Hereditary Diseases and Schemes to control the incidence of these.

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Breeding Dogs

- If we are breeding dogs, it requires us to be responsible in our attitudes. We should leave the breed **in a better state** for future owners.
- We should be aiming for sounder, healthier and better animals in each new generation.
- In order to do this breeders need to understand what problems exist in each breed and what schemes are available to control them.
- With recent developments in DNA technology, the means to help control these diseases fairly quickly (where the disease affects 1 gene) is rapidly becoming within our grasp.

Breeding dogs cont.

- Where polygenetic conditions exist (eg. hip/elbow dysplasia), established schemes where repeatable, and reliable methods of assessing animals by X rays prior to breeding can assist in removing the worst animals from the breeding populations. By doing this we can gradually ***over time*** remove the worst affected animals and improve breed averages. These schemes are long term based.

- **The more diseases we test for at any one time, the slower the rate of progress.**

- **We need to retain *as much genetic diversity as possible* to prevent genetic bottlenecks where new conditions may emerge due to the lack of genetic diversity.**

Recent Developments in Genetics

- Over the last 5-10 years, the dog genome has been undergone a huge amount of investigation, and has finally been fully mapped. There are close to ***400 canine diseases*** that are recognised as being inherited or having significantly inherited components (Patterson 2000) and more are being reported every year. This enormous list also includes those disorders that are considered to have a breed predisposition ie. a higher than normal incidence of the problem compared to the general population.

- Of these recognised diseases, ***more than half are believed to be single gene defects***, and around ***70% of these being inherited as in a simple autosomal recessive mode of inheritance***. Many of the single gene abnormalities that result in canine disease also occur in humans, where the canine disorder mimics either exactly or very closely the human condition.

- Where the canine condition exactly mimics the human condition, the dog model can be used to do a lot of the basic research work in providing genetic material (blood samples, histories etc). Dog generations are very short, they are highly recorded and very traceable across related individuals.

Recent DNA testing developments cont.

- When researchers are looking for genetic defects in the DNA, they start by trying to correlate any known candidate gene that has already been isolated in either the human or mouse genome. Many similar defects are located on the same chromosome or hold a similar position on the chromosome. The more work that is done over time to specifically isolate the causative gene in any of these genomes, can often help decipher similar genetic problems in other species.

- Because *so many of the canine genetic disease conditions are as a result of single gene defects*, this is great hope that eventually there may be many DNA disease specific tests available to dog breeders.

- *Similar diseases* ***within related breeds often have the exact same genetic defect***, but unfortunately this is not always the case. For example what causes PRA (progressive retinal atrophy) in one breed, may not involve exactly the same gene in another breed, which may have the PRA PRCD (progressive rod and cone degeneration) form of the disease.

DNA disease testing cont…

- ***Each test as it is developed has to be checked against known affected dogs and their related siblings/parents etc, to give the very high degree of accuracy necessary (>98%) before the test can be released for that breed.***

DNA Disease Specific Tests

- Once a DNA disease specific test has been developed within a breed, ***it can be used to clear the problem*** from a breed**.** The problem can usually be cleared within several generations without any loss of important breeding stock. Where the DNA test is for conditions such as PRA, where the consequences of breeding an affected dog is blindness at a relatively early age, any such test is a an enormous step forwards for the health and welfare of the breed.

- **Single Dominant Gene DNA test** - If a single dominant gene is affecting an internal organ eg. polycystic kidney disease in Persian cats, the DNA test needs to be able to remove the affected animals (whose condition may not be externally obvious until 3-4 years of age) before they are bred from. With a dominant gene, 50% of all progeny will be affected, the other 50% will be normal. *Once the affected animals are removed from the breeding population and all the remaining breeding animals are normal, then no further testing for this disease is needed.*

DNA disease tests cont…

Simple autosomal recessive gene DNA test –

- With a simple autosomal recessive gene, the DNA test will clearly differentiate between affected, carrier and normal individuals. The beauty of this type of genetic test, is that you do not need to lose **any** valuable animals from your breeding program.

