Hereditary congenital heart defects in dogs

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ABSTRACT

Congenital heart defects is probably the most common class of malformations found in dogs, occurring with a frequency approaching 1 per cent in animals presented to veterinary clinics. The frequency is significantly higher among purebred dogs than in dogs of mixed breeding and specific anatomic malformations occur with highest frequency in certain breeds. Genetic studies of patent ductus arteriosus, pulmonic stenosis, subaortic stenosis, ventricular septal defect, tetralogy of Fallot and persistent aortic arch have confirmed that these are specific heritable defects, the genes for which are concentrated in a number of different breeds. Each of these defects is inherited in a complex manner consistent with a polygenic basis. This paper will describe evidence supporting the view that the common forms of congenital heart disease in the dog are polygenic threshold traits. The general criteria for recognition of polygenic traits and methods for their control will be discussed.

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INTRODUCTION

In both the dog and man, the group of congenital malformations referred to collectively as 'congenital heart disease' is one of the most common classes of birth defects. Estimates in human populations indicate that five to 10 per thousand live-born infants have clinically-significant malformations of the heart (Mitchell and others 1971, Dickinson and others 1981). Estimates of the frequency at birth are not available in dogs, but epidemiological studies have shown that the prevalence of clinically-detectable congenital heart disease in dogs in veterinary clinic populations is also five to 10 per thousand (Detweiler and Patterson 1965, Patterson 1968, 1971, Mulvihill and Priester 1973). In man, and to a lesser extent in the dog, the anatomic and clinical features of congenital heart disease were thoroughly described and surgical treatment had undergone remarkable advances by the mid 1960s. However, the underlying causes of this major class of birth defects were poorly understood. This paper will provide a brief account of the way the aetiology of a number of the common forms of congenital heart disease has been investigated in the dog and shown to have a major genetic component. The knowledge gained from these studies will be used to illustrate the application of a model for polygenic threshold traits. Some general recommendations will be made for the control of congenital heart disease in dogs.

EPIDEMIOLOGY OF CONGENITAL HEART DISEASE

The first attempt to determine the frequency and types of heart disease in dogs on a population basis was an epidemiological study of cardiovascular disease initiated by Detweiler in the Veterinary Clinic of the University of Pennsylvania (Detweiler and Patterson 1965, Patterson 1968, 1971). The relative frequencies of the different anatomical forms of congenital heart disease found in this population and in a later survey of other university veterinary clinics in the USA and Canada (Mulvihill and Priester 1973) are summarised in Table 1. They appear to be representative of dogs in general, at least in North America.

The importance of genetic factors in the aetiology of canine congenital heart disease was first suggested by the observation that its prevalence was significantly greater in purebred dogs (8·9 per thousand) than in mongrels (2·6 per thousand) (Patterson 1968). It was also noted that the five most common anatomical malformations did not occur with equal frequency in different breeds; certain breeds appeared to be predisposed to specific defects (Table 2). These observations gave

Table 1. Comparative frequencies of the common type of congenital heart disease in dogs

Defect	Comparative frequency (% of all congenital heart disease) University of Pennsylvania Clinic N = 276[1]	*National Cancer Institute survey N = 303[2]
Patent ductus arteriosus	25·3	31·0
Pulmonic stenosis	17·6	13·5
Aortic stenosis	12·3	3·0
Persistent right aortic arch	7·1	10·9
Ventricular septal defect	6·2	9·2
Atrial septal defect	3·7	3·0
Tetralogy of Fallot	3·4	†
Other defects	23·4	29·4
All defects	100·0	100·0

* National Cancer Institute survey includes data collected from 10 veterinary schools cooperating in a Veterinary Medical Data Program

† Tetralogy of Fallot frequency not given – included in other defects

(1) Patterson 1968

(2) Mulvihill and Priester 1973

rise to the hypothesis that patent ductus arteriosus, pulmonic stenosis, discrete subaortic stenosis, persistent right aortic arch and tetralogy of Fallot were each due to specific genes that were found predominantly in particular breeds (Patterson 1968, 1971).

GENETIC STUDIES

Family studies and breeding experiments in each of the five common forms of congenital heart disease which appeared to have a specific breed predisposition proved that each was a lesion-specific genetic defect (Patterson 1968, 1980, 1984, Patterson and others 1971, 1974, 1981, Patterson and Pyle 1971). Since the details have been extensively described, this paper will provide only some examples of the findings and a summary of the conclusions.

The most direct and informative test of the hypothesis that each of the five anatomical defects were due to the lesion-specific effects of genes were matings between two individuals of the same breed with the same anatomical defect (Table 3). The offspring of these matings had a high frequency of congenital heart disease and the type of anatomical defect was nearly always the same or developmentally related to that in the parents, confirming the validity of the hypothesis. Further breeding experiments have shown that none of the defects studied are inherited as fully penetrant simple Mendelian traits. Rather, the underlying genetic abnormality in each appears to involve more than one genetic locus and the inheritance patterns tend to fit polygenic models in which the genes involved act additively to increase susceptibility to a specific defect in embryologic development of the heart. Two forms of congenital heart disease, patent ductus arteriosus (PDA) in the poodle and conotruncal defects in the keeshond, will be used to illustrate the features of this type of inheritance.

