Hereditary Patent Ductus Arteriosus and Its Sequelae in the Dog

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ABSTRACT

Further studies of hereditary patent ductus arteriosus (PDA) in the dog show the defect to have a graded phenotypic expression. A high proportion of offspring of test matings had a fully patent ductus arteriosus, while a smaller proportion had a blind diverticulum of the ductus arteriosus which communicated with the aorta. This is considered to be a forme fruste of PDA, representing incomplete closure. Approximately 50% of pups with fully patent ductus arteriosus developed signs of left heart failure, and about 15% developed severe pulmonary hypertension with right-to-left or bidirectional shunts. Genetic analysis indicated that hereditary PDA in the dog is not a simple mendelian trait. Rather, it resembles a quasi-continuous or threshold trait with a high degree of heritability. Results were analyzed using a polygenic model with two developmental thresholds. Liability to defective closure of the ductus arteriosus increased with the proportion of the genome received from dogs with PDA. Moreover, in pups which had PDA, the incidence of serious sequelae (left heart failure and severe pulmonary hypertension) increased in a parallel fashion, suggesting that an increased liability to PDA was accompanied by an increase in the severity of the lesion.

KEY WORDS ductus diverticulum threshold trait heritability quasi-continuous trait left heart failure pulmonary hypertension vascular shunt

■ Persistent patency of the ductus arteriosus after birth (PDA) is one of the most common cardiovascular anomalies found in man (1, 2) and the dog (3-5). A number of reports of the familial occurrence of PDA have implicated genetic factors in the cause of this defect in man (6-11) but the mode of transmission and pathogenetic mechanisms involved are poorly defined. Increased consanguinity in the parents of patients with PDA has suggested that single or multiple genes of a recessive nature may be involved (6), whereas the occasional transmission of PDA through several generations has led other authors to propose a dominant mode of inheritance (8, 11). A recent investigation showed the risk of PDA in offspring of patients with surgically corrected PDA to be about 20 times that in the general population, but the data were not consistent with any simple genetic interpretation (12).

Epidemiologic studies of congenital heart disease in a veterinary clinic population have suggested that genetic factors are important in the etiology of PDA in certain breeds of dogs;
preliminary genetic studies confirmed this hypothesis (5). In the initial genetic studies, it was demonstrated that PDA, unaccompanied by other malformations, was transmitted to the offspring of affected dogs in a manner consistent with autosomal dominant inheritance.

This paper will provide more recent evidence regarding the mode of hereditary transmission of PDA in the dog and will describe the range of gross anatomic and clinical abnormalities produced in the postnatal period.

**Materials and Methods**

**BREEDING STOCK AND HUSBANDRY**

Dogs with PDA and their normal first degree relatives were donated by their owners through the Heart Station of the Veterinary Clinic of the University of Pennsylvania and through cooperating veterinarians. Most of these dogs were purchased miniature or toy poodles, or were partially of poodle ancestry. Normal dogs used in outcrosses were beagles and black and tan coonhounds not known to be related to dogs with PDA. Studies in a clinic population show the prevalence of PDA to be low in these breeds (5). Test matings were designed to determine whether PDA is transmitted as a single gene defect.

The following crosses were made:

1. Reciprocal crosses of dogs with PDA to normal dogs with no family history of PDA (PDA × N, N × PDA).
2. Crosses of normal females that were mothers or full sisters of dogs with PDA to males with PDA [N (1st Rel. PDA) × PDA].
3. Crosses between two dogs with PDA (PDA × PDA).

Although crosses 2 and 3 involved mating pairs in which both members were partially or completely of poodle ancestry, in none of the pairs did the two members have common ancestors within five generations.

In the course of the study it was discovered that the offspring of the foregoing matings could not be placed in two distinct classes as regards patenty of the ductus arteriosus. In addition to normal pups and pups with PDA, an intermediate class appeared in which the ductus arteriosus closed at the pulmonary arterial end, but remained patent over a portion of the rest of its length. This resulted in a blind ductus diverticulum (DD) which communicated with the aorta. Two males and three females with this defect were retained and used in the following crosses:

1. Reciprocal crosses of dogs with ductus diverticulum to normal dogs with no family history of PDA (DD × N and N × DD).
2. Crosses of normal females who were the first-degree relatives of dogs with PDA to males with ductus diverticulum [N (1st Rel. PDA) × DD].
3. Crosses of females with DD to males with PDA (DD × PDA).

