

1938

"THE INHERITANCE OF 'HIGH URIC ACID EXCRETION' IN DOGS"

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INTRODUCTION

This 1938 article is the “Pandora’s Box” of Dalmatian Urate Stone Disease. It is the famous first-telling over 73 years ago to worldwide veterinarians and geneticists that a predisposition to abnormal uric acid in Dalmatian urine was breed-specific. At the time, other breeds were known to excrete high levels of uric acid in their urine. This article introduced explanations of how and why some Dalmatians excreted elevated uric acid levels in their urine differently than how and why other dogs did.

The two Harvard geneticist-authors identified the Dalmatian basic problem of abnormal purine metabolism as being genetic. They were also the first to announce it was a recessive gene. (Abstract reminder: This is a summary of a 1938 article. None of today’s remarkably expanded knowledge of canine stone disease was known when this 1938 breakthrough article was written and published. More explosions of stone disease knowledge would first come decades later after the Minnesota Canine Stone Center was created by Dr. Carl Osborne. It was unknown in 1938, for example, that *“Urinary stone-forming should not be regarded as a single disease with a single cause. Instead, it is a syndrome of many contributing factors combining to progressively increase the risk of insoluble stones in canine urine,”* as taught today by Dr. Osborne. The 1938 revelatory article was nonetheless the impetus for motivating many veterinary researchers to explore the horizons of canine stone forming, their results quickly abolishing prevalent euthanasia as the then predominate

choice to treat dogs whose urinary streams were obstructed by stones.

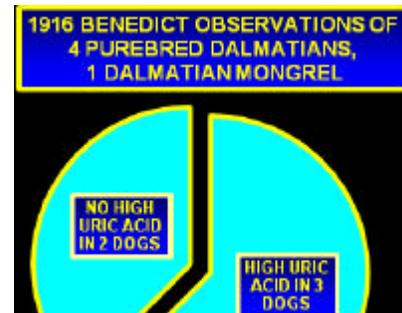
1938 ARTICLE’S REVIEW OF CANINE STONE DISEASE KNOWLEDGE

Different mammals metabolize purines differently. In some, one of many purines (insoluble uric acid) is excreted in urine, in others, purine metabolism continues beyond uric acid into other metabolites which are soluble in urine.

It had been 1914 when the first extensive study of purine metabolism by mammals took place. Man and the chimpanzee were revealed as specific

species which metabolize purines to uric acid and then excrete it in their urine.

Another equally-famous “first time” linking of Dalmatians to abnormal purine metabolism was reported in 1916 as an exception to the 1914 study.



Benedict noticed a Dalmatian on a purine-free diet but in whose urine end-products of purine metabolism did not follow that of other carnivores. He was intrigued so Benedict went further to examine the urine of 4 purebred Dalmatians and 1 Dalmatian-based mongrel. Of those 5 dogs,

3 similarly excreted high amounts of urinary uric acid, 2 did not. (The 1938 authors pointed out Benedict reported his results with these five dogs but without research details.)

The possibility one dog breed, Dalmatians, was metabolizing purines differently than other breeds stimulated immediate studies about canine purine metabolism. Wells found an enzyme formed during purine metabolism, “*uricase*” in a Dalmatian liver but this was no different than other breeds and therefore no credible explanation for the Dalmatian characteristic. Onslow tried heredity studies by outcrossing to other breeds. He bred a Dalmatian dam to a white terrier-based mongrel stud. The two resulting pups (1 male, 1 female) in turn were bred, producing a F₂ generation of 5 females and 1 male who died within a few weeks.

“...it is difficult to postulate the exact course of inheritance from the data given by this one [outcrossed] family alone...the grandfather terrier (probably of mixed breed) carried a dominant factor for destruction of uric acid; also a factor for the inhibition of spotting which is not always entirely dominant in the hybrid.”

PROTOCOL OF THE HARVARD GENETICISTS 1938 EXPERIMENTAL OUTCROSSINGS TO TWO COLLIES

definitely a characteristic of the Dalmatian breed and is inherited in this breed."

Dalmatians in this famous article came from a breedline raised in the authors' laboratories, crossed to two Collie dogs. Before breeding, all dogs were pre-tested to obtain their plateau of uric acid excretions. They were "*entirely typical*" of their breed. Cross no. 1 was a Dalmatian stud with a Collie dam. Cross no. 2 was a Dalmatian dam with a Collie stud.

Purine-free diets were fed to all dogs.

"...[uric acid levels] obtained were not influenced to a significant extent by [diet-induced] variation...provided purines were excluded."

The experiment's Dalmatian population were categorized into two groups by parameters:

1. Low-producers of uric acid (4-10 kg daily)
2. High producers of uric acid (28 or higher kg)

"In most cases, the [urine] specimens analyzed represented the metabolism of a full 24 hour period."

