

INDEPENDENT SCIENTIFIC REVIEW DALMATIAN URINARY URIC ACID ASSESSMENTS BACKCROSS DALMATIAN PROJECT

Date

July 5, 2006

Reviewer

Irvin B. Krukenkamp, MD, FACS, FAHA
Professor of Surgery, Physiology & Biophysics, & Biomedical Engineering
Associate Dean, School of Medicine
State University of New York, Stony Brook
Chairman, Bioengineering, Technology & Surgical Sciences Study Section
National Institutes of Health, Center for Scientific Review
President, Long Island American Heart Association
Principal, The Next Generation (TNG) Dalmatians
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Task

Eva Berg, President of DCAF, approached this reviewer in person, by telephone and by electronic mail circa April through June 2006 to conduct an independent evaluation of various materials relating to Dalmatian urinary uric acid assessments and the Backcross Dalmatian project.

Reviewer's Credentials

Dr. Krukenkamp graduated with a Bachelor of Sciences degree from University of Maryland with a triple major in Physical Chemistry, Biochemistry and Zoology, and a minor in Microbiology. After completion of Medical School at University of Maryland with honors, he entered a seven year program of academic surgical training at University of Illinois and the Cook County Hospital in Chicago during which time he completed a Masters of Science degree, and performed two years of cardiac surgical large animal operative and scientific investigative work in pigs, sheep, baboons and dogs. Three years of clinical academic cardiothoracic surgical training were undertaken in the Harvard system at the New England Deaconess Hospital and the Harvard Medical School during which time Dr. Krukenkamp completed an additional year of scientific research training. He accepted an assistant professorship at Harvard and operated at the Deaconess Hospital in Boston for five years at which time he moved to New York as the Cardiothoracic Surgeon-in-Chief and Director of the Heart Center. Dr. Krukenkamp currently holds academic professorships in Surgery, Physiology and Biophysics and Biomedical Engineering. He is an Associate Dean in the School of Medicine, and is the principal investigator and collaborating investigator of four major scientific research projects in basic and

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translational extramurally funded programs. Dr. Krukenkamp's Curriculum Vitae is available upon request.

This reviewer is not a published scientific expert in canine/Dalmatian urinary stone disease, the veterinary clinical treatment of urolithiasis, or the scientific investigation of canine/Dalmatian uric acid metabolism and excretion. This reviewer is not a published scientific expert in canine/Dalmatian genetics, genomics, proteomics or gene therapy.

This reviewer is, however, a well published expert and senior scientific investigator with over 20 years of basic and clinical research experience, a history of extramural investigator initiated competitive research funding by such agencies as the NIH (National Institutes of Health), NHLBI (National Heart Lung & Blood Institute), AHA (American Heart Association), NSF (National Science Foundation) and others, and he has a publication record exceeding 200 scientific manuscripts, abstracts and national and international scientific conference presentations including a recent scientific presentation at the United Nations (June 2006).

This reviewer has served on scientific review panels for the NIH Center for Scientific Review (CSR) for over 15 years, the American Heart Association, pharmaceutical and device company panels, and on the Board of Directors of the AHA, and other companies (e.g., Astra Zeneca, Raytel & Carbomedics). This reviewer has been the chairman of many scientific review committees, and is presently the permanently appointed Chairman of the Bioengineering, Technology and Surgical Sciences (BTSS) study section at the NIH – CSR. This reviewer is the immediate past chairman of the SBIR/STTR small business innovation study section at the NIH – CSR evaluating emerging bioengineering technologies. In these capacities, this reviewer has written scientific assessments on a broad range of topics outside of the subject matter of the immediate scientific investigations in his own research laboratory. Examples of subjects covered include material sciences, engineered surface blood interfaces, genomics, gene therapy, artificial kidney and heart devices, battery technologies, plastics, steerable catheters, antimicrobial devices, hematological devices and technologies, and many others.

It is respectfully submitted that this reviewer is expert to assess scientific methodology and data, and is properly credentialed to prepare this scientific review statement.

Conflict of Interest Statement

This review was conducted independently. The reviewer had unrestricted access to documentary evidence available through electronic and printed materials. There was no monetary compensation for this report. The reviewer receives no direct or indirect benefit from the preparation of this report. Actions taken by the DCA, DCAF or any other entity with regards to the opinions and recommendations of the report have no direct effect, benefit, inducement or other persuasion to this reviewer. The report represents solely the opinions of this independent reviewer. No other persons or entities reviewed, 'pre' reviewed, edited, modified or in any way influenced these opinions. As stated above, this reviewer is not a published entity nor has he

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made any public statements, writings, lectures or other written, electronic or spoken opinions with respect to the subject matter of this report. There is, therefore, no real, apparent or perceived conflict of interest.

