

An epidemiological approach to prevention and control of three common heritable diseases in canine pedigree breeds in the United Kingdom

J.L.N. Wood *, K.H. Lakhani, W.E. Henley

Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU, UK

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Abstract

This paper reviews recent epidemiological research in the United Kingdom for controlling deafness in Dalmatians, glaucoma in flat coated retrievers and great Danes and hip dysplasia in flat coated retrievers, Newfoundlands, Gordon setters and Labrador retrievers. These studies assessed the prevalence of the disease, identified the factors affecting prevalence, and developed predictive statistical models of offspring/parent relationships. For each disease/breed combination, the research identified those sires and dams that might justifiably be regarded as suitable/unsuitable as potential parents in a selective breeding strategy to control or prevent the disease. Future progress in the control of these diseases is likely to come from greater understanding of their mode of inheritance. Insight, even for these complex diseases, can be derived from further detailed statistical evaluation of datasets such as those described in this paper.

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1. Introduction

Canine pedigree purebred members are predisposed to a variety of heritable diseases because these breed populations are made up of a large number of offspring from sires and/or dams that have ancestors in common. Most such diseases have no cure with afflicted offspring having a highly reduced quality of life.

Distinction can be made between diseases according to the extent to which variation in the trait of interest can be attributed to one or a few 'major genes' (Lynch and Walsh, 1998). Although some inherited disorders, such as von Willebrand's disease (Riehl et al., 2000) and progressive retinal atrophy (Holmes et al., 1999), can be attributed to the action of a single locus, many traits are multifactorial with a complex and generally unknown mode of inheritance. Quantitative geneticists often use a

polygenic model to describe the inheritance of these latter disorders, whereby the trait is assumed to be influenced by a large number of independent loci of roughly equal (and small) effect. Prevention or control of such heritable diseases requires that individuals genetically predisposed to the disease should not be used as potential parents. Developments in molecular genetic technology might, in the future, help identify such individuals, but an immediately available practical approach is to identify genetically susceptible individuals from the dog's phenotypic attributes.

This paper reviews published information on the control of several inherited diseases in pedigree dogs through selective breeding policies based on disease phenotype. In every case, the diseases (deafness in Dalmatians, glaucoma in flat coated retrievers and great Danes and hip dysplasia in Labrador retrievers, Gordon setters, Newfoundlands and flat coated retrievers) were selected because of their likely polygenic mode of inheritance, which makes the prospects for control through programmes based on single genetic marker tests less immediate. The objectives of the paper are to illustrate

* Corresponding author. Tel.: +44-1638-751000; fax: +44-1638-750794.

E-mail address: james.wood@aht.org.uk (J.L.N. Wood).

the potential benefits of taking an epidemiological approach to the control of polygenic canine diseases and to describe the progress that has been made for the three selected disorders in the UK. We review each disease in turn and end with a discussion of common issues and opportunities for further advances through the use of modern quantitative genetic techniques.

2. Deafness: in Dalmatians

Congenital deafness, a problem in several breeds of dog that carry the extreme piebald gene (Cattanach, 1999), was first reported in Dalmatians over a century ago (Rawitz, 1896). Use of the brainstem auditory evoked response (BAER) is a reliable means of testing the hearing status of Dalmatians (Strain et al., 1992; Strain, 1996; Delauche, 1996). The dogs can be categorized as *normal* (no deafness), *unilaterally deaf* (in right or left ear) or *bilaterally deaf* (completely deaf). Whilst unilaterally deaf Dalmatians can lead normal lives, dogs found to be bilaterally deaf are usually euthanased. The deafness results from the collapse of the structures of the inner ear that follows from inadequate migration, during early embryonic development, of neural crest cells, destined to be melanocytes which would normally form the sound-sensitive hair cells in the inner ear.

Research studies at the Animal Health Trust (AHT), conducted by Wood and Lakhani (1997, 1998), with collaboration from colleagues, were based on data from testing 1234 Dalmatians at three hearing testing clinics in the United Kingdom. These clinical deafness data were merged with the Kennel Club's pedigree data on 22,873 registered Dalmatians in the United Kingdom (UK). The resulting composite database contained information on deafness and other attributes of the tested Dalmatians, dams, sires and other ancestors. Detailed statistical analyses were undertaken and the results could be compared with those obtained by other researchers who had used similar analytical approaches (Anderson et al., 1968; Hayes et al., 1981; Holliday et al., 1992; Strain et al., 1992; Yuzbasiyan-Gurkan et al., 1994; Greibrokk, 1994). Wood and Lakhani (1997) also used a generalized logistic regression: logistic-binomial regression model for distinguishable data (Mauritsen, 1984; Egret, 1989), a form of multilevel modelling (Snijders and Bosker, 1999), to allow for the so-called 'litter effects' in the data i.e. the possibility that data from dogs from the same litter might be correlated. Such generalised models (Pierce and Sands, 1975; Kupper and Haseman, 1978; Williams, 1982; McCullagh and Nelder, 1989; Hosmer and Lemeshow, 1989) are now widely used in veterinary research (Curtis et al., 1993; Wood and Burrell, 1993; Mcdermott and Shukken, 1994; Mcdermott et al., 1994b; Atwill et al., 1995; Green et al., 1998; Schukken et al., 2003).

For the 1234 tested Dalmatians, Wood and Lakhani (1997) reported the overall rate of deafness to be 18.4%, of which 13.1% were unilaterally deaf and 5.3% bilaterally deaf. These figures are lower than those reported by Strain et al. (1992) who found a rate of 21.6% unilateral deafness and 8.1% bilateral deafness (29.7% overall deafness) in the USA. These results were from data from three sites, one of which had received "numerous deaf dogs specifically donated for euthanasia and anatomic studies", and this may explain the high prevalence of bilateral deafness (12.7%) at this site. Greibrokk (1994) argued that the relatively low frequency of bilateral deafness in Norway (3.6% after 1986) compared to the rates in the USA, may be due to the use of blue-eyed dogs for breeding in the USA and the absence of selection against unilateral deafness. The rate of unilateral and bilateral deafness in the UK, where breeding from animals with blue eyes is not encouraged, was also clearly lower than the rates in the USA. These figures are entirely consistent with the hypothesis, proposed by Cattanach (1999), that deafness is closely related to all phenotypic markers of melanocyte numbers (i.e. lack of iris pigment and lack of 'patching', which is the term that refers to the presence of pigmented patches at birth in Dalmatians).

Wood and Lakhani (1997) found no association between deafness in Dalmatians and location of testing or coat colour but they found a significant association between the prevalence of deafness and gender: both unilateral and bilateral deafness rates were higher in females, with a significant difference ($P = 0.014$) in overall deafness (i.e., unilateral and bilateral deafness combined). In the modelling variables based upon coat colour and locations of testing were also found to be unimportant (Wood and Lakhani, 1997).

The existing literature of the day was unclear and confused about the effects of gender on deafness in Dalmatians. Various claims included higher prevalence of deafness in male dogs (Anderson et al., 1968); increased risk of deafness among mongrel and English setter females but not in Dalmatian females (Hayes et al., 1981) and no gender effect (Strain et al., 1992). Famula et al. (1996) found the prevalence of deafness in Dalmatians (825 dogs in 111 litters) to be significantly higher in females (29%) than in males (23%). Lakhani and Wood (1997) and Wood and Lakhani (1998) have pointed out that much of the confusion was due to poor statistical interpretation of data, particularly when researchers gave full credence to 'not significant' results.

We have since analysed all data from BAER testing of Dalmatians undertaken at the Centre for Small Animal Studies, AHT. This dataset included test results from 3826 dogs presented by their owners for testing (of which 2461 dogs were successfully matched to the Kennel Club's pedigree database). While many whole litters were presented, some individual adults were also

tested. The frequencies of deafness were 6.3% bilaterally deaf and 15.0% unilaterally deaf with 7.7% of all dogs having a patch. Animals without a patch had a higher prevalence of deafness ($P < 0.001$). Males had a slightly higher rate of patching than females ($P = 0.01$), so that gender effects were examined separately for animals with and without patches. Prevalence of deafness was higher in females than males within both of the subpopulations of dogs (Table 1), although the gender effects just failed to reach significance ($P = 0.12$ and 0.06 for animals with/without patches, respectively). The overall gender effect was judged by combining these two significance probabilities using the well known result that if p_1, p_2, \dots, p_k are k independent significance probabilities then the combined significance can be assessed by the statistic $-2 \sum \log_e(p_i)$, which has a χ^2 distribution with $2k$ degrees of freedom (Kendall and Stuart, 1963).

