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DCA Study Group on Urinary Stones
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RESPONSES TO LUA/HUA QUESTIONS

The committee has done its best to answer the questions objectively and to avoid interjecting any personal opinions.

Dalmatians and Uric Acid Stones

To what extent are stones a problem in the breed?

No study has been done that was extensive enough to provide a definitive answer to the question. It would be necessary to follow a very large number of Dalmatians from a variety of different bloodlines for their entire lives with regular urinalysis and ultrasounds to even determine what percent have any stones/sediment in the bladder and what percent actually obstruct. These dogs would have to be monitored for diet, water intake, opportunity for urination, drugs, etc.

It is important to note that the studies that have been conducted have been conducted primarily with information gathered at Veterinary offices & schools and therefore do not necessarily represent the Dalmatian population as a whole, the premise being that more of these Dalmatians would have some sort of health/stone issues which is why they were at the vet in the first place.

In a project funded by DCAF, Dr. Joseph Bartges conducted a survey on "Urate Urolithiasis in Dalmatians." Spotter, Summer 2006. He reported:

"Of 2,118 dogs, 1,635 (77.2%) had no history of stone disease while 483

(22.8%) had a history of stone disease. The mineral composition of the 483 stones were reported as: Urate = 317 (65.6%)"

Dr. Susanne Hughes did bladder ultrasounds of 377 Dalmatians at the 2005 and 2006 DCA national specialties. 71.3% of males and 25.4% of females had sediment or calculi in their bladders. Dr. Hughes pointed out that these results should not be extrapolated to the entire population of Dalmatians but the figures do seem to indicate that stone forming is a very real problem. However, of the 377 Dalmatian tested only 1 was found to have a stone great that 3 ml. It should also be noted that no evidence has been reported that any of the dogs participating in this study were seen by their home veterinarians for follow up urinalysis or confirmation that the material found was indeed debris/calculi or sludge. Further, no studies to determine if any of the dogs with debris/calculi obstructed or if any of the dogs that were clear developed debris/calculi at a later date.

The following quotations are from "The Rocket Science of Canine Urolithiasis" (Osborne et al, 1999):

From 1981 - 1997 there were 6,144 purine uroliths submitted to the Minnesota Urolith Center. This is 8% of the total 77,191 uroliths submitted during this time period. Purine uroliths include ammonium urate, sodium urate, calcium urate, uric acid and xanthine. p20.

"Male dogs with ammonium urate (90%), sodium and calcium urate (99%), uric acid (88%), and xanthine (81%) uroliths were affected more than female dogs with ammonium urate (10%), " p 161. It was also stated on page 161 that all of the dogs with xanthine uroliths had a history of treatment with allopurinol.

“Sixty-six different breeds were affected with ammonium urate uroliths including Dalmatians (61%), Miniature Schnauzers (7%), Yorkshire Terriers (5%), Shih Tzus (4%), and English Bulldogs (4%). Twelve different breeds had sodium and calcium urate uroliths, but they were primarily encountered in Dalmatians (92%) and English Bulldogs (4%). Six different breeds had uric acid uroliths, but Dalmatians were most commonly affected (80%). Five different breeds had xanthine uroliths, including Dalmatians (56%) and English Bulldogs (35%).” pp161-162.

What is the difference in the levels of uric acid in HUA and LUA Dalmatians?

Non-Dalmatians and Low Uric Acid (“LUA”) Dalmatians produce uric acid levels of 10 – 60 mgs per day. Dalmatians (excluding LUAs) produce uric acid levels of 400-600 mgs per day.

1. Is the HUA gene neuro-protective for something else?

This question was posed to Dr. Bartges who replied he was not aware of any studies indicating the HUA gene protects against any other disease. He added “However, the levels of serum uric acid that Dalmatians reach is “safe” relative to uric acid related diseases in humans (e.g. gout) and I am also unaware that such levels are necessarily bad. The main issue with uric acid in Dalmatians is stone formation.”

Is sludge in the bladder connected to stone forming?

According to the report on the DCA Ultrasound Study by Dr. Susanne Hughes (Spotter, Summer 2007)“It is notable that a large number of male Dalmatians in our study were found to have bladder sediment and/or calculi present. We are unable to predict which of these dogs are likely to obstruct, but it seems safe to conclude that all are at some risk relative to the population of all dogs without bladder debris.”

It is again important to point out that no follow-up studies were conducted and the study did not prove any correlation between sediment & stone formation.

Low Uric Acid Dalmatians

1. How is the LUA gene transmitted?

All Dalmatians (excluding Backcross descendants which have been proven to be LUA) are homozygous for the high uric acid gene (uu). That means they carry two copies of this gene. LUA Dals can be heterozygous (Uu), that is they carry one copy of the high uric acid gene and one copy of the canine normal gene, or homozygous (UU), that is, they carry two copies of the canine normal gene (UU). The HUA gene is a recessive gene (like the liver color) so, when breeding homozygous high uric acid (uu) to heterozygous canine normal uric acid (Uu), statistically 50% of the offspring should inherit one copy of the canine normal gene and have canine normal uric acid. This could be more or less in any one litter but over a sample of many litters should be about 50%.

Homozygous HUA(uu) to homozygous LUA (UU), all of the pups would be heterozygous LUA(Uu).

Heterozygous LUA(Uu) to heterozygous LUA (Uu) = 25% homozygous LUA (UU), 50% heterozygous LUA (Uu), 25% homozygous HUA (uu)

Heterozygous LUA (Uu) x homozygous LUA (UU) = 50% homozygous LUA (UU), 50% heterozygous LUA (Uu).