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Materials Reviewed

1. Bartges JW: "Studies on Urate Urolithiasis in Dalmatians". Final report, report addendum, Lay Abstract and Summary. Provided by e-mail by Eva Berg, June 2006.
2. Bartges JW, Osborne CA, Felice LJ, Unger LK, Bird KA, Koehler LA, Chen M: "Reliability of single urine and serum samples for estimation of 24-hour urinary uric acid excretion in six health Beagles". Am J Vet Res, Vol 55, No 4, April 1994.
3. Schaible, RH: "Genetic Predisposition to Purine Uroliths in Dalmatian Dogs". In Veterinary Clinics of North America, Small Animal Practice, Canine Uroliths: Etiopathogenesis, Detection, Treatment and Prevention", January, 1986.
4. Bartges JW, Osborne CA, Felice LJ, Allen TA, Brown C, Unger LK, Koehler LA, Bird KA, Chen M: "Diet effect on activity product ratios of uric acid, sodium urate, and ammonium urate in urine formed by healthy Beagles". Am J Vet Res, Vol 56, No 3, March, 1995.
5. Safra N, Schaible RH, Bannasch DL: "Linkage analysis with an interbreed backcross maps Dalmatian hyperuricosuria to CFA03". Mammalian Genome: Vol 17, 340-345, 2006.
6. Seltzer, JE: "An Overview of the Backcross Project". Heritage Dalmatian Project Website: <http://www.dalmatianheritage.com/about/Seltzer.htm>, June 2006.
7. Bannasch DL: "The Dalmatian Backcross Project". Heritage Dalmatian Project Website: <http://faculty.vetmed.ucdavis.edu/faculty/dlbannasch/lab/projects/HUU.htm>
8. Various e-mails by Eva Berg, Dr. Bartges, Dr. Seltzer, Carroll Weiss and others on Show-Dals.
9. Power Point presentation on Backcross Dalmatian project to DCA Board 2006.

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Scientific Opinions

AKC Registered Dalmatians

1. It is not valid scientifically nor statistically to report either an incidence or a prevalence statistic for Dalmatian urinary stone disease in the United States. These statistics require knowledge of the total population of Dalmatians, the total number of Dalmatians with various stone-related clinical syndromes by grouping, and the total number of Dalmatians per year presenting with those clinical syndromes by grouping. None of those data points are known for the Dalmatian population in the United States. It is valid, however, to report incidence and/or prevalence data for a given study population of Dalmatians, e.g. for a group of Dalmatians reviewed in a survey, or a group of Dalmatians undergoing a particular study by a veterinarian, scientist, breeder or others.
2. The scientific impact of this critical point is that it remains unknown what the magnitude is of the problem of Dalmatian stone disease in the United States. To be perfectly clear, it remains unknown whether clinically relevant syndromes of stone disease in Dalmatians afflicts 1%, 5%, 10% or more of Dalmatians, either in the total population of Dalmatians (prevalence) or on an annual basis (incidence) in the United States. For the casual reader, this means that it is not known with a high degree of scientific certainty whether this is a highly significant or relatively minor (from a clinical perspective) breed defect. Anecdotal reporting of the last “worst case” is always emotionally heart wrenching, but cannot be scientifically persuasive with regard to the overarching concerns of the breed.
3. Voluntary reporting (e.g., in a voluntary survey) by breeders / owners / handlers / veterinarians or others of Dalmatian stone disease and clinical syndromes by grouping is scientifically inadequate to determine incidence or prevalence statistics for the breed in the United States. Although commendable, such reporting is inherently biased both by under-reporting and over-reporting, and by incomplete reporting. In addition, as noted in #1 above, neither the total population nor the presenting population per year is known. Thus, the exact incidence and prevalence of Dalmatian stone disease and clinical syndromes in the United States is not known, and it is not possible or valid to determine these from voluntary reports through a survey instrument.
4. Again, to be perfectly clear, it is scientifically valid to report the statistical results of a survey or other collection of data if and only if such statistics (e.g., incidence, prevalence, percentages, etc.) are reported with a clear indication that they represent only the study population, which of necessity is a subpopulation of individuals. Scientifically valid reporting should clearly indicate to the casual reader that extrapolation of the results of such study or survey cannot be reasonably made to the larger population of Dalmatians in the United States because of the biases inherent in voluntary surveys or other subpopulations selected on the basis of specific criteria.

