SPECIAL ARTICLE

Genetic Aspects of Cardiovascular Diseases in Animals

By D. K. Detweiler, V.M.D.

The occurrence of specific types of cardiovascular disease in different species, breeds, and strains or families of animals is pertinent to a consideration of the role of heredity in these disorders. Variations in the types and prevalence of cardiac and arterial disease in different genetically related groups of animals are not explainable at present on the basis of environmental influences or known etiologic agents.

The conditions that will be considered are arteriosclerosis (including atherosclerosis), cardiomyopathies, congenital malformations, arrhythmias and conduction disturbances, congestive heart failure, and hypertension.

Although the distribution of a given disease in the sample of the animal population available for study may suggest that inheritance is involved, the criteria for recognizing specific modes of inheritance are ordinarily lacking. Frequently, prevalence and incidence data are not directly comparable because of differences in the methods of study and the introduction of various biases in the selection of cases. Added to this are the difficulty in distinguishing genetic from environmental influences and, frequently, the paucity of information on spontaneous cardiovascular diseases in many animal species. The evidence now available for heritability of cardiovascular diseases consists primarily of observations on unusual aggregations of cases of a given disease among animals related by descent. The obvious advantage in animal material is that, once suggestive evidence for heritability is found, prospective studies can include specific breeding experiments. In a few instances, selective breeding has produced strains of animals in which the incidence of some cardiovascular abnormality is extremely high.

Species Comparisons

Arteriosclerosis

The various animal species studied differ in the types of arteriosclerosis to which they are subject and in their susceptibility to the induction of atherosclerosis by the experimental feeding of fat and cholesterol. Conclusions from reported differences in chronic arterial disease in different species are difficult to evaluate because of lack of agreement on the definition of atherosclerosis and arteriosclerosis, and in the interpretations of lesions. In general, much less work has been done on spontaneous animal arteriosclerosis than on human arteriosclerosis, and relatively small numbers of animals are reported. Since the etiology of these chronic arterial diseases has not been worked out, it is difficult to decide, in most instances, whether the characteristics of a species or its environment are more important in these processes. It is evident, however, that real

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differences exist, some of which apparently result from genetically determined characteristics of the individual species. Atherosclerosis is the most important arterial lesion in man, from the standpoint of clinical disease and mortality; but not in most other species.

Finlayson and co-workers examined a series of 816 exotic animals (mammals, birds, and reptiles), the majority of which died from natural causes in the London Zoological Gardens. Major lesions were found principally in the large elastic arteries and were infrequent in smaller muscular vessels such as coronary arteries. The incidence of these spontaneous arterial lesions was much higher in mammals and birds than in reptiles. Classifying animals as herbivores, carnivores, and omnivores, these authors were unable to find any clear association of arterial lesions with the type of diet. Severe coronary atheromatosis and myocardial infarctions were rare, and the extent of coronary disease was summarized as "minor lesions in minor vessels." Atheromatous plaques were common in birds, which have a relatively high arterial blood pressure, and rare in reptiles, which have a relatively low blood pressure. The median serum cholesterol levels were highest in birds, next in mammals, and lowest in reptiles. Age difference was probably the only factor correlated with fatty streaks and atheroma. The high incidence of atheroma in birds was associated with a greater proportion of lesions in older specimens. Most of the mammals were young specimens in which fatty streaking was common, but atheroma was infrequent. However, spontaneous occurrence of atheroma was seen in some very young mammals and, contrariwise, was absent in several old animals (Felidae, for example).

Ratcliffe et al. reported studies carried out at the Philadelphia Zoological Garden for more than 40 years. Prior to 1935 and the introduction of adequate diets, the most striking form of arteriosclerosis developed in birds as atheromatous of the thoracic aorta and brachiocephalic arteries. During this period, arteriosclerosis of mammals was limited largely to infrahuman primates. In other mammals, the chief arterial disease was segmental necrosis and calcification of the media of the thoracic and abdominal aorta, corresponding more or less to Mönckeberg's sclerosis in man. After the improvement in diet, the large atheromatous of the thoracic aorta and brachiocephalic arteries became rare in birds. They then began to develop smaller, more compact atheromatous, located in the abdominal aorta or its branches. Also since 1935, arteriosclerosis in mammals has increased, in the form of intimal thickening, with or without lipid deposits, in the aorta and its larger branches, as well as in smaller arteries of the myocardium, kidney, spleen, and other organs. Since 1950, intimal thickening of smaller arteries, particularly of the intramural arteries of the heart, became relatively frequent. The authors interpreted these changes as reflecting a response of adequately nourished animals to the stresses of population density.

These two reports from the London and Philadelphia Zoos indicate the pitfalls in drawing conclusions about hereditary factors and environmental influences where animal populations are diverse.