**FIGURE 1**

Ductus diverticulum. Top: Lateral aortic angiogram of a 13-week-old male pup from a cross between a male poodle with a ductus diverticulum and a normal female coonhound. A funnel-shaped ductus diverticulum can be seen over the heart base. The distal extremity of the diverticulum extends well beyond the outer border of the aortic wall. The crista reuniens (CR) is formed by the adjacent walls of the ductus arteriosus and aorta (19). Bottom: Sagittal section of the aorta (A), ductus diverticulum, and pulmonary artery (P) of the same dog. The ductus diverticulum extends beneath the crista reuniens (CR) to about one-half the length of the ductus arteriosus.
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Cross 2 involved a moderate degree of inbreeding (average coefficient of inbreeding of the offspring 0.133). All dogs were maintained indoors under colony conditions, breeding experiments being done by artificial insemination. There was no known exposure of females to teratogenic agents and none showed signs of infectious or other disease during pregnancy.

Pups born of test matings were whelped in heated pens and weighed and examined daily for the first 6 weeks after birth. Electrocardiograms were recorded weekly in selected litters. Immunization for canine distemper and infectious canine hepatitis was carried out at 6 weeks of age. After this time, pups were observed daily and examined at intervals of approximately 1 week. Cardiac catheterization and angiocardiography were performed at 8–10 weeks of age. Following these studies, dogs not retained for further breeding experiments were killed. Complete gross postmortem examinations were performed on all pups that died or were killed; the hearts and great vessels were examined under a dissecting microscope when the pups were small. To preserve them for experiments, a number of pups with PDA were treated by surgical ligation of the ductus arteriosus.

NEONATAL DEATHS

According to previous investigations, the ductus arteriosus in the dog is anatomically closed (no longer probe patent) by the end of the first week of life, although histologic changes in the architecture of the vessel continue for some time after that (13–16). Gross anatomic or clinical evidence of patency of the ductus arteriosus beyond 1 week of age can thus reasonably be assumed to be abnormal in the dog, but patentcy prior to 1 week has uncertain significance. On this basis, only pups that survived the first week are included in the genetic analysis.

DIAGNOSTIC CRITERIA AND DEFINITIONS

In pups that survived the neonatal period but died before 8 weeks of age, final diagnosis was based on postmortem examination. All but one of these pups had unequivocal clinical and postmortem signs of PDA. Final classification of parents and offspring that survived to 8 weeks of age or beyond was based on postmortem examination or cardiac catheterization and angiocardiography or both.

Ductus Diverticulum—This malformation was diagnosed when it was demonstrated by postmor-
not have PDA or in pups that had PDA with severe pulmonary hypertension and right-to-left shunts. The syndrome was characterized by rapid, labored breathing and pulmonary rales, which had their onset between the second and the fifth week after birth. Progressive dyspnea and weight loss ensued, and affected pups invariably died before the end of the fifth week unless surgical ligation of the ductus arteriosus was carried out. On postmortem examination, the lungs were congested and edematous and there was massive enlargement of the pulmonary arteries and veins, left atrium, left ventricle, and ascending aorta.

**Results**

Forty-seven matings produced 247 pups, of which 39 (15.8%) died before 1 week of age and were excluded from this analysis. This neonatal death rate does not exceed that in other colonies of purebred dogs (17, 18). In the 208 pups that survived, postmortem or angiocardiographic evidence of a DD was found at 8 weeks of age or older in 32 (Fig. 1). In 61 other pups, the ductus arteriosus remained patent throughout its length. Of these, 52 (85.2%) had persistent left-to-right shunts (Fig. 2), and 9 (14.8%) developed severe pulmonary hypertension with right-to-left or bidirectional shunts (Fig. 3). Signs of left heart failure occurred in 30 (57.7%) of the 52 pups with left-to-right shunts: 25 died with pulmonary edema, 4 recovered following surgical ligation of the ductus arteriosus, and 1 died during surgery.