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5. Survey results and other anecdotal reports suggest that approximately one fourth to one third of Dalmatians are affected with clinical syndromes of urinary stone disease. It is equally likely that these numbers over-estimate, under-estimate, or correctly estimate both the incidence and prevalence of the problem for the general population of Dalmatians in the United States. Again, since total population statistical data are unavailable, no further scientifically valid statements can be made on these statistics. Proper reporting of these findings must indicate clearly, even to the casual reader, that extrapolation or generalization to the total population of Dalmatians in the United States is neither scientifically valid, nor appropriate. Any author who suggests that their reporting is representative of the total population of Dalmatians in the United States must publish their inclusion and exclusion criteria for the given study, their sampling methodology, power analysis and other statistical methodology to defend such a claim.
6. It is scientifically valid to estimate the converse statistic that two thirds to three quarters of Dalmatians do not exhibit clinically relevant stone disease syndromes. Again, it is equally likely that these numbers over-estimate, under-estimate, or correctly estimate both the incidence and prevalence of the disease free state for the general population of Dalmatians in the United States. However, the absolute ratio cannot be determined for the foregoing reasoning.
7. There appears to be a male preponderance for obstructive stone disease. The exact incidence and prevalence data, and the absolute relative ratio to female Dalmatians are scientifically unobtainable at this point. Male preponderance makes scientific, physiological and anatomical sense, however, due to the presence in the male of the os penis (obviously absent in the female).
8. The reviewer notes that neither in the survey, nor in any other publications on this subject is there clear data regarding the age of castration of male Dalmatians, either in a controlled disease free population, or in a population of Dalmatians with clinically relevant urinary stone disease. If these data are available in the survey, an appropriate analysis and report should be forthcoming. For physiological and anatomical considerations that are logically and medically sound, the development of the os penis is incomplete until about 12 months of age in males. Castration prior to this age impedes the development of the os penis, and the resulting immature, small os penis size may contribute to the development of clinically relevant obstructive urinary stone disease in these animals. This subgroup analysis would be very important to conduct, if possible, from the survey results as it may support the recommendation to breeders, owners and others to delay male Dalmatian castration to one year of age.
9. There appears to be a relationship between the state of hydration of the Dalmatian and the occurrence of clinically relevant, or obstructive, stone disease. Note that this reviewer avoided the use of prevalence or incidence statistics, and loosely used the term occurrence. The subgroup analyses by Dr. Bartges of the survey data revealed an inverse

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relationship (fewer cases) with feeding of kibble food that was made wet at the time of feeding. This provocative finding makes scientific sense from the physiological and biological perspective, although these persuasive data are not scientifically conclusive because of the limitations of inadequate reporting, incomplete numbers, etc. This is a fertile area for future scientific study, and despite the scientific immaturity of the data, the concept should probably be communicated to the Dalmatian community in the United States as wetting food prior to ingestion is a simple, readily adoptable method that may have significant impact on the overall health of the breed.

10. With respect to daily urinary uric acid production, the scientific report (1994) by Dr. Bartges is scientifically persuasive and accurate with regard to 24-hour collection in normal female beagles (n=6). Spot checks, or random samples relating urinary uric acid to creatinine, or other spot methods, are scientifically and convincingly proven to be inadequate for the estimation of total urinary uric acid by this peer reviewed publication. The report scientifically proves that under the conditions of study, the correlation of spot sampling methods to 24-hour total urinary uric acid levels is invalid. However, to be scientifically precise, the results of this study should NOT be extrapolated to the Dalmatian breed, as will be shown subsequently.
11. The urinary uric acid production of the normal canine, including the beagle, is approximately 15 to 40 mg per day. The Dalmatian produces 20 times more urinary uric acid per day, i.e. about 300 to 800 mg/day. In order to validate, or invalidate, spot-checking of urinary uric acid to total daily (24 hour) values in the Dalmatian, a separate study is required. The range of values extrapolation from Dr. Bartges' study exceeds one log rank (10 fold difference), and thus scientifically cannot be applied before experimental validation studies are obtained. The study in normal female beagles considers urinary uric acid levels at the low end of what is a 20 fold or higher overall range. Extrapolations of the findings of this study to the Dalmatian breed assume a linear relationship over the range of values of 24-hour urinary uric acid to the high end where Dalmatian urinary uric acid levels exist. This is NOT a valid assumption, as the statistical inference of linearity may be quite incorrect. Indeed, often in biology such relationships follow exponential or other curvilinear patterns. Thus, it is simply impossible to know what statistical function (linear, curvilinear, exponential, etc.) to use to extrapolate from the data in the report on normal female beagles by Dr. Bartges to abnormal urinary uric acid producing Dalmatians.
12. To be clear, the report in beagles is scientifically valid and well done. The extrapolation of the data to the Dalmatian dog (by others and not by Dr. Bartges) is, however, not scientifically sound until validated in the 20 fold higher range. Again for clarity, this opinion neither validates nor invalidates the use of either test, but simply identifies that the proper scientific correlative study in Dalmatians has yet to be done.