Vastesaeger et al. studied the coronary circulation in 181 hearts from mammals and birds in the Zoological Garden of Antwerp. Occlusive lesions in the large coronary arteries typical of those in man were rare. Disease similar to that described by Ratcliffe was found in intramural coronary arteries in over 20 per cent of the hearts.

In large elastic and musculo-elastic vessels, medial lesions, often with necrosis and calcification, are common in aging horses and cattle, and in rabbits of various ages. Spontaneous atherosclerosis is relatively common in swine, in some avian species, and in certain primates. On the other hand, atherosclerosis is unusual in the dog, and in certain other mammals. In the dog, and in mammals and birds in the Philadelphia Zoo, arteriosclerotic changes of a nonatheromatous type are of greater importance than atherosclerosis.

Kritchevsky has summarized much of the literature on experimental atherosclerosis in animals, and has attempted to explain some of the species' differences. Earlier, Olson had pointed out that resistance of various
species to atherosclerosis is not so much a matter of serum cholesterol level as of lipoprotein distribution. Species with high alpha/beta lipoprotein cholesterol ratios are more resistant to the dietary induction of atherosclerosis. Variations in the pattern of bile acid conjugation may be important also. In mammals resistant to cholesterol and fat-induced atherosclerosis (rat, dog, cat), the bile acids circulate conjugated almost entirely with taunine. In the susceptible species (rabbit, swine, monkey, man), bile acids are conjugated with both taunine and glycine; glycine conjugation is greatly in excess in rabbits and swine, and somewhat in excess in man and monkey.  

**Congenital Malformations**

Prevalence ratio data on the occurrence of congenital cardiac malformations in various species are not directly comparable owing to differences in sampling technics. In humans, prevalence ratios of 5.4 and 8.3 per thousand have been reported for newborn infants" and 2.1 per thousand for elementary school children." In Wistar albino rats, Sobin\(^{16}\) found cardiac defects in 21 per thousand of 2166 spontaneously delivered young. Other workers encountered a much lower incidence of cardiac defects in albino rats.\(^{17}\) The prevalence of congenital heart disease in swine may be as high as 20 to 40 per thousand among animals of slaughter age,\(^{18}\) while a prevalence of 12 per thousand was found in 451 piglets that died or were killed before 2 weeks of age.\(^{19}\) An incidence of 2 congenital cardiac lesions per thousand embryos was determined among 50,000 pig embryos of 18 to 50 cm. in length,\(^{20}\) but the method used was such that internal cardiac defects not affecting the shape of the heart and venous anomalies would not have been detected. The prevalence ratio of detectable congenital heart disease in dogs brought to a veterinary clinic is approximately 5 per thousand.\(^{21}\)

Most of the common types of congenital heart lesions described in man have also been reported in animals.\(^{22-24}\) In man, data based largely on necropsy findings indicate that atrial septal defects (including patent foramen ovale) and ventricular septal defects are most common; patent ductus arteriosus and transposition of the great vessels are next, followed by aortic coarctation and pulmonic stenosis; the remaining lesions include aortic stenosis.\(^{25}\) Two studies have shown that congenital subaortic stenosis of the fibrous ring type is extremely common in swine.\(^{18,26}\) In dogs brought to a veterinary clinic, pulmonic stenosis (either valvular or infundibular) and persistent ductus arteriosus were the most frequent anomalies; subaortic stenosis and persistent right aortic arch were less common, but not rare; while all other types, including atrial and interventricular septal defects were rare.\(^{21,22}\) Ectopia cordis (cervicalis or thoracalis) appears to be much more common among cattle than any other domestic species. In the horse, the most common malformations have been interventricular septal defects and valvular anomalies of various kinds.\(^{21}\)

It is not possible to establish unequivocally characteristic species differences with respect to prevalence and types of congenital malformations. If comparable rather than disparate data were available, the differences suggested by the present information might be confirmed.

**Arterial Blood Pressure**

The giraffe\(^{27}\) and the turkey\(^{28}\) are examples of species that have higher arterial blood pressure than other species. The high pressure in the giraffe is an adaptation required to provide an adequate blood supply to the head, but no such teleologic explanation can be offered for the high pressure found in those breeds of turkeys studied.

