guarantee that the problem is not genetic. Even the larger breeds produce litters of only eight or so, so you would expect only two to be affected. One or three affected would not be considered unusual, and even getting none affected is not considered sufficiently improbable to alarm a geneticist. You might well get no affected pups in one litter and four affected pups in the next!

Dominant mutations having a significant impact on health will, in most cases, result in death before reproductive age is reached. There are exceptions, such as Huntington's Disease in humans. Any late-onset genetic disease, whether dominant or recessive, represents a potential problem. At least with a dominant, you can wait for the progeny to reach an age where the problem would normally have developed, then breed unaffected animals with reasonable assurance that they are not undetected carriers. For example, if the inherited condition develops at six or seven years, you can wait until the dog is three or four years old before breeding it, then not breed any of the progeny until the parents reach seven or eight years of age.

For a dominant mutation that is rare, most crosses will be between a heterozygous affected individual (*Aa*) and a normal one (*aa*). The expectation is that one-half the progeny will be *Aa*. Should both parents be Aa, one-quarter of the progeny will be aa (normal) and three-quarters either *Aa* or *AA*. Sometimes, the *AA* progeny will be affected more severely, or even die before birth.

Doing the necessary crosses to establish the mode of inheritance can be an expensive and time-consuming task, to which is added the thankless prospect of putting down sick puppies and finding pet homes for the remainder. Consequently, test matings are seldom done on a scale sufficient to produce numbers that can be subjected to statistical analysis. [One notable exception is the monumental study by Bourns on day-blindness in Alaskan Malamutes.]

One alternative to test matings is retrospective analysis of the pedigrees of affected animals. As one

generally needs a number of related animals occurring over several generations, the problem will likely already have become fairly common. The accuracy of such analyses is directly affected by the number of relatives for which data exists—a strong argument for the open exchange of information between owners, breeders, veterinarians, and researchers.

References

Little, C.C. "The Inheritance of Coat Color in Dogs", Howell, New York, 1957.

Willis, M.B. "Genetics of the Dog", Whitherby, London, 1989.

Notes

The term **wild-type** literally means the most common type found in the wild. In a Samoyed, it would be the color white. In a Poodle, it would be black. Though we usually equate "wild-type" with "normal," and a white Samoyed is certainly normal for the breed, Samoyeds nevertheless have a genetic deficiency in pigmentation.

Actually, we should not be saying that the **allele functions abnormally**. The allele carries the wrong information. The **consequence** of that information being used results in an **abnormal functioning of some process**.

Agouti is a sort of mottled brown color not seen in most dog breeds. Geneticists try to be consistent in their naming of genes and don't use different symbols for different species, providing the genes are known to have the same action.

II. Breeding Schemes

by John Armstrong

Breeders often talk about inbreeding and outcrossing as though they were the only possibilities -- and generally with negative comments about the latter. There are other possibilities, and I have long been a proponent of assortative mating. It is not a theoretical concept that doesn't work in practice; I know several breeders who do it and achieve good results. This essay will attempt to explain why it is a good idea, but first I need to define the alternatives.

Random Mating

Though random mating is not a common breeding practice, understanding what this implies is important. Random mating is exactly what the name implies: mates are chosen with no regard for similarity or relatedness. (If the population is inbred to some extent, randomly-selected mates may be related.)

Random mating is one of the assumptions behind the **Hardy-Weinberg** formula, which allows one to calculate the frequency of heterozygous carriers from the frequency of individuals expressing some recessive trait in a population. Because inbreeding among purebred dogs and in other small populations decreases the frequency of heterozygotes, these estimates may be higher than the actual incidence.

Inbreeding and Linebreeding

Inbreeding is the practice of breeding two animals that are related (i.e., have one or more common ancestors). The degree of inbreeding may be assigned a value between 0 and 1, called the inbreeding coefficient, where 0 indicates that the animals have no common ancestors. Because the number of ancestors potentially doubles with every generation you go back in a pedigree, you eventually get to a point, even in a very large population, where there are simply not enough ancestors. Thus, all populations are inbred to some degree, and a true **outcross** (the term generally used when two animals are "unrelated") is not really possible. The term is generally misused to describe a cross between two animals with different phenotypes.

In a population with a limited number of founders, a maximum number of ancestors -- the **effective population size** -- is reached in some past generation. This number will be governed by various factors, such as the total population size, how far individuals travel during their lifetime, and whether there are inbreeding taboos or other mechanisms that reduce the likelihood of close relatives mating.

Inbreeding, by itself, does not lead to a change in allele frequencies, but does increase the proportion of homozygotes. Thus, in the absence of other practices, inbreeding will lead to a higher proportion of individuals homozygous for deleterious genes, and these are likely to be removed from the breeding pool by natural selection (if they do not survive to reproductive age) or by man.

Linebreeding is merely a term used for a particular type of inbreeding that often focusses on one ancestor who was considered exceptional. Particularly if it is a male, this exceptional ancestor may end up as grandfather and great-grandfather -- sometimes more than once -- in the same pedigree. Father-daughter, mother-son, and some other combinations also result in a disproportionate number of genes coming from a single ancestor. This type of **close inbreeding** is less common. [In contrast, the mating of full sibs or first cousins doubles up on two ancestors equally.]

As the result of several common practices, most pure-bred domestic animals are more inbred than they really need to be. One is that some breeders own a small number of animals and breed only within their own group. A second is that many breeders have the idea that outstanding animals can be produced by inbreeding -- by doubling up on the good alleles while somehow avoiding the bad. Even if you were to point out that this is a gamble, such breeders might respond that they are simply helping natural selection.

Beyond the conventional close-relative inbreeding, there is another practice that has much the same effect, namely the **popular sire** phenomenon (generally over-use of a well-promoted champion). In fact, many who breed to such a dog believe they are doing a "good thing," as they will be increasing the frequency of occurrence of the genes that made him a champion. What they may not realize is that they are increasing the frequency of **all** genes carried by this animal -- whether they are good, bad, or innocuous -- and that champions, like any other animal, carry a number of undesirable recessive alleles that are masked by wild-type alleles. The result of the popular sire phenomenon is that almost all members of the breed will carry a little bit of Jake Hugelberg, and any undesirable trait carried by Jake will no longer be rare. Finding a safe, unrelated mate then becomes an exercise in futility.

If we lived in a world where all the genes followed the simple rule that there may only be good alleles, which are dominant, and bad alleles, which are recessive, then inbreeding could be an effective tool for improving a breed, providing the latter were rare. (See, however, genetic load.)

Unfortunately, geneticists discovered, fairly early in the game, that there are also alleles that could be described as fair or poor. (They are generally ones that retain a portion of their normal function.) Suppose we have a "mutant" allele that has lost only one-fourth of its normal function. In many cases, this would not even have a noticeable effect. If you made an individual homozygous for this allele, you

would not even be aware that you had done so. Now consider that the same fate may befall a number of genes during an inbreeding program. Eventually, you will have an individual that is considerably less fit than one carrying the normal alleles for all (or even most of) these genes. There is no magic formula for regaining what you have lost. You must start again.

[Sometimes mutant alleles result in an even more dramatic loss of function, but remain undiscovered under normal conditions. A good example is vWD in Dobermans.]

About the only animals that are routinely inbred to a high level are laboratory mice and rats. There, the breeders start breeding many lines simultaneously in the expectation that the majority will die out or will suffer significant **inbreeding depression**, which generally means that they are smaller, produce fewer offspring, are more susceptible to disease, and have a shorter average lifespan. Dogs are no different. If you can start with enough lines, a few may make it through the **genetic bottleneck** with acceptable fitness. However, dog breeders generally don't have the resources to start several dozen or more lines simultaneously.

If that is not sufficient to discourage you, then consider the following. During the past 25 years, geneticists have been going out and measuring genetic diversity in natural populations directly by looking at the DNA or proteins, rather than at the phenotype. They have found that many individuals that cannot easily be distinguished by their phenotypic appearance nevertheless have considerable differences in their genotype. This came as a considerable surprise, as the expectation was that those alleles that reduce function even only marginally should, over time, be selected against in the real world.

This discovery led to the theory of **neutral isoalleles** and the concept that heterozygosity might actually be a good thing -- of itself. Neutral isoalleles produce proteins that are different but that function equally well under normal conditions. In combination, they may function even better. Consider the analogy of a soccer match in which each team is allowed two goalies. One team has identical twins who are good at covering the center, the other fraternal twins, one of whom is better at covering the right and the other the left. All else being equal, which team is going to win?

This is not a universally accepted theory, but today one is hard pressed to find a conservation or zoo biologist concerned with preserving an endangered species who would not list maintaining maximum genetic diversity as one of his/her primary goals. They equate inbreeding depression with loss of heterozygosity.

Assortative Mating

Assortative mating is the mating of individuals that are phenotypically similar. It is a normal practice, to some degree, for humans and various other species. Though phenotype is a product of both genotype and environment, such individuals are more likely to carry the same alleles for genes determining morphology. If we are talking about a conformation that is basically sound from the structural point of view, the genes involved will have been subjected to natural selection for thousands of years and will most likely be dominant. The major characteristics that set one breed apart from another will likely have been **fixed** early in the breed's history. ("Fixed" means that there is only one allele of present in the population. If there is only one allele, the question of dominance does not apply unless you mix breeds.)

Consequently, when you look at a dog, you are looking at his genes. If the conformation (or, for that matter, the temperament, intelligence, or whatever) is not good, then you are very likely looking at a dog or a breed that is homozygous for one or more recessive alleles that you would probably like to get rid of. If it is the dog and not the breed, you may elect not to breed him, or you may look for a mate that covers the problem. If it is the breed, the only solution would be to introduce some genes from another breed. (That would be an outcross!)

Breeding together animals that share dominant good alleles for most of their genes will produce mainly puppies that also carry these genes. Even if the parents are not homozygous for all these good alleles, you should still get many that are suitable. More important, if animals heterozygous for certain genes

are more fit, assortative mating will preserve more heterozygosity than inbreeding. However, unlike inbreeding, assortative mating should not result in an increased risk of the parents sharing hidden recessive mutations. Though we might like to eliminate deleterious recessives, everyone carries a few. Trying to find the "perfect dog" without either visible or hidden flaws is like betting on the lottery. There may conceivably be a big winner out there, but they are certainly not common.

The more you try to cover the deficiencies in one dog with good qualities in another, the less the dogs will have in common. If, then, the results are unsatisfactory, they should not be blamed on assortative mating, as that is no longer what you are doing.

The risks involved

Some trait that breeders consider desirable could be the result of homozygosity for a recessive allele for gene A or gene B. Obviously, crossing an *AAbb* with an *aaBB* will produce *AaBb* progeny that will not express this trait. (However, aside from some of the genes affecting coat color, I can think of no examples.)

If care is not taken to go back far enough in the pedigrees, you may have two animals with similar phenotypes resulting from common ancestry. Whether you are inbreeding unintentionally or intentionally, the consequences are the same. The solution is simple: check the heritage.

Because assortative mating involves selection (you are hopefully mating the best together, and not the worst), you are denying some dogs the opportunity to pass their genes on to the next generation. This is, perhaps, the subtlest of risks, as it does not seem to involve doing anything "wrong." Most would argue that it is merely doing what nature does -- eliminating the least fit. But what if some of these "less-than-best" happen to be the only ones to carry the best allele for some gene? Out goes the good with the bad!

This is primarily a "low-numbers" risk. The larger the population, the less likely we are to find that important alleles are carried by only a few individuals. However, it pays to know where the diversity lies. Do any of you know which, among the current dogs, are most likely to carry the genes of any given founder?

Notes

Inbreeding calculations do not account for the possibility that an allele will become homozygous by "chance," though this, too, can be calculated if the frequency at which an allele occurs in the whole population is known. Most basic Genetics texts explain how. (See, for example, Willis, pp. 293-295, "The Hardy-Weinberg Law.")

I have seen figures of 2500 genetic diseases in man and there are likely to be as many in ***Canis familiaris***, taken as a whole. In man. the vast majority are rare (allele frequencies of < 0.01, which means < 1 in 1000 affected). However, everyone carries three to five "lethal equivalents." This is their "**genetic load.**" Canine breeds are often established with a handful of founders, so we end up with a subset of one or two dozen problems, at frequencies at least 10-fold higher. [If we had five founders, each with a unique set of problems carried as single recessive alleles, the allele frequency of each will initially be ~ 0.1 and ~ 1% will be affected.

III. The Nature of Genetic Disease

by John Armstrong

Many people label any problem that appears to be inherited a "genetic disease." However, though there

are legitimate genetic diseases, there are also a variety of problems that have an inherited component but are of a fundamentally different nature. Dealing effectively with any genetic problem requires an understanding of the relationship between the genes (genotype) and the phenotype. In many cases this is lacking. In this article, I would like to describe some of the differences, in order to give breeders and owners a better understanding of what they are dealing with.

Inborn Errors of Metabolism: The true "genetic diseases"

The first clearly-described relationship between genotype and metabolic deficiencies is credited to Sir Archibald Garrod, an English physician. In 1901, he showed that the inherited disease alkaptonuria results from an inability to metabolize certain amino acids, leading to the accumulation of homogentisic acid. Some of this compound accumulates in skin and cartilage (the latter leading to arthritis). The rest is excreted in the urine, turning it black. Garrod suggested that the metabolic block was caused by an enzyme deficiency, though this was not confirmed until the enzyme (homogentisic acid oxidase) was characterized in 1958.

Since Garrod's time, many other inherited metabolic diseases have been discovered. Some can be managed by careful attention to diet; others cannot. A particularly nasty example is Tay-Sachs disease, which involves an enzyme important in lipid metabolism. Individuals homozygous for a deficiency in this enzyme accumulate a compound called a ganglioside in the nervous system. They appear normal at birth, but progressively lose motor function and die around three years of age. There is no treatment.

Most of these conditions involve mutations that lead to the production of a nonfunctional enzyme, or one that is totally absent. In heterozygotes, the single good copy of the gene is generally able to produce sufficient enzyme to handle the normal workload. However, in a few cases, carriers as well as affected individuals have to be careful about their diet or may exhibit less severe phenotypic effects.

Example of inherited metabolic diseases in dogs include phosphofructokinase deficiency in Cocker and Springer Spaniels, and pyruvate kinase deficiency in Basenjis.

Not all mutations involve metabolic pathways. Some involve proteins that have structural roles in cells and tissues. Others involve regulatory genes that control the correct sequence of events during development. These may lead to such problems as septal defects in the heart or the failure of the embryonic kidney to develop into the adult form. Nevertheless, all can legitimately be considered genetic diseases, as there is a direct one-to-one relationship between a single mutated gene and a particular problem.