**Genetic Analysis**

The distribution of PDA and DD in the offspring of the 47 matings grouped according to parental phenotypes is shown in Table 1. Reciprocal cross differences were not significant, and these data are pooled. Combining data on all matings showed that the incidence of defective ductal closure (DD plus PDA) was not significantly different in males (45.4%) and females (44.1%), although there was a slightly higher incidence in the females of all mating types except N × DD. In further analyses, data on the sexes are combined.

The incidence of defective ductal closure in N × DD offspring (21.4%) did not differ significantly from that in N × PDA offspring.
(21.8%). Likewise, the incidence of defective ductal closure in the offspring of N (1° Rel. PDA) × DD matings (63.2%) was similar to that in N(1° Rel. PDA) × PDA matings (67.5%), indicating that dogs with DD do not differ substantially from those with PDA in their ability to transmit defective ductal closure to their offspring.

The lowest incidence of defective ductal closure occurred in the offspring of N × DD and N × PDA matings (pooled incidence, 21.7%), and the highest in the offspring of PDA × PDA matings (82.9%). The incidence is N(1° Rel. PDA) × DD and N(1° Rel. PDA) × PDA matings was intermediate (pooled incidence, 66.1%).

As noted previously (5), the near 75% incidence of defective ductal closure in the offspring of matings in which both parents have PDA, and the transmission of PDA in outcrosses to normal dogs, are superficially consistent with autosomal dominant inheritance. However, the data in Table 1 differ in two important respects from that expected under the simple dominant hypothesis:

1. Under the simple dominant hypothesis, both fully patent ductus arteriosus and DD might be considered as being due to the same single gene mutation. However, even if DD and PDA are considered as equivalent for the purpose of genetic analysis, the number of offspring manifesting these in outcrosses of PDA and DD dogs to normal dogs with no family history of PDA falls short of the 50% expected. Combining reciprocal DD × N and PDA × N matings, 23 of 106 offspring (21.7%) had evidence of defective closure of the ductus arteriosus, while 53 were expected under the simple dominant hypothesis. (X² = 33.962, P < 0.001)

2. The normal first-degree relatives of dogs with PDA, though phenotypically equivalent, are genetically quite different from normal dogs with no family history of PDA. When mated to dogs with PDA or DD, the normal first-degree relatives of dogs with PDA produced a significantly higher proportion of pups with defective ductal closure (39/59 or 66.1%) than did normal dogs with no family history of PDA (23/106 or 21.7%). The probability of this or more extreme results occurring by chance is less than 0.001 (X² = 31.860). We must, therefore, conclude that the first-degree relatives of dogs with PDA transmitted genetic factors which enhanced the probability of defective ductal closure in the offspring of such matings, but which were in themselves insufficient to produce an overt defect in ductal closure.

These findings exclude any simple genetic interpretation and are similar to the results expected if hereditary PDA is transmitted as a threshold trait. Threshold, or quasi-continuous traits, as they have been called by Grineberg (20), are more or less discrete phenotypic traits, which depend on differences at multiple gene loci and often are influenced by environmental factors. The genetic basis of threshold traits is thus polygenic, as in continuously variable "quantitative" traits such as stature.

### TABLE 1

<table>
<thead>
<tr>
<th>Parental phenotypes (reciprocal crosses pooled)</th>
<th>No. matings</th>
<th>No. surviving 7 days or more</th>
<th>No. with defective ductus</th>
</tr>
</thead>
<tbody>
<tr>
<td>D D × N</td>
<td>4</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>P D A × N</td>
<td>18</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>N (1° Rel. P D A) × D D</td>
<td>6</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>N (1° Rel. P D A) × P D A</td>
<td>7</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>D D × P D A</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>P D A × P D A</td>
<td>10</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>All matings</td>
<td>47</td>
<td>97</td>
<td>12</td>
</tr>
</tbody>
</table>

PDA = patent ductus arteriosus; DD = ductus diverticulum.
and blood pressure, but in contrast to polygenic traits which show continuous variation at the phenotypic level, threshold traits are usually considered as being either “present” or “absent.” In theory, the point of phenotypic discontinuity in threshold traits occurs when some underlying variable exceeds a critical “threshold” value.