**Cardiac Arrhythmias and Conduction Disturbances**

In some species, certain arrhythmias or conduction disturbances occur commonly enough to be considered normal variants characteristic of the species. For example, respiratory sinus arrhythmia is the normal resting rhythm in the dog. The degree of sinus arrhythmia and its relation to heart rate difference characteristically in certain breeds.\(^{29}\) In the horse, incomplete atrioventricular block with dropped beats, sinoatrial block, wandering pacemaker, and sinus arrhythmia all occur.
commonly in animals that show no other evidence of heart disease.\textsuperscript{24} Incomplete atrioventricular block with dropped beats has been observed among otherwise normal elephants\textsuperscript{30} and erratic sinus arrhythmia is present in moles.\textsuperscript{31}

The prevalence of abnormal arrhythmias in individuals of a given population is probably determined by the amount of heart disease present. In a series of 67,375 healthy adult men, the prevalence ratio of arrhythmias was approximately 28 per thousand,\textsuperscript{32} while in a group of dogs examined at a veterinary clinic, the prevalence ratio was approximately 41 per thousand.\textsuperscript{33} In both groups, ventricular premature beats were most common, and atrioventricular block and atrial premature beats were among the most frequent arrhythmias. These groups are not really comparable, since the dogs came from a clinic population and the men were presumably all healthy.

**Breed Comparisons**

**Atherosclerosis**

Loiland and Clarkson have found spontaneous atherosclerosis in certain breeds of pigeons in which only genetic background and age could be correlated with susceptibility to the disease.\textsuperscript{34, 35} In their initial studies, a total of five breeds of pigeons was used: Autosexing Kings, Silver Kings, White Carneaux, Show Racers, and Racing Homers. The White Carneaux have been closely inbred since 1916 and thus might be called a strain rather than a breed. In adult birds 4 to 8 years of age of the three susceptible breeds (Autosexing Kings, Silver Kings, White Carneaux), approximately 10 per cent of the intimal surface of the thoracic aorta (mostly at the distal end) was covered with atherosclerotic plaques.\textsuperscript{35} Atherosclerosis was practically absent in the other two breeds (Show Racers and Racing Homers). The incidence and severity of the disease could not be correlated with levels of serum total, free, and ester cholesterol; total phospholipids; cholesterol; phospholipid ratio; age (within these age groups), sex, diet, or physical exercise.\textsuperscript{34} This led to the conclusion that atherosclerosis in these pigeons is related to a genetic factor.\textsuperscript{35} Subsequent studies in the White Carneaux\textsuperscript{36} demonstrated that the disease increases in prevalence with age, reaching 100 per cent in birds over 3 years old. Prichard and co-workers\textsuperscript{37} have started breeding studies by mating White Carneaux with Racing Homers. Visible atherosclerotic lesions in 2-year-old offspring from these matings have an incidence approximately intermediate between the two breeds, but slightly closer to that of the resistant Show Racers breed. Coronary artery sclerosis is present in about 70 per cent of White Carneaux.\textsuperscript{37} Cholesterol feeding increases the incidence of lesions in accordance with the susceptibility of the breed. Feeding 1 per cent cholesterol supplement in lard to resistant Racing Homers, intermediate Autosexing Kings, and susceptible White Carneaux breeds caused no significant difference in blood cholesterol levels among the groups, but in 6- to 7%-month-old birds the incidence of lesions varied with breed susceptibility: White Carneaux, 100 per cent; Autosexing Kings, 59 per cent; Racing Homers, 9 per cent.\textsuperscript{38}

**Congenital Heart Disease**

In 5,000 dogs examined at the University of Pennsylvania School of Veterinary Medicine, the prevalence of congenital malformations was higher in purebred than in mongrel animals. In this survey, among 4,831 non-referred cases, the prevalence ratio of congenital lesions of the heart and great vessels was 5.6 per 1,000. Additionally, 23 dogs with congenital heart disease were referred to the clinic, giving a total of 50 cases among approximately 5,000 animals. Of the total of 50 cases, 43 occurred in purebred dogs (table 1). Since this sample is biased by the fact that these dogs were brought to a veterinary clinic, it is possible that the prevalence ratio is higher among the purebred than the mongrel animals because the purebred dogs with heart disease are more likely to be brought to a veterinary clinic than are mongrels. Because half of these cases were referred to the clinic, further preselection is introduced. The prevalence ratios in purebred and mongrel dogs under 5 years of age, excluding referred cases, are presented in table 2. This removes the influence...
Table 1

Breed Distribution of 50 Cases of Congenital Heart Disease among 5,000 Dogs

<table>
<thead>
<tr>
<th>Breed</th>
<th>Number examined</th>
<th>Number with congenital heart disease</th>
<th>Prevalence ratio (1/oo)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxer</td>
<td>410</td>
<td>7</td>
<td>17.1</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>272</td>
<td>7</td>
<td>25.7</td>
</tr>
<tr>
<td>Poodle</td>
<td>203</td>
<td>6</td>
<td>29.6</td>
</tr>
<tr>
<td>Chihuahua</td>
<td>123</td>
<td>4</td>
<td>32.5</td>
</tr>
<tr>
<td>Cocker Spaniel</td>
<td>518</td>
<td>3</td>
<td>5.8</td>
</tr>
<tr>
<td>Dachshund</td>
<td>170</td>
<td>3</td>
<td>17.6</td>
</tr>
<tr>
<td>Other purebred</td>
<td>1,696</td>
<td>13</td>
<td>7.7</td>
</tr>
<tr>
<td>Mixed</td>
<td>1,608</td>
<td>7</td>
<td>4.4</td>
</tr>
<tr>
<td>Total</td>
<td>5,000</td>
<td>50</td>
<td>10.0</td>
</tr>
</tbody>
</table>

* Rate per thousand.

