NATURAL PROTECTION OF GENETIC VARIATION

Introduction

Programs to preserve genetic health in dog breeds have been intensively discussed in Sweden in connection with the development of breed specific genetic strategies. Why have breed specific strategies at all become a necessity in dog breeding? In nature there are no special breeding programs or strategies to keep species healthy and vital over very long periods of time. The cause of inherited disorders - observed in so many dog breeds - is that breeders, due to ignorance or extreme breeding forced by various forms of competition trials, break down the protective barriers against genetic disorders that Nature has built over millions of years by means of natural selection. What kind of barriers do we need to know about to avoid such mistakes?

The Cell

The body of an animal - even though it is a unit - is composed of billions of cells. The link between generations is however only one single cell - the fertilized egg cell. Thus everybody involved in breeding ought to know at least a little bit about how the fertilized egg is protected against genetic disorders.

Genes – protein blueprints

The basic function of a gene is to serve as a blueprint for the cell to use when building a specific protein   There are about 30-40 thousands of gene pairs and as many different types of proteins that can be built by the cell. We all need skeletons, muscles, nerve systems, liver, kidneys and all other internal organs. We also need a large number of hormones, enzymes and signal substances to make our bodies work properly.

It would all be very simple if there were never any changes in the environment. There would be no need for any changes in the blueprints to make a specific protein. However, all species have to adapt to a continuous change in the environment or to live under threat by predators. To be able to adapt to such changes all animals must themselves be able to change their physical and mental characteristics. Consequently, there is a need for flexibility of the genetic system.

At the cell level the threat from external enemies is extremely large. Innumerable micro-organisms and viruses are continuously attacking our bodies. Thanks to the very rapid generation turn over these organisms are able to change the way they attack many times during the normal life time of larger organisms such as mammals. To defend oneself against all such attacks each individual needs a defense system which is as unique as possible. Otherwise a successful attack on one individual would spread rapidly.

The Gene system is subjected to three apparently incompatible demands:

A. Stability to guarantee that all organ systems are working correctly
B. Balanced variation for the entire population to make long term adaptation to a changing environment possible.
C. Individual variation to protect every being against diseases and infections.

During the first 3-4 billion years on Earth there were no more complicated forms of life but single cell organisms. Their normal way of reproduction was a non sexual simple cell division.

The DNA molecule, the basic element of genes, is a surprisingly stable chemical compound. This molecule duplicates itself before the cell splits itself in two, thus creating two new cells with identical DNA. After such a division both cells have an identical genetic make up. But if all cells get identical genomes there can be no genetic adaptation to changes in the environment. A sudden change of the DNA molecule, or a single gene, may cause the death of the individual since a vital protein can no longer be produced. A single set of DNA molecules or genes has thus serious disadvantages both for individuals and for the long term adaptation of the species. Only very simple organisms can survive such a lack of genetic variation.

Gender and the duplication of the genome

After several billion of years Nature found a solution to the vulnerable system of simple cell division. Cells with identical genomes joined up two by two to create a new cell. This new type of cell carries then a copy of each single gene. Thus they have an intact copy of the protein blueprint should the other be damaged for some reason. Cells of that kind are much less affected by damage to single genes. Normally, there is a duplicate gene available to guarantee that the right kind of protein will be produced in sufficient amount.

Cells with duplicated genomes can no longer multiply by simple cell division. To make the amount of DNA, and thus the number of genes, constant over generations they have to go through two cell stages. At the first stage, they divide into two cells with only half of the DNA in each of the two new cells. At the next stage two such halved cells melt together in a fertilization to make a new cell which again carries a genome with duplicates of every gene.

Nature's solution was to create two sexes both having special organs, ovaries and testis, where the reduction of the genome to half the normal size takes place when creating ova and sperms. The central advantage of two sexes is the duplication of genes to avoid disastrous results of damage to single genes.