Patent ductus arteriosus

The ductus arteriosus is a short, specialised blood vessel which in fetal life connects the pulmonary artery and descending aorta, providing a shunt around the non-functional lungs. In normal puppies, the onset of breathing at birth causes a rise in arterial oxygen saturation, the abundant smooth muscle of the ductal wall constricts, and the lumen of the vessel is functionally closed a few hours after birth. Within a few days, extensive changes in the ductal wall obliterate the lumen and it is eventually reduced to a fibrous cord, the ligamentum arteriosum. When there is failure of the closure process, the communication between the aorta and pulmonary artery persists after birth as a patent ductus arteriosus (PDA). The consequences to the affected animal depend upon the size of the communication. If small, affected puppies may show no outward signs of disease but auscultation of the heart will reveal a continuous murmur. Somewhat larger ductal openings allow large quantities of blood to be shunted from the aorta into the pulmonary circulation, overloading the left heart and producing heart failure with pulmonary conges-

Table 2. Breed-specific predispositions to congenital heart disease

Defect	Breed	Reference*
Patent ductus arteriosus	Poodle	1,2
	Collie	1
	Pomeranian	1
	Shetland sheepdog	2
Pulmonic stenosis	Bulldog	1
	Fox terrier	1
	Chihuahua	1
	Beagle	1
	Samoyed	2
	Miniature schnauzer	2
Subaortic stenosis	German shepherd dog	1
	Boxer	1,2
	Newfoundland	1,2
	German shorthaired pointer	2
Persistent right aortic arch	German shepherd dog	1,2
	Irish setter	1
Tetralogy of Fallot	Keeshond	1,2
Atrial septal defect	Samoyed	2
Ventricular septal defect	Bulldog	2
Tricuspid insufficiency	Great dane	2
	Weimeraner	2
Mitral insufficiency	Bulldog	2
	Chihuahua	2
	Great dane	2

(1) Patterson 1968 (2) Mulvihill and Priester 1973

Table 3. Incidence and concordance of cardiovascular malformations in the offspring of dogs with congenital heart disease

Parental defect*	Number of matings	Number of offspring	Cardiovascular malformations incidence (%)	% Concordance	Other defects†
PDA (poodles)	10	35	82·9	100·0	Diverticulum of the ductus arteriosus
Pulmonic stenosis (beagles)	10	35	25·7	100·0	None
Subaortic stenosis (Newfoundlands)	5	26	38·5	80·0	Valvular pulmonic stenosis
Persistent right aortic arch (German shepherd dog)	3	30	10·0	66·7	Pulmonic stenosis; PDA; persistent left cranial vena cava
Tetralogy of Fallot (keeshond)	4	11	90·0	100·0	Various conotruncal defects
All defects	32	137	44·5	95·1	

*Both parents had the same type of malformation and were of the same breed.

†Concordant defects were the same as those in the parents or were closely related embryologically.

PDA Patent ductus arteriosus.

tion, oedema and death, often within a few weeks after birth (Patterson 1971). If the ductal communication is very large, there is pulmonary hypertension and a balanced or right-to-left shunt occurs. Animals with the latter form of PDA usually have no detectable murmur, but have pronounced splitting of the second heart sound, right ventricular hypertrophy and cyanosis of the caudal part of the body due to shunting of unoxygenated blood from the pulmonary artery to the descending aorta. They are often polycythaemic and show signs of posterior weakness on exercise.

Initial observations in families of dogs with PDA suggested that inheritance might be simple autosomal dominant, but on further study it became clear that the situation is more complex (Patterson and others 1971). Of particular importance were the following observations:

1 PDA occurred as a graded defect, the size of the lumen ranging from a small channel of little haemodynamic significance to a large vessel with a lumen equal in diameter to the ascending aorta.
2 In addition to PDA of varying lumen size, there occurred a mild forme fruste (aberrant, indistinct form) in which the ductal lumen was closed at the pulmonary arterial end but remained open over the rest of its length, forming a funnel-shaped diverticulum from the aorta (ductus diverticulum).
3 The full spectrum of severity, including ductus diverticulum and PDA of varying size, was often found in members of the same litter.
4 Dogs with ductus diverticulum transmitted both ductus diverticulum and PDA to their offspring in crosses to normal dogs of breeds not known to be at increased risk of PDA.