Table 2

Distribution of Cases of Congenital Heart Disease in Dogs under 5 Years Old between Purebred and Mixed Groups (Excluding Referred Cases)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number examined</th>
<th>Number with congenital heart disease</th>
<th>Prevalence ratio (1/oo)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purebred</td>
<td>1957</td>
<td>19</td>
<td>9.7</td>
</tr>
<tr>
<td>Mixed</td>
<td>976</td>
<td>4</td>
<td>4.1</td>
</tr>
<tr>
<td>Total</td>
<td>2933</td>
<td>23</td>
<td>7.8</td>
</tr>
</tbody>
</table>

* Rate per thousand.

Table 3

Distribution of 105 Cases of Congenital Heart Disease Reported in the Literature with Respect to Breed49

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purebred</td>
<td>68</td>
</tr>
<tr>
<td>No breed given</td>
<td>27</td>
</tr>
<tr>
<td>Miscellaneous *</td>
<td>3</td>
</tr>
<tr>
<td>Mongrel</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
</tr>
</tbody>
</table>


of the referred cases and the difference remains substantial. The data from a partial survey of the literature are presented in table 3.49 Here again, congenital malformations are reported more frequently among purebred than mongrel dogs.

Among the purebred dogs in our series, there is an unusual aggregation of cases of subvalvular, fibrous ring type of aortic stenosis in two breeds. Of 22 cases of subaortic stenosis, 10 were in Boxers, nine in German Shepherds, and three in other breeds.49 None of these dogs was a member of the same family, to our knowledge. All six littermates of one dog with this lesion were examined and none was found to be similarly affected. No cases of the muscular type of subaortic stenosis, reported in man to show a familial occurrence,41, 42 have been recognized.

Chronic Congestive Heart Failure

A total of 97 dogs with chronic congestive heart failure (excluding referred cases) were found among 5,000 dogs screened for heart disease. The majority of them, 71, had acquired valvular or myocardial lesions as the underlying cause of the heart failure. In male Cocker Spaniels the prevalence ratio of congestive failure was approximately four and one-half times that of female Cocker Spaniels and six times that of females of all breeds (table 4). Because of the high prevalence among male Cocker Spaniels, the breed itself and the male sex among all breeds have a higher prevalence ratio of heart failure. Al-
though these data can only apply to the sample of the dog population studied, no biases that can account for the high prevalence of congestive heart failure in male Cocker Spaniels have been discovered as yet.

**Arterial Blood Pressure**

The arterial blood pressures in the breeds of turkeys thus far studied are higher, in general, than those reported for chickens, ducks, and pigeons, and than those of mammals. The arterial blood pressure of the Broad Breasted Bronze Turkey is significantly higher than that of the Jersey Buff. These have been the only two breeds studied to any extent. Whether or not this increased pressure is harmful to the breed is not certain. Spontaneous aortic rupture in turkeys, the etiology and pathogenesis of which are not fully understood, occurs in the Broad Breasted Bronze breed but has not been reported in the Jersey Buff.

**Comparisons of Closely Related Groups of Animals in Strains or Families**

In this context, the term strain is used to mean a group of individuals closely related by consistent inbreeding, and differing in some respects from other members of the breed or species. The term family is used to designate groups of individuals related by descent and thus sharing some common ancestors, but not consistently inbred. In cases where the relationship of animals has not been sufficiently described to make this distinction, the authors' terminology has been adopted.

**Arteriosclerosis and Atherosclerosis**

Rowsell et al. found varying degrees of susceptibility to swine atherosclerosis among individuals of different litters. For example, in one experiment each of three pigs from the same litter was placed in a separate dietary group (control, egg yolk diet, butter diet) and in each group it was the pig from this litter that developed the most extensive atherosclerosis. In general, the Landrace-Yorkshire crosses were less susceptible than the purebred Yorkshires.