- Outstanding examples of the breed that are otherwise sound can be retained even if they are affected once this type of test is available. All you need to do is put any affected or carrier animal to a normal (or clear) animal. With the affected to normal matings, no testing is needed as all offspring will be carriers. With carrier to normal matings all progeny must be tested as half are normal and half will be carriers.

- ***The most important aspect of using this type of DNA test is that no further affected animals will produced provided you know the DNA status of the parents for that disease. Once all dogs in your kennel are clear or normal for the condition, no further testing is needed, provided you keep using normal animals.***

Polygenetic conditions

These will remain a challenge for some time to come in that having several genes affecting one condition eg. hip and/or elbow dysplasia, and involving other environmental effects (eg. diet, weight, rate of growth etc) can all affect the incidence and severity of result seen.

Simple Recessive Mating

- Normal/clear dogs only have the **normal** allele.
- Carriers (heterozygous) have **one copy** of the normal allele ***and one copy*** of the defective allele
- Affected dogs carry **two copies** of the defective allele

- The following diagram shows the outcomes of the different types of matings.

  'A' = normal dominant allele and

  'a' = affected recessive allele.

  One allele comes from each parent.

Simple Recessive Mating cont.

Possible Matings	**Normal AA**	**Carrier Aa**	**Affected aa**
Normal AA	All progeny normal	½ Normal, ½ carrier	All carriers
Carrier Aa	½ Normal, ½ carrier	¼ normal ½ carrier ¼ affected	**½ carrier** **½ affected**
Affected aa	All carriers (B)	**½ carrier** **½ affected**	***All affected***

Determining whether a fault or defect is inherited:-

- 1. Does it affect more than one member of a litter? Obviously the larger the litter the more likely you are to get a significant result.
- 2. Has it recurred in a repeat mating, or in matings that are genetically similar?
- 3. Are there ancestors in common?
- 4. Is it a reported condition in the breed.
- 4. Test breeding can be carried out to see if the fault reappears (last resort).

Clearing an Inherited Disorder from a Breed

- Once breeders have decided that there is significant disease that needs to be brought under control and there is an accepted recognised method of testing that will allow effective monitoring of the disease(s), a breed survey can be carried out Australia wide to determine if all breeders of that breed agree that this is a significant problem in the breed.

- If this is agreed upon, then the disease(s) must be screened for and the results submitted in order to register a litter of that breed. These requirements are called Litter Registration Limitations (LRL's). Once the disease is erradicated or brought under very good control, these requirements may be moderated/reduced to allow a monitoring situation to occur.

- Several diseases have already been successfully controlled by this method.

- Polygenetic conditions such as hip and elbow dysplasia must be looked at in the long term to determine the relative success of these schemes. Regular publication of rolling breed means and ideally sire progeny averages can greatly enhance the success of these schemes.

Applying breed disease schemes.