The concept of threshold traits and methods for their analysis were introduced by Wright (21) and later extended by Falconer (22). In the present analysis, a two-threshold model was utilized. Below the first threshold, closure of the ductus arteriosus is complete and individuals are phenotypically normal. Between the first and second thresholds, there is partial closure of the ductus arteriosus, resulting in a ductus diverticulum. Beyond the second threshold, the ductus arteriosus remains open throughout its length, resulting in PDA. The two thresholds are assumed to represent critical values of some underlying variable important in closure of the ductus arteriosus, such as the concentration of some substance or the rate of growth or differentiation of some tissue element. In theory, if the variable could be measured directly, it would be found to be under polygenic control. Falconer has suggested that the underlying variable in diseases that behave as threshold traits be termed “liability,” indicating not only the innate (genetic) tendency to develop disease, but the influence of environmental factors as well (23). Liability is assumed to be continuous and normally distributed. Its genetic determinants are assumed to consist of a large number of additive genes, each of small effect, or if there are a few genes, their combined effect is supposed to be small in comparison to random environmental sources of variation.

We may think of an individual as having some liability to defective ductal closure, but beyond observing from the phenotype that he lies below, between, or above the two thresholds (normal, DD, or PDA), we cannot determine his exact location on the continuous underlying scale of liability. However, the mean liability of a group of individuals can be

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**Figure 3**

PDA with severe pulmonary hypertension. Two films from an angiogram of a 12-week-old male mixed poodle with a large PDA and severe pulmonary hypertension (pulmonary arterial pressure, 112/90 mm Hg; mean 98 mm Hg; aortic pressure, 106/50 mm Hg, mean 90 mm Hg. All pressures recorded under pentobarbital sodium anesthesia, breathing 100% oxygen). Top: Left lateral angiogram immediately after injection of contrast medium into the right ventricle. The main pulmonary artery (P) and its branches, a large patent ductus arteriosus (D), and the descending aorta (A) are shown. Bottom: Five seconds after the exposure above, contrast medium filled the left atrium (LA), left ventricle (LV), ascending aorta (A), and ductus arteriosus (D). There is some left-to-right flow of contrast medium across the ductus, as indicated by minimal filling of the pulmonary artery (P).
described in terms of its incidence of the three phenotypic classes. The underlying scale is transformed to standard deviation units by referring to tables of the normal curve. With a given incidence, a table of "probits" gives the deviation in standard deviation units of the threshold from the mean of the population (24). To compare different groups with respect to their mean liability to defective ductal closure, the thresholds are used as fixed reference points on the scale of liability, and the mean of each group is determined in relation to these points. The two-threshold model has the advantage of allowing a comparison of standard deviations as well as means of liability (23). This possibility arises from the reasonable assumption that the distance between the two thresholds (threshold interval) represents a difference on the underlying scale which is constant from one group to another.

Threshold intervals are given in Table 2 for offspring grouped according to the proportion of genes they have in common with dogs with PDA. The threshold intervals as determined from the incidences in the three phenotypic classes do not differ significantly between groups \( (X^2 = 1.090, P > 0.80, df = 4) \), and we can assume that the various groups have the same standard deviation. A weighted threshold difference was calculated \( (0.5273) \), corresponding to a standard deviation of \( 1.8965 \pm 0.0912 \). This was used to calculate the mean liability to defective ductal closure in groups of offspring receiving different proportions of their genomes from dogs with PDA (Table 2). The distribution of liability to defective ductal closure in three groups is depicted graphically in Figure 4. The threshold between normal and ductus diverticulum is used as the origin of the scale of liability, which is marked in "threshold standard deviation units" (one unit is equal to the weighted threshold interval). The mean liability of the offspring of PDA \( \times \) PDA matings lies well above both thresholds, and the mean liability of the offspring of PDA \( \times \) N matings lies below them. The mean liability of

<table>
<thead>
<tr>
<th>Threshold Intervals and Mean of Liability to Defective Ductal Closure in Offspring Grouped According to the Proportion of Genes in Common with Dogs with PDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence (%)</strong></td>
</tr>
<tr>
<td><strong>No.</strong></td>
</tr>
<tr>
<td>0.573</td>
</tr>
<tr>
<td>0.900</td>
</tr>
<tr>
<td>1.000</td>
</tr>
<tr>
<td>0.5273</td>
</tr>
</tbody>
</table>

* Deviations of the thresholds from the mean determined from the incidence in the three phenotypic classes, using a table of probits (24). Weighted mean interval = \( \frac{1}{3} = 0.5273 \).

