Congenital and Genetic Disease in Domestic Animals

Farm and household animals can warn of environmental hazards and provide models of human genetic disease.

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By relying upon standard laboratory species for research in genetics and teratology, scientists may be neglecting clues from other species, particularly domestic animals, such as dogs, cats, cattle, sheep, and swine. I shall describe some recent observations on domestic animals that have led to the identification of environmental teratogens, and have provided insights into the pathogenesis of some congenital defects and genetic diseases in man. Most of the chosen examples are recent, unprobed observations, topical and ripe for investigative effort. Since animal models of human diseases have been the subject of a spate of recent symposia, bibliographies, books, and editorials (*1*), an encyclopedic review is not intended.

Malformations Caused by Plant Toxin

For 50 years, farmers in the western United States accepted, indeed apparently concealed, the fact that each year about 1 percent of ewes would deliver monstrous lambs with midfacial malformations or cebocephaly (Fig. 1A). The defects ranged in severity from cyclopia, through maxillary hypoplasia producing the appearance of a monkey's face, to the slightest irregularity of the upper lip. These deformities, popularly known as chattos, which means monkey face, were not considered hereditary, but occurred only in certain Rocky Mountain herds. In order to preserve a breeder's reputation, the lambs that did not die from asphyxiation caused by the defects were slain and lost to scientific study.

In the late 1950's, an epidemic rise in the frequency of chattos in certain herds led Binns and others of the U.S. Department of Agriculture to investigate the cyclopian sheep. In his initial report in 1959, he and his co-workers described the clinical syndrome and crucial breeding experiments, which excluded recessive inheritance and implicated an environmental agent (*2*). In the next report (*3*) necropsy findings were added and the bluetongue vaccine, which was known to produce stillborn and malformed lambs (*4*), was exonerated. Review of environmental factors failed to implicate nutritional excesses or deficiencies and mineral toxins, but foscused attention on the plant *Veratrum californicum,* which grew only in the high altitude ranges grazed by the affected herds (Fig. 1B) (*5*). The feeding of dried *V. californicum* to ewes at low altitudes during the first month of gestation produced the cyclopian syndrome in the offspring (*6*) and established day 14 of gestation as the specific time of susceptibility (*7*). It was significant that experimental feedings in smaller laboratory animals yielded no cyclopian monsters.

Workers in the same laboratory (*8*) pursued the offending plant substance, turning first to extracted alkaloids and later defining the chemical structures and teratogenic activity of compounds purified from *V. californicum.* The active teratogens were cyclopamine, cycloposine, and jervine, all steroids with a rigidly positioned tetrahydrofurylpiperidine side chain at C-17 (Fig. 1C). Appreciating the role of hormonal modification of gene action, Keeler suggested that the teratogenic mechanism might be a competitive inhibition by cyclopamine of hormones which help initiate RNA synthesis at appropriate times during embryogenesis.

Thus, over 15 years, the secret of a disease occurring to excess in isolated flocks of sheep was revealed by an observant veterinarian and skilled chemist. Although their story is still incomplete, they have contributed greatly to the economic welfare of sheep ranchers and to awareness of yet another class of teratogens.

In particular, this account illustrates one worthwhile use of animal models—for distinguishing genetic from environmental causes in a cluster of similar cases. In man, this question must be settled by epidemiological studies, which may be tedious, time consuming, and often inconclusive. In diseases of domestic animals, on the other hand, epidemiology still provides an initial hypothesis which can be tested quickly by definitive breeding experiments. At present, this type of cranial malformation in sheep is well studied and well known, but has no human homolog because an environmental teratogen has not been identified in cases of cyclopia in man.

Minamata Disease: Mercury Poisoning

A disease of man was delineated not long ago through epidemiologic observations by alert clinicians (*9*). The neurologic ailment, now called Minamata disease, was first described after an epidemic in Japan in the mid-1950's. The cause was poisoning by methylmercury, which was discharged as a by-product from a plastics factory into Minamata Bay, and taken up by fish. Neurologic impairments resulting from the ingestion of poisoned fish were present not only in adults and children—in a familial pattern—but also among the fish themselves and among the fish-eating birds and cats. A smaller epidemic of cerebral palsy among newborn infants was overlooked at first, but proved to be the congenital form of Minamata disease, caused by the ingestion of organic mercury by the pregnant mother who did not develop symptoms.

The lessons on mercury pollution from Japan and elsewhere have been learned slowly in the United States. In New Mexico in early 1970, three out of seven children in the Huckleby family became delirious, blind, and eventually comatose (*10*). The illness had the appearance of an acute, lethal encephalitis, although the specific in-

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fectious agent could not be identified. Thorough epidemiological search implicated the grain ingested by the pigs whose meat the children had eaten. This grain had been treated by an organic mercurial called Panogen; the children's sickness was Minamata disease. The mother was in her seventh month of pregnancy when her children first became ill; she remained well, but the boy she delivered had congenital Minamata disease.