Differences in serum cholesterol levels of swine from different litters and from different strains suggest that genetic factors may be involved. Lewis and Page studied cholesterol, lipoprotein, and plasma protein levels in a strain of miniature pigs bred for a short-fat (mesomorphic) somatotype and a strain bred for a long-lean (ectomorphic) somatotype. Higher blood concentrations of lipids and proteins were found in the fat pigs than in the lean pigs. These differences persisted during the period of rapid growth when relative rates of weight gain were similar and diets were identical. Thus different serum cholesterol, lipoprotein, and protein patterns were associated with genetically determined somatotypes (hereditary obesity and leanness) in these two strains. Heidenreich et al. found statistically significant differences in serum cholesterol levels in different litters of swine at older ages (172 and 182 days).

As mentioned previously, the White Carneau pigeon breed is actually a strain, closely inbred for over 40 years, which has developed a high degree of susceptibility to spontaneous atherosclerosis.

It has been known for over 80 years that rabbits develop a type of medial arteriosclerosis involving primarily the thoracic aorta. The majority of workers reporting this lesion have found it in less than 10 per cent of control animals, but reports have varied from none to almost 100 per cent. In Kesten's series practically all the rabbits 8 months of age or older had the lesions. This

**Table 4**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number Female</th>
<th>Number Male</th>
<th>Age-adjusted ratio per 1,000</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dogs</td>
<td>2295</td>
<td>2705</td>
<td>10.8</td>
<td>17.3</td>
</tr>
<tr>
<td>Cocker Spaniels</td>
<td>278</td>
<td>240</td>
<td>16.9</td>
<td>75.7</td>
</tr>
<tr>
<td>Other than Cocker Spaniels</td>
<td>2017</td>
<td>2465</td>
<td>10.0</td>
<td>10.9</td>
</tr>
</tbody>
</table>

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group consisted of 125 individuals raised from one buck and six doe rabbits of the chinchilla breed. Zeek\textsuperscript{51} reported that inbreeding produced a strain relatively free from spontaneous medial sclerosis and another strain with an incidence of about 30 per cent. Kesten\textsuperscript{9} could not account for the high incidence of the disease in his group of related rabbits and suggested that this was another example of the relationship between heredity and disease susceptibility.

**Congenital Malformations**

There are a number of reports of specific congenital malformations occurring in families of animals or developing in selectively bred strains. One of the earliest reports of these in birds was cited by Laubry and Pezzi.\textsuperscript{52} Borghini (1900) observed a family of pigeons in which death of most of the offspring of two generations was attributed to persistent ductus arteriosus with a right-to-left shunt. Siller\textsuperscript{53} discovered a remarkably high incidence of interventricular septal defects in three inbred lines of Brown Leghorn chickens. Eight different strains had been inbred for many years. In three of these, the incidence of the lesion was 84.2, 49.5, and 31.4 per cent, respectively. In three other strains, the incidence ranged from 3.6 to 5.9 per cent. Cross-breeding high with high, and high with low incidence lines resulted in a drop in incidence of the condition. Embryologic studies indicated that the ventricular septal defects could be caused by one or more of several factors observed: stenosis of the right atrioventricular ostium, hypoplasia of its tubercules, an enlarged aortic interstitial cushion, or agenesis of the right fourth aortic arch.\textsuperscript{54} This appears to be a hereditary congenital malformation in which McKusick\textsuperscript{55} has suggested that the inheritance is polygenic.

Fox\textsuperscript{56} is investigating an inbred strain of Long-Evans rats with a high incidence of congenital aneurysm of the membranous interventricular septum. She states that her current findings strongly suggest genetic transmission of this cardiac abnormality.

In swine, Emsbo\textsuperscript{18} found two examples of familial occurrence of subaortic stenosis. In one case, a boar that was shown to have the lesion at death had been bred to three sows. Two of the litter from one sow and one from the second sow exhibited signs before death suggesting fatal cardiac disease. Death was attributed to subaortic stenosis found on postmortem examination of a male offspring from the third sow. In another family, four female littermates were retained for breeding and two of these were found dead at 9 months of age. On postmortem examination, subaortic stenosis was found and established as the cause of death.

Breazile\textsuperscript{57} described eight individuals with aortic arch anomalies and patent ductus arteriosus from two litters of Landrace pigs born on the same farm. Although the Landrace breed is known to be inbred, there was no evidence of inbreeding on this farm for the last 5 years. Although a hereditary factor could be involved in this occurrence, environmental influence affecting the pigs in utero could produce the same result.