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Distribution of liability to defective ductal closure in the offspring of three mating types. Assuming a common standard deviation, the means given in Table 2 are used to depict the distribution of liability to defective ductal closure with respect to the two developmental thresholds in the offspring of three types of matings. The mean liability of PDA × N(1° Rel. PDA) offspring (proportion of genes in common with dogs with PDA = r = 50%) lies approximately midway between the means of PDA × PDA and PDA × N offspring (r = 1 and r = 5, respectively). This information is used to estimate the heritability of liability to defective ductal closure in the Appendix.

PDA × N(1° Rel. PDA) offspring lies between the two thresholds and approximately midway between the means of the other two groups. From this, it is seen that as the proportion of the genome derived from PDA dogs (r value) increased from 1/2 to 3/4 to 1, there was an increasing liability to defective ductal closure. This same relationship is found when offspring having other r values are considered. The liability to defective ductal closure increased with the PDA-derived proportion of the genome as would be expected in polygenic inheritance (Fig. 5).

**HERITABILITY**

Polygenic traits are notoriously susceptible to environmental variation (22). It is therefore of interest to estimate what proportion, if any, of the phenotypic variation seen in hereditary PDA is nongenetic in cause. Heritability is defined as the proportion of total phenotypic variability due to the average or additive effect of genes (heritability = h² = additive genotypic variance/total phenotypic variance = VA/VP). This measure, which excludes nonadditive sources of genetic variance (dominance and interaction), expresses the extent to which the parental phenotypes are transmitted to the offspring. Heritability values range from 0 to 1. A value of 1 attributes all of the observed phenotypic variation in a trait to the additive effects of genes.
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Heritability is estimated by regression analysis of the resemblance between relatives. In the case of hereditary PDA, the information necessary to make a rough estimate of heritability is given in Table 2 and Figure 4. The location of the mean liability of N(1° Rel. PDA) × PDA offspring with respect to the mean of N × PDA and PDA × PDA offspring is a function of heritability. If heritability has a value of 1, the mean liability of N(1° Rel. PDA) × PDA offspring should lie halfway between the other two means. As can be seen in Figure 4, this is approximately the case. The value of heritability obtained using the method in the Appendix is 1.167 ± 0.276. This value is not significantly different from 1. We may conclude from this estimate that the heritability of liability to hereditary canine PDA is high, and that under the conditions of the present experiments, environmental factors were not a major source of variation in determining liability to defective ductal closure.

RELATION OF THE INCIDENCE OF SERIOUS SEQUELAE OF PDA TO MATING TYPE

As already noted, left heart failure and severe pulmonary hypertension with right-to-left or bidirectional shunts occurred as separately identifiable sequelae to PDA in a substantial number of pups. Either of these syndromes can be considered as a sign of serious cardiovascular impairment, indicative of a PDA of large size. A higher incidence of these sequelae among PDA dogs of one group than another would, other factors being equal, suggest a higher proportion of large PDA's. The distribution of left heart failure and severe pulmonary hypertension in the 61 pups with PDA is given in Table 3. Offspring were placed in three groups according to the proportion of their genomes derived from dogs with PDA: 50% or less, 50% to 75%, and 100%. The incidence of serious sequelae increased with the proportion of the genome derived from dogs with PDA. The probability of chance differences as great or greater than those observed is less than 1 in 1000 (X² = 18.776, df = 2). This may be interpreted as evidence of additive effects above the threshold, these effects becoming more severe as the whole population is shifted to the right with respect to the threshold (Fig. 4).

Discussion

The results of this study confirm the previous indications that PDA in poodle dogs is a specific, localized developmental anomaly which is genetically determined. Preliminary test matings previously reported (5) gave results consistent with simple autosomal dominant transmission, but the more extensive studies outlined here indicate that PDA is not inherited as a simple mendelian trait. On closer examination, defective closure of the ductus arteriosus resembles a quasi-continuous or threshold trait of high heritability, both in its graded phenotypic expression and its behavior in test crosses. As the proportion of genes received from dogs with PDA increased,

<table>
<thead>
<tr>
<th>Parental phenotypes (reciprocal crosses pooled)</th>
<th>No. of pups with PDA</th>
<th>No. left heart failure</th>
<th>No. pulmonary hypertension</th>
<th>Total sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD or PDA × N</td>
<td>M 3 6 1 1 0 3 33.3</td>
<td>F 6 1 1 0 3 3 33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD or PDA × N(1° Rel. PDA) and DD × PDA</td>
<td>M 13 16 3 9 3 18 62.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA × PDA</td>
<td>M 16 7 12 4 1 1 18 78.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All matings</td>
<td>M 32 29 16 14 5 4 39 63.93</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

r = Proportion of genes the offspring have in common with dogs with PDA.

