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## Estimating Disease Prevalence with Health Surveys and Genetic Screening

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### I. Background

#### A. HISTORICAL PERSPECTIVE

Most purebred dogs raised today evolved from a relatively small gene pool that established each of the original breeds (Jolly *et al.*, 1981; Patterson *et al.*, 1988; Bell, 1993; Clark and Stainer, 1994; Smith, 1994). Over the years, the common practices of line-breeding

37 dogs were abnormally excitable and 33 were aggressive or irritable (26). Another 18 were considered lethargic and 15 were unstable (erratic or unpredictable).

Other than the more commonly reported autoimmune endocrine diseases, 14 dogs had immune suppressive disorders and a few had AIHA, ITP, SLE, uveitis or VKH syndrome, pemphigus, and rheumatoid arthritis. The most common dental or mouth problems were missing teeth (40 dogs), halitosis (35), retained deciduous teeth (26), and gingivitis (21). Sebaceous cysts were commonly reported (119 dogs), and simple sebaceous adenomas affected 31 dogs. Chronic or persistent ear infections were present in 44 animals, and 19 were deaf. Food hypersensitivity (54) and intolerance (47) were also relatively common. Vaccine reactions were noted in 9 dogs and vaccine failure in 10 dogs.

Reproductive problems most commonly reported were false pregnancy (44 bitches), stillborn puppies (29), vaginitis (30), and abnormal estrous cycles (28). Eighteen males had cryptorchidism and 13 were monorchid. These data generated by bearded collie breeders were strikingly similar to those of the Old English sheepdog and are shown in Tables I–XXI.

#### D. IRISH WOLFHOUSES

The prevalence of von Willebrand's disease and thyroid disease has increased rapidly over the last decade in more than 50 affected breeds despite the collective efforts of conscientious breeders working with veterinarians to test and screen out carriers from their breeding programs. The Irish wolfhound is one of the affected breeds.

The purpose of the present screening study was to determine the prevalence of both disorders in the Irish wolfhound and examine the potential relationship between levels of von Willebrand factor antigen (vWF:Ag) and thyroid hormones in this breed. One hundred seventy-nine dogs participated in the project [the Irish Wolfhound Club of America (IWCA) Physiological Testing Program], which was held at the National Specialty Show in Newport, Rhode Island, May 14–16, 1992. Testing for von Willebrand's disease was performed at the Albany, New York laboratory of the author's associates (Dodds, 1992f); thyroid profiles were measured at the Animal Health Diagnostic Laboratory, Michigan State University, Lansing, Michigan by Dr. Ray Nachreiner and staff (Nachreiner and Refsal, 1992b), and Dr. Neil Harpster of Angell Memorial Animal Hospital in Boston, Massachusetts performed electrocardiograms at the test site. This testing pro-

gram has continued on an annual basis since then, although the aggregate results have yet to be collated and analyzed.

### *1. Age and Sex*

Of the 179 dogs screened, the age of 9 or 5% and sex of 3 or 2% were not provided. Ages were listed for 170 dogs. The youngest dog was 4 months old and the oldest was 10 years old. There were 23 puppies under a year of age, 44 adolescents between 1 and 2 years of age, and 65 adults between 2 and 5 years of age. Another 34 dogs were between 5 and 8 years of age, and 4 dogs were 8 years or older. If the number of adults from 2 to 8 years was combined, the total becomes 99 which represents 58% of those with known age that were screened. Stated another way, most (132 or 74%) of the dogs tested were less than 5 years of age. There were 75 males (43%) and 101 females (57%) among the 176 dogs where the sex was listed. Of these, 3 males were neutered and 9 females were spayed.

### *2. Familial Influence*

As the familial relationship between many of those tested was unknown, the interpretation of test results for vWF:Ag and potentially for thyroid parameters may be biased. For example, if a relatively large number of dogs from the same family, litter, sire, or dam were included, the data base could be skewed as it reflects the influence of a common genotype. If the dogs come from the same owner and environment this could also have some as yet unrecognized influence on results.

### *3. Health History*

Sixty-one dogs (34% of the 179 tested) had a history of various health problems. These included a total of 72 chronic or recurrent conditions, the majority (50 or 69%) of which involved females; only 22 (31%) were males (Table XXII). The remaining 118 dogs (66% of the 179 tested) were presumed to have been healthy throughout their lifetimes, although this is an overestimate because some participants did not complete the health questionnaire.