2. What are the statistics on LUA to LUA breedings?

There have been very few LUA to LUA breedings. At present there are only 7 UU Dalmatians of which we are aware.

3. Is there any documented data of the Backcross descendants through the generations?

There is a very thorough list of the outcomes of most of the LUA breedings that have been done since 2005 on the LUA Dalmatians website www.luadalmatians.com. LUA Dalmatian breeders record their hip, elbow, eye, thyroid, hearing, etc. test results just as AKC breeders do. The information on clearances for a specific dog is available by doing a search on the OFA website www.offa.org. LUA breeders, just like their AKC counterparts, make their own decisions as to which health clearances will be done. No studies have been done on the LUA Dalmatians as a group. As of February 2011, there were 16 LUA dogs with CHIC Numbers.

No comprehensive study has been done to determine if LUA Dalmatians do not produce stones. The question of whether eliminating the gene for uric acid would eliminate the problem of uric acid stones was posed to Dr. Bartges and he replied "Theoretically, "yes" – by lowering urinary uric acid, then stones containing uric acid should not form; however, also "yes" – it would not prevent theoretically a predisposition for stone formation in general (struvite, calcium oxalate, cystine, whatever mineral). The question remains – if all Dalmatians have high uric acid levels in their urine (relative to non-Dalmatian dogs) then why don't all Dalmatians form urate stones? The thought is that there must be something that separates stone-forming from non-stone-forming – therefore, while likelihood of forming urate stones may go down by decreasing uric acid levels, it doesn't necessarily mean Dalmatians won't form stones."

Have any other health or breed type issues been introduced by the Backcross (BC)?

The question of breed type issues in the BC dogs is completely subjective. It appears that the distinct spotting may be related to the HUA gene as the early backcross dogs had more ticking but spotting has improved in recent years in some cases. People would need to look at the LUA Dals to decide the spotting issue for themselves.

As to whether health problems could show up from the mating of a Dalmatian to one Pointer many generations ago, this ShowDals post from Dr. James Seltzer (permission to reprint was granted by Dr. Seltzer) addresses this issue. "At 12 generations removed from the Pointer ancestor a recessive "bad" gene would have had to survive 12 meiotic recombinations. At each recombination the gene would have a 50% chance of being passed to the next generation. The chance that the "bad" gene (assuming it existed ab initio) is still present in the present generation is $(0.5)^{12}$ which is less than one chance in a thousand. Note that the U gene apparently did survive.

A List Member quotes Malcolm Willis: "If an allele is so rare that only 1 pup in 20,000 shows it, then a kennel could carry the allele for generation after generation and not be aware of it, although some intense inbreeding might bring it to the surface."

Dr. Seltzer continues, “I invite you to compute the probability of this happening. First, for 1 in 20,000 to be a meaningful statistic requires that the kennel have a population of significantly more than 20,000 dogs. Next, irrespective of inbreeding, the dog carrying the recessive gene must be paired with another dog carrying that gene. The chance for this to occur randomly is $1/20,000 \times 1/20,000 = 2.5 \times 10^{-9}$ or 2.5 chance in a billion. There were not enough Dals in all of Dalmatian history to find that gene by random matings. Certainly inbreeding modifies the probability....”

4. Is there any form of genetic engineering that could be done to introduce the LUA gene without affecting spotting?

Theoretically this could be done using germline gene transfer. In germline gene transfer, the parents' egg and sperm cells are changed with the goal of passing on the changes to their offspring. The implanted normal uric acid gene would be passed on to the puppies. According to Dr. James Seltzer (“An Overview of the Backcross Project – Part 2”, Spotter, Winter 2006) “Germline gene transfer is not being actively investigated, at least in larger animals and humans, although a great deal of discussion is being conducted about its value and desirability.

There are so many intrinsic technical difficulties and risks associated with germline gene transfer that the process does not offer a practical alternative at this time.”

Adenovirus gene vector insertion techniques have been used to successfully treat some genetic diseases, however, this has not yet been tried on the uric acid condition.

Suggestions for Research

Many of the questions dealt with a need for research and no one has ever determined what type of research is needed. In order to do the research we need to define the specifics of the research, find a researcher who is interested in doing it, finance it, and find participants. This is not an easy task.

- DCAF is currently funding a project to be conducted by Dr. Bartges to try to determine why some Dalmatians form urate stones and others do not. The study will use pairs of male siblings, one a confirmed stone former and the other who has not formed stones. The genome will be screened using a single nucleotide polymorphism (SNP) array. A 5ml sample of blood will be collected into an EDTA-containing collection tube. A microarray analysis will be performed on DNA isolated from nuclear material using a recently available DNA chip. The SNP chips will be processed at the University of Tennessee through the Affymetrix Core Facility. This initial study will probably not answer the question but will hopefully lead to other studies that can provide the answer.
- Perhaps the most critical question about LUA Dalmatians is do any of the LUA Dalmatians have stones/sediment in the bladder? This could be ascertained by doing ultrasounds of all of the living LUA Dalmatians to see if any have debris/calculi in the bladder. If there is any debris/calculi it would need to be analyzed to determine what type of stone it is. There would probably need to be follow up exams over a period of years to determine if (prove that) the LUA Dalmatians will not form uric acid stones.

What diet would be best for a Dalmatian to minimize the possibility of stones and what diet would be best for a confirmed stone former?

Is the tendency to form stones inherited, that is, are stone formers more likely to produce stone formers?

No matter what the outcome of the LUA debate, we will have the problem of trying to minimize the incidence of stone forming and/or obstruction in Dalmatians for many years to come. We can be satisfied with the status quo or we can come up with ways to get research backed answers that can improve the health of our dogs. Above all, we need to be willing to pay for those answers.