For the present data $-2 \times [\log_e p_1 + \log_e p_2]$ should have a χ^2 distribution with 4 degrees of freedom. The calculated value of this statistic was large (9.87) and significant ($P = 0.04$).

We used an identical analytical approach to Wood and Lakhani (1997) in modelling the data described above, but compared the rates of deafness in the offspring of tested normal parents (and even grandparents) to those in the offspring of unilaterally deaf ancestors. Overall deafness was significantly higher in Dalmatians with a deaf dam, sire, dam's sire or dam's dam (Table 2); the number of tested Dalmatians with deaf paternal grandparents was too small to assess the effect of breeding when considering the status of a sire's sire or sire's dam.

Table 3 shows the final model from our analysis of the prevalence of overall deafness using generalized logistic regression with random litter effect terms. The dependent variable (Y) was: *Deaf* = 0 if the Dalmatian had normal hearing, 1 otherwise. The independent variables considered for inclusion were:

Sex = 0 if the Dalmatian was female, 1 if it was male;

Dam's hearing status = 0 if the dog's dam was tested normal, 1 if the dam was deaf;

Sire's hearing status = 0 if the dog's sire was tested normal, 1 if the sire was deaf;

Table 1

The observed number and percentage prevalence rate (\pm S.E.) of deafness categories in females, males and all Dalmatians (both sexes) separately for animals with and without patches

Deafness category	Females ^a		Males ^a		Both sexes	
	Number	Rate \pm S.E.	Number	Rate \pm S.E.	Number	Rate \pm S.E.
<i>Animals with patches</i>						
Normal	114	89.8 \pm 2.7	158	94.6 \pm 1.7	272	92.5 \pm 1.5
Overall deafness	13	10.2 \pm 2.7	9	5.4 \pm 1.7	22	7.5 \pm 1.5
Unilateral	9	7.1 \pm 2.3	9	5.4 \pm 1.7	18	6.1 \pm 1.4
Bilateral	4	3.1 \pm 1.5	0	0 \pm NA	4	1.4 \pm 0.7
Total	127	100%	167	100%	294	100%
<i>Animals without patches</i>						
Normal	1364	76.2 \pm 1.0	1373	78.9 \pm 1.0	2737	77.5 \pm 0.7
Overall deafness	426	23.8 \pm 1.0	368	21.1 \pm 1.0	795	22.5 \pm 0.7
Unilateral	302	16.9 \pm 0.9	255	14.6 \pm 0.8	557	15.8 \pm 0.8
Bilateral	124	6.9 \pm 0.6	113	6.5 \pm 0.6	238	6.7 \pm 0.4
Total	1790	100%	1741	100%	3532	100%

^a One animal with missing gender was excluded from the columns for males and females.

Table 2

The estimated percent prevalence of combined unilateral and bilateral deafness (and its standard error) for Dalmatian subsets from the AHT data defined by whether the Dalmatian's dam, sire, dam's dam or dam's sire were tested normal, compared with the prevalence of deafness when these relatives were unilaterally deaf

Parental relatives	Relative's status				Significance probability
	Tested normal		Unilaterally deaf		
	Prevalence	S.E.	Prevalence	S.E.	
Dam	18.6	0.84	32.6	3.91	<0.0001
Sire	19.3	0.85	31.1	4.24	<0.0001
Dam's dam	17.4	1.10	30.1	4.14	0.0006
Dam's sire	18.9	0.96	34.6	6.60	0.0047

Table 3

Maximum likelihood estimates of the parameters (β) from the selected generalised logistic regression model of the probability of deafness from AHT data

Model terms	Sample size	$\beta \pm$ S.E.	Odds ratio (95% confidence interval)	Significance: P
Intercept	1613	-1.59 ± 0.12		<0.001
<i>Dam's hearing status</i>				
Deaf	87	0.62 ± 0.31	1.85 (1.01, 3.40)	0.048
Normal	1526	0.00	1.00	
<i>Sire's hearing status</i>				
Deaf	86	0.88 ± 0.37	2.40 (1.16, 4.97)	0.022
Normal	1527	0.00	1.00	
<i>Patched (at birth)</i>				
Yes	118	-1.52 ± 0.43	0.22 (0.09, 0.51)	0.001
No	1495	0.00	1.00	
Random litter effect ($0, \sigma_{\text{litter}}$)		0.20 ± 0.10		0.037

Patch = 0 if the dog did not have a colour patch, 1 otherwise.

All models were fitted in SAS using PROC NLMIXED, using the approach described by Wood and Lakhani (1997).

The variable *Sex* was significant by itself ($P = 0.03$) and after the addition of *Dam's hearing status* ($P = 0.03$), but it failed to reach significance in the presence of *Sire's hearing status* ($P = 0.32$). The final model (Table 3) was further enlarged by also including *Sex* as an additional term. This enlarged model showed the coefficient for *Sex* to be -0.13 ± 0.13 and not significant ($P = 0.34$) but all the other coefficients in the model remained unchanged. *Sire's hearing status* and *Dam's hearing status* were significant when included individually and together in multivariable models. The presence of colour patching was associated with a reduction in prevalence of deafness after adjusting for the effects of parental hearing status ($P = 0.001$), consistent with the inheritance of deafness being a multifactorial trait. Our results support earlier studies that have found an association between deafness prevalence and colour patching (Strain et al., 1992; Greibrokk, 1994; Famula et al., 1996, 2000) and are consistent with the biological model, proposed by Cattanaach (1999) and referred to above, that relates deafness to the genetic mechanism responsible for low melanocyte numbers.

Wood and Lakhani (1997) echoed the recommendations of Strain et al. (1992) that breeders should ensure that *both* potential parents were tested and bilaterally hearing. This would be facilitated by using a published hearing database, and it will be of interest to British breeders that such a scheme is currently being considered by the Kennel Club. The analyses of Wood and Lakhani (1997), based on the generalized logistic-binomial regression model yielded reduced estimates for deafness prevalence: for the offspring of normal parents, the prevalence of overall deafness was 11.9% (with an

upper 95% confidence limit of 16.8%) and for bilateral deafness the prevalence estimate was 1.1% (with an upper 95% confidence limit of 3.4%). It is worth noting that Greibrokk (1994), in advocating selection against blue-eyed (and bilateral deaf) dogs, argued that "if bilateral deafness can be reduced to 3–4%" then "further measures may not be considered worthwhile". Our recent analysis of the AHT data gave consistent but slightly higher prevalence estimates for the offspring of normal parents despite the presence of dogs with patches, which were expected to have lower prevalence: a prevalence of overall deafness of 15.9% (upper confidence limit of 19.3%) and for bilateral deafness a prevalence estimate of 3.8% (upper confidence limit of 5.5%). These results clearly emphasize the benefits of breeding only from tested-normal dams and sires. Despite the recommendations to date, estimates from the AHT data of the rate of breeding from tested/untested parents are disappointing: only 41% of offspring in 2000 and 22% of offspring in 2001 came from parents where both had been tested for deafness. This contrasts with hip dysplasia where encouraging progress has been made in implementing a control scheme across a number of breeds (see below).

Insights into the mode of inheritance may assist the selection process and aid the development of DNA testing. Muhle et al. (2002) found evidence for a recessive allele at a single biallelic major locus with incomplete penetrance of the recessive homozygotes. If future studies support this hypothesis and the recessive allele is found to explain a substantial proportion of the genetic variance, then a control programme would need to incorporate genetic marker information in order to eradicate or efficiently control the disease, given that carrier animals of the recessive allele (heterozygotes) are clinically normal.