The most common health problem listed by respondents was chronic infections (48 dogs or 67% of the conditions listed). As was true for the total group with health problems, the majority (41 or 85%) involved females. The next most common disorders involved the reproductive tract and allergies, which affected 28 (39%) and 22 (31%) of the group, respectively. Females were represented more frequently in these cate-

TABLE XXII  
HEALTH HISTORY OF IRISH WOLFHOUSES

Rank	Condition	Number of dogs	Sex <sup>a</sup>		Frequency diseased (%)	Frequency of total ( <i>n</i> = 179,%)
			M <sup>b</sup>	F <sup>c</sup>		
1	Presumed healthy	118	50	65	—	66
2	All health problems <sup>d</sup>	72	22	50	100	40
3	Chronic infections	48	7	41	67	27
4	Reproductive disorders	28	3	25	39	16
5	Allergies	22	7	15	31	12
6	Haircoat or pigment change	13	2	11	18	7
7	Diarrhea	8	5	3	11	4
8	Thyroid disease	7	2	5	10	4
9	Arthritis	7	4	3	10	4
10	All other conditions	24	15	9	33	13

<sup>a</sup> Another 3, unknown sex.

<sup>b</sup> Male.

<sup>c</sup> Female.

<sup>d</sup> Includes those with more than one condition.

gories as well (25 or 89% and 15 or 68%, respectively). Chronic problems with hair coat and pigmentation were reported in 13 dogs (18%). Of these, 11 (85%) were females and 2 (15%) were males. Hypothyroidism was reported in 7 dogs (10% of total), and 5 were on thyroid replacement therapy when tested. The other 2 affected dogs were not receiving therapy, for reasons that are unclear. The majority of affected dogs (5 or 71%) were females (Table XXII).

Diarrhea of chronic nature was noted in 8 dogs (11%), 5 males and 3 females. Several had chronic giardiasis. Seven dogs had chronic arthritic disease, and another 24 dogs had miscellaneous conditions including chronic parasitism(8), halitosis(4), cardiac disease(3), vaccine failure and canine kennel cough(3), excessive bleeding(2), inability to maintain weight(1), seizures(1), muscle weakness(1), and liver and kidney disease(1).

Table XXIII describes the specific diseases of the four most common disease categories. Chronic infectious disorders, involving the skin (21) and reproductive tract (17), were most often reported. The most common reproductive disorder was vaginitis (15), followed by sterility or infertility (7), pseudopregnancy (7), and abnormal heat cycles (5), two cases of metritis, and one case of monorchidism. The most commonly reported allergy was to fleas (13). Changes in hair coat texture,

TABLE XXIII  
SPECIFIC DISEASES OF IRISH WOLFHOUNDS

Rank	Condition	Number of dogs <sup>a</sup>	Sex		Frequency diseased (%)	Frequency of total (n = 179,%)
			M <sup>b</sup>	F <sup>c</sup>		
1	Chronic infections	48	7	41	67	27
	Skin	21	6	15	29	12
	Reproductive tract	17	0	17	24	9
	Anal glands	7	3	4	10	4
	Ears	6	2	4	8	3
	Urinary tract	5	0	5	7	3
	Pneumonia	3	0	3	4	2
2	Reproductive disorders	28	3	25	39	16
	Vaginitis	15	0	10	21	8
	Sterility or infertility	7	2	5	10	4
	Pseudopregnancy	7	0	5	10	4
	Abnormal cycles	5	0	5	7	3
	Metritis	2	0	2	3	1
	Monorchidism	1	1	0	1	<1
3	Allergies	22	7	15	31	12
	Fleas	13	5	8	18	7
	Diet	4	0	4	6	2
	Atopy	3	0	3	4	2
	Drug (sulfonamides)	2	1	1	3	1
4	Haircoat or pigment change	13	2	11	18	7
	Poor, dry, thin coat	7	2	5	10	4
	Coat color change	4	1	3	6	2
	Vitiligo (loss of pigment)	3	0	3	4	2

<sup>a</sup> Includes those with more than one condition.

<sup>b</sup> Male.

<sup>c</sup> Female.

quality, color, and amount were the fourth most frequently noted category of health problem. Seven dogs had poor, dry, or thin coats, four had a noticeable change in coat color, and three had vitiligo (depigmentation of nose, lips, and eye rims or skin).

#### 4. von Willebrand Factor Antigen Results

Results of plasma vWF:Ag levels for the 179 dogs tested were disappointing because only 11 dogs (6%) had values within the established normal ranges. Another 57 dogs (29%) had borderline normal or equivocal test results (50–69% vWF:Ag), while the majority of Irish wolf-

hounds tested had levels below 50% (117 dogs or 65%) (Table XXIVA). The lowest test reading was 6% and the highest was 120% vWF:Ag.

As discussed earlier, results obtained from members of the same family or litter could potentially bias interpretation of the overall findings. Specifically with respect to vWF:Ag, presence of the congenital inherited form of vWD would be reflected in an increased number of affected animals within that family. As the overall number of animals having abnormal results was high in this population, it is difficult to assess potential influence of the von Willebrand's disease gene in related family members. This would be particularly relevant if an individual vWD carrier sire and several of his offspring were included in the clinic (i.e., the "founder" effect).