A system with two sexes has another important advantage. At the stage when germs cells (ova and sperm) are created, the DNA molecules, resembling long strings, wrap around each other. As everybody knows it may be a complicated matter to untangle strings. This is also the case for the cells, where the paired chromosomes break and exchange parts with each other. This is called crossover. Thanks to this crossover, new gene combinations are formed every generation, and in all individuals, within all species having two sexes. Sex thus both has the function of protection against gene damage and as an important source of new genetic variation to facilitate necessary genetic adaptation to changing environmental conditions.

Most but not all chromosome changes are harmful. If there is only a minor change in the composition of a protein due to a mutation, a sudden change in a gene, the new protein may do well in spite of the change. In rare cases the new protein composition might lead to advantages for the animal. Such advantages will rarely show immediately but might result from later crossing over and rearrangements of genes along the chromosomes. In cases where such mutated genes cause increased vitality of animals the carriers will on average produce more offspring and the favorable gene will be incorporated into the gene pool of the breed or species. In the opposite case, where gene changes are harmful, the mutated gene will be rapidly erased from the population by natural selection. The main selection force is again changes in vitality resulting in less progenies produced by affected animals.

Male to female bond affects male reproduction

Evolution throughout millions of years has shown that the division of animals into males and females has been indispensable for the creation of highly developed animals. There is however a problem connected to the way bisexual mammals reproduce. The reproductive capacity of females is generally restricted to produce progeny in tens rather than in hundreds. Males may however mate with a large number of females and thus have much more progeny than females. Such sexual behavior reintroduces the risk that two genes with identical origin will come together in succeeding generations. Male sexual behavior may thus violate the protective force of the duplicated gene structure.

Natural selection again found a solution by creating more or less strong bonding between reproducing males and females. It does not matter if such bonds are for life or only for one reproductive season. The effect will be the same. The upper limit for male reproduction is set by the number of progeny an average female may give birth to and rear. The creation of male/female bonds is a simple and brilliant way in which Nature reinforces the protection caused by the duplicated gene structure in spite of the fact that males have the capacity of producing a dangerously large number of progeny.

In Sweden an overproducing male with too much progeny is called a “Matador”. Matador was an intensively used bull in the northerly part of Sweden. He carried a gene for testicular hypoplasia, too small testicles, causing reduced fertility. Due to the intensive use of the bull the deleterious gene spread rapidly over the entire local bovine population. I took several decades of selection against the gene to repair the damage caused by too intensive use of what once seemed to be a male of exceptional high quality as a breeding animal.

MHC – the ID card

The cooperation of billions of cells in a body can only take place if there is a way for all the cells to identify each other as belonging to the same unit. Otherwise there is no way to identify enemies and defend the body against invasion of other cells causing diseases or damage to the body. Thus each cell in the body needs an identity card. The identity code of the card should vary as little as possible among cells belonging to the same animal but at the same time be as unique as possible for each animal.

Nature has solved the problem by creating a special set of genes called MHC, where MHC stands for Major Histocompatibility Complex. Together the MHC genes form the unique "identity card" carried by all cells of an individual and make it possible for the cells to cooperate without harming or attacking each other. The MHC genes constitute the basis for our immune system and play an important role in reproduction.

The genes of the MHC system create special proteins on the surface of each cell. It is the special combination of these proteins that make up the identity code, alike for all cells of an individual. The cells can "read" each others identity code and cooperate without any risk with cells carrying the same code as themselves. If cells carrying another code penetrate into the body they are attacked by special guard cells called T-cells or murder cells. The T-cells are continuously moving around and looking for cells with deviating identity code and kill such cells immediately when found. Together the combination of the MHC proteins and the T-cells make up one of the most important defense mechanism against invasion of pathogenic cells.

It is now obvious that the more unique identity code an individual carries the better it is protected against diseases. Pathogenic cells will always try to copy the identity code to fool the T-cells that they belong to the body. But if they succeed and all individuals carry different identity codes the pathogenic cells cannot spread easily from one individual to another. They will be discovered by the T-cells of any individual carrying another identity code.