Further improvements could in theory be achieved by adopting a quantitative genetics approach, using deeper

pedigree information to calculate indices for selecting potential parents. For example, estimated breeding values (EBV) could be calculated using best linear unbiased prediction (BLUP; Lynch and Walsh, 1998) to predict random effects in a general mixed model of canine deafness. If this recommendation were taken up, it would be possible to produce EBV's for each established breeding animal. Such an approach might enable quantified benefits to be promoted and accrued from the breeding of individuals seen to have a low prevalence of deafness in their offspring (Strain et al., 1992).

Another key issue in reducing the prevalence of deafness in Dalmatians to lower levels is that breeders are most reluctant to consider using 'patched' animals in their programmes, despite the clear arguments for this being beneficial (Cattanach, 1999). This reluctance reflects the fact that, within the context of the breed standard, a patch is regarded as a defect and breeders have been trying to select against patches and hence, unwittingly, towards deafness for many years. Perhaps the fact that the star of the new Disney cartoon, the sequel to 'One Hundred and One Dalmatians' not only appears to be patched, but is also called 'Patch', might go some way to increase the popularity of these 'imperfect' dogs. Let us hope so.

3. Glaucoma: in flat coated retrievers and great Danes

Primary, 'closed angle' glaucoma is a painful, acute onset condition, associated with raised intraocular pressure leading to blindness, for which there is no effective treatment (Martin and Wyman, 1978). The most common form of primary glaucoma in dogs is 'closed angle', in contrast to man, where it is the 'open angle' form that predominates. Primary, 'open angle' glaucoma is rare in dogs, although it has been reported, for instance in elkhounds.

Goniodysgenesis (GD), or pectinate ligament dysplasia (PLD), as it has previously been described, is a congenital ocular abnormality in dogs affecting the iridocorneal angle, the presence of which is associated with the development of adult-onset glaucoma (Gelatt, 1991). Often, both eyes become affected with glaucoma, resulting in complete blindness in afflicted dogs. Affected pedigree breeds include flat coated retrievers, great Danes, golden retrievers and Welsh springer spaniels.

3.1. Flat coated retrievers

Read et al. (1998) described the results of a survey of GD (which they referred to as PLD) and glaucoma in flat coated retrievers in the UK, including the technique used for gonioscopic assessment of the degree of GD. A novel and important aspect of this work was an attempt

to grade the severity of GD by assessing the proportion of the visible irido-corneal angle affected by GD.

The data were derived from: (i) a sample of 389 flat coated retrievers with no prior evidence of ocular disease, mostly selected at dog shows, and included GD, intraocular pressure, and the presence/absence of glaucoma; (ii) a 'target' sample of 48 flat coated retrievers, which included close relatives of those flat coated retrievers which had high values of GD in the first dataset and any dogs presented with GD related primary glaucoma; and (iii) a 'control' sample of 100 GD dogs from about 30 other breeds that were selected due to their availability for examination in a private clinic for non-ophthalmic problems. The degree of GD was recorded as equally spaced values: <25% (assumed 12.5%), 25%, 37.5%, and so on in steps of 12.5%, the degree of GD could be ranked as 0, 1, 2, up to 7. The frequency of GD in flat coated retrievers was compared with that in other breeds, and the association between GD and glaucoma in flat coated retrievers determined after adjusting for the age of the animal at testing.

The frequency of GD in the 'random' sample, defined as the percentage of dogs with GD score at least 1, was 34.7% compared to a figure of 6.0% in the 'control' sample. The frequency in the 'target' sample was even higher at 83.3%. Intraocular pressure was normal in dogs unaffected with glaucoma, even if they had a high degree of GD. Ekestén and Narfström (1991, 1992) also found no significant difference in intraocular pressure of samoyeds with normal angles and that of samoyeds with dysplastic changes in the iridocorneal angle.

Wood et al. (1998) followed up the preliminary results with a detailed study to assess the heritability of GD in flat coated retrievers and to quantify the relationship between GD and glaucoma, using the above data merged with the Kennel Club database of 19,036 registered flat coated retrievers in the UK. Their objectives were to quantify the relationship between GD and glaucoma and to show that this relationship was unlikely to be spurious due to the dependence of the degree of GD upon the age of the animal. In addition, the association between the degree of GD in parents and the degree of GD in offspring was assessed and the heritability of GD estimated. Such objectives are critical for determining the usefulness of a selective breeding strategy based on breeding only from screened animals with an absence or low degree of GD.

There was a clear correlation between the degree of GD and glaucoma: out of 16 cases of glaucoma, 14 occurred when the degree of GD >75%, i.e. the ranked value of GD was >5. With respect to the effect of age on GD, they found that although the degree of GD increased with age, this increase was very slow: their regression analysis yielded the predictive model: Degree of GD = 0.383 + (0.144 × age in years). Under this model the GD score for animals born with a zero score was

expected to be 1.8 for age = 10 years, and 3.3 for age = 20 years. As the incidence of glaucoma was associated with much larger values of GD, the increase in GD with age was, on average, not large enough to cause the disease in initially totally unaffected animals. Bearing in mind that many of the cases of glaucoma in these flat coated retrievers occurred when animals were aged around six years, it could however be of significant biological importance in pushing animals from moderate classes of GD into those severe classes where glaucoma becomes likely.

Subsequent modelling confirmed the importance of the degree of GD, but not of age, in predicting the probability of glaucoma, $P(\text{glaucoma})$.

$$P(\text{glaucoma}) = \frac{\exp(-12.95 + 2.17 \times \text{GD})}{[1 + (\exp(-12.95 + 2.17 \times \text{GD}))]} \quad (1)$$

There was a significant positive linear relationship between the degree of GD in offspring and parents; there were some differences between the genders (shown in the original paper) and the final model for offspring GD (both sexes) was based on both parental variables SGD (sire GD score) and DGD (dam GD score):

$$\text{GD} = 0.30 \times \text{SGD} + 0.43 \times \text{DGD} \quad (2)$$

These results suggested that it might be possible to have a beneficial selective breeding strategy in which the degree of GD in potential breeding dogs and bitches is measured while they are relatively young and before they are used for breeding. Selection indices could be based on the phenotypes of the selection candidate and its mate or could be extended to incorporate phenotypic information from other relatives in the pedigree (see Section 6). It is not possible to develop a similar strategy based on presence/absence of glaucoma in potential dams and sires because the onset of glaucoma occurs after the animals, particularly bitches, have passed their peak reproductive age.

The data were too sparse to directly assess the heritability of glaucoma in the flat coated retrievers, although the heritability of GD could be assessed and this was done using regression analysis of mean litter GD on mid-parental values, as well as each parent separately (Falconer and Mackay, 1995). Whichever way the data were analysed, the degree of heritability was high, being greater than 0.7 with standard errors ranging from 0.12 to 0.27 (Wood et al., 1998).

The results did not prove that GD was the actual cause of primary glaucoma in the flat coated retrievers, but they showed that GD was a highly useful clinical marker for the risk of developing glaucoma. The high values of heritability indicated that breeding from animals that have been screened and proven to have low values of GD should have a significantly beneficial effect, reducing the incidence of glaucoma to less than a fifth of the then current rate even when non-stringent

criteria were adopted (a score of 4 or less). The reduction would be even greater if a more stringent GD cut off point was chosen. Again, as in the case of deafness, further improvements might be achieved through the use of EBV's for each animal, rather than simply relying on its phenotypic attributes.

3.2. Great Danes

Wood et al. (2001) carried out a similar study in great Danes, where there is also a high frequency of primary, closed angle glaucoma. In this study, GD and glaucoma data were measured in 180 great Danes. For 30 of these animals, a further three ocular measurements (depth of the anterior chamber, vitreal body length and the total depth of the globe) were also recorded ultrasonically. All the clinical data were merged for statistical analyses with pedigree data from the 43,371 Kennel Club registered great Danes. The main difference between this work and that in flat coated retrievers was that GD was scored on a percentage scale (0–100%) rather than being graded from 0 to 7.