Under the hypothesis that the incidence of left heart failure and pulmonary hypertension combined is not different in the three groups, the observed or more extreme distribution would be expected with P < 0.001 (X² = 18.776, df = 2).

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there was an increase in both the incidence of defective ductal closure and the incidence of serious sequelae to PDA, indicating that an increasing liability to PDA was accompanied by an increase in the severity of the lesion. In quasi-continuous traits, an increase in the percent of abnormals usually goes together with the appearance of more severely affected individuals (20).

It should be understood that the threshold model used in the present analysis is a convenient simplification which is at the opposite extreme from fully penetrant single-gene inheritance. The results of test matings, though not consistent with single-factor inheritance and in reasonable agreement with the polygenic threshold model, do not insure that all of the conditions of the threshold model are in fact satisfied. In particular, the assumption of “a large number of genes, each of small effect,” is not proved. It might be argued that the results presented are consistent with transmission of a single dominant gene with “variable penetrance and expressivity,” but if this is so, the normal first-degree relatives of dogs with PDA must possess specific modifiers which enhance the penetrance and expressivity of that gene, while other normal dogs must have modifiers which limit its full expression. As has been pointed out by Edwards (25), the model of a single gene with penetrance may yield numerical results that are difficult or impossible to distinguish from those of the true quasi-continuous model, if the penetrance is assumed to vary with modifying genes in the genetic background. The concept of a single gene with penetrance thus approaches the true quasicontinuous model as other genes in the genetic background have an increasing influence on its expression (25).

It should also be emphasized that while the present data are consistent with a high degree of heritability, and thus indicate that environmental factors were not a major source of variability under the conditions of these experiments, they do not rule out the possibility that the genetically determined processes involved in ductal closure might be subject to
environmental variation. Particularly where genetically determined liability to PDA lies just below threshold for abnormal ductal closure, certain environmental conditions (e.g., neonatal hypoxia) might have sufficient influence on the underlying developmental mechanisms to shift the individual beyond the threshold.

The superficial resemblance to simple dominant inheritance exhibited by hereditary PDA in the dog can be explained by the polygenic threshold model when it is understood that the liability of an individual to develop a threshold trait may lie in any position with respect to the threshold at which phenotypic discontinuity occurs. When an affected animal, whose liability lies above the threshold, is mated to a normal animal, a proportion of their offspring approximating 50% may fall above the threshold, depending upon the heritability of the trait and the position of both parents' liabilities with respect to the threshold. It is also possible for the pattern of transmission of threshold traits to simulate simple recessive inheritance. If the parents are themselves clinically unaffected, but their liabilities to the trait lie near the threshold, the mean liability of their offspring will be shifted to the right of the general population, and some proportion may fall above the threshold. If that proportion is near 4%, the trait will appear to be inherited as a simple recessive in those families. An increase in the incidence of a trait with inbreeding (consanguinity) is well known as a feature of simple recessive inheritance, but it is no less characteristic of threshold traits, since the multiple genes responsible may be concentrated by the same process.

The confusing results of family studies of PDA in man also are perhaps best explained by the threshold model. The slightly increased rate of consanguinity in the parents of patients with PDA noted by Lamy et al. (6) and by Polani and Campbell (7) would be expected if the defect were inherited as a simple recessive trait, but Wilkins's observations that the incidence in siblings of patients with PDA is on the same order as that in their offspring is not consistent with that interpretation (12). Furthermore, although family pedigrees occasionally resemble dominant inheritance (8, 11), the low incidence of PDA in the offspring of patients (1.7%) is not expected with simple dominant transmission (12). These seemingly conflicting findings are, however, characteristic of threshold traits. Depending upon the mean liabilities of the parents of individual families, threshold traits behave sometimes as recessives and sometimes as dominants, but on careful examination fail to satisfy the criteria for either.