The basic consequence of inbreeding is to duplicate genes of the same origin. Such duplication will inevitably reduce the number if genes with different blueprints for protein production and hence also reduce the possible variation of genes in the MHC system. With fewer proteins as a basis the identity code will be less unique and easier to copy just as very short keys in a computer system. This is why inbred individuals are more susceptible to infectious diseases.

Genetic scent signals

Nature has created a special protection against dangerous reduction of genetic variation in the MHC gene system. Again the solution is brilliantly simple. The genes of the MHC system take part in the production of the scent substances called pheromones. The pheromones are important sexual signals and make it possible for animals to "smell" part of the genetic set up of the MHC genes carried by a possible mating partner. It has been shown by experiments that all kinds of animals from insects to mammals use the pheromones to avoid mating with close relatives carrying all too much of the same genes in the MHC system. Thus the bond between the pheromones and the MHC genes protects the genetic variation of the immune system. This kind of protection will be effective only when there is a free choice of mating partners and the number of possible partners is large enough. If the number of available partners is low females may choose to mate also with closely related males rather than not mate at all. A less viable progeny may be better than to become barren.

It is important to accept when the bitches distinctly signal that they do not accept a male. The females know better than the breeder if the male carries MHC genes which are favourable for her progeny. Forced mating is an effective way to violate one of the most important protections of genetic variability.

Fertility and inbreeding

Most breeders are well aware of the fact that strong inbreeding has negative effects on viability, health and fertility. But what do the immune system and reproduction have in common to make them both sensitive to inbreeding?

The foetus is protected from being rejected

Everybody is well aware of the problems in transplantation surgery to get the receiver accepting foreign tissue. The basic reason for the rejection of foreign tissue is that all its cells carry another ID code and hence they will be attacked by the immune system of the receiver to avoid an unwanted invasion of possibly malignant cells. When transplanting organs from one individual to another the process is facilitated if the genetic system of the donor is as much alike as possible to the genetic system of the receiver. But even in cases where donor and receiver are closely related it is necessary to use cytotoxin to avoid the rejection of the transplanted tissue.

The genes of a fertilized egg are 50 % inherited from the mother and 50 % from the father. Hence the genetic system of the fertilized ova normally deviates to a large extent from that of the mother. As a consequence the fertilized egg ought to be repelled by the immune defense system of the mother. As a matter of fact should there be no other mechanism at work pregnancy would not be possible. But again Nature has found a solution. A very special type of protein is produced in the mother to prepare her for pregnancy. That protein has the function of guarding the fetuses against attacks from the immune system of the mother. The special protein will guard the fetuses continuously during pregnancy. It is an interesting fact that the total amount of fetal tissue, including the placenta, shows a rather similar proportion to the weight of the pregnant female. One of the probable mechanisms that releases delivery might then be that the total amount of fetal tissue exceeds the capacity of protection from the special protective protein.

The protection of the fetuses has a negative side effect. At the time when the delivery is finished the protective protein still remains in the body of the mother for 2-3 days. During this period she is extremely susceptible to infections since her own immune response is seriously lowered by the remaining protective protein. It is thus necessary to supply the bitch with a clean and dry environment especially during the first few days after delivery.

One might think that fetuses with gene systems very like their mothers, i.e. for example those that are heavily inbred, would benefit from their genetic likeness to the mother. There should be a less strong tendency to reject such fetuses from the womb. But if there is a very strong genetic likeness between the mother and her fertilized eggs another problem arises.
How should the uterus of the mother be able to identify fertilized eggs as deviating from any other cells of the mother's body floating through?
One of the prerequisites for the adhesion of the egg to the uterus wall and the formation of the placenta is the difference in genotype between the fertilized egg and the mother.