The objectives of the study were similar to those for flat coated retrievers (Wood et al., 1998) but an additional objective was to assess the usefulness of other ocular measurements as potential predictors of the likelihood of glaucoma in great Danes.

In this breed, regression of the degree of GD on age explained only one percent of the variation in GD values. In contrast, the degree of GD was significantly and positively associated with $P(\text{glaucoma})$: all glaucoma cases had high degree of GD (at least 60%). Their logistic regression model related the probability of glaucoma, $P(\text{glaucoma})$, to the degree of GD:

$$P(\text{glaucoma}) = \frac{\exp(-13.2 + 0.16 \times \text{GD})}{[1 + (\exp(-13.2 + 0.16 \times \text{GD}))]} \quad (3)$$

For the 30 animals with ocular measurements, the association of glaucoma was strongest and negative with the depth of the anterior chamber, X_1 ; even for this relatively small data set, there was a strong association between glaucoma and the degree of GD. The logistic relationship between $P(\text{glaucoma})$ and the depth in mm of the anterior chamber, X_1 , was:

$$P(\text{glaucoma}) = \frac{\exp(143.2 - 38.9 \times X_1)}{[1 + (\exp(143.2 - 38.9 \times X_1))]} \quad (4)$$

The regression relationship between the degree of GD and the depth of the anterior chamber, X_1 , was quadratic, namely:

$$\text{GD} = -3461.1 + 2067.2 \times X_1 - 299.9 \times X_1^2 \quad (5)$$

Because the degree of GD, measured as a percentage, must range from 0% to 100%, Eq. (5) is subject to the condition that $3.52 \text{ mm} < X_1 < 4.02 \text{ mm}$; if $X_1 < 3.52 \text{ mm}$, then $\text{GD} = 100$ and if $X_1 > 4.02 \text{ mm}$, then $\text{GD} = 0$.

There was a significant association between the degree of GD in offspring and parents and the offspring/parent regression relationship for great Danes, similar to Eq. (2) for flat coated retrievers, was:

$$GD = 0.167 \times SGD + 0.402 \times DGD. \quad (6)$$

The heritability, h^2 , of GD, based upon data from 12 pairs of parents comprising 59 offspring, was high and significant: $h^2 = 0.52$ from both parents with standard error 0.23 and $P = 0.045$ (Wood et al., 2001).

The relationships between various variables for great Danes were remarkably similar to those found in flat coated retrievers. Hence, the conclusions were also similar to those for flat coated retrievers:

- (i) A close association was found between the degree of GD in any given great Dane and the probability that it will develop glaucoma. The degree of GD was inversely related to the depth of the anterior chamber, which may also be used to predict the probability of glaucoma.
- (ii) The association between GD and glaucoma was not because of any strong correlation between GD and the covariate age of the great Dane.
- (iii) The heritability of GD in the great Dane was significant and high. This suggested, as it did for flat coated retrievers, that glaucoma might also be heritable.
- (iv) Given that heritability for glaucoma is likely to be high, selective breeding using sires and dams screened for a low degree of GD should be effective in reducing the incidence of glaucoma. As before, more complex breeding programs could be designed based on developing selection indices, such as EBV, using phenotypic data on wider pedigree relationships. Such a selective strategy can also be based upon ensuring that the anterior chamber depth values for sires and dams are large. More accurate predictions of the status of an animal for breeding could potentially be obtained by combining the information from the correlated measures, GD and anterior chamber depth, into a composite selection index.

4. Practical control of glaucoma

A great strength of the work in flat coated retrievers (Read et al., 1998; Wood et al., 1998) and great Danes (Wood et al., 2001) was that clinical measurements in each study were all taken by single experienced and well qualified ophthalmologists, so that the issue of inter-observer measurement variation did not need to be considered.

Since the publication of the work in flat coated retrievers, this breed was listed in the 1991 British Veter-

inary Association (BVA)/Kennel Club (KC) eye schemes as one that should be screened for the presence of goniodysgenesis prior to breeding. It rapidly became clear that breeders considered that there was significant variation between the results recorded by different eye panellists, each of whom examines dogs as an individual and with few easily assessed criteria by which to score them. If such schemes are to prove effective and sustainable, it is clear that there is a need for them to be based on clear and reproducible criteria with more quality control. Although this issue has been grasped by some breed clubs, it is important that it is also taken up by the BVA as the co-ordinators of the eye testing schemes.

5. Hip dysplasia: in flat coated retrievers, Newfoundlands, Gordon setters and Labrador retrievers

Hip dysplasia, or malformation of the coxofemoral joint in dogs, is a major canine health problem. The hip joint consists of a rounded femoral head lying in a cup-shaped socket, the acetabulum. Surrounding soft tissues hold the bones together, and the looseness of these tissues can result in the dislocation or partial dislocation (subluxation) of the joint. Schnelle (1937), found a number of large dog breeds with defective hip joints, describing this condition before the Second World War. The subject was given greater publicity and the high prevalence of this condition was recognised by Schales (1956) and Henricson and Olsson (1959). Schemes were set up in Sweden, UK, USA and Germany to combat the problem. The current BVA/KC scheme (British Veterinary Association/Kennel Club, 1991) is voluntary and depends upon co-operation by dog-owners/breeders. The scheme relies on submission of radiographs from animals that are over one year old to ensure adequate skeletal maturity. The control scheme and the scoring of radiographs are described fully by Gibbs (1997), Willis (1997) and Dennis (1998). Briefly, under this scheme, nine specific radiographic features (components of the radiograph), which are considered collectively to define the condition of the coxofemoral joint, are examined by a panel of veterinarians and awarded a numerical score. These components are acetabular fossa, cranial acetabular edge, caudal acetabular edge, cranial effective acetabular rim, dorsal acetabular edge, femoral head and neck exostosis, femoral head recontouring, Norberg angle and subluxation. All components are scored on a scale from 0 (ideal) to 6 (worst) except for caudal acetabular edge, which is scored on a scale from 0 to 5. Hence, the score for each hip ranges from 0 to 53, and the total score over both hips (hip score) ranges from 0 to 106. By early 1998, over 108,000 dogs, representing 97 breeds, had been examined and scored (Dennis, 1998).

The UK scheme uses criteria to score the degree or presence of hip dysplasia that are different to those used in other countries, e.g. Sweden (Swenson et al., 1997) and different parts of the USA (Lust, 1997 and Smith, 1997). A drawback of all of the scoring systems is that none of them take into account the differing basic anatomy of the different breeds and none have been correlated quantitatively with the degree of discomfort experienced by dogs with hip dysplasia in different breeds.

With support from both the KC and the BVA, Wood, Lakhani and colleagues at the AHT have studied hip dysplasia in flat coated retrievers, Newfoundlands, Gordon setters and Labrador retrievers (Wood et al., 2000a,b, 2002; Wood and Lakhani, 2003a,b). Clinical hip score data (from the scheme) were merged with the KC pedigree database for the breed to obtain a composite data base which included information about the hip score and other attributes (sex, date of birth, age when examined, etc.) for the dog, as well as for those relatives which had been examined.

The main objectives of the research were (a) to estimate the degree of hip dysplasia in the four breeds and any effects of gender and to assess the effects of the hip dysplasia control scheme; (b) to identify any association between the offspring and parental hip scores and to develop statistical models to predict the offspring hip scores from the parental hip scores; and, importantly, (d) to estimate the heritability of hip dysplasia. The research was undertaken in order to provide scientific evidence-based breeding policies for prevention of the condition.

The values of hip scores varied with the breeds; the mean values ranged from 10 for flat coated retrievers to 30 for Newfoundlands. The results are summarised in Table 4, which also shows that, with the exception of Gordon setters, the mean hip score values were significantly higher for females compared with males. The three dominant components were cranial acetabular edge, Norberg angle and subluxation (Wood et al., 2002; Wood and Lakhani, 2003a,b). The scores for these components added up to over 60% of the hip score for Gordon setters (GS), and nearly 70% of the hip score for Labrador retrievers (LR).