RESEARCH QUESTIONS INFLUENCING CONCLUSIONS

Is high uric acid hereditary?
 If so, what is the mode by which it is inherited?
 If dominant, only 1 mutant for each pair of genes?
 If recessive, both members must be mutant?
 Like many mammalian genes, are those of Dalmatians 100% dominant or 100% recessive?
 Is the uric acid gene gender-linked?
 Are co-existing multiple genetic factors required?
 Is Dalmatian spotting linked to the uric acid gene?
 If not, does it reside in the same chromosome to link that way?

RESULTS AND CONCLUSIONS

For one comparison, "*... 21 dogs from three generations in a particular family of Dalmatians*" tested out to be high uric acid producers.

"When we consider that many dogs not of the Dalmatian breed have been tested and none has been found to possess the character, these facts become more convincing and indicate that the 'high uric acid excretion' is

Two outcross breedings indicated **the mode of inheritance**. A low-uric acid Collie bitch was mated to a high-uric acid Dalmatian male. The litter of 5 males and 1 female all tested out as low-uric acid. The hybrid progeny excreted only slightly higher uric acid than their low-uric acid Collie dam. (This litter was not evaluated for spotting.)

The second experimental breeding was between a high-uric acid Dalmatian dam and a low-uric acid Collie sire. Their litter of 1 male and 4 females were all low-uric acid.

"The fact that the quantity of uric acid excreted is reduced so sharply in F₁ hybrids of Dalmatian outcrosses is sufficient to prove that the 'high uric acid excretion' is due to almost completely recessive factors..."

No intermediate grades of uric acid excretion in the 11 outcrossed hybrids was observed. The hybrids were either high-excreting or low-excreting.

Gender-linkage was ruled out by the authors on the basis of several genetic reasonings applied to analyzing an extensive pedigree chart, published as one of the article's many tabulations.

No more than two pairs of recessive genes are responsible for high-uric acid excretion, based on pedigree results when two types of backcross breedings took place. In the first, a F₁ hybrid male was crossed to two F₁ females. An additional F₃ litter was produced by crossing 2 backcrossed hybrids. In the second type, 3 F₁ females were bred back to their maternal grandfather. One F₁ male was backcrossed to his maternal grandfather's sister.

"... 'high uric acid excretion' is not determined by the same pair of genes that produces...spotting...in purebred Dalmatians."

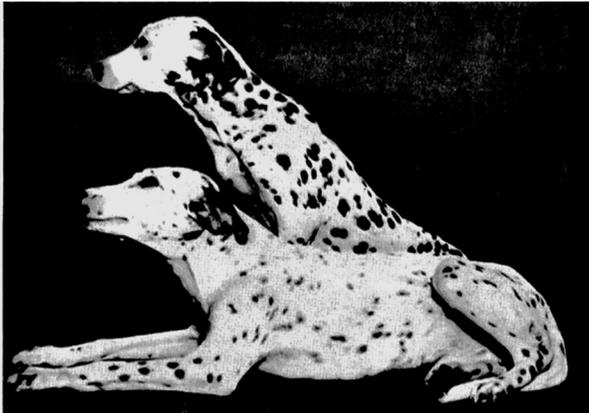
PIGMENTATION IN HYBRIDS

The authors acknowledge the sought-after spotting pigmentation in purebred Dalmatians:

1. *"The spots of the most prized [Dalmatians] are clearly defined and intensely black.*
2. *"These are sharply delimited in that there is no diffusion of pigment into the adjacent white areas.*

3. *“We do not know any cases in which pedigreed Dalmatians have white hairs interspersed among the black hairs of their pigmented spots.”*

In contrast, they observed some hybrid progeny of the experimental cross-breeding with white hairs distributed evenly among the black hairs of their pigmented spots. Such invasion of white hairs did not take place within hybrid patches. The hybrids with the diffusing white hairs *“have been consistently ‘low-producers’ of uric acid...”* High-uric acid hybrids *“have had uniform black pigment in their spots. (See photographs.)”*



LIGHT AND NORMAL DALMATIAN SPOTTING

Figure 4

In this study some of the Dalmatian segregates had diffuse spots in which white hairs were interspersed, as in the dog in front. The normal Dalmatian spots are solid black, as is shown in the other dog. The light spotting was associated with low uric acid excretion in the animals observed in these experiments.

Dalmatian-type spotting and high-uric-acid-excretion are not effects produced by the same gene, nor seem to be genetically linked by being on the same chromosome. The latter conclusion was a difficult one because the Collie breed was known to carry recessive spotting.

“This complication merely means greater variation of spotting expression in individuals bearing one or both genes for Collie spotting, in addition to one or both genes for Dalmatian spotting.”