Conformational Diseases: The result of unnatural selection

Problems such as bloat (gastric dilatation-volvulus, or GDV) and hip dysplasia clearly have a genetic component, but also an environmental component and, perhaps, a behavioral one, as well (which also may be determined partially by the genes).

Bloat is not a "genetic disease" in the same sense as the metabolic and other disorders described above, and it seems unlikely that a single gene is responsible for bloat. One might better compare a bloat attack to a bad case of indigestion in a human. Some people are more prone to such attacks than others, and there may well be an inherited component, but other factors also come into play. Research into bloat suggests that diet, behavior, and conformation may all play a role.

Leaving aside the question of the role of genetics in behavior, the results suggest that the incidence of bloat increases with the size of the dog and the depth-to-width ratio of the chest cavity. This is a conformational problem, not a genetic disease. Certainly, the overall conformation is, ultimately, determined by the genes, but not by a single gene. There are probably dozens or hundreds of genes that go into determining the shape and size of the head, trunk, and limbs. Wherever there is genetic variability, one can select for larger, smaller, narrower, wider, etc. If the fancy as a whole decides that a taller, narrower dog looks more "refined," more of that description will be kept for breeding purposes, and the population will be shifted toward a more bloat-prone conformation.

When it comes to the question of correcting this problem, the solution, in theory, is simple. We stop breeding for a bloat-prone conformation and select for a slightly smaller dog with a chest cavity that is not so deep or narrow. Some may regard this as a retrogressive step, but we have to decide which we want to sacrifice.

I do not rule out the possibility that two dogs of identical conformation may have one or more genes that lead to one being more bloat-prone than the other. If we could identify these genes, we might be able to reduce the incidence of GDV somewhat while retaining some of the desired "refinement."

While it may be argued that there is nothing wrong with a tall, narrow dog aside from the greater risk for bloat, selecting for a conformation that is not **functionally** sound is a recipe for disaster. Wild canids do not move awkwardly. Any that did would be eliminated by natural selection. After thousands of years of evolution, the musculoskeletal system of the average wolf has found a combination that works efficiently. Because there is diversity in the gene pool, there is always the possibility of a chance combination of genes that produces an individual that can move more quickly and efficiently. There is also the possibility that a less efficient combination may arise, but it is not likely to be favored.

In the artificial world of the show dog, one can insulate an individual from natural selection and favor a conformational extreme, because the breeder or the public thinks it looks more attractive or just different. Two such extreme dogs, bred together, may lead to something even more extreme and more popular. However, the changes in one component must be accompanied by changes in others, or the result, from a structural standpoint, may impose stresses that the components are not designed for. The result will be components easily damaged or deformed while the puppy is still growing.

In such a case, one may not be dealing with genes that are "bad" and make a nonfunctional or defective product, just with a bad combination of genes. But if, during this "unnatural selection," the genes necessary to make a good combination have been discarded, where does this leave the breed?

All in the Family (Part 4)

Reprinted from **"Bloat Notes", Jan. 1998**
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School of Veterinary Medicine, Purdue University
W. Lafayette IN 47907-1243

We continue to follow a family of Irish Setters in which several dogs have already bloated. This family study is another attempt to better understand genetic influences on bloat, which can cluster within certain families (familial bloat) or occur in unrelated animals (sporadic bloat). Geneticist Dr. Robert Schaible and Irish Setter breeder Jan Ziech collaborated with the Purdue Bloat Research Team in this study.

Measurement data and bloat histories were collected for all but 1 of 15 surviving pups in 2 litters, whelped in 1988 and 1991, respectively, that had the same dam but different sires. The parents' measurements and bloat histories were obtained. The pedigree was plotted on a scale of chest depth/width ratios. The ratios in this family are spread across a wide range of values for Irish Setters enrolled in the ongoing prospective study.

The pattern suggested that incomplete dominance of a major gene is the mode of inheritance of chest depth/width ratio. The data support the hypothesis that dogs with a deeper chest relative to width are at greater risk of developing bloat than dogs of the same breed with smaller chest depth/width ratios. The pattern for this family will not be complete, however, until all dogs have been followed throughout their lifetime. Breeders who want to do a similar family study can call Dr. Schaible at 812-876-9884.

Reference: RH Schaible et al. *J Am Animal Hosp Assoc* 33:379-383, 1997

IV. Diversity and the Purebred Dog

(The Poodle and the Chocolate Cake)

by John Armstrong

The Nature of Diversity

Think of genes as recipes. They carry the instructions for the various components that go into making up an organism. Each recipe specifies a particular component, and different individuals may carry different versions of the same recipe. (In the jargon of genetics, we say that they carry different alleles of a particular gene.) Individuals within a population often carry similar or identical recipes, for example, chocolate cake for a Poodle, lemon cake for a Beagle, and white cake for a Samoyed. A different canine species might be represented by a fruit cake. When you consider animals that are quite different, such as frogs and chickens, you will generally find "homologous" recipes, say for pies or puddings. Thus, there is more diversity among mammals than among carnivores, more among the carnivores than among the Canidae, and more among the Canidae than among the wolf group.

An organism carries a collection of recipes, and the collection defines the organism. The great diversity in the possible collections of recipes is the reason for the great diversity in the animal and plant kingdoms. The more closely related two individuals are, the greater the similarity in their collections. The number of combinations is huge, and during evolution, the recipe collection was undoubtedly reshuffled many times. The combinations that worked well survived and multiplied. Those that did not work quickly died out. In theory, one may make a meal of Champagne with tacos and Yorkshire pudding, but they don't really belong together. As time passed, exchange of recipes became difficult between animals that differed substantially in their physical and behavioural characteristics. Different groups, therefore, became constrained to work with only a subset of the total possible collection of recipes.

One definition of a species is that members of two different species bred to each other cannot produce a fertile hybrid. However, a more modern definition is that two species are geographically, physiologically, or behaviourally isolated such that they do not normally produce hybrids. Additionally, they should have features that differ sufficiently to allow them to be distinguished from each other. The domestic dog, wolf, coyote, and jackal can all mate with each others (barring size constraints) to produce viable and fertile hybrids. Yet, they have been considered different species (within the genus Canis) because they normally live in different places, behave differently, and can usually be told apart. (Though there has been a recent move to change *Canis familiaris* to a subspecies of *Canis lupus*.) However, a jackal will not mate with a dog unless they have been raised together from pups (presumably due to a learned behavioural difference). Furthermore, no Canis species can produce a hybrid with a fox. This is not because the kinds of genetic recipes are greatly different, but because foxes do not share the same number of chromosomes. (In other words, their recipes are filed under a different, incompatible system — somewhat akin to filing one under DOS and the other on a Mac.)

Genetic recipes may get modified when they are passed on. Many of the modifications will make no noticeable difference, or only a very subtle one. Some may improve the recipe and others will not. If we are making a chocolate cake and a critical ingredient is forgotten, or the cake is baked too long or at the wrong temperature, we end up with a disaster. (If we don't understand what has gone wrong, we will likely throw out the recipe and look for a new one.) We may even make deliberate modifications in an attempt to get a more memorable cake. Among the "chocolate cake" population, there will be a variety — or diversity — of recipes and, therefore, of cakes.

This, I would say, is a "good" thing. Do we always want the **same** chocolate cake? Surely we will tire

of it, and even if we don't, we lose the pleasure of anticipation. If, for some unforseen reason, everyone suddenly loses their taste for **THE** chocolate cake, it will surely go extinct. *To have the potential for evolution and adaptation, we must risk the possibility of the bad.* That is the "cost."

In a large, naturally breeding population, we will end up with a number of versions (alleles), some so slightly different that we will never notice, some perceptibly different (but still functional), and some that just don't work at all. However, if we remove the diversity we lose the potential for evolution and for surviving unexpected change. To have the potential for evolution and adaptation, we must risk the possibility of the bad. Geneticists call that cost **genetic load**. (This "bad" group persists because every individual carries two copies of every recipe, and often having just one "good" copy is enough for normal function.) In most populations, every individual carries a portion of the load — three to five bad recipes out of several thousand. The load is so well distributed that if two individuals compare their recipe collections they will generally not have two copies of the same bad recipe.

Loss of Diversity

Suppose we start a new population with only six or eight founders. (A number of breeds have started with that few.) We will get rid of hundreds of bad recipes, but the remaining dozen or two will be encountered much more frequently. Furthermore, if there are several good or excellent recipes, the chance of dropping one of these from the collection grows greater as the number of founders diminishes, and the risk of losing one remains high as long as the effective population size remains low. Working with small numbers will inevitably decrease the diversity, simply because individuals do not pass on their recipes equally to the next generation and some recipes are accidentally lost. This has the superficially desirable result of giving a more reproducible phenotype, but at the expense of an overall reduction in quality, health, and longevity.

If breeders had the ability to recognize each individual recipe and choose only those that were excellent, breeds could be produced with a small number of individuals that lacked genetic problems. However, what we see (the phenotype) is the product of all the recipes and, for the most part, we cannot distinguish the individual recipes. Moreover, we do not have the option of selecting recipes individually. When we select an animal for breeding, we are forced to accept a complete set. Even in those few cases where we now have a DNA test for a bad recipe (allele), we do not possess the ability to correct or selectively discarded it. We are therefore forced to work around it, or to discard the whole collection, with the attendant risk of discarding something excellent along with it.

The common practice of almost everyone rushing to breed to the currently-popular male show champion is probably the most significant factor reducing whatever diversity remains. Consider your own breed (the situation for most breeds is similar). Can you find one or more males that appear in most pedigrees? Almost everyone decides they like the recipes of (*insert name*) — or at least the ones they can see readily — and abandons other recipes with little thought to the eventual consequences. In a few generations, almost everyone has a substantial number of his recipes, though not necessarily his exceptional ones, and many excellent alternatives are very hard to find.

How precious is the individual that comes along with some of the missing recipes and relatively few of the "popular" collection? Do we hesitate because there are also a few bad recipes in this alternate collection? Are we now so accustomed to dealing with the more-popular collection that we have lost the vision of the "memorable" chocolate cake?

Population Genetics and the Breeder

What is often called **Mendelian** genetics deals with the outcome of specific crosses. **Population genetics** deals with the distribution of alleles in a population and the effects of mutation, selection, inbreeding, etc., on this distribution. As a breeder, you are a practicing geneticist. A knowledge of both Mendelian genetics and population genetics is critical, not only to your own success, but also to the survival of your breed.

Because many early geneticists believed that there were only two possible alternatives for a gene — "good" alleles that functioned normally and "bad" alleles that didn't — they expected to find little

genetic variability in a population. The majority of individuals were expected to be homozygous for the good allele for most genes.

But with the advent of modern biochemical and molecular tools, geneticists studying populations found far more variability (diversity) than they had expected. There are a number of possible reasons for this, and even the experts are not in total agreement on the most likely reason(s). However, geneticists have also discovered that populations lacking genetic diversity often have significant problems and are at greater risk from disease and other changes in their environment. The conclusion is that genetic diversity is desirable for the health and long-term survival of a population.

Are purebreds dogs genetically diverse? Some may regard that as a contradiction in terms. The very concept of creating a breed with characteristics that are distinctly different from other breeds implies a certain limitation on diversity. Nevertheless, within the standards for a breed, diversity should still be possible for genes that do not affect the essential characteristics that distinguish one breed from another. If, in order to maintain breed identity, one has to compromise on genes that relate to general structural soundness, good health, intelligence, and temperament, perhaps this breed should not exist. However, as long as these essentials are not compromised, I see no reason why one cannot have different breeds with different appearances and different talents.

For those genes that establish breed identity, there will be markedly less variability within a breed than within *Canis familiaris* as a whole. The tricky bit is restricting variability for those genes that make a breed distinctive without sacrificing the variability/diversity that is necessary for good health and long-term survival of the breed. In many cases, this has not been achieved, and we are now paying the price in terms of high incidence of specific genetic diseases and increased susceptibility to other diseases, reduced litter sizes, reduced lifespan, inability to conceive naturally, etc.

Why has this happened, and do we have to accept it as an inevitable consequence of creating a breed? I don't think we do.

The principal reasons for limited genetic diversity are:

1. Many breeds have been established with too few founders or ones that are already too closely related.
2. The registries (stud books) are closed for most breeds; therefore you cannot introduce diversity from outside the existing population.
3. Most selective breeding practices have the effect of reducing the diversity further. In addition, the wrong things are often selected for.
4. Even if the founders were sufficiently diverse genetically, almost no one knows how their genetic contributions are distributed among the present day population. Consequently, breeding is done without regard to conserving these contributions, which may be of value to the general health and survival of the breed.

A role for the breed clubs

Each breed needs a database with all the breedable animals recorded with all their ancestors back to the founders. This would most appropriately be the task of the breed club. Are any actually doing this (outside some of the rare breeds)?

Such a database would enable breeders to identify which individuals are most likely to carry the genes from each founder. At the level of the individual breeder, it would enable him/her to make intelligent, informed choices when selecting mates. Measures might also be considered to re-balance the breed, in order to ensure that the remaining diversity is more evenly distributed and that, therefore, there is less risk of loss.

References

Hartl, D.L. A Primer of Population Genetics, Sinauer, Sunderland, MA, 1988.

Notes

A population is regarded as genetically diverse if a substantial proportion of the genes are polymorphic. A polymorphic gene is one for which the most common allele has a frequency of less than 0.95 (95%). Mammals are about 15% polymorphic.

A gene that is not "polymorphic" is called "monomorphic", but this does not imply only one allele. Most monomorphic genes have rare alleles, generally occurring at frequencies below 0.005.

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Significant Relationships

by John Armstrong

How would you determine the impact of a famous Champion on his breed?

A dog who has won many shows and earned many titles may have been quite popular as a stud and may have sired more winning progeny than other contemporary males. However, that does not guarantee that he will have more impact five or ten generations down the line than another dog who was bred only two or three times.

Percent Contribution

If sufficient data is available, one way of determining the significance of an ancestor is to calculate his percent contribution to the current dogs. The % contribution (aka **percentage of blood**) is determined by the way genes are passed from the parents to the progeny. An individual inherits one set of chromosomes, and the genes they carry, from his or her sire and a second, homologous (equivalent) set from the dam. Thus, each parent makes a 50% contribution. As the parents in any generation always contribute 50% of their genes to their progeny, it seems reasonable to expect that 25% will come from each grandparent, 12.5% from each great-grandparent, and so on. However, once we are past the parents, we are dealing in probabilities, not certainties. This is not like mixing paint! When dad passes you one set of his chromosomes, they will include a selection of ones inherited from both his parents, but there is no guarantee that the selection will be exactly equal. There is even a small chance (very small) that he will pass on those from only one of his parents.

By the time we get back 10 generations, the contribution from each of the 1024 ancestors would, in theory, amount to slightly less than 0.1%. However, in the pedigree of the average purebred dog, there are seldom more than 100-200 different names and some appear 50 times or more. These are the significant ancestors that make the major genetic contributions.