Twelve of the dogs tested for vWF:Ag levels had one or more previous tests. Eleven of them had levels below the normal range (less than 50%), and one was in the borderline range (50–69%) in the current study. The previous test results were identical or similar in five dogs. In this group one animal had been tested twice, one three times, and one four times previously. These five dogs have had consistently abnormal vWF:Ag levels within a narrow range of test values. In six animals results of the previous tests were higher than the present ones. In four of them, original results were within the normal range (70–88%), whereas for two dogs values were borderline normal (59–60%). Another animal that tested within the normal range 5 years ago subsequently tested below the normal range and currently had even lower levels of vWF:Ag. None of these six dogs had any significant illness noted on their health history, and none had been neutered or spayed; both sexes were represented. Thyroid function on five of the six was within normal limits, and was borderline normal on the other dog. Thus, no explanation could be found for their drop in vWF:Ag levels. Some genetic or physiological influence had presumably altered the ability of their endothelial cells to produce or release vWF protein (Dodds, 1989, 1992d; Brooks *et al.*, 1992; Panciera and Johnson, 1994). Whether this had any potential clinical significance for the future health of these dogs is unknown.

Table XXIVB provides a breakdown of the vWF:Ag levels by age (170 dogs). Of the 23 dogs less than 1 year of age at the time of testing, 10 or 43% had levels below the normal range. Another 12 or 52% were borderline normal and only 1 animal had normal levels. Of the 44 dogs between 1 and 2 years of age, 29 or 66% had abnormal levels of vWF:Ag, 14 or 32% had borderline levels, and again just 1 animal had normal levels. Of the 65 young adults between 2 and 5 years of age, 41 or 63% had low levels, 20 or 31% had borderline levels, and 4 or 6% had

TABLE XXIV  
vWF:Ag ASSAY RESULTS IN IRISH WOLFHOUNDS

A. Summary				
	Total number	Number of Dogs		
		vWF:Ag(%):	0-49	50-69
	179	117 (65%)	51 (21%)	11 (6%)
B. vWF:Ag and Age				
Years	170			
Less than 1	23	13 (57)	9 (39)	1 (4)
1-2	44	29 (66)	14 (32)	1 (2)
2-5	64	41 (64)	19 (30)	4 (6)
5-8	35	26 (74)	7 (20)	2 (6)
8+	4	4 (100)	0 —	0 —
C. vWF:Ag and Sex				
Sex	176			
Males, intact	72	50 (69)	15 (21)	7 (9)
Males, neutered	3	2 —	1 —	0 —
Females, intact	92	54 (61)	35 (35)	3 (4)
Females, spayed	9	8 —	0 —	1 —
D. vWF:Ag and Health Problems				
Condition				
Presumed healthy	118	73 (62)	35 (30)	10 (8)
All health problems <sup>a</sup>	72	52 (72)	18 (25)	2 (3)
Chronic infections	48	38	9	1
Reproductive disorders	28	22	6	0
Allergies	22	21	1	0
Haircoat or pigment change	13	11	2	0
Diarrhea	8	5	3	0
Thyroid disease	7	7	0	0
Arthritis	7	6	1	0
All other conditions	24	16	6	2
E. vWF:Ag and Thyroid Levels				
Thyroid level				
Within normal ranges <sup>b</sup>	95	63 (54)	29 (57)	3 (27)
Borderline normal <sup>c</sup>	61	39 (33)	17 (33)	5 (10)
Below normal <sup>b</sup>	23	15 (13)	5 (10)	3 (27)

<sup>a</sup> Includes those with more than one condition.

<sup>b</sup> For all 6 thyroid analytes tested.

<sup>c</sup> For one or more analytes tested.

normal levels of vWF:Ag. Of the middle aged dogs between 5 and 8 years of age, 26 or 74% had abnormal levels, 7 or 20% had borderline levels, and 2 or 6% had normal levels. All 4 dogs over 8 years of age or higher had abnormal levels of vWF:Ag.

The sex breakdown for vWF:Ag levels is shown in Table XXIVC. For the 176 animals whose sex was known, the data show no sex difference in the test results. Levels of vWF:Ag in the 118 animals presumed to be healthy are compared to those of the 61 dogs exhibiting 72 health problems in Table XXIVD. There was no significant difference between these two population groups. Thus, there did not appear to be any significant influence of age, sex or health problems on test results.