The penetration of the hip dysplasia control scheme in the different breeds can be seen in Table 5. Over the years, the percentage of puppies born to tested animals rose for all four breeds. It was encouraging to note that while initially, just one parent was often tested, more latterly, both parents were much more commonly tested. The proportion of breeding animals tested was far higher than the overall proportion of dogs tested; clearly it is breeding, rather than non-breeding animals that are important when considering the possible impact of any scheme that operates through genetic improvement.

The regression modelling of offspring/parent relationships was detailed and complex (see original papers for full details). The models for LR and GS were extended to include explanatory environmental variables, such as the age of the animal at the time of examination and the month of birth of the animal, in the models as well as genetic effects due to the parental hip scores (Wood and Lakhani, 2003a,b). Table 6 shows examples of such models for LR and illustrates the benefits of such detailed modelling. The similarity of the coefficients of the parental scores in Models 1, 2 and 3 (as labelled in Table 6), and the similarity of the coefficients of the term *Period* in Models 2 and 3 indicate that the parental scores, period and age effects operated independently of one another. Predictions based on Model 3 are the sum of both genetic and environmental components. Hanssen (1991) and Ohlerth et al. (2001) have commented upon the effects of the month of birth upon hip dysplasia, but they studied this effect in isolation, ignoring the important parental effects. Nevertheless, Wood and Lakhani's (2003a,b) results on the effects of the month of birth agree *qualitatively* with the results in Hanssen (1991) and in Ohlerth et al. (2001) – “dogs born in summer or fall had significantly less CHD than dogs born in spring or winter”.

The estimates of hip score heritability are shown in Table 7. In all breeds, except Labrador retrievers, heritability was higher from dam and both parents compared with heritability from sires. The heritability estimate for Labrador retrievers was lower than the heritability estimate of about 0.55 reported by Swenson et al. (1997), but lower still in Gordon setters. For this breed, analysis of the data for the nine components separately (using data from 283 litters), showed significant heritability for four

Table 4
Number of observation used (*N*) and mean hip scores (\pm standard errors) for flat coated retrievers (FCR), Newfoundlands (NF), Gordon setters (GS) and Labrador retrievers (LR), shown using all data and for the two sexes separately

Breed	Both sexes		Male		Female		<i>P</i>
	<i>N</i>	Mean (S.E.)	<i>N</i>	Mean (S.E.)	<i>N</i>	Mean (S.E.)	
FCR	1258	9.9 (0.2)	317	9.2 (0.3)	890	10.2 (0.3)	0.02
NF	1566	30.0 (0.6)	546	28.3 (1.0)	988	30.8 (0.8)	0.05
GS	1188	25.4 (0.6)	432	27.0 (1.0)	756	24.5 (0.7)	0.03
LR	29,610	15.9 (0.2)	7754	14.9 (0.3)	21,854	16.2 (0.1)	<0.001

Table 5

Trends in the percentage of offspring born from parents where at least one parent was tested, P_1 , and where both parents were tested, P_2 , for different breeds

Year	FCR ^a		NF ^a		GS ^a		LR ^a	
	P_1	P_2	P_1	P_2	P_1	P_2	P_1	P_2
1982	1.9	0	13.3	0	29.3	4.8	7.3	0.4
1985	5.5	0	42.7	11.5	67.7	23.3	29.4	5.5
1990	35.1	6.8	69.6	23.4	82.1	54.2	53.1	21.0
1995	92.4	70.7	87.6	62.4	93.0	69.3	68.2	36.5
1999 ^b	–	–	–	–	–	–	75.9	52.0

^aFCR, flat coated retrievers; NF, Newfoundlands; GS, Gordon setters; LR, Labrador retrievers.

^bThe study extended up to 1999 for Labrador retrievers only.

Table 6

Regression models showing the dependence of hip scores of Labrador retrievers on the hip scores of parents, their months of birth and their age when scored

Model No.	Model terms	n	Parameter estimates	S.E.	P
1	Intercept	13,291	10.90	0.239	<0.0001
	Sire hip score		0.21	0.016	<0.0001
	Dam hip score		0.16	0.013	<0.0001
2	Intercept	13,291	8.47	0.475	<0.0001
	Sire hip score		0.21	0.016	<0.0001
	Dam hip score		0.16	0.013	<0.0001
	Period		1.43	0.241	<0.0001
3	Intercept	13,291	5.99	0.564	<0.0001
	Sire hip score		0.21	0.016	<0.0001
	Dam hip score		0.16	0.013	<0.0001
	Period		1.44	0.241	<0.0001
	Age ^a		0.99	0.122	<0.0001

Period, 1 for Labrador retrievers born during the four months July to October.

Period, 2 for Labrador retrievers born during the eight months November to June.

^aVariable age, year of life, e.g. age = 3 if age in years >2 but <3.

Table 7

Three estimates of heritability of hip score in flat coated retrievers, Newfoundlands, Gordon setters and Labrador retrievers by regressing offspring litter means on mid-parental score, sire's score or dam's score

Breed name and parental variable	Number of litters	Heritability ^a $h^2 \pm$ S.E.	P	Comment on heritability
<i>Flat coated retrievers</i>				
Mid-parental score	73	0.74 \pm 0.25	0.004	Very high and significant
Sire's score	73	0.41 \pm 0.50	0.49	Not significant
Dam's score	73	0.93 \pm 0.29	0.002	Very high and significant
<i>Newfoundlands</i>				
Mid-parental score	244	0.49 \pm 0.08	<0.0001	Very high and significant
Sire's score	244	0.40 \pm 0.15	0.009	High and significant
Dam's score	244	0.59 \pm 0.11	<0.0001	Very high and significant
<i>Gordon setters</i>				
Mid-parental score	287	0.21 \pm 0.11	0.04	Significant
Sire's score	287	-0.01 \pm 0.13	0.94	Zero and not significant
Dam's score	287	0.40 \pm 0.14	0.005	High and significant
<i>Labrador retrievers</i>				
Mid-parental score	7185	0.34 \pm 0.02	<0.0001	Very high and significant
Sire's score	7185	0.41 \pm 0.04	<0.0001	Very high and significant
Dam's score	7185	0.30 \pm 0.03	<0.0001	Very high and significant

^aHeritability $h^2 = b$ or $2 \times b$ depending upon whether b is the regression slope of offspring on mid-parent or one parent.

components: cranial effective acetabular rim (mid-parental = 0.21, dam = 0.30), femoral head and neck exostosis (mid-parental = 0.17, dam = 0.40), Norberg angle (mid-parental = 0.19, dam = 0.26) and subluxation (mid-parental = 0.24, dam = 0.26); but for all components the heritability from sires was not significant. In contrast, for Labrador retrievers, the significant results were: cranial acetabular edge (mid-parental = 0.17, sire = 0.17, dam = 0.18), femoral head and neck exostosis (mid-parental = 0.14, sire = 0.25), Norberg angle (mid-parental = 0.29, sire = 0.42, dam = 0.20) and subluxation (mid-parental = 0.26, sire = 0.29, dam = 0.24).

The heritability estimates shown in Table 7 were derived from unweighted regression analyses of mean litter hip score on mid-parental values, as well as each parent separately (Falconer and Mackay, 1995). Weighting each litter according to its size in the regression analysis can reduce the standard error of the heritability estimate (Lynch and Walsh, 1998). To test the impact of this refinement, we implemented an iterative algorithm, described by Lynch and Walsh (1998), whereby the weight allocated to each litter is inversely proportional to the estimated variance of the litter hip score. Overall heritability estimates were calculated for Labrador retrievers using this algorithm and were found to be very similar to the unweighted results (mid-parental = 0.35 ± 0.02 , sire = 0.43 ± 0.04 , dam = 0.31 ± 0.03). Although not material in this case, the effect of a weighted analysis could be more substantial when the sample size is smaller and/or there is a wider distribution of litter sizes (80% of the LR litters contained 1 or 2 dogs).