In cattle, genetic influence is suggested by the occurrence of interventricular septal defects\textsuperscript{58, 59} in closely related individuals. Bellin\textsuperscript{58} found five calves with interventricular septal defects complicated by various other associated cardiac malformations in two closely related herds of Hereford cattle. Pedigree analysis indicated that the genes responsible came from both parents and were not sex-linked. Two of the calves were sired by the same bull, and another bull was the sire of one defective calf and great-grand sire, on both sides, of another defective calf. In addition, another calf had a congenital malformation of the tricuspid valve and a second calf had a fenestrated foramen ovale. The latter condition is common in calves in general, owing to the normal process of closure of the foramen ovale in this species. Currently, three living heifers and one bull calf have cardiac murmurs, but a definite diagnosis has not been made. Because routine necropsies have been done in these herds only since 1958, the total incidence of congenital heart disease is not known.

Regan et al.\textsuperscript{56} suggested from inadequate evidence that a single autosomal recessive
GENETICS OF CARDIOVASCULAR DISEASE

Gene might be responsible for the occurrence of patent foramen ovale and interventricular septal defect in Jersey cattle. Terman and co-workers concluded that congenital heart disease might be responsible for early deaths in a herd of Holstein-Fresian cattle, but the data obtained were too meager to be certain that any cardiac malformations were present.

Sybesma has published a study of a bull and its progeny in which fatal hemorrhages from congenital aneurysms of the celiac and cephalic mesenteric arteries occurred frequently. Apparently, the aneurysms formed as the result of faulty fusion of the embryonic pairs of these vessels. Of 125 sons and daughters of this bull, data were available on 63. Five of these cattle are still living, and 58 died or were slaughtered. Twenty-four of the 58 died of hemorrhages or were slaughtered because hemorrhage had started. Three cows showed the arterial abnormalities, although rupture and hemorrhage had not occurred. The author concluded that a dominant gene carried by the bull caused a simple autosomal form of heredity, resulting in transmission of the lethal anomaly.

Congenital cardiac malformations in families of dogs have been observed only rarely. Milks and Williams reported an example in which persistent right aortic arch occurred in three Boston Terriers from the same kennel, two of which had the same sire. Naylor found this same lesion in a German Shepherd and in a puppy in a later litter from the same dam. We have observed patent ductus arteriosus in both a mother and son of the Cocker Spaniel breed.

In recent studies, a family of Keeshonden has been discovered, in which there are multiple members with congenital cardiovascular malformations. Two female littermates were bred to the same male, approximately half of the offspring from these matings have various cardiac malformations including pulmonic stenosis, interventricular septal defect, patent ductus arteriosus, anomalous right subclavian artery, and persistent left cephalic vena cava. The two dams, the sire, and various other members of the family have been examined clinically and do not appear to be affected. Two pups from an accidental brother-sister mating in a branch of the same family died soon after birth and were also found to have cardiac malformations.

Cardiomyopathies

Homburger and associates have discovered a generalized polymyopathy and myocardial necrosis in all of 100 individuals studied thus far in a line of Syrian golden hamsters developed through 25 generations of brother-sister matings. The myocardial lesions resemble those produced experimentally in rats by Selye.

The myocardial necrosis was usually the cause of relatively early and sudden death in these animals. Whether this condition represents a genetically determined muscular dystrophy, an infectious polymyositis, or a metabolic or toxic myopathy is unknown. The authors' working hypothesis is that the disease or the susceptibility to it is inherited, as are previously reported muscular dystrophies in mice, chickens, and man. Hummel is studying a dystrophic calcification of the myocardium and testicular blood vessels that has appeared in a strain of inbred mice (identified as C3HeB/Fe). Myocardial lesions are found in 100 per cent of breeding females and, when severe, the skeletal muscle is also involved. Fewer male and virgin females are affected and in these the disease is less severe. The probable interaction of heredity and environmental factors in this condition remain to be worked out. Other strains of mice (DBA/1 and DBA/2) in this laboratory also show this lesion. Meier and Hoag have reported the occurrence of left atrial thrombosis in a strain of mice (strain BALB/c). This is restricted to breeding females and is attributed to postpartum hyperprothrombinemia.

Connective Tissue Disorders

Heritable generalized connective-tissue disorders, for the most part, have not been clearly identified and characterized in animals.
other than man. Diseases thought to be similar or related to connective-tissue disorders in man have been reported from time to time: for example, fibrodyplasia ossificans progressiva in the dog; osteogenesis imperfecta in the cat; ox, dog; and “snorter” dwarfism in cattle, which has certain features similar to the Hurler syndrome in man.

“Snorter” dwarfism in cattle is inherited as a simple autosomal recessive. The condition is currently encountered most commonly in Hereford and Angus breeds in the United States. Lorinez found that urinary acid mucopolysaccharides were elevated in “snorter” dwarf cattle, and McIlwain and Eveleth reported a higher excretion of chondroitin sulfate-B.

