Pituitary Dwarfism - A bigger problem than expected

Pituitary dwarfism is thought to have originated as a spontaneous mutation (*University of Utrecht*) sometime during the 1940's. When the GSD was seriously depleted during and after World War 2, there was a period of intensive inbreeding, the recessive allele occurred and was quickly spread. Much research has been done including the use of Max von Stephanitz own notes but no recorded trace of PD prior to this period could be found. It cannot however be totally discounted that this was a very rare allele that was present in the founders at the formation of the breed and has increased within the population through genetic drift, unlikely but possible.

A small number of people over the years have attempted to highlight the problem most notably Fred Lanting and John Walker in the 1980's and 90's, at this time however they had relatively little scientific information to go on other than their own experiences of dwarfs. Things are much different now with clear scientific evidence of the harmful genetic effects to the German Shepherd population from this defective recessive gene.

But what is Pituitary Dwarfism, why the concern?

Pituitary Dwarfism is an autosomal recessive inherited disorder of the Pituitary Gland caused by a mutation of the LHX3 gene on Chromosome 9 (deleted base pair sequence GCGCCCC at Intron 5) and is encountered most often in the pastoral breeds particularly the German shepherd dog where 20% (source: University of Utrecht) are now estimated to carry the faulty gene. The pituitary is a hormone producing endocrine gland at the base of the brain, this pea-sized gland is composed of the anterior lobe and the posterior lobe. The anterior pituitary synthesizes many of the essential hormones which are then secreted for numerous body functions such as growth, reproduction, lactation and metabolism.

Hormones secreted by the pituitary gland from the anterior lobe are: growth hormone (GH), which is essential for growth, Thyroid Stimulating Hormone (TSH), which regulates thyroid function, Prolactin (PRL), which is essential for lactation Follicle Stimulating Hormone (FSH) hair growth, Luteinizing Hormone (LH), which is essential for ovulation in female dogs and sperm production in male dogs and Adrenocorticotroph Hormone (ACTH), which stimulates the adrenal cortex

Any defect in the development of the pituitary gland creates enormous problems for the dog the most obvious example of hormone deficiency is the small proportionate stature and hair loss but there are also many hidden problems. Dogs that are carriers of the recessive gene do not have any visible symptoms and look exactly the same as the dogs that are not carriers and this is the problem. The birth of an affected dog means that both parents are carriers each with a single copy of the gene and of

course with a recessive gene when two carriers are mated on average 50% of their progeny will be carriers, 25% clear and 25% of their offspring will be affected that is they will be pituitary dwarfs.

The clinical symptoms of dwarf dogs are not limited to their visible appearance; they suffer from a whole range of detrimental hormonal conditions particularly from under development of the liver and kidneys causing chronic renal failure, cardiovascular problems such as Patent Ductus Arteriosus (PDA) and also for many a range of neurological conditions. The deficiency of Thyroid Stimulating Hormone (TSH) results in an underactive thyroid gland (hypothyroidism) causing many animals to be slow, dull with some aggressive tendencies due to the lack of TSH, this is not true of all dwarf dogs as many are alert and easily trainable as with a normal dog and with no temperament issues. Additionally the reduced level of gonadotrophins may result in failure of one or both testis to move or "descend" into the scrotum (cryptorchidism) in male dwarves while female dwarves do go into heat more often and for longer than normal but they do not ovulate, females are particularly prone to urinary tract infections.

'Hobbit' and Normal Litter mate at age 8 weeks

Without proper treatment, the long term survival rate is generally poor, many dwarfs will not live to more than 4 to 5 years of age. However, there are a significant number of dogs that do live longer even untreated with reported examples up to 14, probably because in some cases the pituitary gland still produces enough of the required hormones to survive.