The main points emerging from these studies were:

- (i) For Gordon setters the hip scores were higher in males compared with females; but for all other breeds the scores were higher in females compared with males.
- (ii) Both the percentage of registered dogs tested and the percentage of the number of animals born from tested parents increased in time for all four breeds. These positive trends demonstrate the extent of the penetration of the BVA/KC hip dysplasia scheme in these breeds.
- (iii) The heritability of hip score was high and significant for all four breeds (when derived from mid-parental regressions). It was higher from dams for flat coated retrievers, Newfoundlands and Gordon setters; but higher from sires, for Labrador retrievers. The higher heritability estimates from the dam for three of the four breeds may indicate that maternal effects play a role in the development of hip dysplasia, although there is currently no plausible biological model to support this hypothesis.

Since hip-score is likely to be positively correlated with the probability of occurrence and the severity of hip dysplasia (Smith et al., 1995; Swenson et al.,

1997; Cardinett and Lust, 1997; Lust, 1997; Fluckiger et al., 1998), there is clearly a great potential for control of hip score, and hence of hip dysplasia, by selective breeding, from only those potential parents who have been examined and found to have low hip scores.

- (iv) Since 1984 it has been mandatory in Sweden that hip joint status of both parents is published before the Swedish Kennel Club (SKC) registers the puppies. Swenson et al. (1997) pointed out that these measures have led to a shift towards using only those potential sires and dams that do not have hip dysplasia, and this has been accompanied by a decreased prevalence of hip dysplasia in most breeds. Similar benefits should follow in the UK because all hip score results have been published since 1991. The changes over time in mean hip score emphasise the need for the BVA / KC scheme to publish central scores (preferably median due to the skewed nature of the hip score distributions) only from recently tested animals in all breeds, rather than historical mean values.
- (v) Further work should be done to determine the underlying pathogenesis of the environmental effects, such as month of birth and nutrition, on hip scores. In addition, it is important that an understanding of the quantitative relationships between hip score, or radiographic evidence of dysplasia, is developed by further research.
- (vi) Future breeding should be from sires and dams *both* with low hip scores; if this is done over time, then future canine populations will be from parents, grandparents and earlier parental ancestors with low hip scores. Regression models, such as those presented above, can be used to estimate the size of the gain derived from breeding from animals with low scores. More work is needed to assess the potential for deriving selection indices, such as EBV, using information from wider pedigree relationships.

The same practical issues relating to inter-observer measurement discrepancies do not exist for control of hip dysplasia as in glaucoma, as radiographs are all scored (and if challenged by breeders, re-scored) by a central panel of radiological experts. However, the schemes are not entirely fool-proof, in that dogs are identified only by their owners; it has been pointed out that the lack of independent means of identification lays the schemes open to abuse by unscrupulous dog breeders (Guilliard, 2003). As with all of the control schemes above, dedicated breeders can improve the health of their lines through following the advice, but the schemes remain voluntary and human nature thus dictates that not all dogs are likely to benefit from them.

6. Discussion

This paper has reviewed recent epidemiological research into three canine inherited disorders: deafness, glaucoma and hip dysplasia. These diseases were chosen because they represent a significant problem in the selected breeds and because their unknown, and probably polygenic, modes of inheritance make them suitable for taking an epidemiological approach to prevention and control.

The chosen method of selection was based on identification of potential parents with suitable phenotype. Such an approach requires that we first verify a clear association between the phenotypic attribute and the disease; second, we need to show that the offspring/parent relationship of the particular attribute is positive, and both biologically and statistically significant. This can provide an evidence-based selective breeding strategy under which only those potential sires and dams are selected for breeding that have been clinically examined and tested and are proven to be wholly satisfactory with respect to the phenotypic attribute. The progeny of such parents would be expected to be satisfactory with respect to the phenotypic attribute, and hence have a much-reduced likelihood of having the particular disease.

The strategy outlined above makes use of standard epidemiological methods and can be applied to any polygenic canine diseases. The impact of genetic factors is summarised through the estimation of heritability. In our previous work, heritability has been estimated from the parent–offspring regression, an approach that has several strengths: it is well understood, only requires information on offspring and parents, is not influenced by dominance nor linkage and is unbiased by selection on parents (Lynch and Walsh, 1998). In addition, given that the objective is to select parents so as to improve the offspring phenotype, it makes intuitive sense to estimate heritability directly from the parent offspring resemblance. However, this is now no longer the method of choice for the analysis of populations under arbitrary conditions, including unbalanced family sizes, assortative mating and fragmentary data from different relationship types. In particular, efficient estimates of quantitative genetic parameters, including heritability, can be obtained for extended pedigrees by fitting general mixed models with variance components estimated by restricted maximum likelihood (REML; Lynch and Walsh, 1998). These methods utilize all the relationships within the pedigree and can also account for common environmental factors. The application of these methods to the canine pedigree datasets described in this paper is an area for further research and one that we are currently undertaking.

The polygenic model assumed in this review is widely used in animal breeding and has been shown to be very

effective for predicting breeding values of candidates for selection (Martinez et al., 2000). However, the assumption of a very large number of independent loci with each locus contributing additively is only an approximation. In practice there may be one or more genes segregating in the population that have a large effect on the genetic variance (so-called ‘major genes’). The mode of action of such genetic effects can be studied using an approach known as complex segregation analysis (Lynch and Walsh, 1998). Several previous studies have used segregation analysis to identify major genes associated with canine diseases, including deafness in Dalmatians (Muhle et al., 2002; Famula et al., 1996) and epilepsy in the Belgian tervueren (Famula and Oberbauer, 2000). Despite the limitations of this approach, including the limited power of the method for detecting major genes and a lack of robustness (Go et al., 1978), knowledge of the mode of inheritance could have important implications for the design of breeding programs for the diseases considered in this review. In addition, inclusion of information on genetic markers would add power to the analyses and thereby assist with the detection of major genes (Lynch and Walsh, 1998).

In the present paper we recommend that breeding decisions be based on the phenotype of the selection candidate and its mate. This approach is sometimes referred to as a ‘mass selection’ strategy and is effective when the heritability is high, as was the case for the diseases considered. However, as has been mentioned earlier, when the heritability is low it is more effective to base selection on an index, such as the EBV, that also includes information from other relatives. EBV can be estimated by using BLUP to predict random effects from a general mixed model that includes a combination of major gene and polygenic effects (Lynch and Walsh, 1998). By utilising information on all pedigree relationships, EBV may also help to improve breeding decisions for traits, such as deafness and hip dysplasia, with high heritability and low inter-observer measurement error. The approach is likely to be less effective when making breeding decisions for goniodysgenesis, because inter-observer measurement discrepancies are likely to be significant relative to the size of genetic effects.

One of the practical benefits of quantitative genetic theory is that not only can it provide estimates of breeding value but it can also make predictions about the effectiveness of different selection strategies. We have already mentioned that the success of mass selection depends on the heritability of the traits. More generally, one can make predictions about the rate of genetic gain from a breeding strategy (Falconer and Mackay, 1995) and these predictions should play an important role in providing advice to breeders. Software is now available that uses deterministic simulation to predict response to selection on BLUP estimators of breeding values (Rut-

ten et al., 2002). Use of these predictions in evaluating breeding strategies should enable breeders to focus resources on schemes that offer the greatest potential for improvement.

Advances in molecular genetics also provide opportunities for improvements in the design of breeding programmes. In humans and in livestock these approaches are successfully used for traits with a complex mode of inheritance (QTL studies; Lynch and Walsh, 1998). Canine molecular genetic resources have improved dramatically in recent years so that this promises to be an area for useful developments in the future.

Much of the discussion in this review has concentrated on methodological aspects of developing a breeding program. However, the success of an epidemiological-based selective breeding strategy is also crucially dependent on the quality and quantity of data available. In these studies the datasets were of sufficient size to permit detailed modelling of important genetic and environmental effects. As regards data quality, non-random sampling of animals for testing can introduce bias into model parameters, unless account is taken of the ascertainment mechanism by which families are selected from the population (Lynch and Walsh, 1998). In the glaucoma study for flat coated retrievers, probands, defined as individuals causing a particular family to enter the sample, were selected with no prior evidence of ocular disease. They could therefore be considered as a random sample with respect to ophthalmic variables so that ascertainment bias was likely to be small. Selection of animals was much broader in the deafness and hip dysplasia datasets, particularly for hip dysplasia, with the vast majority of potential breeding animals being screened for the condition.