If you have a pedigree, you can calculate % contribution of any repeats simply by multiplying the number of times each ancestor appears in any generation by the appropriate percentage for that generation and then add together all of the calculated percentage of contributions from each generation. The table listed below shows the percentage of blood inherited from each ancestor at the given generation levels. Generation "1" is the parents.

Genetic Contribution of Ancestors										
Generation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
% Contribution	**50.0**	**25.0**	**12.5**	**6.25**	**3.125**	**1.563**	**0.781**	**0.391**	**0.195**	**0.098**

You should get a number between 0 and 1; multiply by 100% to get the % contribution.

Databases exist for many breeds that will contain the data enabling you to extend a pedigree to 10 generations or more. Manual computation, though tedious, is still possible, but hardly convenient. Several pedigree programs (e.g. CompuPed) will quickly calculate % contribution for selected ancestors or all ancestors for a specified number of generations, providing you with information on

which dogs have been most influential.

Inbreeding Coefficients

While most breeders recognize that a mating between half-sibs or cousins represents inbreeding, the majority probably have no idea which is the closer relationship. This is not helped by the non-standard definition of inbreeding in some books (e.g. Onstott's "Breeding Better Dogs").

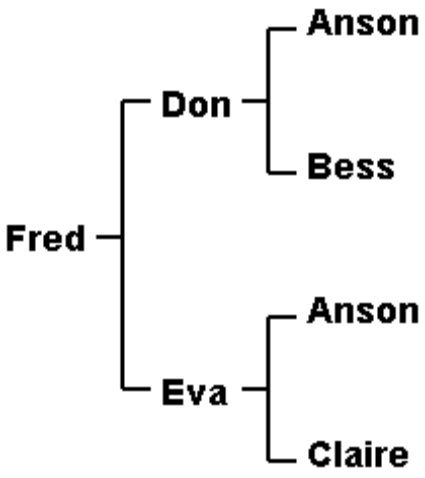
The standard definition of inbreeding is that it is any scheme which results in the sire and the dam having common ancestors. Many breeders use the term "inbreeding" for close relatives and "linebreeding" for more distantly related individuals, but there is no fundamental difference.

The parameter used to express this common heritage is called the **inbreeding coefficient** and was first proposed by Sewell Wright in 1922. Designated **F** by Wright (but more commonly IC or COI by breeders), it can theoretically range from 0 to 100%, and indicates the probability that the two alleles for any gene are **identical by descent**.

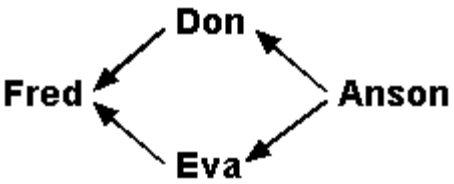
The primary consequence of inbreeding is to increase homozygosity. However, the IC is not a direct measure of homozygosity because the two alleles passed down from different ancestors may be functionally the same. Furthermore, some proportion of all the genes will be the homozygous because there is only one allele. The IC serves as an indicator of what proportion of the remainder may have been made homozygous by inbreeding.

The inbreeding coefficient is a function of the number and location of the common ancestors in a pedigree. It is **not** a function, except indirectly, of the inbreeding of the parents. Thus, one can mate two highly inbred individuals who share little common ancestry and produce a litter with a very low IC. (Because the potential number of ancestors doubles every generation, eventually you reach a point where the number of ancestors exceeds the number of individuals alive at that time. You are, therefore, bound to find some common ancestors if you go back far enough.) Conversely, it is possible to mate two closely related dogs, both of which have low ICs, and boost the IC substantially.

The most widely used approach for calculating inbreeding coefficients is Wright's "paths" method (see note), best illustrated by a simple example. Suppose we mate half-sibs, the common ancestor, Anson, being the father. Don is the son of Anson and Bess; Eva the daughter of Anson and Claire. Fred is one of their progeny.



To simplify, we don't show the ancestors that aren't shared:



Now we consider a gene for which Anson carries two different alleles, *a1* and *a2*. There is a 50% probability of the allele Anson passed to Don being passed on to Fred. There is also a 50% probability that the same allele will be passed from Anson to Eva, and a 50% probability of it being passed from Eva to Fred, if Eva got it. When dealing with events that are contingent (this ***and*** that must happen), we multiply the probabilities - in this case 0.5 x 0.5 x 0.5 = 0.125 (12.5%). This final number is the probability that Fred will be homozygous for either *a1* or *a2* because of the common grandfather.

In general, Wright's method is to determine the path from Fred to the common ancestor, Anson, and back again on the other side of the pedigree (Fred-Don-Anson-Eva-Fred), count the number of individuals in the path, excluding Fred (there are 3, Don-Anson-Eva) and then calculate $\mathbf{½^n}$, where n is that number. So, in the present case, we have $(½)^3$ or (½ x ½ x ½) = 1/8, or 12.5%. If this were the only common ancestor, the inbreeding coefficient for Fred would be 12.5%.

Now, suppose the common ancestor was one of the grandfathers of the parents (i.e. a great-grandfather of the litter). This adds an individual on each side of the pedigree, so that we will get a path of the type Fred-X-Don-Anson-Eva-Y-Fred, and the inbreeding on Anson will be $(1/2)^5$ or 1/32 (3.125%).

Like many other genetic calculations, the IC is based on probabilities, not certainties. An individual may be more or less highly inbred than the number computed.

If we had only a single common ancestor to deal with, life would be relatively simple. However, there are two complications to deal with. The first is that there will be more than one common ancestor. Let's consider the case of first cousins. In human populations such a pairing is prohibited in some societies but allowed in others. We have already calculated the inbreeding for a single shared grandparent. First cousins have two shared grandparents, and we simply add the inbreeding coefficient for each to get 6.25%.

The second complication is that the common ancestor may be inbred. If so, his or her inbreeding coefficient will have to be calculated. To account for this we have to multiply the inbreeding coefficient calculated for Fred by $(1 + F_A)$, where F_A is the inbreeding coefficient calculated for Anson. For example, if Anson is the product of a mating of first cousins, the total inbreeding for Fred will be 0.125 x 1.0625 = 0.133 (13.3%) **if** there are no other shared ancestors in the pedigree.

Unfortunately, in the average pedigree, there are a large number of shared ancestors. Therefore, the total inbreeding for a dog cannot generally be calculated manually and appropriate software must be used (e.g. CompuPed). Calculating inbreeding for only the first few generations is not particularly useful. If there are more than one or two common ancestors in four or five generation pedigree, the inbreeding is probably already higher than desirable. Unfortunately, having none is no guarantee that common ancestors will not occur in abundance further back, and some pedigrees of this type still achieve moderately high inbreeding coefficients. Neither can be number of shared ancestors be used as a reliable guide, as the inbreeding coefficient is very sensitive to when and where they occur in a pedigree.

Is there a quick way of determining how genetically similar two dogs are?

Suppose a breeder has two bitches (A and B) she wants to mate to different males. After careful research she has identified three potentially suitable males (C, D and E), all of which look equally good. She hopes to get a male puppy from one litter and a female from the other, and would like to eventually breed them to each other. The objective could be to pick the combination that will minimize the potential inbreeding. Alternatively, she may be looking for two dogs that are not close relatives yet have similar heritage.

One approach would be to produce hypothetical litters for all combinations: AC, AD, AE, BC, BD and BE. Then we would have to look at the possibilities for the second generation. There will be six if we don't permit shared grandparents, and 36 if there are no restrictions. These potential litters could then be evaluated for inbreeding or the % contribution of significant ancestors. This will certainly provide the data, but is unnecessarily tedious.

The Coefficient of Relationship

The coefficient of relationship (RC) provides a way of objectively assessing the similarity of two pedigrees by giving a number that is a direct measure of shared ancestry. In most human populations, two individuals picked at random would likely have a RC of 0, a brother and sister 50% and identical twins 100%. Other relationships would fall between 0 and 50%.

The number generated may be viewed as analogous to the % composition, except that you are comparing two dogs instead of looking at one. A brother and sister will give a value of 50% as long as an ancestor is not repeated. Once ancestors start to repeat, the individuals no longer have an inbreeding coefficient of zero. Two sibs from a highly inbred line may have an RC of 80% or more, and two dogs that are not sibs may have an RC above 50%.

The formula for the RC is:

$$R_{AB} = 2f_{AB} \div [(1 + F_A)(1 + F_B)]^{½}$$

where f_{AB} is the inbreeding coefficient of a hypothetical litter between A and B, and F_A and F_B are the inbreeding coefficients for the two individuals, A and B.

A simpler approach to the breeder's problem would be to compute the RCs for C vs D and E, and D vs E. This is not a pencil and paper calculation. However, presented with just such a problem, it took me about 2 minutes to obtain the three RCs with the latest version of CompuPed. My results were R_{CD} 10.4%, R_{CE} 13.4%, R_{DE} 17.2%.

As D and E share the most common ancestry, so would the progeny from their two prospective litters, while C and D share the least. To minimize inbreeding and maximize diversity, they would be my choice, all else being equal. (These values actually all fall below the average for the breed, which is ~ 23%.)

The Kinship Coefficient

The f_{AB} term in the RC equation is sometimes called the "kinship coefficient" and may also be used as a measure of the relationship between two individuals. It's computation is the same as that of an inbreeding coefficient for a hypothetical litter between the two dogs. (It doesn't matter if they are the same sex.)

The mean kinship (mk_i) for individual *i* is is the average of the kinship coefficients (f_{ij}) between *i*

and all the other breedable individuals in the population:

$$mk_i = \frac{\sum_{j=1}^{N} f_{ij}}{\mathbf{N}}$$

A conservation biologist would consider the individual with the lowest mean kinship to be the most genetically valuable in terms of maintaining diversity in the population, and would try to favor that individual in a breeding program.

Note: An alternative approach, often referred to as the "tabular" method, calculates inbreeding from the ealiest ancestor forward to the current dog (or dogs).

>

Demystifying Inbreeding Coefficients

John Armstrong

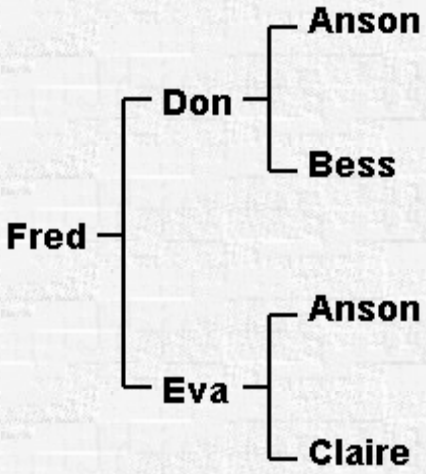
While most breeders recognize that a mating between half-sibs or cousins represents inbreeding, the majority probably have no idea which represents the closer inbreeding. This is not helped by the non-standard definition of inbreeding in some books (e.g. Onstott's "Breeding Better Dogs").

The standard definition of inbreeding is that it is any scheme which results in the sire and the dam having common ancestors. This common heritage is expressed by a parameter called the **inbreeding coefficient**, first proposed by Sewell Wright in 1922. Designated **F** by Wright (but more commonly IC or IBC by breeders), it can theoretically range from 0 to 100%, and indicates the probability that the two alleles for any gene are **identical by descent**. Though the primary consequence of inbreeding is to increase homozygosity, the IC is not a direct measure of homozygosity because the two alleles may be the same for other reasons. Within a breed, some proportion of all the genes will be the homozygous because there was only one allele to start with. In that sense, the IC may be regarded as indicating what proportion of the remainder have been made homozygous by inbreeding.

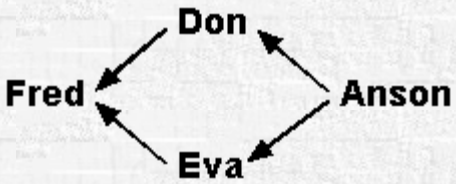
The inbreeding coefficient is a function of the number and location of the common ancestors in a pedigree. It is **not** a function, except indirectly, of the inbreeding of the parents. Thus, one can mate two highly inbred individuals who share little common ancestry and produce a litter with a very low IC. (Because the potential number of ancestors doubles every generation, eventually you reach a point where the number of ancestors exceeds the number of individuals alive at that time. You are, therefore, bound to find some common ancestors if you go back far enough.) Conversely, it is possible to mate two closely related dogs, both of which have low ICs, and boost the IC substantially.

Calculating inbreeding coefficients

The accepted method is best illustrated by a simple example. Suppose we mate half-sibs, the common ancestor, Anson, being the father. Don is the son of Anson and Bess; Eva the daughter of Anson and Claire. Fred is one of their progeny.



To simplify, we don't show the ancestors that aren't shared:



Now we consider a gene for which Anson carries two different alleles, *a1* and *a2*. Whichever one is passed to Don has a 50% probability of being passed to Fred. There is also a 50% probability that the same allele will be passed from Anson to Eva, and a 50% probability of it being passed from Eva to Fred, if Eva got it. When dealing with events that are contingent (this ***and*** that must happen), we multiply the probabilities - in this case 0.5 x 0.5 x 0.5 = 0.125 (12.5%). This final number is the probability that Fred will be homozygous for either *a1* or *a2* because of the common grandfather. If this were the only common ancestor, the inbreeding coefficient for Fred would be 12.5%.

In general, Wright's method is to determine the path from Fred to the common ancestor, Anson, and back again on the other side of the pedigree (Fred-Don-Anson-Eva-Fred), count the number of individuals in the path, excluding Fred (there are 3, Don-Anson-Eva) and then calculate 1/2 to the power n, where n is that number. So, in the present case, we have $(1/2)^3$ or (1/2 x 1/2 x 1/2) = 1/8, which is 12.5% as we calculated above.

Now, suppose the common ancestor was one of the grandfathers of the parents (i.e. a great-grandfather of the litter). This adds an individual on each side of the pedigree, so that we will get a path of the type Fred-X-Don-Anson-Eva-Y-Fred, and the inbreeding on Anson will be $(1/2)^5$ or 1/32 (3.125%).

Complications

If we had only a single common ancestor to deal with, life would be relatively simple. However, there are two complications to deal with. The first is that there will be more than one common ancestor. Let's consider the case of first cousins. In human populations such a pairing is prohibited in some societies but allowed in others. We have already calculated the inbreeding for a single shared grandparent. First cousins have two shared grandparents, and we simply add the inbreeding coefficient for each to get 6.25%.

The second complication is that the common ancestor may be inbred. If so, his or her inbreeding coefficient will have to be calculated. To account for this we have to multiply the inbreeding coefficient calculated for Fred by $(1 + F_A)$, where F_A is the inbreeding coefficient calculated for Anson. For example, if Anson is the product of a mating of first cousins, the total inbreeding for Fred will be 0.125 x 1.0625 = 0.133 (13.3%) **if** there are no other shared ancestors in the pedigree.