The results of initial breeding studies are shown in Table 4. It is clear from these data that all simple genetic hypotheses must be rejected. Matings between two affected dogs produced a high frequency of dogs with defective ductal closure, but less than the 100 per cent expected with fully penetrant autosomal or X-linked recessive inheritance. Although outcrosses to normal dogs produced some affected offspring, the number was too small to be consistent with fully penetrant autosomal or X-linked dominant inheritance. Furthermore, when dogs with either PDA or ductus diverticulum were mated to the normal first degree relatives of dogs with PDA, the proportion of offspring with defective ductal closure was intermediate between that produced in outcross matings and matings between two dogs with PDA. The latter result indicates that close relatives of dogs with PDA, although themselves phenotypically normal, carry genes which increase the probability of defective ductal closure. It was also noted that as the proportion of affected offspring increased, there was a concomitant increase in the proportion of affected dogs having the more severe form of the defect (PDA). This can be described as an increase in expressivity that is positively correlated with an increase in incidence of the defect (Table 4). Taken together, the results of breeding studies are consistent with a polygenic threshold model similar to that first proposed by Wright (1934) and subsequently used by Falconer (1965) and others to explain the inheritance of traits that

Table 4. Distribution of patent ductus arteriosus (PDA) and ductus diverticulum (DD) in surviving offspring of various mating types

Parental phenotypes	Offspring number	DD (%)	PDA (%)	Total % defective	Expressivity† (%)
DD × N	28	17·9	3·6	21·5	16·7
PDA × N	78	11·5	10·2	21·8	47·1
DD × N(1°Rel PDA)	19	15·8	47·4	63·2	75·0
PDA × N(1°Rel PDA)	40	22·5	45·0	67·5	66·7
PDA × PDA	35	17·1	65·7	82·8	79·3

*Adapted from Patterson and others 1971

†Expressivity defined as the percentage of affected puppies with the more severe form of the defect (PDA)

have a high frequency within families but do not follow simple Mendelian inheritance.

According to the model, genes at more than one locus are assumed to act additively to influence some underlying variable that can be termed, 'liability'. If it could be measured, liability would be found to be continuous and normally distributed. Discontinuity at the phenotypic level (in this case failure of ductal closure) results when liability exceeds a critical, threshold value. The interpretation of the breeding results from Table 4 in terms of a polygenic model with two thresholds is illustrated in Fig 1. Liability to defective ductal closure is measured on the X axis and the Gaussian curves represent the distribution of phenotypes in the offspring of different mating types. In puppies falling below the first threshold, ductal closure is complete (normal), while in those above the second threshold, the ductus remains patent throughout its length (PDA). Between the two thresholds, ductal closure is partial and a ductus diverticulum results. The areas under each part of the curve represent the proportions of offspring falling into each of the three phenotypic classes. The curve at the top of Fig 1 represents the offspring of matings in which both parents have PDA (r = 1 is the proportion of genes the offspring have in common with dogs with PDA). In this mating type, the mean liability to defective ductal closure lies well to the right of both thresholds; a high proportion of offspring have a fully patent ductus, and a small proportion have ductus diverticulum. The bottom curve represents offspring of matings in which one parent has PDA and the other is normal and unrelated to PDA dogs (r = ½); the mean liability of the offspring lies well below both thresholds and the proportions with DD and PDA are approximately equal. The middle curve represents offspring of matings in which one parent has PDA and the other is phenotypically normal but is a first degree relative of a dog with PDA (r = ¾). The mean liability of these offspring lies approximately halfway between those of the other matings. (Note that the mean liability of the offspring of each mating type is approximately proportional to the proportion of their genes derived from dogs with PDA.)