### 5. *Thyroid Profile Results*

Complete baseline thyroid profiles were run by Drs. Nachreiner and Refsal at Michigan State University (1992b). As to the question of whether the established thyroid hormone concentrations for normal dogs apply generally to all breeds, the present study assessed values for Irish wolfhounds in comparison to these reference ranges. Of the 179 animals tested at the clinic, 95 or 53% of them had values for all thyroid parameters within the normal ranges for adult dogs established by Michigan State University (Nachreiner and Refsal, 1992b; Dodds, 1992f). Another 61 or 34% of the dogs had one or more test values below these published normal limits. Twenty-three animals or 13% had levels that were all below the established normal ranges for this laboratory. In the latter instance, two of the dogs had elevated levels of T4 and T3 autoantibodies. One dog had elevated T4 and T3 autoantibodies whereas the second dog only had an elevated T3 autoantibody.

When thyroid test profiles were examined by specific analyte, all but the free T3 values appeared to have a somewhat lower distribution than the established canine reference ranges (Nachreiner and Refsal, 1992a; Refsal and Nachreiner, 1993). For example, values for the majority of the tested Irish wolfhound population (i.e., representative of their true normal range) were 15–40 nmol/liter for total T4; 1.0–1.75 nmol/liter for total T3; 6–16 pmol/liter for free T4; 1.75–3.25 pmol/liter for free T3; <20 for T4 autoantibody, and <10 for T3 autoantibody.

To determine whether other variables such as age, sex, health status, and type of heartworm preventive used affected thyroid values in this population group, separate analyses were made for each variable (Nachreiner and Refsal, 1992a). With respect to age, there was no significant population correlation seen with any of the thyroid analytes except for a trend toward lower levels in the few animals over 8

years old. However, when values for all six analytes were assessed for dogs within different age groupings, 32 or 73% of dogs between 1 and 2 years of age had all results with the reference ranges, 29 or 45% of 2–5 year olds had all normal values, and even fewer (12 or 34%) of those between 5 and 8 years of age had normal levels (Dodds, 1992f). Whether this trend represents an influence of aging on thyroid levels and/or the effect of chronic diseases such as reproductive or subclinical thyroid dysfunction is unknown (Reimers *et al.*, 1990). If these results reflected subtle early changes of thyroid disease, one would have expected an increased frequency of lower values as the animals approach midlife.

There was no influence of sex on the results for thyroid profiles whether or not the dogs were intact or neutered. Similarly, no significant differences were found among dogs taking heartworm preventives daily, monthly, or seasonally (Nachreiner and Refsal, 1992a).

Health problems are known to influence thyroid hormone concentrations (Feldman and Nelson, 1987; Ferguson, 1988; Larsson, 1988; Chastain, 1990; Nelson *et al.*, 1991; Torres *et al.*, 1991). For the 118 animals that were presumed healthy, 68 or 58% had all thyroid values within the established reference ranges. Another 32 or 27% had borderline normal levels (i.e., one or more test analyte fell below the normal range), and 18 or 15% animals had all of the analytes below the established ranges. The 61 dogs described as having 72 chronic health problems had thyroid values as follows: 30 or 42% had values in the normal range, an identical number had values in the borderline range, and 12 or 17% were below normal. While this suggests that fewer animals had thyroid values in the normal range when health problems coexisted, no significant differences were found (Dodds, 1992f; Nachreiner and Refsal, 1992a). The reasons probably reflect the relatively small numbers involved and the fact that the presumed healthy dogs included those where no information was given on the health questionnaire.

Lastly, Table XXIVE compares thyroid values and vWF:Ag levels. Of the 117 animals with abnormal levels of vWF:Ag, 63 or 54% had thyroid analytes all within the established normal ranges, 39 or 33% had borderline normal levels of thyroid hormones, and 15 or 13% had levels below the established normal limits. Similar results were obtained for the group of dogs that tested with borderline normal vWF:Ag levels (between 50 and 69%). As only a small number of animals had vWF:Ag levels in the normal ranges (70% or higher), no interpretation can be made about these data in relationship to thyroid hormone levels. These findings fail to show any significant influence of thyroid hormone concentrations on the high proportion of Irish wolfhounds in

this study population found to have abnormal or borderline normal levels of vWF:Ag. This suggested that in the Irish wolfhound breed, congenital and inherited and/or physiological influences on production of von Willebrand factor are responsible for the observed results.

The production, storage, and secretion of von Willebrand factor are known to be under complex physiological control in health and disease (Avgeris *et al.*, 1990; Panciera and Johnson, 1994). Though well established in clinical and experimental settings, the relationship between thyroid function, von Willebrand factor, and von Willebrand's disease is not well understood (Ziegler *et al.*, 1986; Dalton *et al.*, 1987; Dodds, 1988, 1989, 1992d; Brooks *et al.*, 1992; Panciera and Johnson, 1994). It would be important to follow the health status and vWF:Ag levels of this Irish wolfhound cohort as the animals age in order to assess the influence of low levels of vWF:Ag on their health and longevity.