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13. To emphasize a point to be made later, the use of spot testing (UUA:UC) advocated by Dr. Schaible for the evaluation of urinary uric acid in backcrossed Dalmatians may NOT be independently valid, as proven by the study discussed above in normal female beagles, because the level of urinary uric acid in such backcrossed Dalmatians approaches that of the normal female beagle. However, to be fair to the advocates of the use of this test in litter analyses, their interest is to discriminate between backcrossed [Uu] genotype and normal Dalmatian [uu] genotype. This usage of spot urinary uric acid to urinary creatinine ratio may be scientifically valid, as will be discussed below.
14. The issue of alkalization of Dalmatian urine to increase solubility of uric acid has been considered by Dr. Bartges to be invalid because systemic alkalization actually increases urinary uric acid excretion. The increased urinary uric acid concentration in the Dalmatian bladder (or urine) exacerbates the possibility for urate crystal and stone formation. This point is raised because it can be confused with the contention of Dr. Schaible that alkalization of urine SAMPLES is important to maintain uric acid solubility for laboratory assay. Once a sample of urine is obtained, it appears scientifically valid to alkalize the sample to high pH to maintain the solubility of uric acid to facilitate a correct assay. This point is important and specific to the laboratory assay technology which in Dr. Bartes report is by High Pressure Liquid Chromatography (HPLC), and which is undefined by Dr. Schaible.
15. The current state of scientific investigation on Dalmatian urinary uric acid and stone disease appears to not be focused on the observations that a large number or percentage of Dalmatians with known high uric acid do not develop clinically relevant syndromes. Moreover, observations of the range of 24-hour urinary uric acid production in Dalmatians vary from 200 to 800 mg/day. Whether these observed variances in urinary uric acid production or clinical stone disease are under genetic control, or instead are significantly influenced by environmental factors, or quite possibly affected by hormonal or other physiological influences appears elusive. These areas would appear fertile for scientific investigation.

Backcross Dalmatians

1. The genetic defect resulting in abnormal urinary uric acid in Dalmatians appears to follow a simple Mendelian recessive inheritance pattern, akin to liver coat color in Dalmatians. AKC registered Dalmatians are homozygous recessive and may be represented as [uu]. This genotypic representation is likely to be scientifically sound, but it does not wholly explain the wide range of phenotypic expression as noted above. Dalmatian urinary uric acid daily totals vary widely from 200 to 800 mg/day. To be specific, the [uu] genotype may not completely control all of the known phenotypic defects of uric acid in the Dalmatian which include defective hepatic metabolism of purines to uric acid instead of to allantoin, defective renal tubular absorption/excretion of uric acid, and defective solubility of uric acid in urine related to specific inhibitors and

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promoters.