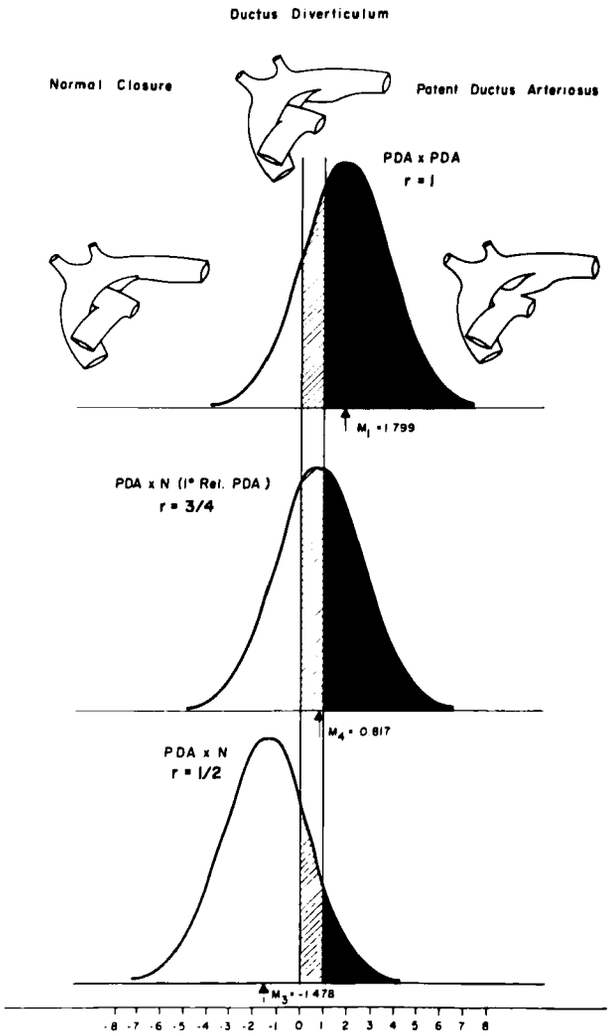

FIG 1. Threshold model of inheritance of patent ductus arteriosus (PDA). The offspring of three mating types are depicted as Gaussian curves overlapping two thresholds along a scale of liability to defective closure of the ductus arteriosus. In offspring lying below the lowest threshold to the left, the ductus closes throughout its length. Between the two thresholds, closure is abnormal, taking place only at the pulmonary arterial end and producing a ductus diverticulum. To the right of the second threshold the ductus remains patent throughout its length, producing a PDA. The distance between the two thresholds is taken as one standard deviation unit and the location of the mean liability of each group is measured in threshold standard deviation units from the lower threshold. At the top, the offspring resulted from the mating of two dogs with PDA (r = 1 is proportion of the offspring's genes derived from dogs with PDA). This group has the highest mean liability to defective ductal closure. The curve at bottom represents the offspring of matings between a dog with PDA and an unrelated normal dog (r = ½). The mean liability of this group lies below the lowest threshold. The middle curve represents the offspring of matings between a dog with PDA and the normal first degree relative of a dog with PDA (r = ¾). The mean liability of this group lies midway between the other two. From Patterson and others (1971) with permission

One of the chief distinguishing characteristics of multiple-threshold models of polygenic inheritance is that there is a correlation between the proportion of affected offspring and the degree of severity of the defect. This is seen clearly in Fig 1. As the distribution is shifted to the right, there is not only an increase in the proportion of defective offspring, but in those that are defective there is an increasing risk of having the more severe form of the defect (full PDA rather than ductus diverticulum). Although the two-threshold model in Fig 1 does not distinguish increases in severity beyond the threshold for PDA, other evidence suggests that there is an increase in the size of the PDA as the proportion of the offspring's genes derived from PDA parents increases. This evidence relates to the incidence of left heart failure and pulmonary hypertension, two sequelae of PDA that are associated with ductal lumens of large size. Considering only puppies with PDA, the combined incidences