While the Japanese experience makes this tragedy all the more devastating, it is especially so since the makings for a similar calamity were reported, but apparently overlooked, 2 years previously (*11*). Here the victims did not include human beings, but the story was quite similar to the New Mexican episode. Pigs on a New York farm suddenly became febrile, anoretic, and listless for 3 to 5 days before dying in coma; some were incoordinate and blind as well. Because several swine had not been vaccinated, hog cholera was initially diagnosed. Necropsy results failed to support that diagnosis, but suggested mercurial poisoning, which toxicologic tests later confirmed. This confirmation came only after seven of the animals had been sold for food. Ultimately, the whole herd died as did other farm animals and birds. During the epidemic, only five piglets were born alive from five litters of 10 to 14 each; the five young pigs died soon after weaning. As in New Mexico, the feed contained wheat grain that had been coated with the mercurial, Panogen. Let us hope, in the face of this overwhelming evidence, that Minamata disease in domestic animals will henceforth be a model for an extinct human disease.

Monitoring the Environment

Minamata disease and cyclopamine-induced cebocephaly are examples of spontaneous diseases whose causes have been shown to be environmental by epidemiologic observations. Teratologic events in one species cannot be extrapolated to all species, but results in animals can hardly be ignored in watching for environmental dangers to man. In fact, because of their place in man's ecology, domestic animals may well be the best sentries for environmental toxins and teratogens. Spontaneously occurring epidemics of congenital malformations among domestic animals should be brought quickly to the attention of biomedical scientists, so that clues to environmental hazards are not overlooked. The report of Minamata disease among pigs on a New York farm could have prevented the outbreak in the family in New Mexico, if regulatory measures had been taken.

One epidemic now deserving prompt elucidation began in 1967 in central Kentucky (*12*, *13*). Over 500 pigs on nine farms were born with stiff and deformed joints resembling the human condition of arthrogryposis multiplex congenita (Fig. 2). Genetic causes were considered unlikely because different boars were used. Epidemiologic search was focused on burley tobacco stalks, which were ingested during pregnancy by all the mothers of the malformed swine. The teratogenic agent remains unknown, but might prove to be natural plant chemicals, as suggested by a report of a similar microepidemic in Missouri (*14*), or compounds sprayed on the plants, such as various insecti-