Unfortunately, in the average pedigree, there are a large number of shared ancestors. Therefore, the total inbreeding for a dog cannot generally be calculated manually and appropriate software must be used (e.g. CompuPed). Calculating inbreeding for only the first few generations is not particularly useful. If there are more than one or two common ancestors in four or five generation pedigree, the inbreeding is probably already higher than desirable. Unfortunately, having none is no guarantee that common ancestors will not occur in abundance further back, and some pedigrees of this type still achieve moderately high inbreeding coefficients. Neither can be number of shared ancestors be used as a reliable guide, as the inbreeding coefficient is very sensitive to when and where they occur in a pedigree.

ELIMINATING MUTATION
THE IMPOSSIBLE DREAM

by John Armstrong

Though it is not practical to eliminate all deleterious mutation, the incidence of affected individuals may be significantly reduced through a combination of intelligent breeding practice and the development of DNA tests.

Why do we have mutations?

Mutations are changes in an organism's DNA that potentially affect the correct functioning of genes. They occur naturally due to replication errors, mispairing of homologous chromosomes, or through unavoidable exposure to natural radiation (e.g., cosmic rays). Mutations can occur anywhere in the DNA and in any cell. They are **heritable** only when they occur in the germ cells (eggs and sperm), but mutations in the DNA of other (somatic) cells may lead to cancer. Even though the DNA replication enzymes are very accurate, and there are also supplementary systems for detecting and correcting damage, no system is perfect. We should, therefore, recognize that some level of mutation is inevitable. However, the mutation rate is increased by radiation, including ultraviolet light, and exposure to certain toxic chemicals. We can, therefore, take some precautions to minimize the risk..

The **mutation rate** for dogs cannot be determined readily, but from indirect evidence and extrapolation from other species, geneticists believe that mutation rates are normally on the order of 1 in 100,000 or less. For a sexually reproducing mammal, that would mean a new mutation in a particular gene would likely not occur more often than once in every 100,000 gametes. That may not seem like a high probability, but consider that most mammals are estimated to carry 80-100,000 genes. This suggests that every individual born has a good chance of carrying one new mutation in some gene.

What happens to new mutations?

Identical mutations are unlikely to occur simultaneously in the same gene from both parents (probability: < 1 in 10 billion), so any progeny will be heterozygous. (The exception being sex-linked genes, as the X and Y chromosomes are not homologous.) Dominant mutations will be expressed and any that are deleterious will be eliminated almost immediately from the population. If the mutation is advantageous, and this advantage is noticed by breeder or "nature", the mutation may survive and its frequency gradually increase. If a mutation neutral, which is to say, neither good nor bad (just different), its survival will be determined by "genetic drift". New recessive mutations remain hidden from selection until they reach a frequency where some homozygous individuals begin to appear. However, this does not prevent drift loss, which doesn't depend on phenotype.

Drift is a consequence of the random nature of genetic events. For example, if you breed a brown

bitch to a black dog carrying brown, you would expect ¸ the progeny to be black and ¸ brown, but probably wouldn't be too surprised if you got 7 blacks and 3 browns in a litter of 10. It works the same way for any gene that has two or more alleles. Suppose that we have only one black dog (Bb), all the rest being bb. The one Bb dog may pass the B allele to none or all of his progeny, or to any number in between. If he has more than 5 black progeny, the frequency of black will go up providing all contribute equally to the next generation. In subsequent generations the frequency may drift even higher, or back down.

In a large population, the frequency will tend to fluctuate by only a small amount. However, small populations are inherently unstable and, if other factors don't intervene, one allele will eventually take over. This is called fixation. How long this takes depends on population size. With a rare breed, fixation may easily occur within 25 generations (~ 100 yrs.)

Many recessive mutations persist for a few generations at low levels before being lost again. Only very rarely do they reach a significant level in the population (> 1 in 1000). In terms of estimates of genetic diversity based on average heterozygosity, these genes are effectively monomorphic, as a screen of 50 or 100 individuals from the population would generally fail to reveal any differences for the majority of the these loci. When two individuals appear to carry the same mutation, it may well be due to independent mutations. However, unless there is some common ancestry, the chance of producing affected progeny should be no more than 1 in a million. [Notably, in the first study of an "inborn error of metabolism", Garrod (1902) observed that "among the families of parents who do not themselves exhibit the anomaly a proportion corresponding to 60 per cent are the offspring of marriages of first cousins." He estimates that only about 3% of all marriages are between first cousins.]

These estimates assume equal use of all individuals in the population, and we all know how common that is. If a particularly popular sire produces 10 times his "share" of sons and daughters, whatever deleterious allele(s) he carried will get a substantial boost in the next generation. A new mutation may be promoted from one-of-a-kind to moderately frequent in this way. As long as we insist on making mate choice a popularity contest, we risk introducing new problems as fast as we can develop tests for the old ones.

Genetic "load" and the founder effect

The human population carries at least 2500 deleterious mutant genes (or, more correctly, alleles of genes) causing significant health problems. For the most part they are fairly evenly distributed in the population. For the entire *Canis familiaris* population, the situation is likely fairly similar. Each individual is estimated to carry a "genetic load" of three or four "lethal equivalents", which implies recessive alleles that would kill of the bearer if they were homozygous. As long as they are recessive, they should not cause problems.

However, consider what happens if we form a subpopulation by choosing 10 individuals from a much larger population. Though these individuals will not carry the vast majority of the unwanted deleterious recessive alleles found in the wider population, the few they do carry will be promoted instantly from rare alleles (0.1% or less) to at least 5% in our example (or more generally, 1/2N, where N is the number of founders).

Because random drift has a greater impact on a small population, the population needs to grow rapidly, to at least several hundred breeding individuals, so as to minimize the loss of valuable alleles. During this time, we should select cautiously. While it is true that fixing "type" is one of the prime objectives of purebred dog breeders, too rigorous selection during the early generations

increases the possibility of accidental loss of a valuable gene closely linked to one of the genes under selection. Dalmatians, for example, are all deficient in an enzyme required for correct uric acid metabolism. The mutant gene appears to be closely linked to one of the genes for the characteristic spotted pattern and was likely inadvertently fixed when early breeders selected for that pattern (Nash, 1990).

Recognizing mutation

Though, at an allele frequency of 5%, affected individuals should only make up about 0.25% of the population, this would be a good time to stop it from increasing further. However, would a mutation occurring at that frequency be recognized as such? If we are talking about breed with average litter size of four, then we are only looking at about one litter in 100 with one affected puppy. If there have been no other reports, the breeder may simply write it off as "one of those things". In a breed with larger litters, the probability of two or more affected pups occurring in the same litter is greater, but even in these cases, lack of exchange of information between breeders and lack of education in genetics may result in a failure to identify the problem as genetic.

Selection

Selection is only effective if we are dealing with easily recognized phenotypes. However, undesirable mutations are not always that accommodating. There is a full range of possibilities from silent mutations, that have no noticeable effect on proteins coded for, to mutations that fail to make any functional product. There is even a small possibility of improvement. Those, and the silent class, are no threat to us. However, those that prevent normal function but do not eliminate it completely are likely to present a substantial problem. One example is the vWD mutation in Dobermans. This mutation eliminates 85-90% of the active clotting factor, but this low level is still sufficient to protect a homozygous affected individual from excessive bleeding in most situations. A dog that is "lucky" enough to avoid a major injury or surgery may not be recognized and may even be bred. Consequently, the frequency of the mutant allele rose to slightly over 50% in the population (Brewer, 1999).

This should not be regarded as an exception. Fewer than one in three mutations appear to be fully lethal, and that the others cover the full spectrum from the 0-100% activity. In addition to dealing with a handful of easily-recognized genetic diseases in a breed, we are also likely to be dealing with scores of others that reduce fitness but present no obvious phenotype that can be used to identify them. If we can miss a gene that is only 10-15% functional, how well are we likely to do with those that retain 80 or 90% of their normal function?

Why should this be a problem?

In a small population, drift inevitably leads to fixation for one allele. Computer simulations show that if we start with a neutral allele with a frequency of 5% in the population, as would be the case if it was originally carried by 1 of 10 founders, it will be fixed 5% of the time (surprise, surprise!). As the fitness of the homozygous phenotype decreases, its chances of being the winning allele decline. At a 5% reduction in fitness, 3.5-4% will still be fixed, most within 25 generations. At 15% the computer says the other allele will almost always win - if our slightly deleterious allele gets no boost from being linked to a selected gene or spread by a popular sire. However, one or both these conditions are usually violated, as discussed above. Furthermore, there is no guarantee that our selection will discriminate as finely as the computer.

If each such gene reduced fitness by only 5%, and the effects are additive, we could easily be facing a population with significantly lower litter sizes, shortened lifespans and greater susceptibility to non-genetic problems. Yet we would have no easily identifiable gene to pin it on.

Conclusions

Longevity and fertility, commonly regarded as indicators of "inbreeding depression", are reduced in canine populations which ave been inbred over a relatively short time period (Laikre and Ryman, 1991; Nordrum, 1994). However, most of the inbreeding in domestic dog populations does not appear to be due to breeders intentionally mating close relatives[1] (though there are certainly exceptions), but to the loss of diversity due to drift and selection. The resultant loss of choices makes every individual a close relative, no matter what breeding strategy is employed.

The outcome for any breed will depend on both luck and on the breed's history. What is the effective population size? How many founders were there? Over how long a period prior to the closure of the stud books had the breed been refined? How intensive was the selection used to define type? Have there been any bottlenecks? How strong an influence have popular sires had?

What can we do?

1. We can control many of the obvious genetic diseases by supporting research aimed at locating the genes and developing direct DNA tests for the mutant alleles. Test results should be employed to make certain that carriers are only mated to clear individuals, rather than for wholesale elimination of carriers, which would further impoverish the gene pool.

2. We can explain to breeders that mutations will always be with us, and are not an indication of failure or bad breeding practice, and that an open exchange of information will produce the greatest rewards. We can also show them ways to achieve their personal goals without making choices that are detrimental to their breed.

3. We can attempt to educate breed clubs on the importance of maximizing diversity in the gene pool. As the keynote speaker at the recent AKC/CHF conference, Dr. Malcolm Willis, pointed out, few breeds even have a good idea of what their major genetic problems are, how many pups are in an average litter, or how long their dogs live. Fewer still have any idea of how to retain existing diversity or reduce the average inbreeding.

Notes:

1. Based on a study of 3 and 5-generation pedigrees of Australian Shepherds, Clumber Spaniels, Standard Poodles and Malamutes.

References

Brewer, G.M. (1999) DNA Studies in Doberman von Willebrand's Disease. Available online at: http://www.VetGen.com/vwdrpt.html

Garrod, A.E. (1902) The incidence of alkaptonuria: a study in chemical individuality. Lancet 2: 1616-1620. Available online at: http://www.esp.org/foundations/genetics/classical/ag-02.pdf

Laikre, L. and N. Ryman (1991) Inbreeding depression in a captive wolf (*Canis lupus*) population. Conservation Biology 5: 33-40.

Nash, J. (1990) "The Backcross Project" in The Dalmatian Quarterly, Fall 1990, Hoflin Publishing Ltd.

Nordrum, NMV (1994) Effect of inbreeding on reproductive performance in blue fox (*Alopex lagopus*). Acta Agriculturae Scandinavica, Sect. A, Animal Sci. 44: 214-221.

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RESEARCH ON CANINE LONGEVITY & DOG BREEDING

Many Boxer breeders are concerned about the apparent decrease in the average life span of our breed. But has the average life span of the Boxer really decreased and if so, what can breeders do to reverse this trend? John Armstrong, Ph.D., of the University of Ottawa dept. of Biology, a geneticist and a dog fancier, is currently engaged in a research project on canine longevity and its genetic components. Dr. Armstrong is head of the Canine Diversity Project and the list owner of the Cangen list (Canine Genetics list). I had an opportunity to speak with him recently about his research.

LS: Dr. Armstrong, many breeders, not just of Boxers but of a number of purebreds, are concerned by an apparent decrease in their breeds average life span. Is this what prompted your research and how do you go about proving if this assumption is true and if it is, what may be causing it?

JA: First, we need to establish what the reasonable life expectancy for a domestic dog is. This is not information readily available, as neither owners nor veterinarians are obliged to report deaths, and the kennel clubs keep no records. Where such data exists, it has been collected by surveys, and the results depend on how representative the sample is of the population. For example, a Swedish study (Bonnett et al., 1997) based on insurance claims ignores all past age 10 as they are no longer insurable, while an American study (Patronek et al, 1997) is based on deaths at veterinary teaching hospitals and will likely not include many that die of old age.

Breed health surveys avoid these biases, but may be biased by either under-reporting of dogs that lived relatively problem-free lives or, particularly when it comes to looking at longevity earlier in the century, "selective memory" – i.e. ones that died very young have been forgotten. Furthermore, most breed surveys of health that have led to longevity estimates don't analyze the data correctly. In fact, they generally underestimate the median lifespan because they do not account for the dogs that are still living while including contemporaries that have died.

Some of the questions I would like to attempt to answer include the one of whether mixed breed dogs live longer and also whether smaller dogs live longer. Patronek's study seems to support these beliefs. We started with the Standard Poodle (because I am a poodle owner and the subject came up on one of the discussion groups), and expanded to include Clumber Spaniels and Australian Shepherds because of interest expressed by individuals active in these breeds. I won't claim that these are representative of all purebred dogs, but they are all approximately in the same size range while having quite different breed histories. Clumbers and Poodles are probably among the least likely large dogs to be maltreated. (When was the last time you heard of a Poodle being chained outside during bad weather? It may happen, but not often, and probably not by people who are involved with their dogs to the extent that they participate in Internet discussion groups or would visit the Diversity web site.) Both are old breeds, but the Clumber has never been as numerous and went through a serious bottleneck at the end of WW II. In contrast, the SP has a much broader base, but a serious problem with popular sires (and a popular kennel) that has reduced genetic diversity considerably. Aussies are a much more recent breed, at

least with respect to kennel club recognition and one might hope that they are more diverse.

My working hypothesis is that the major factor affecting purebred longevity is inbreeding depression. The history of the breed will dictate the inbreeding and thus the lifespan to a greater extent than other factors, including size. One reason large dogs live shorter lives may be that they are often less numerous than the smaller dogs and are more subject to abuses such as the overuse of popular sires.

Once the stud book is closed, inbreeding goes up – even if breeders are not deliberately inbreeding – simply because there are not enough dogs in a breed for every dog to have unique ancestors. If dogs are living shorter lives than they once were, this is likely part of the reason.

LS: How have you conducted your survey to collect relevant information?