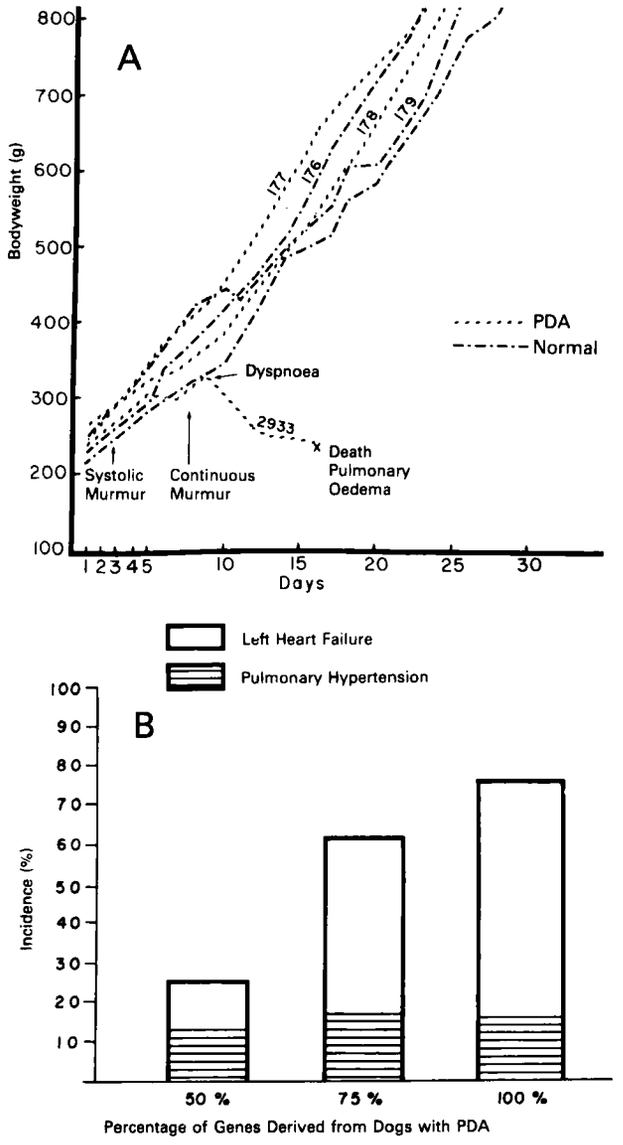

FIG 2. Incidence of serious sequelae in puppies with patent ductus ateriosus (PDA). A. Growth curves and clinical signs in a litter of poodles with PDA. Three puppies had PDA with left to right shunts. Systolic murmurs could be detected in all three at three to four days of age and became continuous by the end of the first week. One of the affected puppies began to have difficulty in breathing at eight days, steadily lost weight and died at 17 days with pulmonary oedema, despite treatment with oxygen and digitalis glycosides. B. The incidence of left heart failure (pulmonary congestion, oedema) and severe pulmonary hypertension is compared in the three groups of puppies with PDA shown in Fig 1. Only puppies with PDA are included. The increasing incidence from left to right indicates that the severity of the lesion (size of the ductus arteriosus) increased with the proportion of the genome that was derived from dogs with PDA. From Paterson and Pyle (1971) with permission

of these two sequelae increased from 25 per cent in those which received 50 per cent of their genes from dogs with PDA, to 78 per cent in affected puppies which receive 100 per cent of their genes from PDA dogs (Fig 2). As would be predicted, in puppies which received 75 per cent their genes from PDA dogs, the incidence of the sequelae was intermediate (approximately 60 per cent).

There is another feature of hereditary PDA in poodles that requires some explanation. In clinic population studies, the frequency of PDA in females is approximately twice that in males. It is interesting that in humans, PDA is also more common in females (Record and McKeown 1953, Polani and Campbell 1960). In the initial breeding experiments described in Table 4, most mating types showed a slightly greater frequency of defective ductal closure in females than males, but the difference was not statistically significant. However, analysis of a larger series (Patterson 1979) showed that this difference is real. Although the biological mechanism for the sex difference is unknown, the situation can be viewed operationally as one in which females have a lower threshold for PDA than males. If such a mechanism were operating in the case of a polygenic threshold trait, it follows that the less frequently-affected sex must have inherited a higher liability to the defect in order to be affected. Consequently, we would expect the offspring of males with PDA to have a higher risk of PDA than the offspring of affected females. The most direct test of this hypothesis would be to perform reciprocal crosses between dogs with PDA and normal dogs having no relatives with the defect. These studies were done and indeed show that the frequency of defective ductal closure is greater when the father has PDA than when the mother is the affected parent (Patterson 1979).

The underlying abnormality in ductal closure in hereditary PDA of the poodle has been shown to be a localised genetic defect in the histodifferentiation of the ductus arteriosus. There is a decrease in number and an abnormal arrangement of smooth muscle cells in the media of the affected ductus, associated with an increase in elastic fibres (Buchanan 1978). The normal separation of the endothelial cells from the internal elastic membrane and expansion of the subendothelial region, producing the intimal cushions that precede normal closure does not occur (Gittenberger-De Groot and others 1985, De Reeder and others 1988). The histological findings provide a simple explanation for the ductus diverticulum that occurs in some dogs genetically-predisposed to PDA. In serial sections, the histological defect is a graded phenomenon, the most severe degrees of which occur at the aortic end. Dogs with ductus diverticulum are simply those in which enough normal ductal tissue remains at the pulmonary arterial end to allow closure at that point.

Physiological studies of isolated ductuses from PDA-predisposed and normal puppies indicate that in the defective ductuses, there is impairment of the capacity to constrict following exposure to oxygen or other agents which normally cause contraction of ductal smooth muscle (Knight and others 1973). Prostaglandin inhibitors cannot be