Another feature of the datasets discussed in this review was incomplete recording of phenotypic information for some litters. This is a common characteristic of animal breeding datasets with breeders often choosing not to test specific animals, often for unspecified reasons. This may have introduced some degree of sample selection bias into the prevalence estimates presented. Further work is needed to assess the impact of the sampling scheme on estimates of heritability and other genetic parameters.

In conclusion, epidemiological methods can be used to develop a practical strategy for prevention and control of polygenic canine diseases with high heritability. This review has focused on glaucoma, deafness and hip dysplasia in a number of pedigree breeds and shown how selection based on parental phenotype can lead to a reduction in disease prevalence. Further improvements could be made through the application of modern quantitative genetic techniques including the calculation of EBV and the analysis of mode of inheritance. Practical problems remain in introducing

strict selection criteria into dog breeding programs including difficulties in removing inter-observer measurement variation and ensuring owner compliance with voluntary schemes.

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References

- Anderson, H., Henricson, B., Lundquist, P.G., Wedenberg, E., Wersall, J., 1968. Genetic hearing impairment in the Dalmatian dog. *Acta Oto-laryngologica* (Suppl. 232), 1–33.
- Atwill, E.R., Mohammed, H.O., Scarlett, J.M., McCulloch, C.E., 1995. Extending the interpretation and utility of mixed effects logistic regression models. *Preventive Veterinary Medicine* 24, 187–201.
- British Veterinary Association/The Kennel Club., 1991. BVA/KC Hip Dysplasia Scoring Scheme. *Veterinary Record* 128, 63–64.
- Cardinett, G.H., Lust, G., 1997. The International Symposium on hip dysplasia and osteoarthritis in dogs. *Journal of the American Veterinary Medical Association* 210, 1417–1418.
- Cattanach, B., 1999. The 'Dalmatian dilemma': white coat colour and deafness. *Journal of Small Animal Practice* 40, 193–200.
- Curtis, C.R., Mauritsen, R.H., Kass, P.H., Salman, M.D., Erb, H.N., 1993. Ordinary versus random-effects multiple logistic regression for analyzing herd-level calf morbidity and mortality data. *Preventive Veterinary Medicine* 16, 207–222.
- Delauche, A., 1996. Brainstem auditory evoked response. A test with potential. *British Veterinary Journal* 152, 13–14.
- Dennis, R., 1998. A scheme to control hip dysplasia. *Veterinary Nursing* 13, 55–60.
- Egret, 1989. *Statistical Package User's Manual*. Statistics and Epidemiology Research Corporation, Seattle, WA.
- Ekesten, B., Narfstrom, K., 1991. Correlation of morphologic features of the iridocorneal angle to intraocular pressure in samoyeds. *American Journal of Veterinary Research* 52, 1875–1878.
- Ekesten, B., Narfstrom, K., 1992. Age-related changes in intraocular pressure and iridocorneal angle in samoyeds. *Progress in Veterinary and Comparative Ophthalmology* 2, 37–40.
- Falconer, D.S., Mackay, 1995. *Introduction to quantitative genetics*, fourth ed. Longman, London.
- Famula, T.R., Oberbauer, A.M., 2000. Segregation analysis of epilepsy in the Belgian tervueren dog. *The Veterinary Record* 147, 218–221.

- Famula, T.R., Oberbauer, A.M., Sausa, C.A., 1996. A threshold model analysis of deafness in Dalmatians. *Mammalian Genome* 7, 650–653.
- Famula, T.R., Oberbauer, A.M., Sausa, C.A., 2000. Complex segregation analysis of deafness in Dalmatians. *American Journal of Veterinary Research* 61, 550–553.
- Fluckiger, M.A., Friedrich, G.A., Binder, H., 1998. Correlation between hip joint laxity and subsequent coxarthrosis in dogs. *Journal of Veterinary Medicine* 45, 199–207.
- Gelatt, K.N., 1991. The canine glaucomas. In: Gelatt, K.N. (Ed.), *Veterinary Ophthalmology*, second ed. Lea & Febiger, Philadelphia, pp. 396–428.
- Gibbs, C., 1997. The BVA/KC oring heme for control of hip dysplasia: interpretation of criteria. *Veterinary Record* 141, 275–284.
- Go, R.C.P., Elston, R.C., Kaplan, E.B., 1978. Efficiency and robustness of pedigree segregation analysis. *American Journal of Human Genetics* 30, 28–37.
- Green, L.E., Berriatua, E., Morgan, K.L., 1998. A multi-level model of data with repeated measures of the effect of lamb diarrhoea on weight. *Preventive Veterinary Medicine* 36, 85–94.
- Greibrokk, T., 1994. Hereditary deafness in the Dalmatian: relationship to eye and coat color. *Journal of the American Animal Hospital Association* 30, 170–176.
- Guilliard, M.J., 2003. Hip dysplasia in dogs. *Veterinary Record* 152, 120.
- Hanssen, I., 1991. Hip dysplasia in dogs in relation to their month of birth. *Veterinary Record* 128, 425–426.
- Hayes, H.M., Wilson, G.P., Fenner, W.R., Wyman, M., 1981. Canine congenital deafness: epidemiologic study of 272 cases. *Journal of the American Animal Hospital Association* 17, 473–476.
- Henricson, B., Olsson, S-E., 1959. Hereditary acetabular dysplasia in German Shepherd dogs. *Journal of the American Veterinary Medical Association* 135, 207–210.
- Holliday, T.A., Nelson, H.J., Williams, D.C., Willits, N., 1992. Unilateral and bilateral brainstem auditory evoked response abnormalities in 900 Dalmatian dogs. *Journal of Veterinary Internal Medicine* 6, 166–174.
- Holmes, N.G., Wood, J.L.N., Binns, M.M., 1999. DNA markers for generalised PRA in Labrador retrievers. *Veterinary Record* 144, 160.
- Hosmer, D.W., Lemeshow, S., 1989. *Applied Logistic Regression*. Wiley, New York.
- Kendall, M.G., Stuart, A., 1963. The advanced theory of statistics. In: *Distribution Theory*, vol. 1. Charles Griffin, London. p. 394.
- Kupper, L.L., Haseman, J.K., 1978. The use of a correlated binomial model for the analysis of certain toxicological experiments. *Biometrics* 34, 69–76.
- Lakhani, K.H., Wood, J.L.N., 1997. Fundamental sampling and statistical considerations for epidemiological studies. *Epidemiologie et Sante Animale* 31–32, 13.C.54.
- Lust, G., 1997. An overview of the pathogenesis of canine hip dysplasia. *Journal of the American Veterinary Medical Association* 210, 1443–1445.
- Lynch, M., Walsh, B., 1998. *Genetics and Analysis of Quantitative Traits*. Sinauer, Sunderland, MA.
- Martin, C.L., Wyman, M., 1978. Primary glaucoma in the dog. *The Veterinary Clinics of North America. Small Animal Practice* 8, 257–286.
- Martinez, V., Bunger, L., Hill, W.G., 2000. Analysis of response to 20 generations of selection for body composition in mice: fit to infinitesimal model. *Genetics, Selection, Evolution* 32, 3–21.
- Mauritsen, R.H., 1984. *Logistic regression with random effects*. Ph.D. thesis, Department of Biostatistics, University of Washington.
- McCullagh, P., Nelder, J.A., 1989. *Generalized Linear Models*, second ed. Chapman & Hall, London.
- Mcdermott, J.J., Shukken, Y.H., 1994. A review of methods used to adjust for cluster effects in explanatory epidemiological studies of animal populations. *Preventive Veterinary Medicine* 18, 155–173.
- Mcdermott, J.J., Shukken, Y.H., Shoukri, M.M., 1994b. Study design and analytic methods for data collected from clusters of animals. *Preventive Veterinary Medicine* 18, 175–191.
- Muhle, A.C., Jaggy, A., Stricker, C., Steffen, F., Gaudenz, D., Busato, A., Kornberg, M., Srenk, P., Gaillard, C., 2002. Further contributions to the genetic aspect of congenital sensorineural deafness in Dalmatians. *The Veterinary Journal* 163, 311–318.
- Ohlerth, S., Lang, J., Busato, A., Gaillard, C., 2001. Estimation of genetic population variables for six radiographic criteria of hip dysplasia in a colony of Labrador Retrievers. *American Journal of Veterinary Research* 62, 846–852.
- Pierce, D.A., Sands, B.R., 1975. Extra-Bernoulli variation in binary data. Technical Report 46, Department of Statistics, Oregon State University.
- Rawitz, B., 1896. Gehororgan und Gehrin eines weissen Hundes mit blauen Auge. *Morphologische Arbeiten* 6, 545–554.
- Read, R.A., Wood, J.L.N., Lakhani, K.H., 1998. Pectinate ligament dysplasia (PLD) and glaucoma in flat coated retrievers. I. Objectives, technique and results of a PLD survey. *Veterinary Ophthalmology* 1, 85–90.
- Riehl, J., Okura, M., Mignot, E., Nishino, S., 2000. Inheritance of von Willebrand's disease in a colony of Doberman Pinchers. *American Journal of Veterinary Research* 61, 115–120.
- Rutten, M.J., Bijma, P., Woolliams, J.A., Van Arendonk, J.A., 2002. SelAction: software to predict selection response and rate of inbreeding in livestock breeding programs. *Journal of Heredity* 93, 456–458.
- Schales, O., 1956. Hereditary patterns in dysplasia of the hip. *North American Veterinarian* 38, 152–155.
- Schnelle, G.B., 1937. The veterinary radiologist: regional radiography – the pelvic region – Part I. *North American Veterinarian* 18, 53–56.
- Schukken, Y.H., Grohn, Y.T., Mcdermott, B., Mcdermott, J.J., 2003. Analysis of correlated discrete observations: background, examples and solutions. *Preventive Veterinary Medicine* 59, 223–240.
- Smith, G.K., 1997. Advances in diagnosing canine hip dysplasia. *Journal of the American Veterinary Medical Association* 210, 1451–1457.
- Smith, G.K., Popovitch, C.A., Gregor, T.P., Shofer, F.S., 1995. Evaluation of risk factors for degenerative joint disease associated with hip dysplasia in dogs. *Journal of the American Veterinary Medical Association* 206, 642–647.
- Snijders, T.A.B., Bosker, R.J., 1999. *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modelling*. Sage, London.
- Strain, G.M., 1996. Aetiology, prevalence and diagnosis of deafness in dogs and cats. *British Veterinary Journal* 152, 17–36.
- Strain, G.M., Kearney, M.T., Gignac, I.J., Levesque, D.C., Nelson, H.J., Tedford, B.L., Remsen, L.G., 1992. Brainstem auditory-evoked potential assessment of congenital deafness in Dalmatians: associations with phenotypic markers. *Journal of Veterinary Internal Medicine* 6, 175–182.
- Swenson, L., Audell, L., Hedhammar, A., 1997. Prevalence and inheritance of and selection for hip dysplasia in seven breeds of dogs in Sweden and benefit:cost analysis of a screening and control program. *Journal of the American Veterinary Medical Association* 210, 207–214.
- Williams, D.A., 1982. Extra-binomial variation in logistic linear models. *Applied Statistics* 31, 144–148.
- Willis, M.B., 1997. A review of the progress in canine hip dysplasia control in Britain. *Journal of the American Veterinary Medical Association* 210, 1480–1482.
- Wood, J.L.N., Burrell, M.H., 1993. Epidemiological studies with multiple episodes as outcome: a suggested analytical technique using a cohort study of respiratory disease in horses. *Proceedings of*