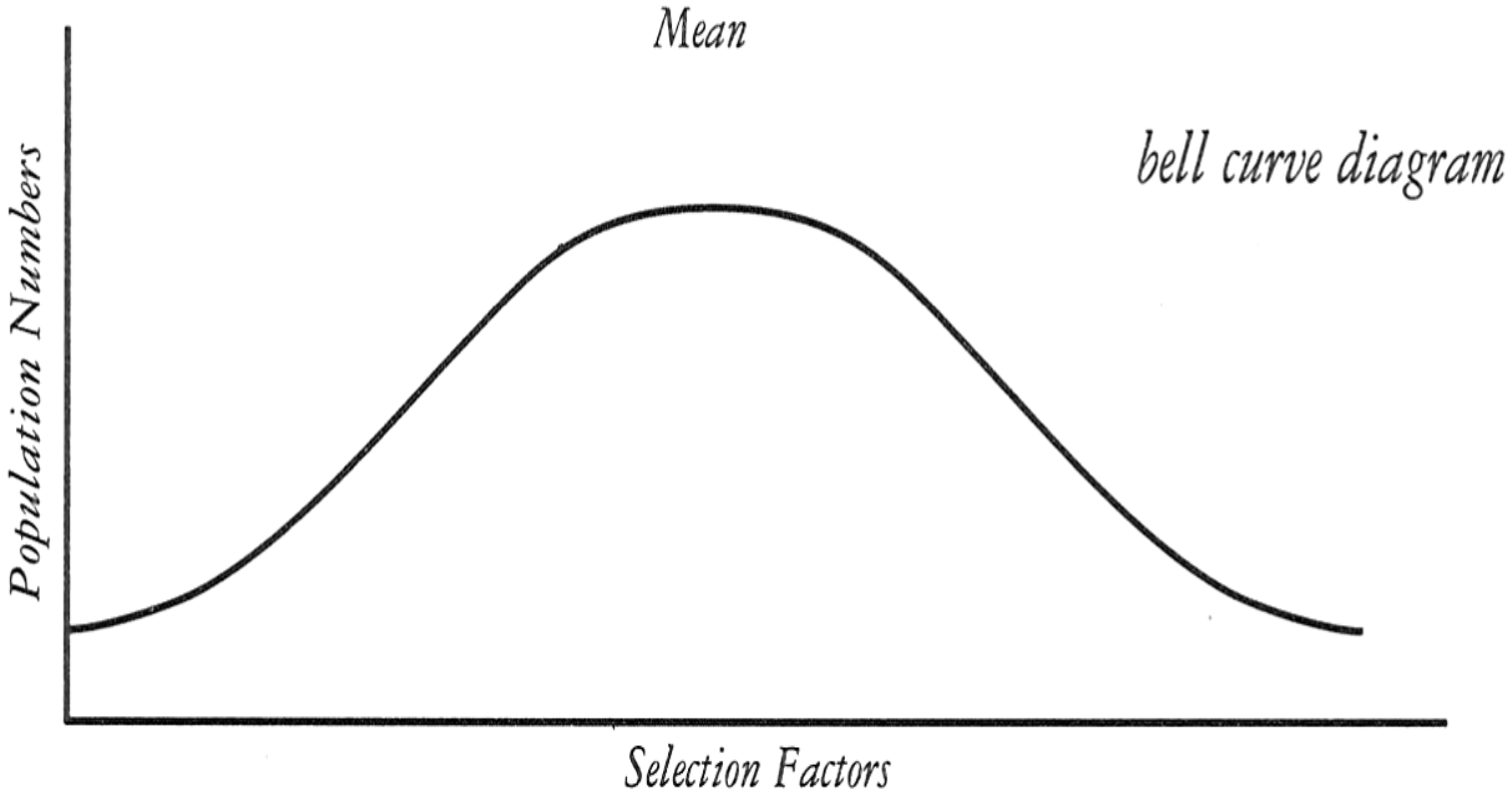
- When applying a breed improvement scheme one must always look ***at the overall and long term picture***. Attempting to change entire breed averages or affected/carrier to normal percentages with DNA tests is generally going to take generations of breeding stock (5-10 on average) ie. time!!
- The more schemes that are applied, the slower the overall rate of progress.
- The aim should be to remove the worst affected individuals (empirical schemes X rays etc) or prevent the occurrence of severely affected individuals where DNA tests are available.
- ***Removing carriers and mildly affected individuals is not generally the aim.*** Removal of such animals would in most cases severely restrict future genetic diversity.
- With DNA testing we can in most cases (recessive conditions) avoid loosing any genetic diversity, in many cases even using affected animals, provided they are put to normal (unaffected/clear) partners.

Populations

- Populations can be described by a bell curve which can apply to any feature you wish to look at, be it height through a breed, litter size, hip dysplasia (HD) scores and so on. With this curve, the top of the curve is the mean of the population factor being assessed eg. height with the extremes at either end of the scale ie. the shortest and tallest.