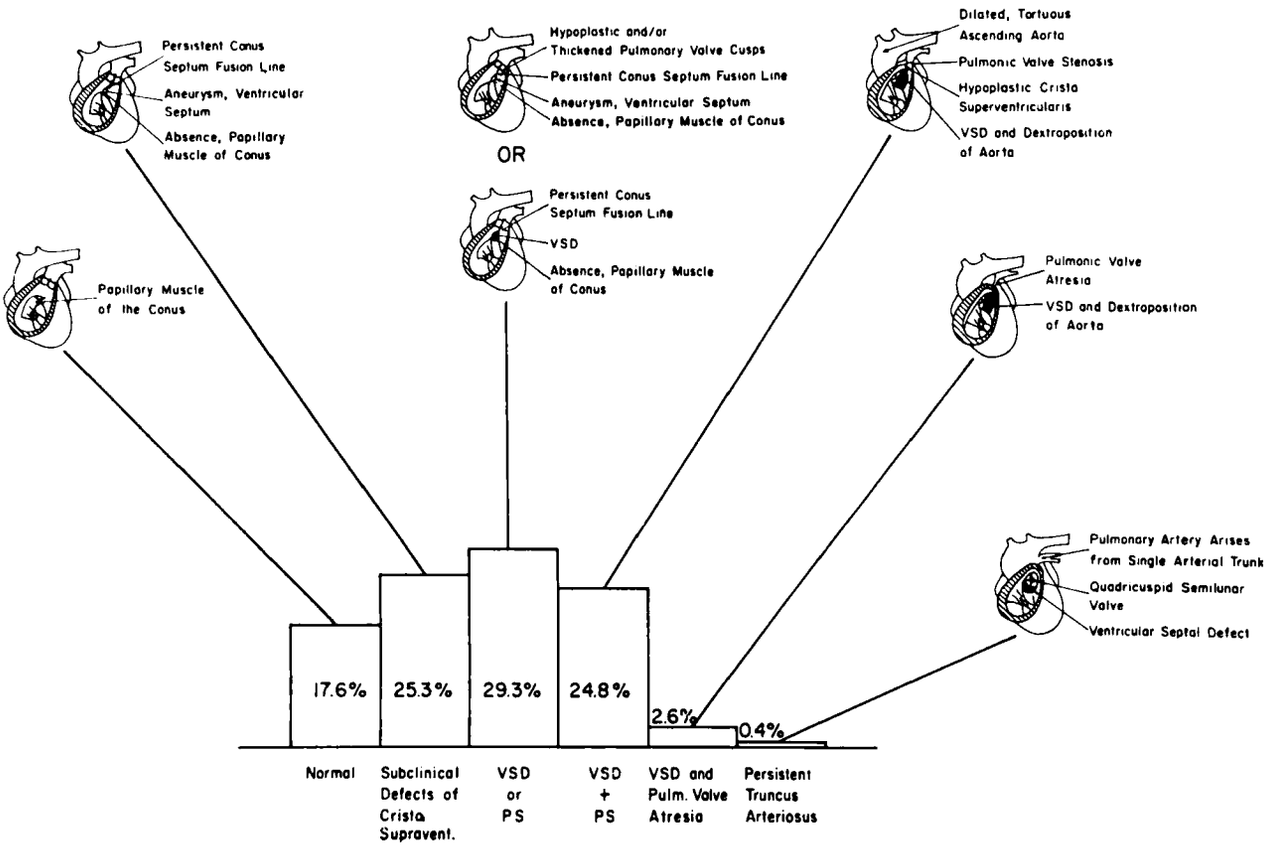

FIG 3. Distribution of conotruncal defects. The frequency distribution of cardiovascular phenotypes in 474 consecutive offspring of a line of keeshond dogs is shown. The line was developed by selection of affected dogs from a family with a high incidence of conotruncal anomalies and has been maintained mainly by matings between affected animals and their close relatives. From Patterson (1980) with permission. PS Pulmonary stenosis, VSD Ventricular septal defect.

expected to cause closure of the structurally and functionally abnormal ductus of hereditary PDA as they do in premature human infants who have an immature, but otherwise normal ductus arteriosus (Patterson 1979).

Conotruncal defects in keeshond dogs

In epidemiological studies, the defect found to occur with unusually high prevalence in keeshond dogs was tetralogy of Fallot (Table 2). In the classical form of tetralogy, there is a ventricular septal defect with overriding aorta and pulmonary stenosis. If the pulmonary stenosis is severe, there is marked right ventricular hypertrophy and affected dogs are cyanotic due to shunting of unoxygenated blood from the right ventricle to the aorta through the ventricular septal defect. In the process of family studies and breeding experiments it became apparent that although tetralogy of Fallot was a frequent anomaly, related keeshond puppies had a spectrum of other cardiac malformations. The entire spectrum included clinically silent defects of the right ventricular outflow tract, ventricular septal defect, tetralogy of Fallot, and persistent truncus arteriosus (Patterson and others 1974, Patterson 1980). The distribution of lesions observed in a large family studied over a number of years is shown in Fig 3.

Although the variability in lesions at first seemed to be an exception to the lesion-specificity of genes underlying canine congenital heart disease, it was soon recognised that all of the anatomical defects in affected keeshond families could be explained by varying degrees of abnormality in a single embryological process: the growth and fusion of the conotruncal septum. The conotruncal septum is formed from embryonal mesenchymal cushions or ridges that grow together to separate the right and left ventricular outflow tracts and proximal portions of the pulmonary artery and aorta (Fig 4). Embryological studies in the keeshond confirmed that the underlying embryological abnormality is hypoplasia of the conotruncal septal ridges (Van Mierop and others 1977). More recent studies indicate that the hypoplasia of the conotruncal septum in the keeshond defect is part of a more generalised growth failure of the right ventricular myocardium which occurs at a critical stage of cardiac development during the process of septation of the outflow tracts (Pexieder and Patterson 1984, Alaili and others 1985). Because the conotruncal septum plays such a central role in the partitioning of the right ventricular outflow tract and great arteries, even slight deficiencies in its development have important anatomical consequences, and small variations in the severity of the hypoplasia result in malformations in the completed heart which have different functional consequences. This no doubt accounts for the fact that these embryologically-related defects have often

been viewed by the anatomist and the clinician as separate aetiologic entities. This new perspective on conotruncal malformations has been one of the important contributions of studies in the dog to the understanding of human congenital heart disease. Indeed, the clustering of tetralogy of Fallot with related defects in human families can be explained by the same mechanism (Fraser and Hunter 1975).