- the Society for Veterinary Epidemiology and Preventive Medicine 11, 213–224.
- Wood, J.L.N., Lakhani, K.H., 1997. Prevalence and prevention of deafness in the Dalmatian, assessing the effect of parental hearing status and sex using ordinary logistic and generalized random litter effects models. *The Veterinary Journal* 154, 121–133.
- Wood, J.L.N., Lakhani, K.H., 1998. Deafness in Dalmatians: does sex matter? *Preventive Veterinary Medicine* 36, 39–50.
- Wood, J.L.N., Lakhani, K.H., 2003a. Hip dysplasia in Labrador Retrievers: the effects of age at scoring. *Veterinary Record* 151, 37–40.
- Wood, J.L.N., Lakhani, K.H., 2003b. The effect of month of birth on hip dysplasia in Labrador Retrievers and Gordon Setters. *Veterinary Record* 151, 69–72.
- Wood, J.L.N., Lakhani, K.H., Dennis, R., 2000a. Heritability and epidemiology of canine hip-dysplasia score in flat coated retriever and Newfoundlands in the United Kingdom. *Preventive Veterinary Medicine* 46, 75–86.
- Wood, J.L.N., Lakhani, K.H., Dennis, R., 2000b. Heritability of canine hip-dysplasia score and its components in Gordon Setters. *Preventive Veterinary Medicine* 46, 87–97.
- Wood, J.L.N., Lakhani, K.H., Read, R.A., 1998. Pectinate ligament dysplasia (PLD) and glaucoma in flat coated Retrievers. II. Assessment of prevalence and heritability. *Veterinary Ophthalmology* 1, 91–99.
- Wood, J.L.N., Lakhani, K.H., Rogers, K., 2002. Heritability and epidemiology of canine hip-dysplasia score and its components in Labrador Retrievers in the United Kingdom. *Preventive Veterinary Medicine* 55, 95–105.
- Wood, J.L.N., Lakhani, K.H., Mason, I., Barnett, K.C., 2001. Relationship of the degree of goniodysgenesis and other ocular measurements to glaucoma in great Danes. *American Journal of Veterinary Research* 62, 1493–1499.
- Yuzbasiyan-Gurkan, V., Robinson, E., Gurkan, M., Venta, P., Brewer, G., Dolan, D., 1994. Hereditary hearing loss in Dalmatians: a candidate gene approach. Personal communication.

Book review

Diseases of Small Domestic Rodents.

V.C.G. Richardson (Ed.); Blackwell Publishing, Oxford, second edition, 2003, 272 pages (soft) ISBN 1405109211 (£24.99)

Chinchillas, chipmunks, degus, gerbils, jirds, hamsters, mice and rats are covered in alphabetical rather than taxonomic order in this small, user-friendly book. In place of guinea pigs, which the author covers in another book, and (by custom) rabbits, which are the subject of a separate BSAVA manual, Richardson's second edition includes degus and jirds, recent additions to the pet superstore. These are not yet described in detail in the larger texts, although some of these are currently under revision.

Each section includes a species outline and three chapters: husbandry and nutrition, systems and diseases, and anaesthesia and drug treatments culminating in a dosing table. Degus were used to model diabetes mellitus, which they develop if fed a diet containing simple sugars; jirds require a significantly hotter environment than do gerbils. Inevitably there is some repetition between nutrition and disease, but little information is given that is only of academic interest (except possibly chinchilla choline deficiency which is described without

giving a practical remedy). Topics about the familiar species from hand-rearing to exercise wheel design are discussed.

Omitting baseline species differences and emerging case reports on the treatment of chronic systemic disease seems a pity, but clinical pathology is seldom practicable (any blood removal from a mouse comprises more than a 'sample'). The dosing tables are well laid out but not as comprehensive as in some other books and it needs to be pointed out that many clinicians prefer not to inject into the gluteals of small animals. The anaesthesia pages mention ether, methoxyflurane and yohimbine. These agents could, I think, have been replaced with a stronger recommendation for isoflurane (safer than halothane in tiny animals where there is less control over anaesthetic depth), pulse oximetry where feasible, and injectable regimens using currently available drugs.

Despite the proliferation of animal care courses, husbandry error continues to dominate disease in rodent pets. The strength of this concise book is in its quality and quantity of applied animal health information. It will be a welcome complement to the practice bookshelf whether or not this already holds larger texts.

Henrietta Price