Another risk with to much genetic likeness between the mother and her progeny is that the labour pains during delivery will be seriously lowered leading to a prolonged delivery time. There is thus a threefold advantage in divergent MHC genotype between the mother and her progeny. The foetus will get a better start in the mother's uterus, the delivery process will be shortened and thus less trying and finally the newborn animal will have a more unique ID code making it more viable and less prone to infectious diseases.

Number of puppies and size of the mother

One of the fascinating consequences of the fact that total fetal tissue has a rather close relation to the size of the mother is that it affects litter size in dogs. Normally there is a negative relationship between the size of the mother and the number of progeny in all litters, i.e. the larger the mother the fewer her progeny in each litter. Small animals like mice tend to have large litters while large animals like elephants normally give birth to only one young at a time. In dogs this rather general rule is reversed, as in most breeds of domesticated pigs. The reason seems to be that our breeding efforts have been much more effective in changing adult size of our dogs than changing the size of their newborn puppies. Thus with the same proportion of fetal tissue compared to the body weight of the female a large female will be able to carry more puppies.

The ova and her selection of sperm

Is there any way in which an unfertilized egg may have any influence upon its genetic variation after fertilization? Anybody who has seen pictures of an egg just before fertilization knows that the egg is surrounded by a crowd of sperm. It is not just a coincidence or an act of Nature's superabundance that there are millions of sperm produced to fertilize only one or a few eggs. The large amount of sperm is a guarantee that enough sperm will reach the egg in time for fertilization. The identity code of all cells will then make it possible for the egg to select a sperm among all available that best matches her own MHS complex so as to produce as viable a progeny as possible.

It might sound strange that an unfertilized egg should be able to select the sperm that is allowed to fertilize her. But fertilization is not a violent process where the sperm forces its way into the egg. The cell wall of the egg has to open up to allow the sperm to pass its DNA content into the egg cell. Thus the egg cell takes an active, and probably dominant, part in the fertilization.
Similar mechanisms of cross-fertilization in plants are well known since long. If pollen from the flowers of a plant reach the stigma of flowers on the same plant the pollen tube will not grow due to blocking chemical reactions. Thus the stigmas of flowers are able to identify the genotype of pollen and avoid close inbreeding and self-fertilization.

The large number of sperm produced by mammal males has the same function as the large number of pollen produced by plants. It gives the female egg the possibility to select a partner producing progeny with the highest possible viability. Large number of sperm is thus another of Nature's guarding system to preserve genetic variability in a breed or species. The use of strong inbreeding will however again break down the protective systems since all the sperm will be too alike in genotype and thus reduce the possibility for the egg to select a proper sperm.

Artificial reduction of number of sperm

The very large number of sperm normally produced by a male has since long been considered as just a surplus overflow with no effect whatsoever in breeding. The argument being that as there is need for only one viable sperm to fertilize one egg why not try to make fertilization more effective. The number of sperm produced at one occasion will certainly be enough to get many more females pregnant. Prominent males can then be used to produce a much larger number of progeny than ever seen in Nature.

When using artificial insemination in cattle breeding, one normally dilutes the ejaculate 1/100, i.e. the number of sperm is reduced to only one hundred of the normal number. Although such a reduction may not have any dramatic short term effects it is obvious to anybody thinking clearly that in the long term perspective the effect might be deleterious to the genetic variation and thus to the viability of animals.

With our selves the experimentation has gone much further. It started by test-tube fertilization. With this method, as with insemination, the fertilization as such is quite normal although the number of sperm is often reduced. Today one often uses what is called micro injection. In that case some scientist or doctor is looking through a microscope trying to find a viable sperm, i.e. one that swims around and appears alert. Such a sperm is then picked up into a micro pipette which is forced through the wall of the unfertilized egg. When using micro injection to fertilize the egg, the latter is totally depleted of all possibilities to select a sperm that matches its own genotype to guarantee as viable progeny as possible.