- This same principle can be applied to any genetic problem within a breed. If the incidence of a problem is small across the whole breed, eg. affecting 5-10%, it can be fairly easy for breeders or clubs to say not to breed with affected animals. If however, the problem has a variable expression and/or a complex means (polygenetic) of inheritance, this can affect virtually every member of the breed eg. hip dysplasia, to some degree.

Diagram - Bell curve population spread



The most important point is to keep the problems a breed has within perspective.

- This means that if there is a minor problem that does not affect the animal's soundness, either as a working animal or its quality and length of life, *it should be kept in proportion relative to other problems* within the breed.

- ****Genetic problems that result in a high incidence of blindness, crippling arthritis, a vastly shortened life span (eg. the storage diseases), or there is pain and suffering for both the dog and the owner (be it monetary or emotional stress), then efforts should be made by breeders and breed clubs to decrease the incidence of these problems.***

Populations cont…

- The major task facing any breed inherited disorder, is ***establishing the mode of inheritance***. If you are lucky, it may affect a single gene, with a recessive/normal pattern, and if you are really lucky, there may be a DNA marker or specific gene test found that can identify all three states of the gene ie. affected, carrier and normal. This still allows a breed club to keep its genetic pool and breed the problem out within two to three generations if they want to.

- Many breed specific diseases have already been found to be as a result of a single gene defect eg. PRA (Progressive Retinal Atrophy). Much work is being done to isolate genetic markers or the specific gene that causes these diseases. By studying dog breeding populations and related individuals carrying or being affected by the disorder, the abnormal gene or its marker may eventually be isolated (after a lot of hard work).

Populations cont…

- Inherited problems may have ***two or more genes affecting the inheritance pattern.*** Dominant genes can express one problem and hide another problem. The normal gene usually carries sufficient enzyme-making ability to hide the effects of the defective gene. The animal will appear normal but is in fact a 'carrier' of the abnormal gene.
- This can often be seen in sex-linked genetic problems eg. Haemophilia A. As this gene is carried on the X chromosome, the problem can be carried or hidden by a bitch (XX) on to the next generation as she has two X chromosomes. If a male (XY) carries the affected X chromosome, the problem will be expressed as there is no other X chromosome to provide the correct enzyme to allow normal blood clotting to occur. There is at present no definitive test to determine carrier status in females for Haemophilia A (humans or canines).

Populations cont…

- *Multiple gene problems* are called ***polygenetic*** and are much harder to clear from the population as they are often a blend of effects of the genes and the environment acting together. The more genes that are involved, the greater the chance that the environmental factors will affect the end result. Environmental factors include diet, rate of weight gain, level of activity and stress factors.

- As stated above, ***the overall picture should be remembered.*** Trying to eliminate all dogs with hip dysplasia (HD) did not work (attempted in both German Shepherds and Labradors) and the end result was a greatly reduced genetic pool. Cases of HD were still occurring and breeds no longer resembled the standard.

  The main aim today of most hip schemes is *a gradual reduction in the breed average while at the same time allowing breeders to preserve valuable bloodlines and decrease the incidence of really severe HD.* The inheritance of HD varies in different breeds. The higher the degree of inheritance, the more rapidly changes can occur within a breed when selecting for the characteristic. Also, a dog that has a good hip score, may not necessarily throw low scores in his progeny, while a litter brother with a slightly higher score may have a far lower progeny average.

Summary

- Beautiful, healthy dogs who are sound in temperament and body, are the aim of all dedicated dog breeders. The end result is often a compromise of various factors, including economic ones. Where soundness relates to the dog's quality of life, we must make honest attempts to decrease the incidence of any problems.
- The more we know of all the factors concerned, the quicker we can find solutions and reduce the numbers of unsound dogs being produced. It has benefits for all, particularly for the dogs.
- *###Remember when breeding, aim for soundness, evenness and reliability as the age of guarantees is upon us.*
- Law suits abound