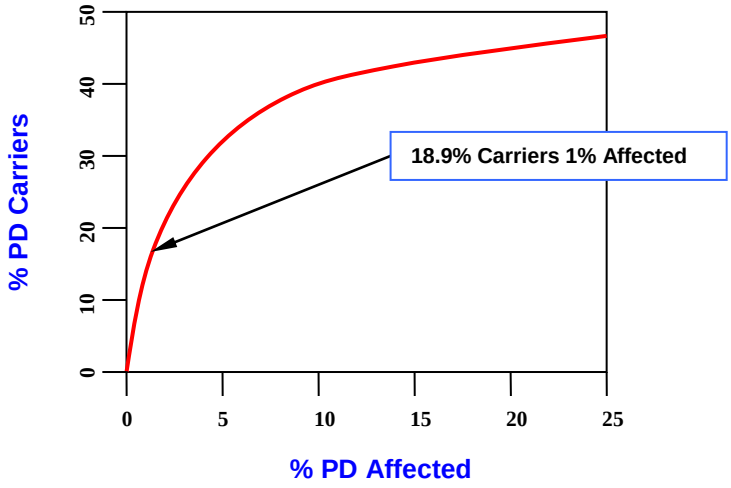
'Hobbit' aged 2 years - Treatment with proligestone from age 8 months has made great improvements to coat and appearance, but Hobbit still has many internal problems

Treatment with porcine growth hormones will not increase the size of a pituitary dwarf, what it will do is aid the development of the renal system and also help retain their coat.

As already stated in most cases dwarf dogs to date are not known to be capable of breeding as they are mostly infertile and therefore automatically excluded. Even if

some were found to be fertile as is suspected a small minority are, the physical stature of a female dwarf would make it impossible to carry a litter of pups to full term as the developing dwarf pups in the womb are virtually the same size as normal GSD's. Reports of a normal sire to a dwarf dam mating resulted in the death of both dam and pups. Most dwarfs can in fact be very difficult to tell apart from their litter mates at birth in terms of size and appearance. There have been many instances where the largest pup at birth has turned out to be the dwarf which is contrary to what many people believe. Managing the recessive gene would however be quite different from most undesirable genes in that those affected are already lost to the gene pool so there is no conflict of interest in their use for breeding programs, it's all about managing the carriers.

What is known is that if left to continue then this defect will become a breed trait and hence impossible to eliminate without irreparable damage to the genetic diversity of the GSD. The gene could have been dealt with much sooner, I fear all that can be done now at best is to reduce its occurrence, but even this would take many generations to complete assuming there is actually the will to do so, as it is the PD gene will only increase relentlessly over time. The graph below shows where we are now 18.9% carriers taken from a random sample by the University of Utrecht and also where we are heading using the Hardy - Weinberg principle:



This has now become a global issue with dwarf dogs being reported to us every week, increasingly from North America and Australia, it seems that no country is immune from this condition and such is the extent that isolated populations are quite possibly now unlikely to exist certainly in the show lines, the data is presented across all GSD lines such as Show and Working lines through to Pet lines including White Shepherds in Europe and the USA.

There is not just a potentially heavy financial burden involving dwarf dogs but also a forgotten emotional cost. The potential for unscrupulous intentional breeding to own a dog that mistakenly appears to be forever a puppy brings out the best and worst in human nature. Despite the health costs to the dog, the worrying thing is by further highlighting this issue we at the Saartje Foundation have a moral dilemma in that we could inadvertently create a demand for dwarf dogs as knowledge of these dogs becomes more widespread. On meeting these dogs for the first time the general public often ask; "Where can I get one of those?", "How much do they cost?" or "I want one of those aren't they cute" The attractiveness of dogs that remain apparent puppies can be quite irresistible to many potential owners particularly now as their coats have a good chance of being retained unlike the recent past where these dogs appeared quite unappealing except to those owners who loved them for what they are - sick dogs. We have even heard of some breeders asking for premiums for them because of their 'rarity value' but without regard for their health, and sold to unsuspecting buyers who have little or no knowledge of their requirements, this is without doubt not a good outcome for the dogs or for the potential owners of such dogs.