The fact that it might not be possible to immediately, or in a few generations, detect serious negative effects due to such violent break down of the natural security mechanism is not proof that the technique is not harmful in a long term perspective. Evolution works through many small steps. Each of those steps may seem to be of minor importance but added over a large number of generations they may have profound effects on the development of a breed or a species. Therefore one cannot by the experiences from but a few generations conclude that it is harmless to pull down all security mechanisms built into the system of fertilization to preserve vital genetic variation.

Surplus of eggs at each mating

Among multiparous animals there is also another and simpler mechanism to enhance viability among the newborn progeny. The number of ova shed by the females during the heat period is normally about twice the number born as fully developed young ones. If the female is mated during a favorable time of heat all the ova will be fertilized. But there is rarely enough place for all the fertilized eggs in the tubes of the uterus. There will thus be a competition among the eggs for a place where they can adhere to the uterine wall and start the formation of a placenta. Less viable eggs, for example such eggs that have got duplicated genes with negative effects in very early development, will lose the competition. Hence the young ones borne have a little less of genetic burden to carry. The actual inbreeding is a little bit less than the one that may be calculated from their pedigrees. This type of selection will never be as strong as the one based on selection among millions of sperms. But it will guarantee that genes with profound negative effects in early development cannot easily spread in a population.

Natural selection

Natural selection, or the forces applied by nature to make individuals as viable as possible in their environment, will not preserve genetic variation in all gene systems. In some cases there is need for genetic stability. As living creatures we all need lungs, hearts, stomachs, skeletons, nerve systems and brains and so forth. It would be too harmful to the development of our basic organs to have too much genetic variation in the genetic systems responsible for their development.

What we in everyday speech call the natural selection is a force with the purpose to balance the genome in order to give it the best combined effect on viability. In nature a creature has to find food, protect itself against enemies including micro organisms. It is also necessary to be able to adapt to environmental factors such as heat or cold, rain or lack of continuous supply of water. If an individual shall have any impact on the genetic future of the species to which it belongs it has to find itself a mating partner and produce and rear progeny. For the females also the very complicated process of pregnancy and delivery has to work without problems. A lot fewer animals than people normally realize survive long enough under natural selection to pass all the necessary stages as contributors to future generations.

It is of profound importance that all breeders of animals do understand that the basic principle of natural selection is to stabilize the genetic system to be effective during normal environmental circumstances. The struggle for life in nature has very little to do with fights between individuals. The main fights are the fights for survival and reproduction. Only those who in the long run produce viable progeny are the winners and in nature extreme individuals are not among the winners. The most prolific individuals will win the race and those are the ones best adapted to the present environment, i.e. the normal individuals closer to the population average. In a case where changes never take place in the environment natural selection would probably result in a very far going genetic identity between individuals of the same species. But environmental circumstances always change and over long time periods the changes may be very large. Species that have lost their genetic variation will not be able to adapt to those changes in environment and hence their destiny is extinction. For this reason Nature will always favor those species that have the power both to preserve the genetic variation necessary for adaptation and to preserve the genetic stability to form all vital organs of the body.

Normally there is genetic variation in systems responsible for body size and form, color, length and thickness of the fur and so forth. It would be advantageous for this kind of traits to be able to change rather rapidly if environmental conditions undergo sudden changes. Other gene systems, as for example those who are responsible for reproduction, may be more stable. Food supply may for example vary quite a bit between years and it would not be an advantage if that had an immediate genetic effect to reduce reproductive capacity.

In wild animals the selective force will under all normal circumstances be directed towards the centre of the population – the average individual is rewarded. Extreme individuals may have advantages only in cases where the environment changes dramatically. If the temperature for example drops heavily, such as it did 65 million years ago, animals with long and protective fur may get a selective advantage and form the new centre of a population. Should the change be large enough a new species is actually created. In cases where such environmental changes are very rapid or too large, there might be no animals carrying the necessary genes and characteristics to survive. Then the entire population or species will become extinct. That has actually happened to over 98-99 % of all species ever existing on Earth.