Tyler et al. fractionated the mucopolysaccharides from two “snorter” dwarf cattle and found only chondroitin sulfate present. Neither chondroitin sulfate-B nor heparitin sulfate was identified, and the concentration of total polysaccharides in the cattle was lower than that found in humans with gargoylism. In Hurler’s disease of man, “gargoyle” or clear cells storing sulfated mucopolysaccharides are found in histologic sections of the liver, spleen, pituitary glands, and elsewhere. Tyler and associates failed to find these cells, and they have not been reported by others. Since excessive excretion of chondroitin sulfate-B and heparitin sulfate and the presence of “gargoyle” cells are reported to be characteristic of Hurler’s syndrome in man, these authors concluded that “snorter” dwarfism is not a homolog of the human disease.

Mortality among “snorter” dwarfs is high. They exhibit labored breathing from birth (hence the term “snorter”) and bloat readily. Cardiac hypertrophy and valvular fibrosis have been reported in these animals. The relative importance of the cardiovascular disorders in these animals has not been determined.

**Hypertension**

Through selective breeding, strains of rabbits and rats and chickens with arterial hypertension have been developed.

Alexander et al. screened 553 rabbits of New Zealand White, Dutch, and Californian breeds and found 2.7 per cent with systolic pressures of 160 mm. Hg or higher. These individuals were selected for breeding stock. The colony was started with eight separate matings and interbred. New, spontaneously hypertensive rabbits were introduced into the original groups. Twelve families were established and blood pressure determinations were made on two to four generations of each. These rabbits were moderately hypertensive like their parents and the trend continued in two subsequent generations which were followed. In this latter group, the systolic/diastolic blood pressure by direct arterial puncture averaged 151/97 mm. Hg compared with 128/87 mm. Hg for normotensive stock rabbits.

Smirk and Hall developed several families of rats with a high incidence of hypertension by selective crossbreeding followed by intensive inbreeding, using brother-sister matings. As the colony was continued, over 50 per cent of the male rats came to have tail pressures exceeding 150 mm. Hg, compared with a mean of 124 mm. Hg for control males in the original colony.

Recently, Dahl and associates produced two strains of rats by selective inbreeding for three generations: one was resistant and one was sensitive to experimental hypertension induced by chronic, excess salt ingestion. The sensitive strain was normotensive on the control diet.

Sturkie and co-workers observed a wide range of blood pressures in unselected White Leghorn chickens. Hypotensive and hypertensive groups of birds were then chosen and bred selectively without inbreeding for three generations. There was a significant difference in the blood pressure of the progeny of the two lines in each of the generations. These data from breeding experiments in three species indicate that the level of arterial blood pressure is a heritable characteristic.

**Discussion**

The interplay of genetic and environmental influences in the pathogenesis of disease is
well known, both with respect to congenital malformations and the so-called acquired diseases.\textsuperscript{55, 93–97} All diseases are influenced by genetic factors, and environment plays a role of variable importance in hereditary disorders.

Clearly, genetic factors operate in determining individual and group variations in susceptibility to diseases, such as arteriosclerosis or atherosclerosis. The case of atherosclerosis in swine, induced by dietary butter and egg yolk feeding, is an example in which heightened susceptibility in one litter resulted in an increase in degree of the disease produced.\textsuperscript{46} A similar response was noted in the breeds of pigeons with varying susceptibilities to cholesterol and lard feeding.\textsuperscript{58} It is possible that the cardiomyopathies described in rats and hamsters represent an inherited predisposition to toxic agents in the environment.\textsuperscript{64, 70} If increased susceptibility to a disease or condition is inherited, the abnormality cannot appear unless the etiologic agent is present in the environment. For example, the strain of rats susceptible to dietary salt-induced hypertension was normotensive on the control diet.\textsuperscript{90}

An example of environmental influence on congenital disease is the increased incidence of cardiac malformations in a strain of rats, when the pregnant females were exposed to such stress as tumbling.\textsuperscript{18}

The environmental factors that could account for cardiac malformations include a host of teratogenic agents and influences.\textsuperscript{94–97} The effect of rubella in humans suggests that in lower animals certain malformations may result from virus infection in the pregnant female. Hog cholera virus in pregnant sows can produce various congenital malformations\textsuperscript{98} and vaccination of pregnant ewes with modified blue tongue virus may induce congenital lesions.\textsuperscript{99} Cardiac malformations have not been specifically reported, but presumably can be so caused. Virus infections in the pregnant dam, however, have not been identified as a significant cause of cardiac malformations in mammals other than man. It has been shown experimentally that viruses produce congenital malformations in chick embryos.\textsuperscript{93} Whether other teratogenic influences, such as nutritional deficiencies and various chemicals, are important in the etiology of naturally occurring malformations in animals is not known.