Currently well over six hundred hereditary deviations are known in dogs of which pituitary dwarfism is just one (*University of Sydney*), but only a small number of these are caused by a single recessive gene. Most genetic deviations are caused by a collaboration of a whole series of gene pairs and dogs carry both many known and unknown genetic diseases. What we see in carriers are phenotypically healthy dogs but genotypically those same dogs are a risk for the unwary breeder without testing, what is certain is that something needs to be done regarding not just this problem with pituitary dwarfism but also with other deleterious genes within the GSD population.

The estimate is that 90% of all PD affected dogs die in the womb or shortly after birth and are seen as fading puppies but of course some survive and are often sold before the condition is recognised. This is exactly why many breeders often say " there is no PD in my lines I have never seen or had a live dwarf ", but for every still born or fading puppy that they do see then there is a high probability that this might be the cause and as the condition is not recognised within a breeders lines then the carrier rate as a consequence continues to increase. Normally, the solution would be to select against the undesirable alleles by excluding the affected dogs from breeding programmes and within a few generations the number of affected would reduce. After two generations the number of affected dogs would halve, after ten generations the number would or should become negligible - Success, problem solved or has it been? We know with Pituitary Dwarfism that the dogs in effect exclude themselves from breeding by virtue of their infertility (this is not entirely true) or their physical structure, yet why is the number of those affected rising? It is rising because we have done in most cases virtually nothing to manage both the known and unknown carriers

out there within the GSD population that is except for those good Breeders that in fact do test. The genetic issue surrounding pituitary dwarfism is now not a difficult one, if all German Shepherd organisations recommended DNA testing for pituitary dwarfism. The solution to this problem and other issues caused by recessive genes within the GSD population needs to be debated at all levels within the breed, not just for current issues but also for those unknown deleterious genes that will inevitably appear in the future. We are close to a point where decisions need to be made before it is too late to make the necessary changes to protect the breed's long term future.

Currently a dwarfism database with all reported affected dogs together with all DNA tested clear and known carriers is now being centralised in Holland the home of dwarfism research. This programme as a matter of urgency needs the assistance of not only the Breed Council but all organisations with an interest in the breed to ascertain the true extent of the problem which at present we believe is grossly under estimated except by those of us at the Saartje Foundation and the University of Utrecht who are having to deal with this condition on a day to day basis. The biggest single thing that could be done to reduce the incidence of pituitary dwarfism would be to ensure that all VA and V rated dogs are tested for PD before breeding, the testing of all dogs is not really feasible but those that are popular sires tend to be the largest single group of carriers and have a disproportionate influence on the breed. This group frequently have progeny of over a thousand and it is not unusual to have numbers over two thousand and spreading both good and bad genes all over the world. Breeding for phenotype and not knowing the genetic status of these dogs for this condition is spreading it far and wide.

The use of popular sires has been identified as the single most important contributor to the spread of genetic diseases in purebred dogs Leroy (2011). The Popular Sire syndrome has been known about for a very long time in population genetics and serious consideration needs to be given to its consequences with regard to not only simple recessive mutations but also the more difficult complex traits such as DM and Epilepsy by making more use of Estimated Breeding Values (EBV's) and co-efficients of inbreeding (COI's). But unlike DM and Epilepsy we know what the mode of inheritance is with PD and have a DNA test, therefore theoretically it should be relatively easy to reduce its occurrence to negligible levels relatively quickly. New genetic problems will inevitably arise in the future and can be quickly spread amongst the population, the question is when they do arise as pituitary dwarfism has done do we have the desire to tackle these issues quickly and effectively for the benefit of the German Shepherd breed before its too late.

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For further information on pituitary dwarfism in the German Shepherd see:

http://gsdpituitarydwarfism.weebly.com/introduction-to-pituitary-dwarfism.html