In Nature a stabilizing selection, adapted to small and slow environmental changes is the normal state. The rapid environmental changes are rare but most of them cause widely spread extinction of living species. The very rapid loss of species today, as a consequence of our civilization and its effect on the environment, may serve as a commonly known effect of the difficulties species have to adapt to too sudden changes of their living conditions.

Artificial selection

Artificial selection is the selection of animals by man. When breeding farm animals there is a steadily ongoing selection for faster growth, more milk or eggs and meatier animals. The most extreme individuals are those who win the race provided they are able to cope with the burden of rapid change placed upon them. Breeding pet animals should be possible without such an ambition to rapidly change animals. For most pet animals however the breeding is governed by show competitions or other trials such as hunting trials and working trials for dogs. In a contest there is no way to favor the most average individual, as happens in natural selection,. In a contest the extreme individuals are the winners. Too often we reward small differences in characteristics, characteristics which have no impact on health, or which might even have negative impact on health. As a matter of fact the kind of artificial selection applied to our animals, also to pet animals, is very much like the type of natural selection during environmental catastrophes. Extreme individuals are primarily the ones selected for breeding. The negative effect of such a selection policy over a long period of time is well known. The problem in pet and dog breeding is that most people do not plan for more than decades at best, very few for longer periods than that and none that care for the effects measured in evolutionary time perspective.

If we seriously want to breed and rear healthy and vital pet animals we have to learn all the ways Nature preserves viability in wild animals. We must abandon breeding techniques that invariably violate all the security mechanisms invented by Nature. If we are not willing to learn how these security systems are built, and how we can use them in favor of our loved animals, both breeds of farm- and pet animals may get a depressing future. Breeding is not primarily a matter of complicated genetic theory. Nature has no theoretical knowledge of genetics. Successful breeding, with the intention to create healthy and viable animals, is a matter of adopting and stick to some few and very simple principles of selection and breeding.

Summary and some practical consequences

At this stage it ought to be evident that the overriding cause to genetic defects and inherited diseases in animals is not due to some unhappy coincidence. It is the direct and unavoidable consequence of lack of knowledge among breeders about some basic rules of Nature. They have not had knowledge enough to foresee the consequences of the way they have used their animals in breeding. The most responsible driving force for all the mistakes made is the basically unsound breeding practices and contests and trials where rapid genetic changes are desired and where these aims have been given higher priority than the health and viability of the animals. The rewarding system applied in competitions also stimulates to split breeds into steadily larger number of breeds or varieties of breeds. This inevitably produces a large number of populations all too small for any kind of proper breeding. When the number of breeding individuals gets below critical levels the loss of genetic variation is very rapid. Genetical disorders may be a problem in such a short time as about ten generation or 30-50 years. Most breeds are not older as pure breeds than about 100 years. The steadily growing problem with genetic disorders in our pet breeds is thus exactly what we can expect from what we know about breeding practices in many breeds.

Those who are looking for advanced breeding programs to correct all the genetic problems we see today are looking in all the wrong directions. They should try to understand exactly what has gone wrong and start to learn from Nature how animals can be kept viable over hundreds and thousands of years without any theoretical knowledge at all.

1. The size of a population must be large enough to carry and preserve genetic variation. There is no way to succeed when a breeding population has less than about 100-150 breeding animals and twice the number is preferable.

2. Only viable animals in good physical and mental condition and with all natural functions still present should be allowed to breed.

3. In highly developed creatures the basic rule is that separate individuals are not allowed to have more than a restricted number of progeny during its life.

Those are the three simple basic rules of Nature, rules when properly applied will keep any population of animals healthy over very long periods of time. The one and only reason for the genetic disorders in our breeds of dogs and other pet animals is that we neglect to consider the mechanisms to protect genetic variation created by natural selection during billions of years.

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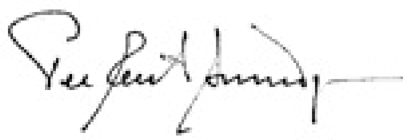

Per-Erik Sundgren
Dr. Agric.