Appendix

A METHOD FOR THE ESTIMATION OF HERITABILITY OF THRESHOLD TRAITS

As pointed out by Falconer (23), an estimate of the heritability ($h^2$) of a threshold trait can be obtained from the incidence of the trait in the general population and that in the near relatives of affected individuals. Assuming a continuous, normal distribution of multiple genetic and environmental determinants with a fixed threshold beyond which individuals are affected, incidence data are converted to means on a scale of standard deviation units by referring to a table of probits (24). The scale may be thought of as one of "liability" to the trait in question. By analogy with a selection experiment, the distance along the scale between the mean liability of affected individuals in the general population and the mean of the normal individuals may be thought of as the "selection differential." The distance between the mean of the normal individuals in the population and the mean of the near-relatives of affected individuals may be considered analogous to the "response to selection," that response being a function of the degree of relationship to affected individuals and the heritability of the trait. First-degree relatives have half of their genes in common. If heritability had a value of 1 (100% of phenotypic variance due to the additive effects of genes), the mean liability of the first-degree relatives of affected individuals would be expected to lie halfway between the mean of the normal individuals in the general population and the mean of the affected individuals. If heritability was zero, the mean liability of relatives would be the same as that of the normal individuals in the general population (there would be no response to selection).

In the present analysis, accurate data on the incidence of PDA in the general dog population are not available, precluding Falconer's method of estimating the mean liabilities of either normal or
abnormal individuals. However, an estimate of the mean liability of affected animals can be obtained from the incidence of the trait in the offspring of matings between two affected individuals, and heritability can be estimated from the relative positions of this mean and the mean liabilities of two other classes of relatives.

Three types of mating must be performed, and the mean liability of each group of offspring is determined from a probit transformation of the proportion falling beyond the threshold (Table 2 and Fig. 4). Inbreeding effects are minimized by choosing mating pairs that are not closely related (in the present study, mating pairs were not related within five generations).

The three mating types selected in the present study were:

<table>
<thead>
<tr>
<th>Type of Mating</th>
<th>Liability of Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected × Affected</td>
<td>M₁</td>
</tr>
<tr>
<td>Affected × Normal (unrelated)</td>
<td>M₂</td>
</tr>
<tr>
<td>Affected × Normal (1° Rel. of Affected)</td>
<td>M₄</td>
</tr>
</tbody>
</table>

The position of M₁ on the scale of liability is assumed to represent the mean liability of affected animals. The mean liability of unrelated normal animals (M₂) is unknown. The positions of M₃ and M₄ would be expected to lie between M₁ and M₂ on the liability scale.

By analogy with a selection experiment, the following relationships are meaningful: D = M₁ - M₄ = Selection Differential. From the relationships in Figure 4 let A = M₁ - M₄ and C = M₁ - M₄.

Y₁ = the shift in the mean liability to the trait due to selection of genes for the trait. Therefore: Y₁ = D - A; this would represent the shift when affected animals are mated to normal unrelated animals. The offspring would have one-half of their genes in common with affected animals (rₐ = 0.50). Y₂ = D - C; this would represent the shift when affected animals are mated to phenotypically normal first-degree relatives of affected animals. The offspring would have three-fourths of their genes in common with affected dogs (r₄ = 0.75).

From formula 6 we obtain:

- Variance of X₁ = Var.(X₁) = 0.0995;
- Variance of X₄ = Var.(X₄) = 0.0136;
- Variance of X₃ = Var.(X₃) = 0.0370.

From formulas 4 and 5 it follows that:

- Variance of G = 16(Var.(X₃) + Var.(X₄)) = 0.8096 and,
- Variance of B = 9(Var.(X₃) + 4Var.(X₆) + Var.(X₆)) = 0.3699.

Substituting now into formula 1 we find the estimate of heritability to be:

\[ h^2 = \frac{0.817 + 1.478}{0.817 + 1.478} = 1.1669, \]

or by means of formula 2,

\[ h^2 = 1.1669, \]

and the standard error of the estimate of heritability is obtained from formula 3.

\[ SE(h^2) = \sqrt{\left(1.1669^2 \cdot \frac{0.8096}{4.84^2} + 0.3699 \cdot \frac{0.3699}{4.1478^2}\right)}, \]

\[ SE(h^2) = 0.2763. \]
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