JA: Data on these three breeds has been collected almost exclusively over the Internet with the project being advertised on breed-specific discussions groups and in breed newsletters. There is no fool-proof way of establishing whether this sample is representative, but we now have on the order of 10% of the registered Clumbers from the last 25-30 years and probably a similar percentage of Standard Poodles. (The exact number of SPs is unknown because the poodles are not registered by variety. The number of Aussies is also uncertain because there are several registries.)

We have also been collecting data on a potential control group of mixed breed dogs. This last group is not intended to be representative of mongrels, but rather the potential life expectancy of a mixed breed dogs owned by a caring and responsible pet owner. Although this is an assumption, the responses come from visitors to the Diversity site and from those who own one of the survey breeds.

LS: Have you reached any conclusions regarding the data you have already studied?

JA: My expectation is that the mixed-breed dogs should live the longest and the Clumbers the shortest as they represent the lowest and highest inbreeding, respectively. The data collected to date supports this expectation.

Perhaps the most significant discovery, however, was that the survivorship curve for Poodles inbred to less than 10% (10 gen. calculation) is a close match to that for the Mixed group, with a median of 14 yrs. In contrast, those over 30% have a median of about 11 years. This is longer than the average Clumber (COI 24%) lives, but there are undoubtedly other factors involved.

The other trend of interest is the reduction of 1-1.5 yrs from the recent to the early poodles. However, there could be reasons for this in addition to higher inbreeding. For one thing, current dogs are likely exposed to more environmental toxins. Another factor could be "selective memory". People may have forgotten some of the dogs that died young and tend to remember the ones that lived a long time.

LS: There seems to be a rather distinct correlation between inbreeding level and longevity, has this held true for all the breeds you have studied?

JA: The Clumbers do not have a wide enough range – 15-40% compared to 1-70% for the poodles – for a trend to be apparent. Unfortunately, we don't have enough pedigree data yet for the Aussies.

When you compare the recent to the older poodles, the inbreeding actually appears to go down, but this is misleading. We are comparing pedigrees for their last 10 generations rather than from a fixed time point. If I go back 15 generations from the 90s I get back about as far as 10 generations from the 70s and the average IC increases from ~ 17% to 22%. However, I do not feel this is large enough to account for the difference.

A preliminary analysis suggests that longevity can be inherited. This is independent of the inbreeding effect.

LS: Dr. Armstrong, a lot of breeders struggle when it comes to the genetic implications of conditions we see in our dogs, especially if we don't have a background in scientific training. Earlier books on breeding that were directed to dog breeders advocated inbreeding and linebreeding as the preferred method. Almost every author stated that "doubling up" on the preferred traits would "fix" them and that by doing so, you would bring problems to the surface, where you could work to eliminate them. The stated goal was to "purify" your line in order to be successful. People followed this advice to a large degree because it seemed to make sense. But now, if you look around, breeds every where are in trouble. Genetic diseases seem rampant and even the popular press is full of articles criticizing purebred dog breeders. Why didn't this work? Could you give us a brief explanation of how traits are inherited?

JA: When Mendel established the basic rules of genetics, he based his conclusions on a study of the inheritance of seven easily-recognized morphological traits in the pea – things like height, flower color and seed color. There were two alternatives for each trait (tall vs. short, purple vs. white, etc), but neither was deleterious, and there were no other complications such as multiple alleles or incomplete dominance.

If we were breeding peas instead of poodles (or Boxers), the popular "type" might be tall with yellow seeds and purple flowers. If this were the overwhelmingly preferred type, some of the other phenotypes might eventually disappear. Would it matter if green peas disappeared? You might think "no" (unless you were particularly fond of green), but the answer is not that simple. It depends on what other genes are closely linked to these traits, how large the population is, and how rapidly this occurs.

All populations of sexually reproducing organisms have some genetic variation. In mammals, around 10% of the genes are estimated to be polymorphic. By that we mean that they have more than one common allele. Many of these are like the traits Mendel studied in the pea, resulting in phenotypic differences that do not impair survival and reproduction. Lets call these Group A variants (or mutants, if you prefer). The remaining 90% or so of the genes are also susceptible to mutation, but the mutant alleles are generally found at frequencies below 0.1% (1 in 1000) and are frequently deleterious (lets call these Group B)

All animals are believed to carry several deleterious recessive alleles. This is called "genetic load." The unanswered question is whether this is in the form of 3 or 4 recessive lethals, or a greater number of genes with alleles that diminish fitness but are not individually lethal when homozygous. This group may include subtle differences detectable only with sophisticated biochemical techniques.

When breeders, be they of peas or dogs, attempt to create a line (variety, breed), they are focused on a particular set of the visible (group A) traits. Ideally, none of these traits reduce fitness. If a breed is founded by 100 individuals, we should eliminate 90% or more of the group B mutations, but will boost the frequency of those carried by the founders by 10 fold or more. At frequencies now on the order of 1%, these should still not be a major problem. However, most populations are genetically smaller than the actual number of individuals due to unequal contributions. For example, if one popular sire services 10% of the available bitches, 10% of the males will not be bred, and their genes will be lost. If they include some alleles that are not well-represented in the breed, there is a risk these alleles may be lost. Even at the replacement level – 2 progeny replacing 2 parents – there is a 50% probability that one allele from each parent will not be carried by either of the progeny. If there is only one son or daughter, half of each parent's collection of genetic recipes will be lost. Of course if all were either lethal or harmless, we would not miss the former and the loss of the latter would only matter esthetically.

The need to maintain relatively large, diverse populations arises largely from the existence of mutations that diminish fitness by a small amount. The smaller the population, the greater the chance of one allele being fixed (taking over). If a mutation reduces fitness by only a small amount, the loss of the better allele may not

be noticed. As suboptimal mutations accumulate over time, we may, however, begin to notice that our dogs don't live as long and are not as healthy as in the "old days". In a large population, there is less chance of any allele being fixed. Consequently, some individuals will be healthy, and some may not be, but as long as we do not favor the latter, the survival of the population should not be at risk.

LS: Right now a great many Boxer breeders are trying to deal with a very serious heart condition in our breed that is certainly affecting it's longevity. Although there are other cardiac conditions that are present, the one most troubling is Boxer Cardiac Conduction disease. Until recently it was referred to as Boxer Cardiomyopathy but as more information about it has come to light many in the Boxer community are using this alternative term to distinguish it from Dilative Cardiomyopathy. There are three things that have made this particularly difficult to deal with; first, many dogs are asymptotic until they drop dead unexpectedly. Second, there wasn't any good screening procedure available until last year when the researchers at Ohio State University told us that a 24 hour Holter monitor test was the best way to screen for it. And third, it is often a late onset disease, which appears after a dog has been bred.

Additionally, Dr. Kate Meurs (the head of the research project) told us this year that they aren't sure that a Holter reading of clear this year will accurately predict future health. Furthermore, no one is sure exactly how many ectopic beats in a 24-hour period are indicative of the condition. Because we don't yet have any concrete answers many breeders are understandably worried about the best way to deal with this disease.

As a geneticist, if you were advising the American Boxer Club, what would you tell it's members?

JA: Share information.

Get numbers. If the Holter test looks promising, pursue it. Get a second opinion on the inheritance. (It may make no difference to how you proceed, but it can't hurt. I would suggest this no matter who did the initial analysis.)

Share information. One approach may be to not breed progeny until parents are an age where they should have developed the problem. If it normally appears at 4 or 5, don't breed before they are 3. By the time the progeny are 3 the parents will be 6. (Obviously this doesn't work if a substantial number don't show a problem till 8 or 10.) Whenever everyone rushes to breed to the currently popular stud, and many are two generations down the road by the time he is 4, there is a potential for disaster.

Share information. I can't say it too many times. When breeders start accepting that there are no "perfect" dogs, that genetic problems can occur in anyone's line, and that they don't have to hide it or face ruin, then they will have the power to bring any problem under control.

LS: Some people have suggested the best course of action would be to get as many Boxers holtered as possible so we can find what the breed average is. And then, to try to use those dogs that are in the upper 50% percentile for breeding (I believe this is the approach advocated with things like hip dysplasia). They are concerned that eliminating too many dogs from the gene pool would cause more problems in the future. How do you feel about this?

JA: I agree that testing a fairly large and representative sample (different ages, both sexes, and different lines) would be a good idea. If there is an indication that clear now does not mean clear forever, then it should be an ongoing study, where the same dogs are assessed yearly. I do not think it would be wise to eliminate those who do not score in the top 50%, especially if there are no long-term guarantees.

I suspect that if there is a range in scores, and breeders start publicizing the results, you won't have to do much else. The conscientious ones will look for mates with the best scores, while those who breed carelessly will continue to do so. The problem

may be preventing the overcautious from using only the top 10%

If the score turns out to be a reliable indicator, then setting a suggested cutoff score should be dictated to some extent by the effects it would have on breed diversity. I would proceed very cautiously and 50% seems high. You really need to do a study on genetic diversity in the breed before you get carried away with extensive culling.

LS: There seems to be increasing evidence that heterozygosity, especially with regard to immune system function, may be optimal for the overall health of an animal. How can breeders try to get the most diversity in things like the Major Histological Complex (MHC) without losing breed specific traits or traits particular to their own line that they value?

JA: With respect to the latter, the advice I always give Poodle breeders who ask which dog to breed to is to evaluate their own dog as objectively as possible with reference to the breed standard (or their vision of the ideal poodle). Then look at as many potential mates as possible evaluating them in the same way. Rank them in order of closest match to the most distant (which may not be the same as best to worst). It is alright to try for improvement, but avoid many and/or large differences. (You can't make a silk purse...). Give me your list and I will determine how closely they are related. Then the breeder has to decide how much weight to place on type and how much on health. In my opinion, little weight should be given to show titles and none to popularity or how impressive the pedigree looks. (If you want evidence that it works, read "Inbreeding and Diversity" at the Diversity web site.)

Breed specific traits should have been fixed when the breed was established. If they prove difficult to maintain, then something is wrong. You are probably trying to do something that goes against thousands of years of canine evolution. The look you want may be due to an inherently unstable combination of genes, particularly if the breed was established from dissimilar founders over a short period.

by: Liz Sullivan

Longevity in the Standard Poodle

by John B. Armstrong, Ph.D.
Department of Biology
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What is a reasonable life expectancy for a Poodle? ...or, for that matter, any domestic dog? This is not information readily available, as neither owners nor veterinarians are obliged to report deaths, and the kennel clubs keep no records. Where such data exists, it has been collected by surveys, and the results depend on how representative the sample is of the population. For example, a Swedish study (Bonnett et al., 1997) based on insurance claims ignores all past age 10 as they are no longer insurable, while an American study (Patronek et al, 1997) is based on deaths at veterinary teaching hospitals and will likely not include many that die of old age. Nevertheless, both rank the Standard and Miniature Poodle among the most long-lived dogs.

Data collection

We collected data from breeders and owners responding to requests placed in breed-specific publications, Internet discussion groups, and on the Canine Diversity Web site. Many of the older reports were from obituaries placed in breed publications. Respondents were also asked to give the ages of living dogs. Though these are not truly random samples, I believe they are large enough to be considered representative of the population. As data collection progressed, we found that the means changed very little after the first 150-200 reports.

Longevity then and now

The determination of the median lifespan is straightforward if one has sufficient data and the period covered is sufficiently far in the past that no individuals are still living. For more recent dogs, one can look at the percent still living from any year and attempt to determine the year for which 50% are still alive. The oldest dog reported still living in 1999 was born in 1982. Analysis of % survival over that period suggests a median lifespan of close to 11 years (Fig. 1).

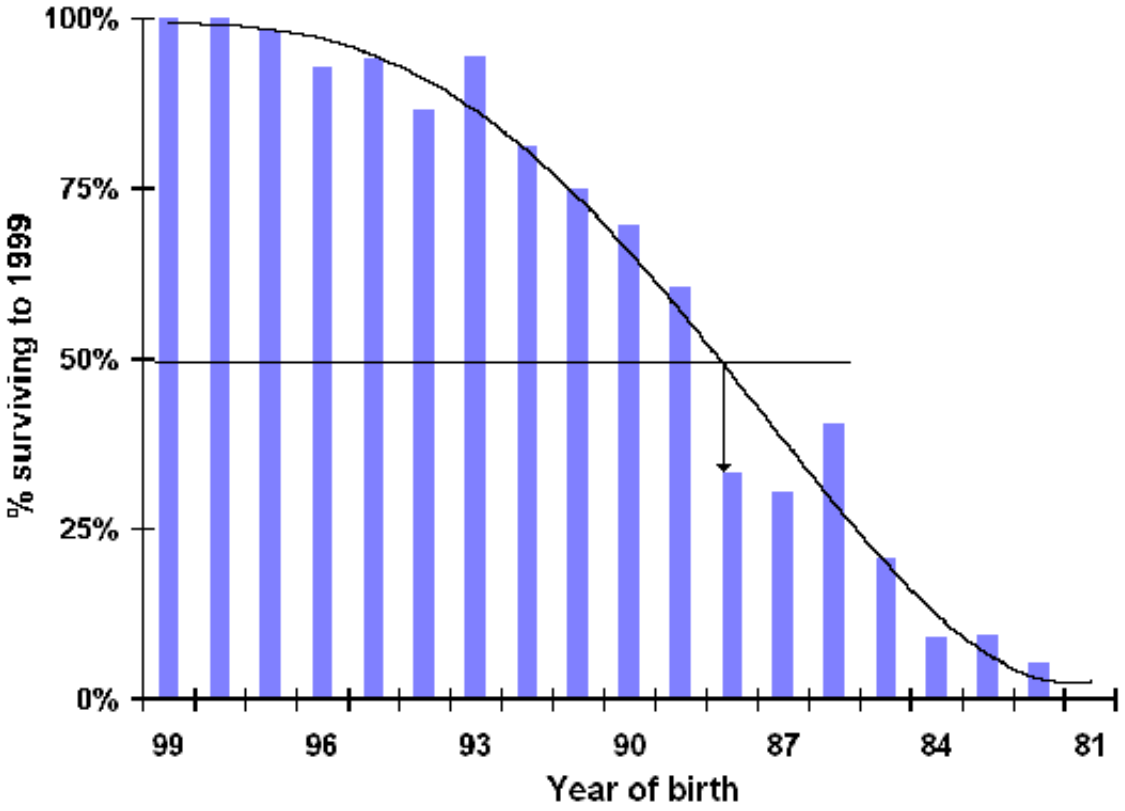


Fig. 1. Survival of recent Standard Poodles. The data was collected during 1999. The curve is a best-fit polynomial calculated with Microsoft Excel. N = 627

For older data, the number of reported deaths at each age may be taken as a percentage of the total reported, and is probably most clearly visualized by plotting the data as cumulative mortality, or a survivorship (% still living at age N). The data shown in Fig. 2 shows the survivorship of this group, compared to the recent group.