The mode of inheritance of conotruncal malformations in the keeshond resembles that of hereditary PDA in poodles, fitting a similar polygenic model with multiple thresholds (Patterson and others 1974). In this case, the various grades of conotruncal malformation as depicted in Fig 2 can be considered to represent different developmental thresholds along a continuum of increasing liability to hypoplasia of the conotruncal septum. The most extreme class is represented by persistent truncus arteriosus, in which the conotruncal septum is entirely missing. The most severe defects in the keeshond are lethal early in life. However, animals with subclinical defects, ventricular septal defects, pulmonic stenosis, or tetralogy of Fallot with minimal pulmonic stenosis, often survive and can reproduce. As expected from the polygenic threshold model, the more severe the defect in the parent, the greater is the frequency of affected offspring and the more likely it is that they will be severely affected (Patterson 1974).

A few genes or many, and what about environmental effects?

In the polygenic model used for the analysis of PDA and conotruncal defects, a major simplifying assumption was that many gene loci are involved, each with small additive effects. It should be pointed out that although the observations made in PDA in poodles and conotruncal defects in the keeshond do fit the model, they could also be explained by models involving a smaller number of genes, particularly if dominance and epistasis (ie, super-imposition of one hereditary character to conceal another) are introduced as variables (Trojak and Murphy 1983). The fact that some affected offspring are produced in outcrosses and that such high frequencies of affected offspring can be obtained by mating affected animals and their close relatives suggests that although the congenital heart defects studied are not simple Mendelian traits, the number of genes involved may not be large. The use of the threshold models as given here should therefore be regarded mainly as a descriptive method which contributes to the understanding of how the variation in frequency and severity of the malformation can be related to an underlying genetic defect in development involving more than one gene locus. The models also are of some help in the development of control measures, but they are

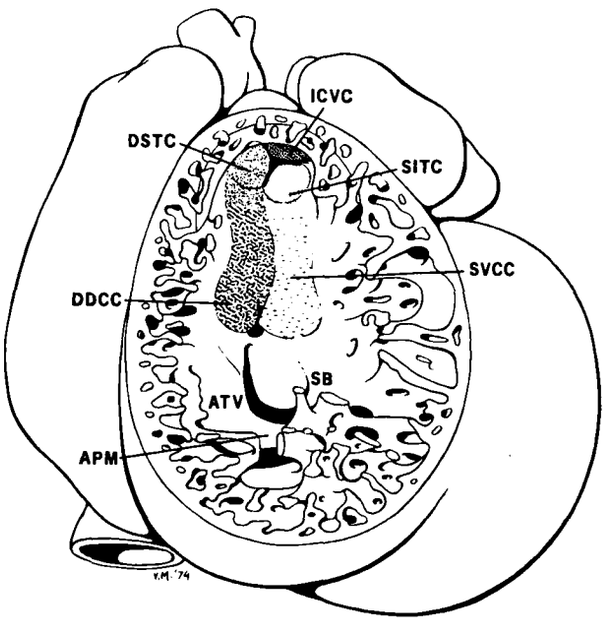

FIG 4. Embryonic conotruncal septum. Drawing of a wax plate reconstruction of the heart of a normal dog embryo of approximately 28 days. The right ventricular wall has been removed to show the conotruncal septum, which is nearing completion of its development. The dextrodorsal conus cushion (DDCC) is stippled to show its fusion with the sinistroventral conus cushion (SVCC) to form the conus septum. Fusion is not yet complete at the bottom of the conus septum, leaving a small opening between the two ventricles. Note that the dextrosuperior truncus cushion (DSTC) gives rise to the right leaflet of the pulmonary valve and the sinistroinferior truncus cushion (SVTC) forms the left pulmonary valve leaflet. The anterior leaflet of the pulmonary valve is formed from the intercalated valve cushion (ICVC).

When the conotruncal cushions are hypoplastic, the septum between the right and left ventricular outflow tracts does not close and the pulmonary valve develops abnormally. Varying degrees of hypoplasia give rise to the spectrum of anomalies shown in Fig 3. From Van Mierop and others (1977) with permission

not particularly useful in predicting recurrence risks of defects in different families. This is because the exact genotype of the parents is never known, as it can be when a single dominant or recessive gene is involved. In effect, all we can deduce about the parental genotype is that those animals which produce the most affected offspring are themselves nearest the threshold of liability for the defect. This can vary from family to family.