Of the evidence suggesting the importance of genetic factors in cardiovascular disease, the most convincing is the development of strains of animals with a high incidence of some specific disease or condition. Examples of this are congenital cardiac malformations in chickens\textsuperscript{53} and rats,\textsuperscript{56} cardiomyopathies in hamsters\textsuperscript{64} and mice,\textsuperscript{70} and hypertension in rabbits,\textsuperscript{85} rats,\textsuperscript{86} and chickens.\textsuperscript{87} This direct approach to the problems of identifying heritable disease and studying modes of inheritance has been surprisingly infrequent in the cardiovascular field. Since analogs and counterparts of many human diseases of the heart and blood vessels occur in the lower species, this type of research should contribute to a better understanding of the role of genetic factors in the pathogenesis of cardiovascular diseases of man and other animals.

Summary

When the incidences and types of cardiovascular disease present in various species, breeds, and strains, or families of animals are compared, certain differences are apparent. It is often difficult, however, to separate hereditary from environmental influences.

Studies of vascular disease in zoo animals have shown that changing environmental conditions can alter the incidence of certain types of lesions in various species. Species differences, however, in resistance to diet-induced atherosclerosis appear to be genetically determined. The prevalence and types of congenital cardiac malformations appear to differ from species to species, but further systematic study is required. Arterial blood pressure is higher in the giraffe and turkey than in other species, and normal variants in cardiac rhythm are characteristic of the dog, horse, and mole.

Relatively high incidences of specific cardiovascular diseases are found in certain breeds of animals. The White Carneaux, Auto-sexing King, and Silver King breeds of pigeons have a high incidence of atherosclerosis. Congenital heart disease appears to be more common in purebred than in mongrel dogs, and
an unusual aggregation of cases of subaortic stenosis in the Boxer and German Shepherd breeds has been found. In a survey of heart disease in dogs, the prevalence of chronic congestive heart failure in the male Cocker Spaniel greatly exceeded that in the male and female of all other breeds. Arterial blood pressure is higher in Broad Breasted Bronze turkeys than in the Jersey Buff breed. This is associated in the former breed with a relatively high incidence of spontaneous aortic rupture.

The occurrence of cardiovascular disease is unusually high in certain families and strains of animals. Among swine, litter and strain differences in serum cholesterol levels and in susceptibility to atherogenic diets occur. The White Carneaux breed of pigeons is actually a highly inbred strain with a remarkable predisposition to the development of atherosclerosis. Strains of chickens and rats with high incidences of interventricular septal defects have been developed by selective breeding. The familial occurrence of congenital heart disease in dogs and swine has been observed, and an inherited vascular anomaly in cattle has been described. Through selective breeding of laboratory rodents, strains with various types of cardiomyopathies have been developed. Certain diseases thought to be similar to the heritable disorders of connective tissue in man have been identified in domestic species. The level of arterial blood pressure is a heritable characteristic, and strains of rabbits, rats, and chickens with relative hypertension have been produced by selective breeding.

Many of these observations indicate the importance of inheritance in determining susceptibility to various types of acquired cardiovascular disease. Genetic factors appear to operate in determining the occurrence of certain congenital malformations. Breeding experiments provide the most convincing evidence of genetic influence on the development of specific cardiovascular lesions. This experimental approach holds the greatest promise for furthering knowledge and understanding of the role of inheritance in the etiology of disease of the heart and blood vessels.

Addendum
Since this manuscript was prepared, the following information has come to hand: Behrer and Goldring\textsuperscript{100} have observed a familial incidence of subaortic stenosis in German Shepherd dogs and Weidman\textsuperscript{101} has worked with a strain of purebred Beagles which have a high prevalence of interventricular septal defects.

Okamoto and Aoki\textsuperscript{102} have obtained a Wistar rat strain in which the incidence of hypertension is 100 per cent.

A male Beagle with a serum cholesterol level of 1,760 mg per 100 ml of serum has been discovered which produced seven daughters with serum cholesterol levels exceeding 200 mg per 100 ml.\textsuperscript{103}

References

Circulation, Volume XXX, July 1964
GENETICS OF CARDIOVASCULAR DISEASE

39. Bradley, J.: Partial bibliography of congenital heart disease in dogs. Comparative Cardiovascular Studies Unit, School of Veterinary Medicine, University of Pennsylvania, 1963.*

* This list will be sent on request to interested readers (author).


70. HUMMEL, K. P.: Personal communication, 1963.


Circulation, Volume XXX, July 1964
100. Behrer, M. R., and Goldring, D.: [St. Louis Children's Hospital, St. Louis, Mo.] Personal communication, 1963.
Genetic Aspects of Cardiovascular Diseases in Animals
D. K. DETWEILER

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