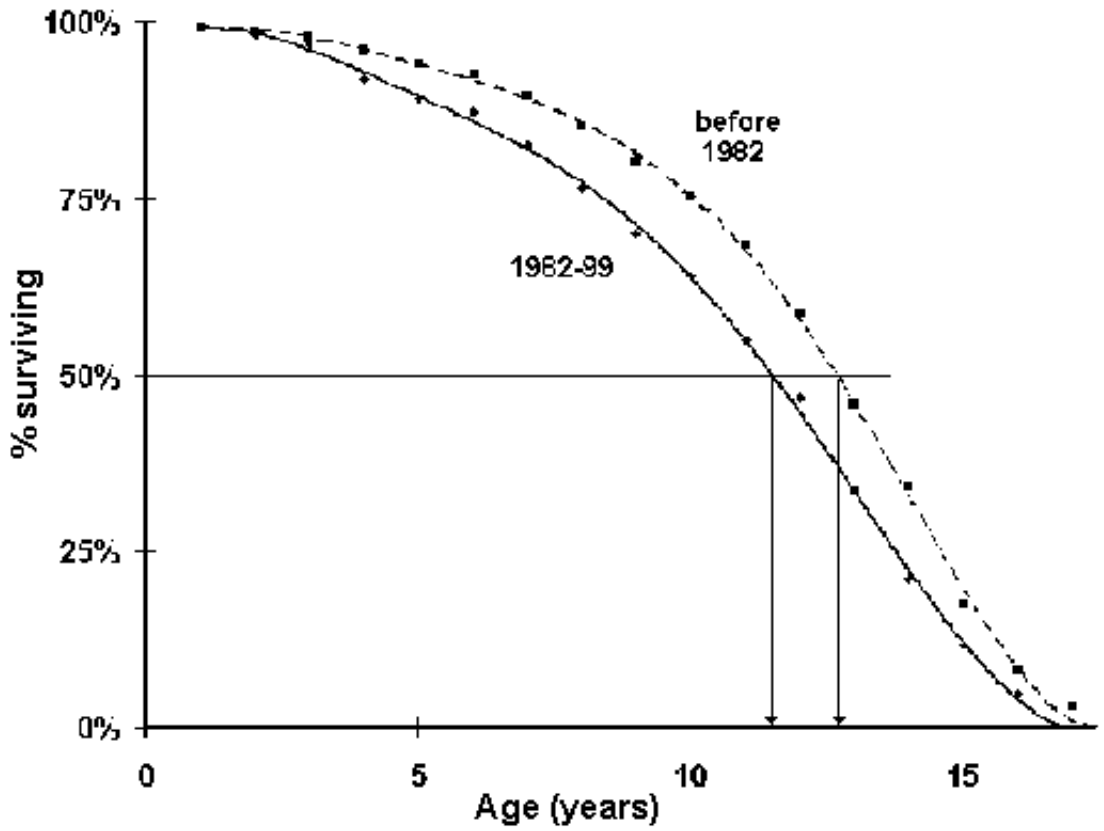


Fig. 2. Comparison of survival of poodles born before 1982 (N = 361), median lifespan 12.7 yrs, with those born more recently (N = 627), median lifespan 11.5 yrs.

The difference of 0.5 yrs between the two results for the recent group is probably accounted for by the latter analysis weighting the years according to the number of reports. The difference between the recent and the earlier poodles is a more worrisome 1.2-1.8 years. Is this difference real, and if so, what could account for it?

The artifact possibilities include:

- sampling error - one or both groups are not representative of the whole population.
- selective memory - dogs that died young may have been forgotten and/or older dogs may have had an extra year or two added.
- analytical error - due to the difficulty of correcting the recent group for dogs still living. (Without correction, the median lifespan of the recent group is 8.4 years.)

The remaining possibilities would include:

- environment - such as a higher level of toxic substances in the environment, poorer nutrition or over-agressive vaccination.
- genetics - a higher level of genetic abnormalities resulting from loss of genetic diversity, possibly due to line/inbreeding.

Though inbreeding has an impact on longevity (see below), the inbreeding coefficients of the two groups were not significantly different.

Effects of Inbreeding - Expectations

A second objective of this study was to evaluate the impact of inbreeding on lifespan and the incidence of genetic problems. Among dogs that are only very slightly inbred, I would expect to find that some die from genetic and others from non-genetic problems. The frequency with which the former appear will depend on how common the "bad gene" is in the population. The frequency will be increased by inbreeding, because inbreeding increases homozygosity. However, if the problem leads to early mortality, continued inbreeding should tend to eliminate it. One might therefore predict that the highly inbred dog could be substantially free of genetic diseases. In contrast, nongenetic problems should be largely unaffected by inbreeding.

However, though I agree that inbreeding can be used to identify undesirable mutant genes, there are several complicating factors. First, a genetic problem may be dismissed as nongenetic, particularly if it is not fully penetrant. Second, a dog may be bred, and it's progeny bred, before a late-onset problem is evident. Unfortunately, even a well-publicized announcement by the owner may not discourage the use of the descendants. These factors may actually increase the incidence of the problem in a highly inbred line.

As an added complication, inbred lines may accumulate sub-lethal alleles that, individually, have no particularly obvious effect (and are not selected against) but collectively reduce overall fitness. The relative frequencies of the different primary causes of death may or may not change as a result.

Effects of Inbreeding - Results

When we break down the results into 4 subgroups according to the level of inbreeding (based on a 10-generation pedigree that is at least 95% complete), the survival of those inbred to less than 6.25% (the equivalent of first cousins who shared no other common ancestry) is significantly greater than for the more highly inbred dogs.

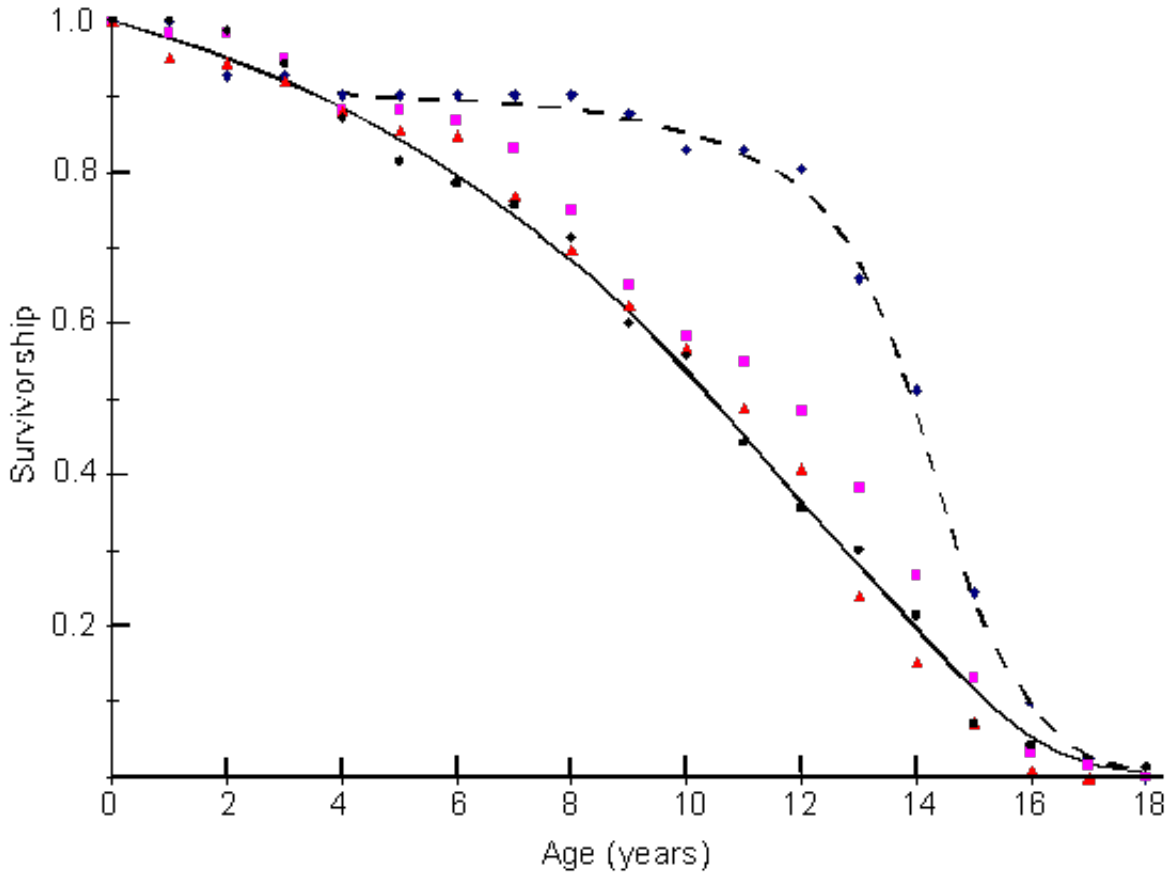


Fig. 3. Standard Poodle survivorship at different levels of inbreeding. Blue diamonds: < 6.25% (N=39); pink squares: 6.25%-12.5% (N=65); red triangles: 12.5-25% (N=141); black circles: > 25% N=71). The solid line is fitted to the > 25% group.

The least inbred group survive, on average, 14 years -- approximately 4 years longer than the most highly inbred. The shape of the survivorship curve more closely resembles that of a non-inbred population.

Cause of Death

Cause of death was indicated for 355 of the dogs surveyed. The most frequent cause cited for the pre-1982 dogs was "old age" (42.7%), whereas cancer was the most common cause in the 1982-99 group (33.7%), with old age only being cited 9.1% of the time. Table 1 shows the incidence of the most common causes of death, treating "old age" deaths as unknown.

	before 1982	1982-99
Addison's	2.8%	5.9%
Cancer	41.5%	37.1%
GDV (bloat)	20.8%	27.6%
Immune-mediated	0.9%	7.6%
Kidney failure	5.7%	8.2%
Seizures	5.7%	1.2%

Cardiovascular*	6.5%	3.5%
All other	16.1%	16.5%

* includes stroke

Bloat kills about 30% of the affected dogs (Jan. 1998 Bloat Notes, Fig. 3). That would mean that the risk of a Standard Poodle bloating at least once during its lifetime may be as high as 90%.

There is a very strong correlation between the incidence of bloat and inbreeding (Fig. 4). However, one should not conclude that a dog that has a low inbreeding coefficient is at no risk. The correlation may be due to the genetic predisposition to bloat being carried by those lines that have, in the past, practiced the closest inbreeding. If this predisposition is inherited as a dominant trait, only one parent need be a carrier (see Bloat in the Standard Poodle).

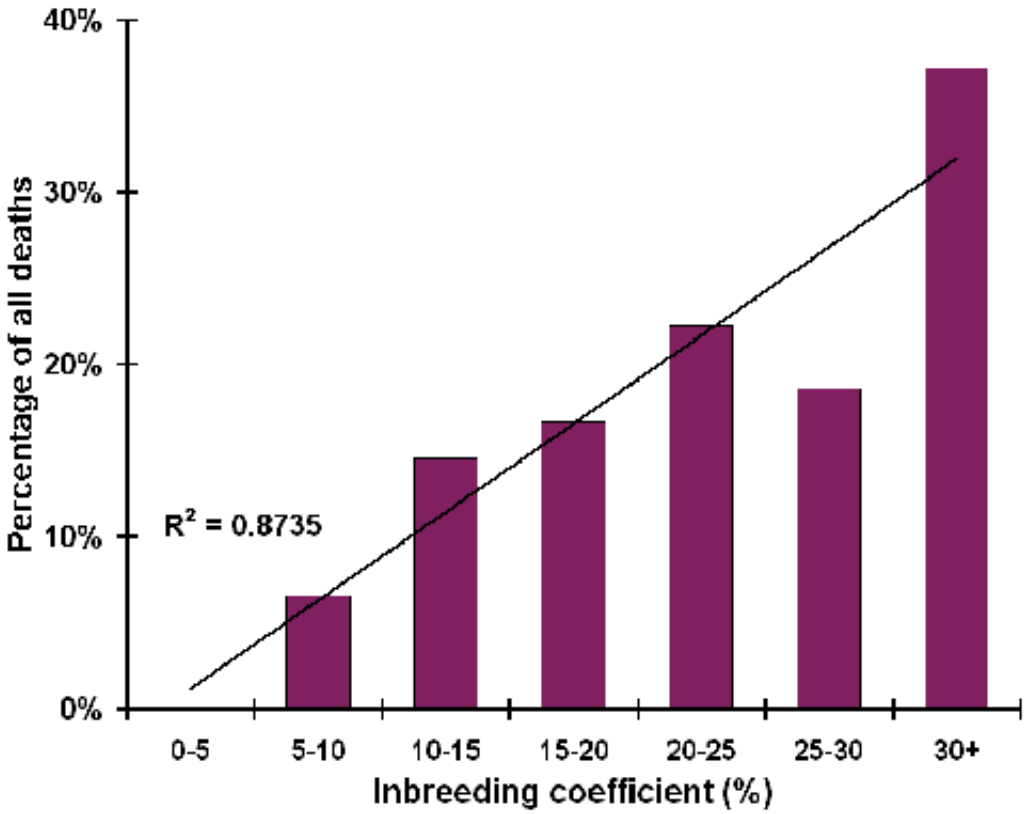


Fig. 4. Percentage of dogs in a particular inbreeding range that were reported as dying of bloat.

The incidence of cancer is also likely to be higher than shown, as there are some dogs who survive cancer. Additionally some proportion of the dogs reported as dying of old age probably have cancer. Cancer shows a slight negative correlation with inbreeding, but the difference between the least and most inbred dogs is not statistically significant.

Cancer is not inherited *per se*, but the predisposition to a particular cancer may be. To sort this out, we desperately need more data on specific types. If you have a SP with cancer, or had one in the past, please consider registering it with the Standard Poodle Cancer Registry.