The multifactorial threshold model has been used extensively to explain the occurrence of congenital heart disease in human families (Nora 1968, Nora and Nora 1978). This model is essentially the same as the polygenic model, but emphasises the potential importance of environmental 'triggers' that might act in concert with the polygenically-determined liability to thrust an embryo beyond a critical threshold. In this situation, teratogenic agents not usually causing cardiac defects might do so in individuals that lie precariously near a threshold because of their

genotype. Breeding studies in the dog were done largely under controlled laboratory conditions with no known exposure to teratogens. It is possible that subtle environmental effects might have some influence on the frequency and severity of cardiac malformations in genetically-predisposed dogs, but their role does not appear to be great. The major source of variation appears to be the additive effects of genes and, at least in the case of PDA, this is both a necessary and sufficient cause of the malformation (Patterson 1971).

OTHER CONGENITAL HEART DEFECTS

Extensive genetic studies have also been made in discrete subaortic stenosis of Newfoundlands (Pyle and others 1976), pulmonary valve stenosis of beagles (Patterson 1984), and persistent right aortic arch of German shepherd dogs (Patterson 1968). While the details vary among the different anatomic defects, they too are inherited in patterns not consistent with a fully penetrant single gene model. For the present, they can be considered to be polygenic threshold traits inherited in a manner similar to PDA, though lacking any evidence of a difference between the sexes.

Other apparent breed predispositions to congenital heart disease are suggested by clinic population data (Table 2), but have not been investigated by family studies or breeding experiments. In addition, new defects may emerge as genetic disorders in breeds in which they have not been previously reported. Subaortic stenosis, for example, has increased to a noticeably high frequency in golden retrievers in the USA within the past few years. Although it appears to be similar in its clinical and pathological features and pattern of inheritance to that in Newfoundlands, definitive genetic studies have not yet been made.

SUMMARY

Hereditary congenital heart defects in the dog have the following features that are characteristic of polygenic threshold inheritance:

1 The defects are often congenital malformations whose pathogenesis is explained by a failure of coordinated growth during development.
2 There is a higher risk of the same or a developmentally-related defect in close relatives than in the general population.
3 On careful genetic analysis, the pattern of occurrence within families is not consistent with any model of fully-penetrant single-gene inheritance.
4 Relatives of the most severely-affected individuals have the highest risk of being affected and tend to have the most severe defects.
5 In contrast with the situation in single-gene traits, where the risk is always predictable from the mode of inheritance (eg, 25 per cent for *each* offspring of two carriers of an autosomal recessive trait), the risk in polygenic traits varies from family to family. The higher the proportion of affected offspring in a given family, the higher the risk to subsequent offspring.
6 In families or lines with genes predisposing to a given defect, the frequency of the defect may increase with inbreeding.
7 In some defects, the risk may vary between males and females. When this is the case, close relatives of affected individuals of the least affected sex are at highest risk.

CONTROL MEASURES

The incidence of congenital heart defects can reach high levels within a kennel and sometimes within a whole breed. Reduction in their frequency, as in all genetic defects, can only be accomplished by selection to reduce the frequency of the genes involved. Programmes for this purpose must rely on two major principles:

1 The identification and elimination from breeding of all affected animals.
2 Avoidance of the breeding of animals that are clinically normal but carry the genes involved.

The first principle requires careful clinical evaluation of the cardiovascular system in all potential breeding stock, particularly in breeds in which there is a known hereditary malformation of the heart. Fortunately, most significant congenital heart defects produce heart murmurs that can be detected by auscultation and this is the most efficient screening method. If a murmur is found, further examinations are usually required to make a definitive diagnosis. It is important to make a specific anatomic diagnosis wherever possible. Not all congenital heart defects are genetic in cause and the occurrence of a form not known to be present in a given breed could indicate that it is of a non-genetic aetiology. As we have seen in the case of PDA and the conotruncal defects, there will be some animals that appear clinically normal but which have a subclinical forme fruste (aberrant form). There is no ready solution to this problem and such animals may be suspected only after they have produced a high frequency of defective offspring.

Because there are as yet no laboratory means for detection of carriers of polygenic defects, it can only be done by progeny testing. In effect, this approach reveals the genotype of the parent through the phenotype of the offspring. A formal scheme of progeny testing, as is done for single

recessive gene defects, is usually not practical because no simple way exists to define the number of normal offspring needed to reduce the probability of failing to detect the carrier state to a known level. A practical approach is to breed only clinically-normal dogs and monitor the cardiovascular status of all offspring, eliminating from further breeding those parents which produce a high frequency of defective offspring. One should usually avoid the breeding of the clinically-normal siblings of animals with congenital heart defects. An exception to this can be made if an animal is in other ways unusually desirable, but its offspring should be carefully examined for evidence of heart disease and the parent eliminated from further breeding if affected puppies are produced.

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