Determining the number of involved genes used certain guidelines of evaluation:

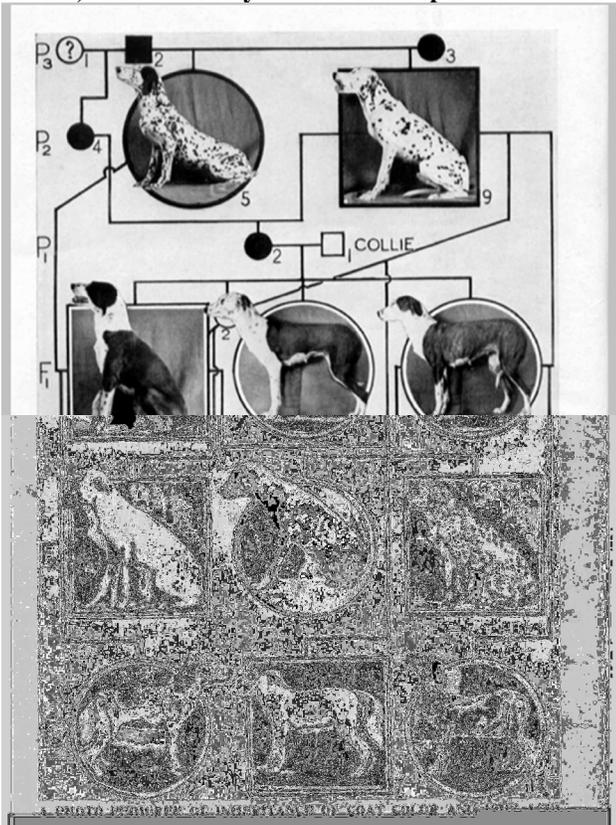
1. Two spotting genes, if the Dalmatian had a black patch on the head or the ears, *only*.
2. One spotting gene if the Dalmatian had black patches on the body *in addition* to on the head.
3. Equal numbers of both anatomical sites were expected in the backcross population.

“...we find...relatively equal numbers of pups bearing one Dalmatian spotting pattern gene and pups bearing two Dalmatian pattern genes. Of 7 pups having one Dalmatian spotting gene, 2 bear ‘low uric acid excretions’ and 5 have ‘high uric acid excretion.’ Of 8 bearing two genes for Dalmatian spotting pattern, 6 have ‘low uric acid excretion’ character and 2 have ‘high uric acid excretion.’ Of 8 bearing two genes for Dalmatian spotting pattern, 6 have ‘low uric acid excretion’ and 2 have ‘high uric acid excretion’...if any linkage existed...the four classes should be relatively equal in numbers.”

Four detailed tabulations are presented by the authors reconciling pigmentation, patches, outcrossed pups vs backcrossed pups.

“To summarize our genetic findings, we may say that ‘high uric acid excretion’ is inherited as an almost completely recessive, non-sex-linked unit character, dependent for its expression upon the presence of a single pair of Mendelizing genes...Our linkage tests indicate...the genes underlying ‘high uric acid excretion’ and [that of] the production of Dalmatian spotting are resident in independent pairs of chromosomes.”

PICTORIAL PEDIGREE SHOWING PIGMENTATION AND PATCHES PRODUCED BY HYBRID BREEDING



Dalmatians are the only reason they form urate stones. The propaganda theorizes *uric acid* and *urate stone forming* are disease synonyms, which they are not! The three U.S. stone experts are unanimous, "...*only a small percentage* [of Dalmatians with elevated uric acid levels] *form urate stones.*"

4. The exact cause of Dalmatian Uric Acid Stone Disease continues to be exasperatingly unknown, including that **abnormal uric acid is not the isolated culprit!** Most non-backcross purebred Dalmatians do **not** progress into uric acid stone forming, according to the U.S. stone experts and their 20 clinical years of diagnosing and treating a half-million stone-forming patients. Despite the unknown cause, simple preventative measures enable urate stone-forming Dalmatians to become easily symptom-free for the rest of their lifetimes. Just hydration (floating kibble in water) and minimizing purine food ingredients may be effective.

IMPORTANT April 2010 ADDENDUM

Backcross vs What is the Actual Dal "Defect?"

The past 71 years since this 1938 discovery article has not changed what is unknown and scientifically unproven as to the cause of Dalmatian Urate Stone Disease. Uric acid - alone - is **not** the cause of urate stone forming despite theoretical conjectures.

1. Fundamentally, it is **not** "*uric acid*" which is the basic Dalmatian-unique defect, but "*defective purine metabolism.*" (Insoluble uric acid is one result when Dalmatians are fed purine-yielding proteins which they digest incompletely and metabolize abnormally.)
2. Published research cites a pre-disposition to abnormal uric acid levels (note "*pre-disposition*") resulting from the underlying purine abnormality. No study in the past century of vet research has ever (repeat "*ever*") proved all Dalmatians progress beyond that inborn "*pre-disposition*" into active urate crystal/stone forming.
3. The most misleading allegation asserts - without proof - abnormal levels of uric acid in purebred