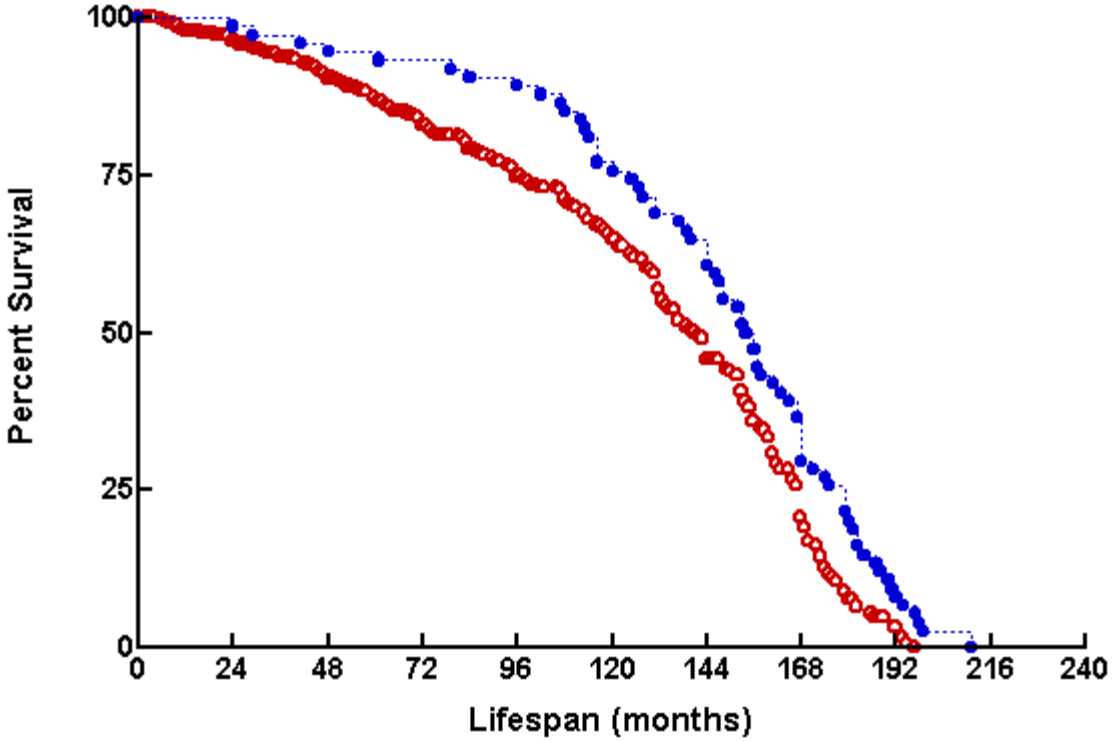
References:

- Bonnett, B.N., A. Egenvall, P. Olson and A. Hedhammar (1997) Mortality in insured Swedish dogs: Rates and causes of death in various breeds. Vet. Record **141**: 40-44.
- Patronek, G.J., D.J. Waters and L.T. Glickman (1997) Comparative longevity of pet dogs and humans: Implications for gerontological research. J. Gerontology **52A**: B171-B178.

Revised April 17, 2000

[The Canine Diversity Project]

Australian Shepherd Longevity



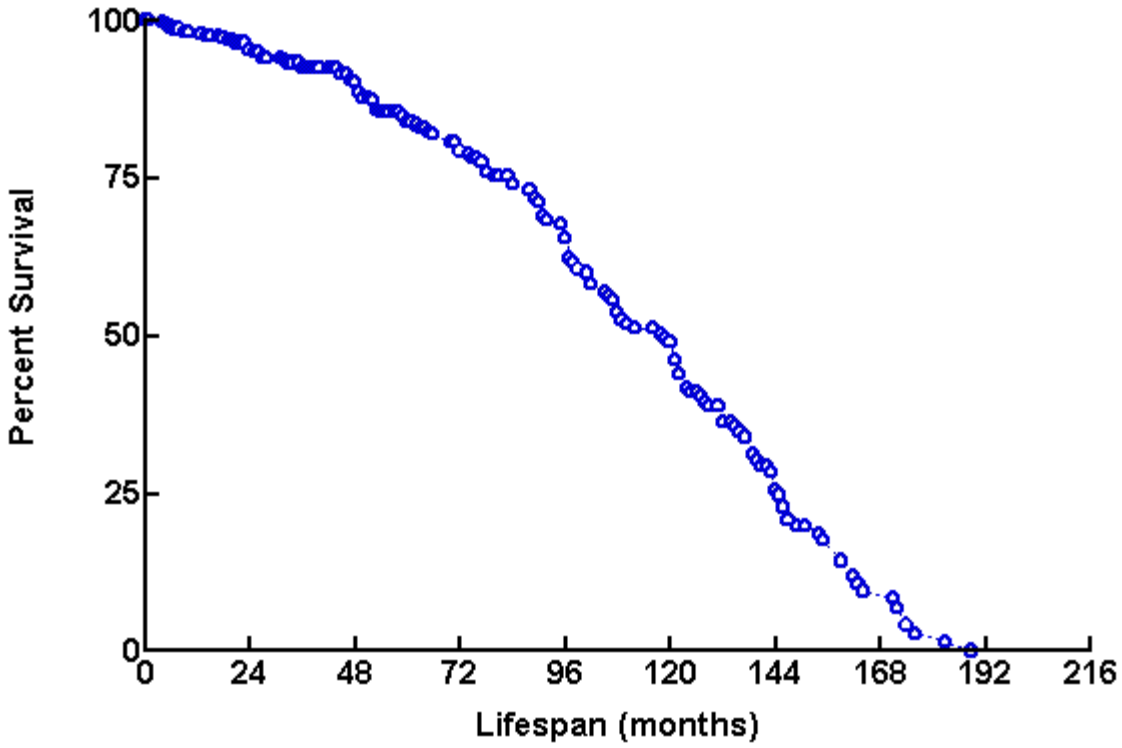
Kaplan-Meier survival curves comparing Australian Shepherds born before 1980 (closed circles), median lifespan 156 months, with those born more recently (open circles), median lifespan 142 months. N = 619.

For a description of the methods and possible interpretations, see Longevity in the Standard Poodle. All analyses were performed using GraphPad Prism 3.02, GraphPad Software, San Diego.

Updated Oct. 18, 2000

[The Canine Diversity Project]

Clumber Spaniel Longevity



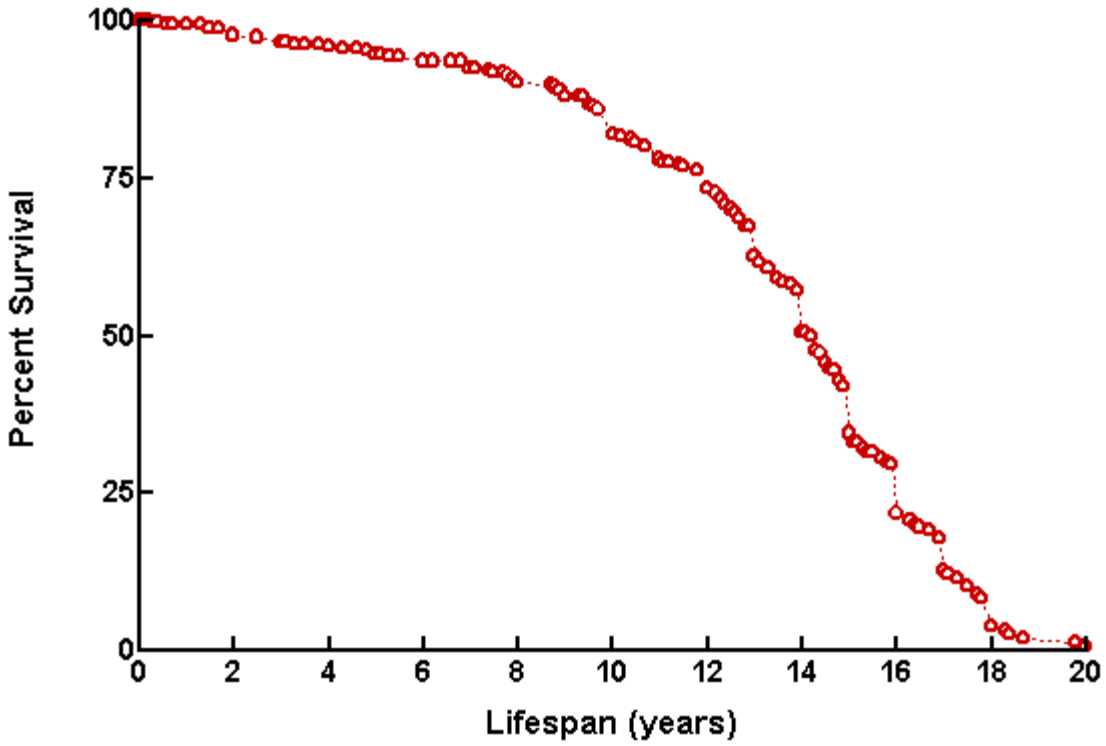
Kaplan-Meier survival curve for the Clumber Spaniel, based on data for 301 dogs. The median lifespan is about 10 years.

For a description of the methods and possible interpretations, see Longevity in the Standard Poodle. All analyses were performed using GraphPad Prism 3.02, GraphPad Software, San Diego.

Updated Oct. 18, 2000

The Canine Diversity Project

Mixed-breed Longevity



Kaplan-Meier survival curve for 328 mixed-breed dogs. The median lifespan is just over 14 years.

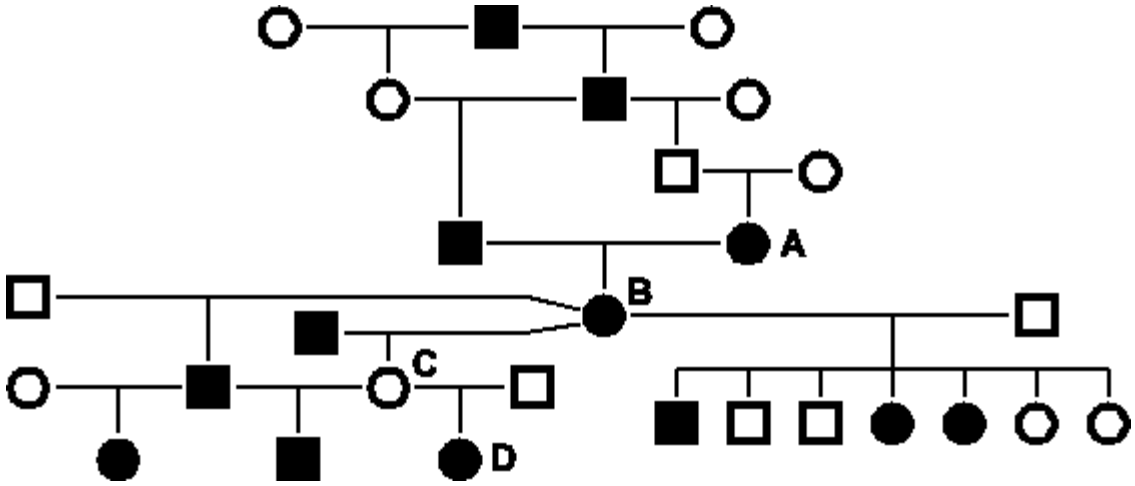
For a description of the methods and possible interpretations, see Longevity in the Standard Poodle. All analyses were performed using GraphPad Prism 3.02, GraphPad Software, San Diego.

Updated Oct. 18, 2000

The Canine Diversity Project

INHERITANCE OF BLOAT
in the Standard Poodle

by Dr. John Armstrong



Standard Poodle bloat pedigree. Circles indicate females, squares indicate males. Solid symbols indicate dogs that have bloated. Except for the litter of 7 (lower right), the status of the sibs of other individuals in the pedigree is not known.

Analysis of the pedigree

When attempting to establish the mode of inheritance from a pedigree, the objective should be to come up with the simplest model that will explain the data. Therefore, we should first ask whether bloat can be explained as a single-gene dominant or recessive trait.

Recessive trait (***AA*** and ***Aa*** normal, ***aa*** bloats)	**Dominant trait** (***AA*** and ***Aa*** affected, ***aa*** normal.)
Expectations	
• two affected individuals should produce only affected progeny	• two affected individuals may produce unaffected progeny if both are heterozygous (***Aa***)
• one affected and one normal should produce 1/2 affected and 1/2 normal progeny if the normal is a carrier (***Aa***)	• one affected and one normal should produce 1/2 affected and 1/2 normal progeny if the affected is heterozygous
• two normal may produce 1/4 affected progeny if both are carriers	• two normal individuals should not produce any affected progeny

Data

- C (unaffected) is the daughter of two affected individuals. To account for this, we would have to say that that the trait is not fully penetrant (an individual genetically predisposed to bloat does not necessarily do so).
- C (unaffected) is the daughter of two affected individuals. As we lack data on sibs, we cannot establish whether this occurs about 25% of the time.
- The litter of seven has 3 affected - acceptably close to the expected 1/2 for either a dominant or recessive trait.
- We have two examples (A and D) of affected individuals produced by normal parents, but lack data on sibs and cannot establish whether the proportion is approx. 1/4.
- Affected individuals A and D are from two normal parents. To account for this, we would have to say that that the trait is not fully penetrant, and that at least one of the parents is heterozygous.
- We also have to suppose that every non-bloating individual that has an affected son or daughter is a carrier. There are nine of them, only two of which are known to have a parent that bloated.
- In this case no restrictions are placed on the "unrelated" non-bloating parents of dogs that bloated.

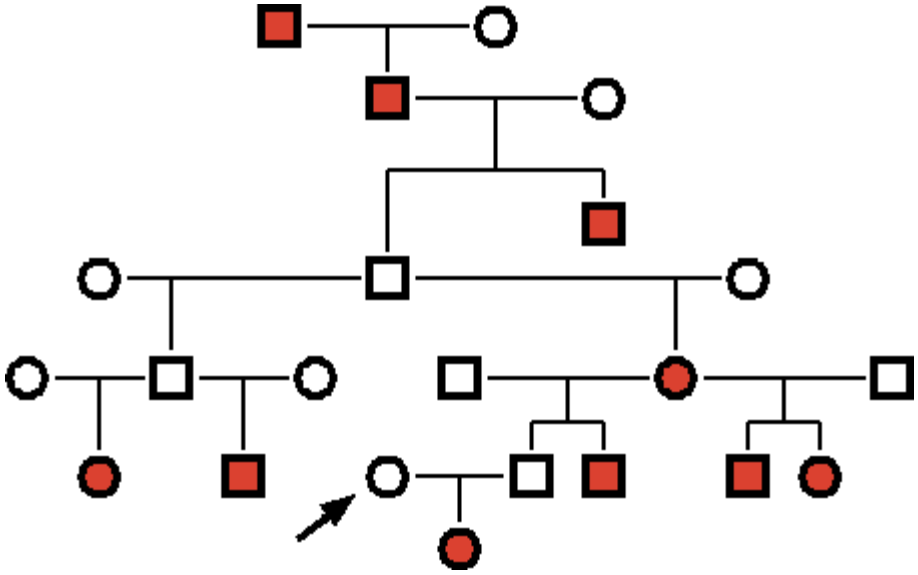
Conclusion

Both the dominant and recessive model require us to propose that dogs with a "bloat" genotype do not necessarily bloat. In light of the Purdue study which indicates that stress, diet and other environmental factors play a role, this requirement is not unreasonable. What a dog inherits is a predisposition to bloat, not bloat itself.

