Eliminating Mutation
The Impossible Dream

by Dr. 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 ½ the progeny to be black and ½ 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 have 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 (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

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