2. A scientifically valid hypothesis is that the [uu] genotype may control only one albeit major aspect of the defective uric acid metabolism, for example hepatic conversion of purine protein to uric acid. This makes scientific sense because other genes may also impact upon urate oxidase transcription or translation such that any individual Dalmatian may have a different genetic expression resulting in phenotypically different levels of the enzyme, and its activity, to produce the observed variances in Dalmatian daily uric acid.
3. Dr. Schaible hypothesized that producing a Dalmatian of the heterozygous genotype [Uu] would correct the uric acid defect and restore urinary uric acid levels of the progeny to normal canine levels. A single Pointer to Dalmatian backcross was conducted in 1973, and subsequent matings of offspring are presently in the 11th generation.
4. Spot urinary uric acid testing of Backcross Dalmatians has been conducted using the UUA:UC (urinary uric acid to urinary creatinine ratio) method. To be scientifically critical, this methodology has been proven inaccurate to estimate total daily urinary uric acid production by Dr. Bartges in a study of normal female beagles. The comparison with allegedly normal urinary uric acid producing Dalmatians is scientifically valid because both the Backcrossed Dalmatians and the Beagles produce (in theory) comparable levels of urinary uric acid – roughly 10 to 40 mg/day.
5. One must also be critical of the conditions of urinary uric acid assay in the 5 to 7 week old backcrossed puppies. No information is available to this reviewer regarding diet, purine level in the diet, control of calories or purine/protein percentage, state of hydration, access to water, activity level, other medications administered, time of day when sampled, urine collection methodology, urine sample volume, volume of urine, puppy weight and size, and other sampling considerations.
6. There were only two anecdotal reports available to this reviewer to evaluate the UUA:UC methodology distinguishing backcrossed “low” from backcrossed “high” uric acid puppies. In a website report by Dr. Bannasch, the results of this testing in 28 puppies is depicted graphically. Fourteen “low” and fourteen “high” puppies were compared. The author indicates that duplicate samples were studied because of the high variability in the testing results attributed to metabolism in the high uric acid backcross puppies. The statistically significant differences (by T test, $P < 0.0001$) are apparent, with a 10-fold difference in the results distinguishing the two groups. Notwithstanding the obvious variability in the “high” grouping, the error bars do not overlap. It is, however, not indicated in that document whether the error bars represent standard error of the mean (SEM) or standard deviation (SD), or whether they depict one or two deviations. This is not a small point; because if they represent only one SEM, then it is quite probable that significant overlap occurs with the “low” grouping despite the ten-fold difference in mean value. This will require clarification. In another website report, Dr. James Seltzer

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identifies the result for an August 2005 backcrossed litter of 8 pups. Again, the UUA:UC ratios depict a roughly 10-fold separation between individuals.

7. Notwithstanding the provocative data noted above, the UUA:UC results in Backcross Dalmatian puppies at 5 to 7 weeks should not be considered scientifically determinative of their urinary uric acid production. If future properly controlled investigations of the conditions under which these assays were/are made continue to identify the anecdotal reporting of a 10-fold statistically significant discrimination between individuals, then this evaluation may be entirely useful to segregate puppies at this time point.
8. It remains completely unknown, however, what the relationship is between a “low” urinary uric acid puppy by this testing technique and future urinary uric acid or stone formation probabilities in adulthood. To be specific, there were no data available to this reviewer (either anecdotal, scientific or probabilistic) that support whether the normal canine phenotype of urinary uric acid and clinical stone formation continues in to adulthood in these Backcross Dalmatians. This remains a fertile area for future investigation.
9. It should also be noted that the “low vs. high” uric acid segregation methodology based on UUA:UC spot urine sampling has not been scientifically reviewed or subjected to peer reviewed publication. This is a critically important step. Such scientific reporting will necessitate careful writing of the methodology utilized, and thereby must meet important minimum requirements for scientific and statistical review. This critique is not meant to imply that the method is invaluable, but instead is intended to clearly identify that the technique must be viewed with great caution until a future time when it is scientifically validated.
10. Doctors Safra, Schaible and Bannasch have recently reported (2006) a linkage between Backcross Dalmatian testing of urinary uric acid at 5 to 7 weeks by UUA:UC analysis and a specific genetic marker REN153PO3 located on chromosome CFAO3. This finding is particularly provocative because it hones down one genetic locus for the Dalmatian specific defect to approximately 24 candidate genes. Moreover it yields a genetic marker that may be useful to distinguish [uu] from [Uu] animals. Notwithstanding this provocative finding, one must be very cautious to not over interpret the results. Whether this marker will be proven effective to distinguish adult Dalmatians producing low uric acid from high uric acid remains to be proven.
11. The writings and presentations available for review on Backcross Dalmatians have focused upon the production of the heterozygote [Uu]. One must consider that outcross breeding to these individuals in successive generations will produce more [Uu] individuals in certain breeding lines, which if cross bred will yield homozygous [UU] Dalmatians. It is unclear to this reviewer what impact such genotype will have on phenotypic expression with respect to uric acid metabolism, urinary uric acid levels, and

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future stone formation. It is scientifically sound to expect that the [UU] genotype, as the [Uu] genotype, will be expressed phenotypically as low uric acid production. However, the impact upon other breed specific characteristics, such as spotting pattern, conformation, temperament, etc, remains to be elucidated.