As we can get a bloat genotype among the progeny of a normal and an affected parent, we cannot use this data to distinguish between the two possibilities. However, the recessive model requires that all these normal dogs be heterozygous carriers, whereas the dominant model places no restrictions. Therefore, on balance, I favor a dominant model.

Another bloat pedigree

Last revision Jan. 2001



Standard Poodle bloat pedigree. Circles indicate females, squares indicate males. Solid symbols indicate dogs that have bloated. All the affected individuals have additional brothers and/or sisters, not shown, the status of which is unknown.

The first affected dog (at the top) was an AKC Champion and top-producer. His son was exported to Europe and the balance of the pedigree is comprised of Swedish and Finnish poodles.

Though most of the unaffected dogs are related to some degree to the ones that bloated, the bitch indiated with the arrow is Polish and shares no recent ancestry with the others. Though we cannot exclude the possibility that she carries the same recessive allele as the others, we are not forced to suppose this if the trait is dominant.

January 28, 1998

The Diversity Newsletter - July 3, 1997

Striking a Balance

John Armstrong Ph.D.
Department of Biology ~ University of Ottawa

Contents

1. Lessons from the wolves

Too many breeders follow the "breeding for extinction" paradigm. Start with too few founders, close the registry to new imports, inbreed and breed your preeminent males as many times as possible. It is a guaranteed recipe for degrading the gene pool. Breeders will visit the Diversity web site, read some of the information, and come away still believing that what I propose will lead to deterioration of their line, often insisting that the best and most successful breeders don't breed this way. They don't see the relevance of the strategies for saving endangered species or populations, and maintain that the factors taken into consideration for the Mexican or Ethiopian wolf don't apply to Canis familiaris.

To be sure, the domestic dog, as a species, has considerable genetic diversity, and is not in any danger of extinction. However, I see no fundamental difference between breeds of domestic dog and subspecies of wolf. If the Mexican wolf is distinctly different from the Ethiopian wolf, and if there is merit in trying to save both, is there not also merit in trying to preserve the Poodle, the KyiApso, the Malamute, etc. The difference is only that the evolution of the different wolves has been determined less by man and more by nature, and that man has generally done a worse job.

It is amazing how many breeders accept that "fading" puppies, stillbirths, small litters, inability to conceive, and even the occasional disaster litter (where most or all are lost) are "normal". They will dismiss the statistic that, for example, a Standard Poodle lives, on the average, two years less than a Miniature Poodle with the statement that "big dogs don't live as long as small dogs". They never question the logic. Do small animals live longer in the wild? (Don't tell me that such a comparison is not relevant unless you can come up with a logical reason for why a smaller animal should live longer.)

I have been asked, several times, what to tell such a person. I'm afraid that my reaction is largely one that you make someone aware of alternative possibilities, but if they insist on clinging to their old beliefs it is pointless to persist. Altering someone's fundamental beliefs is not easy. The best you can do is to show them that there are alternatives to consider, and hope that they will wake up and recognize the reality of the situation.

2. How many founders? (see also The Diversity Newsletter - May 16)

This question has come up again in relation to the attempts of a few breeders to rescue the KyiApso, which I will describe, probably unfairly, as an overgrown Lhasa Apso (~ 26", 80 lb.). Six have been imported to North America and bred. There are now about two dozen breedable animals including four of the original imports. Is this sufficient to establish (and possibly save) the breed, which may be threatened with extinction in Tibet?

In "The Millenium Ark", Soulé et al. conclude that 6 is the absolute minimum number of founders, and that with fewer, the group will lose more than 10% of its genetic diversity as soon as it reproduces. Twenty is a much safer number. Furthermore, the population size should be increased to 200-300 as quickly as possible to prevent significant loss of diversity. The necessity for increasing the population

size is to prevent random loss of alleles that may be important.

In genetics we deal in probabilities. Each fertilization is an independent event, and one does not influence another. Sometimes probabilities seem counterintuitive. Surely if I keep tossing this coin, and it keeps coming up heads, the probability of getting a tail must be increasing. The answer is "no, it is 1/2 each time". What does change with an increased number of trials is the probability of getting all heads (or all tails). If we toss that coin twice, the probability of getting a tail is 1/2 each time, but the question should be "what is the probability of getting two tails when you toss it twice." In effect, you are asking "what is the probability of getting a tail on the first toss AND ALSO getting a tail on the second toss." If you ask the probability of two independent events, A and B, both happening, you multiply the probabilities: 1/2 x 1/2 = 1/4.

From the practical perspective of planning what matings need to be done to retain founder alleles, the numbers game is much the same. We want to know how many progeny are necessary to be reasonably certain of retaining a desirable allele for some gene. If you have only one son or daughter that carries on the line, the probability is 1/2 that the allele will be "dropped" (not passed on). If you retain six progeny, the probability is reduced to (1/2 x 1/2 x 1/2 x 1/2 x 1/2 x 1/2) = 1/64 (~ 1.6%). This should assure that the allele is retained better than 98% of the time.

Once the population size reaches several hundred, we no longer need to keep 6 progeny - as long as the number of animals carrying the desired allele is reasonably high and everyone has a fairly equal chance of contributing to the next generation. However, once you impose selection, the rules change. Even the decision not to breed an affected individual, while desirable from the viewpoint of reducing the incidence of that particular problem, also eliminates all the other genes carried by that individual. In effect, you are hoping that other, unaffected individuals carry the good alleles you are discarding. A program to eliminate all the carriers of a "bad" allele for some gene carries, in my opinion, an unacceptably high risk.

3. The preeminent male

I repeat -- The decision NOT to breed an individual also eliminates all the other genes carried by that individual. Such a decision may be largely taken out of the hands of the owner, as everyone flocks to the current star. This is a form of selection. Intentionally or otherwise, when you select for one thing you are selecting against others. If one line gains a significant advantage and maintains it, the others will be denied the opportunity to pass on their genes and diversity will be lost.

Some might argue that if this line is really the outstanding one, we are improving the quality of the breed. To take a real example, let's argue that Annsown Sir Gay (b. 1949) was the best black poodle ever bred and that anyone who wants a good black poodle would be overjoyed at having a Sir Gay. However, even if he truly represents perfection in the breed, favoring his line is not producing clones of Sir Gay.

Recently, a visitor to the Diversity Website put forward the argument that surely the outstanding males from his line produced enough offspring that most of his genes should be preserved in the gene pool of today -- and that it would not be just his bad genes that were passed on. Though that may be true, she has missed the point. Even if all his genes have been preserved, when you sample the gene pool to create a new puppy you are not going to get the exact "Sir Gay collection." If the gene pool is only Sir Gay's, and if he carried only one bad gene, the laws of genetics predict that 25% of our new creations are going to get 2 copies. Too bad! (Pun intended)

Something for the poodle-people to think about: the top 10 (and very likely the top 20 or more) top-producing Standard males of the past 40 years - ALL colors included - are direct descendants of Sir Gay.

My own attitude toward breeding is that one should try to breed like to like and best to best while at

the same time minimizing common ancestry. Practiced consistently, it does work. I know of a number of breeders who breed this way and will tell you that they are pleased with their results.

Articles or news items of possible interest are always welcome. Comments, submissions, and requests to be added or removed from the mailing list should be directed to the Editor (John Armstrong) at the address below.

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Visit "The Canine Diversity Project" at http://www.magmacom.com/~kaitlin/diverse.html

The Canine Diversity Project

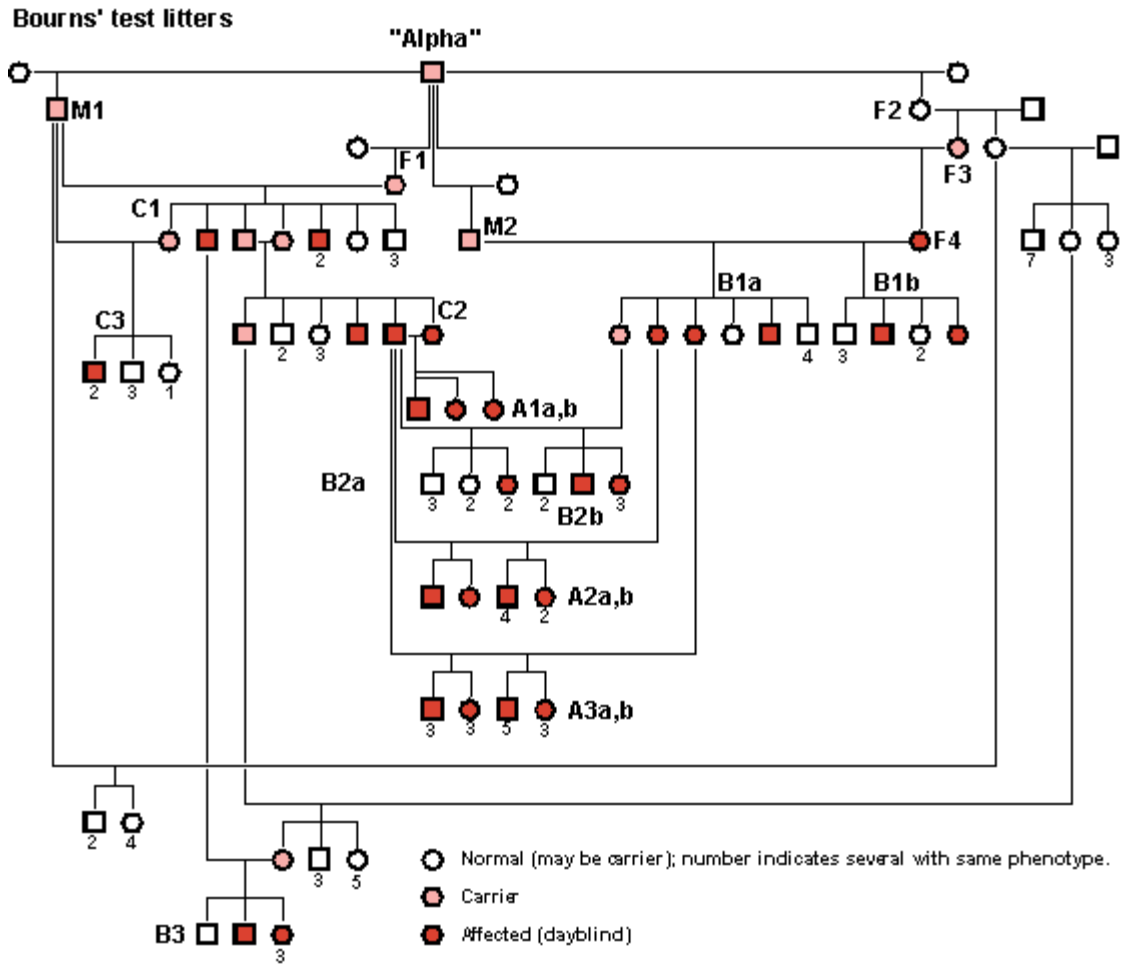
The Bourns Test Litters for Dayblindness in Malamutes

Around 1960, Dr. Kenneth Bourns, then an assistant professor of Zoology at the University of Western Ontario, and a breeder of Alaskan Malamutes, had 3 puppies in a litter of 10 that seemed to have problems seeing during the day, but not at night. Dr. Bourns went to Dr. L.H. Lord of the Ontario Veterinary College at Guelph for assistance. They started on a series of test matings that expanded to include a second kennel and Dr. Lionel Rubin, well-known for his work on inherited eye diseases. The disorder, given the name **hemeralopia**, is now also known as **inherited cone dysplasia**.

The story actually begins in the mid-50s, with the mating of a male to four different females. In the published account, the dogs are not identified either by name or even by number, which makes the story somewhat difficult to follow. To simplify things, I will call this male Alpha. As his mates are not critical to the remaining account, they can remain nameless. However, four of their progeny (one from each dam) will be designated M1, M2 (male), F1 and F2 (female).

[The litters between two dayblind dogs are designated "A", those between a dayblind and a carrier "B", and those between two carriers "C".]

When M1 was mated to half-sister F1, a litter (C1) of 10 was obtained which included 3 dayblind pups. This would be Bourns' litter, described above. Subsequently, two unaffected sibs from the C1 litter were bred to each other producing a litter (C2) of 9, with 3 dayblind. A third unaffected bitch from the litter was bred back to her father (M1) and produced a litter (C3) of 6, of which 2 were dayblind. The three litters, together, produced 25 pups, 8 of which were affected. As this is about as close as you can get to the perfect Mendelian 1/4 for a recessive trait, that mode of inheritance was strongly suggested.



The second group appears to be from the other kennel, though the paper does not clearly indicate which litters are from which kennel. F2 was mated to an unrelated male. One of the females (F3) from this litter was subsequently mated to her grandfather (Alpha) and produced at least one dayblind pup (F4). I believe it likely that F4 was acquired by Bourns and his colleagues for the test breedings. [Animals from both kennels were used for the test litters, but are not identified. However, one may make an educated guess as to which these were.]

F4 was bred twice to her grandmother's half-brother (M2) to give 16 pups, 5 of which were dayblind (litters B1a and B1b). Two of the dayblind bitches were then crossed to a dayblind male from the C2 litter, and he was also crossed to one of his dayblind sisters. Each mating was repeated to give a total of 6 litters where both parents were dayblind. If the trait is recessive, then the parents would have to be homozygous, and only homozygous pups would be expected. If the trait is fully penetrant, all should be dayblind. All 25 pups from these six litters were dayblind.

The same dayblind male was also mated with a phenotypically normal bitch from the B1a litter to produce litters B2a and B2b - total 13 pups, 6 affected (indicating that she was a carrier).

One additional litter included in the data is between a dayblind male from the C1 litter and a phenotypically normal cousin. This litter produced 4 live and 1 stillborn pup. All four were dayblind! However, when the 5 "B" litters are added together, there are 15 dayblind and 17 normal progeny, which is in good agreement with the expected 50:50 ratio. Thus, though some of the litters show surprising deviations from the expected ratios, the numbers are too small from any one litter to draw firm conclusions. [Ideally, one would like at least 30 in each group before attempting any statistical testing.]

In summary:

Group A (affected x affected: expect all affected)

total 25	affected 25	normal 0

Group B (affected x carrier: expect 50% affected)

total 32	affected 15	normal 17

Group C (carrier x carrier: expect 25% affected)

total 25	affected 8	normal 17

Because all these dogs are inbred on Alpha, the simplest conclusion would be that Alpha was a carrier. However, the possibility cannot be ruled out that the bitches to which he was mated were all carriers and that he was clear. Be that as it may, though I would be very surprised if any of the dogs from the test litters produced descendants, there is no indication that Alpha did not have other descendants or relatives who continued to pass on the defective gene.

Summary based on "Hemeralopia in Dogs: Heredity of Hemeralopia in Alaskan Malamutes" by Lionel Rubin, T.K.R. Bourns and L.H. Lord, American Journal of Veterinary Research, Mar. 1967, pp. 355-357.

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