12. It is also important to identify that Dr. Schaible has linked the genetic domain of the breed specific uric acid defect to the T locus, that genetic area controlling spotting or 'ticking'. Spot pattern is an extremely important type specific matter for Dalmatians. Indeed, photographs of early Backcross Dalmatians provided in a Power Point presentation to the DCA Board (May 2006) and generally available on the Internet identifies concerning deficiencies in spotting size and pattern. Photographs of a young Backcross Dalmatian Bitch taken by this reviewer at the 2006 DCA National Specialty are attached herewith, and are illustrative of the potential issue.

Overall Conclusions and Recommendations

AKC registered Dalmatians exhibit urinary uric acid production exceeding that of normal canines by approximately 20 fold. This problem leads to urinary uric acid related clinical stone disease syndromes in a minority of Dalmatians. The majority of Dalmatians do not exhibit clinically relevant stone disease syndromes. There appears to be a male preponderance, which makes scientific, biological and physiological sense because of the presence of the os penis. There appears to be a relationship with the overall hydration state of the dog, and the DCA and DCAF should consider advising Dalmatian breeders/owners/handlers/veterinarians and all others that feeding dry food to Dalmatians should be avoided. The precise incidence and prevalence of Dalmatian stone disease syndromes in the United States is unknown and likely unobtainable. Presently available urinary uric acid testing in Dalmatians has been extrapolated from data investigated in other normal breeds (the Beagle), and has not been scientifically validated in the Dalmatian where urinary uric acid levels are 20 fold higher. The pathophysiology of Dalmatian urinary uric acid and stone disease is poorly understood. New theories focused upon instantaneous urinary uric acid levels, and upon 24 hour ROC curve analysis may prove useful to develop regimes that limit stone formation. Further, characterization of promoter and inhibitor substances or conditions, including environmental conditions, may also increase the repertoire of available methods to control the Dalmatian breed specific defect. Finally, based on the comprehensive materials reviewed for this report, this reviewer is in complete agreement with a statement made by Dr. Bartges that "It would seem to me to be possible to breed 'non-back-crossed' Dalmatians and still end up with very little, if any, urate stone disease depending on the presence/absence of other environmental and genetic risk factors. It would be interesting to run through several generations in fairly closed pedigrees of 'full' Dalmatians to see if there is urate stone disease present." These and the other scientific considerations noted above should be critically evaluated, and perhaps pursued by the appropriate groupings within DCA and DCAF.

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With respect to Backcrossed Dalmatians, significant progress has been achieved since the single breeding to a Pointer in 1973. The data available to this reviewer are quite provocative. Notwithstanding the appropriate scientific considerations of some methodologies, particularly related to spot urine testing, there appears to be a reproducible method in 5 to 7 week old puppies to identify “low” uric acid producers AT THAT TIME POINT. Interestingly, quite provocative data regarding a putative genetic marker have just been reported. Whether these data hold up to appropriate scientific scrutiny over time, and whether these findings are relevant to urinary uric acid production and stone formation in ADULT Backcrossed Dalmatians remains to be evaluated. This reviewer respectfully requests the reader to maintain objectivity and appropriate skepticism with regard to these provocative results, for the reasons identified. Nevertheless, it is an inescapable conclusion that further studies, with scientific veracity, are warranted. As above, these and other scientific considerations should be critically evaluated, and perhaps pursued by appropriate groupings within the DCA and DCAF. Noteworthy in this recommendation is that appropriate scientific expertise and absence of conflicts of interest are paramount.

Two final thoughts require expression. First, this reviewer would strongly urge the DCA or DCAF to develop a certification process, akin to OFA or CERF, which would either identify high urinary uric acid producing Dalmatians phenotypically (e.g., 24 hour urinary uric acid level) or genotypically (e.g., by the presence or absence of the REN153PO3 marker). Such information could in theory be registered with the AKC. This would be one mechanism for Dalmatian breeders to address the breed specific uric acid defect in their own breed lines. This recommendation is scientifically sound, and is easily adoptable.

The second final thought is that production of the [Uu] or [UU] genotype may have desirable effects upon phenotypic expression of uric acid, but other correlated effects upon Dalmatian type, spotting pattern, conformation or temperament are as yet to be clearly catalogued or defined. It will require a highly integrative and cooperative approach amongst breeders, owners, handlers, judges, etc., which has been historically a politically and emotionally charged subject. This reviewer suggests that completely transparent data collection and presentation using such readily available media as the Internet, and the tremendous advantages of digital photography and videography, may greatly aid in the process.

This report is respectfully submitted July 5, 2006.

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**DIGITAL PHOTOGRAPHS OF BACKCROSS DALMATIAN BITCH
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