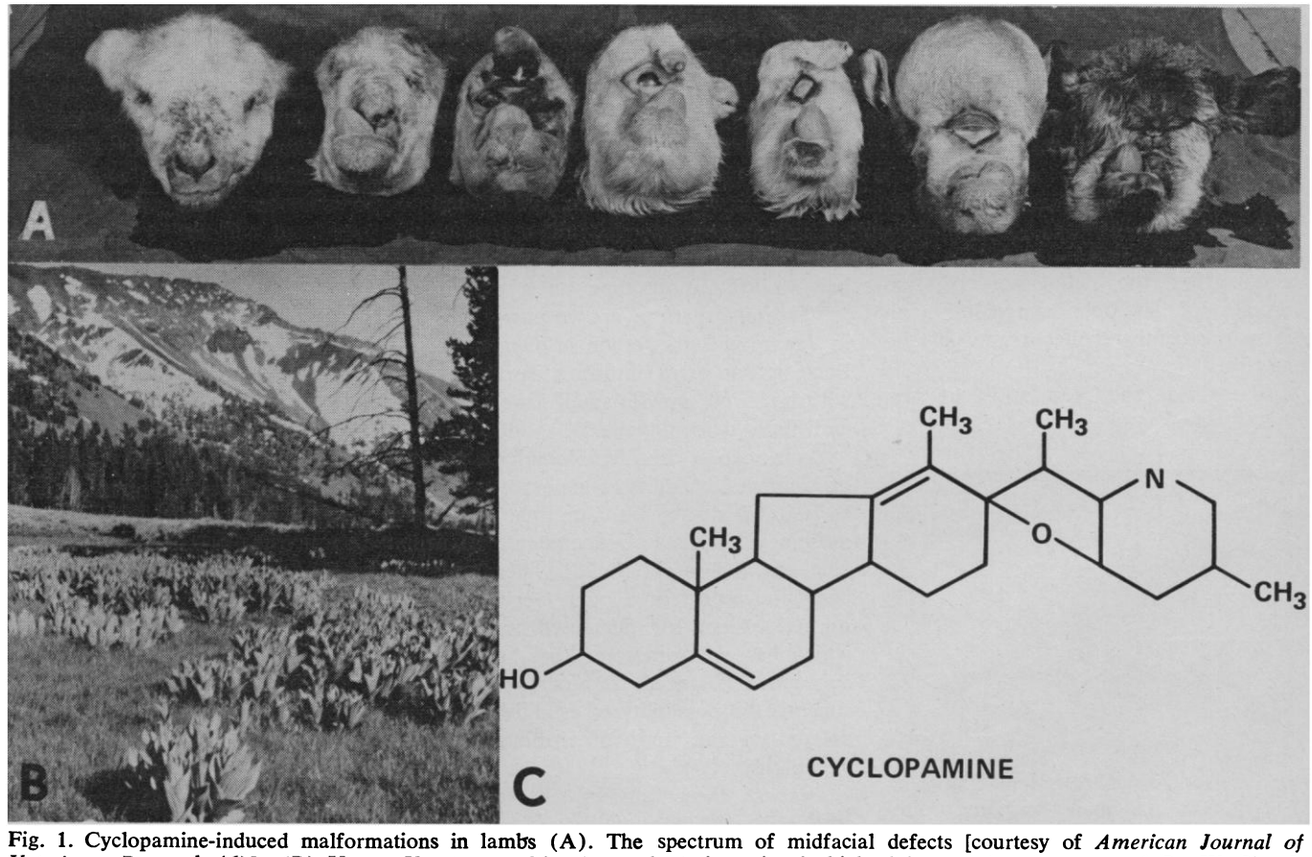

Fig. 1. Cyclopamine-induced malformations in lambs (A). The spectrum of midfacial defects [courtesy of *American Journal of Veterinary Research* (*6*)]. (B) Young *Veratrum californicum* plants in spring in high alpine meadow [courtesy of Dr. W. Binns]. (C) Chemical structure of cyclopamine.

Table 1. The XXY phenotype in man, sheep, cat, and dog (*17, 18*).

Feature	Man	Sheep	Cat	Dog
Frequency among males	1/350	1/000	?	?
Body size	Tall	Small	Variable	Small
Sterile	Yes	Yes	Usually	Yes
Testicular size compared to normal	One-half	One-ninth	One-half	One-half
Spermatogenesis	Some	None	Rare	None
Testicular histology	Tubular hyalinization	Normal	Prominent interstitium	Tubular dysgenesis
Other defects	Mental deficiency plus behavioral aberrations	Normal "mental" abilities	Tortoiseshell color	Cardiac ventricular septal defect
Buccal smear for chromatin	Positive	Positive	Positive	Positive
Type of late-labeling chromosome	Metacentric*	Acrocentric*	Large submetacentric (*18*)*	Submetacentric*

* This is the same type as the X chromosome of this species.

cides and growth-regulating hormones. It is hoped that these outbreaks of arthrogrypotic pigs can stimulate sufficient research so that rational regulation might prevent an epidemic of human malformations.

Homologous Genetic Diseases

Teratogens may act differently in dissimilar species, and extrapolation of findings in animals to cases of human malformation is hazardous. By contrast, the principles of genetic mechanisms are universal—"even down to the fine print," commented *Nature* in citing the fact that, in protein synthesis, most polypeptide chains begin with the same amino acid, methionine, in species as far apart as bacteria, yeast, trout, and rabbit (*15*). Perhaps no other comparative science enjoys a more fundamental unity than mammalian genetics.

Of the contributions made to medical genetics by comparative mammalian cytogenetics (*16*), two are especially noteworthy: the delineation of syndromes of multiple congenital malformations and the phenomenon of chimerism.

The tortoiseshell tomcat is the best known animal that has one extra X chromosome as do men with Klinefelter's syndrome. The XXY chromosomal complement has been found in at least four species and the similarities of their phenotypes are sufficiently impressive to allow the term "Klinefelter's syndrome" (Table 1) (*17, 18*). On the other hand, the contrasts are intriguing. Why are the sheep and dog with the XXY chromosomes small, while the human XXY individual is tall? Why is there no hyalinization in the postpubertal ovine or canine testes? Our ability to find the answers is not impeded by a lack of experimental models.

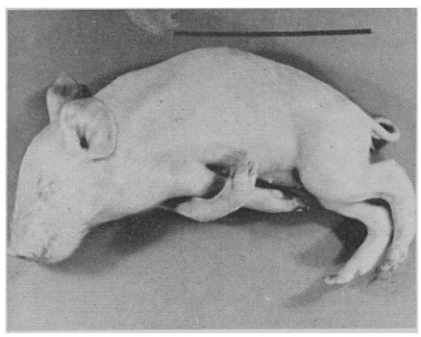

Fig. 2. One of many newborn arthrogrypotic pigs from a Kentucky tobacco farm [courtesy of Dr. M. W. Crowe (*13*)]. Scale 30 cm.

Other chromosomal anomalies have been reported in 2 out of 18 dogs with congenital heart disease and in most domestic species (*19–21*). Chromosomes were analyzed in these animals because they had traits, such as problems of reproductive performance, growth, or development, which have been associated with chromosomal disorders in man. However, no syndrome of anomalies has occurred more than once, except for a similar pattern in two cows, one in Japan and the other in Germany. Each had an extra autosome associated with impaired growth, small lower jaw, and limb deformity (*20*).

As in man, a considerable percentage of animals that die in embryonic or early fetal stages has abnormal chromosomes; this is well documented for chickens and pigs (*21, 22*). There has been one report of a boar, apparently normal except for decreased fertility, which has a chromosome that has undergone a balanced translocation; this suggests the possibility of establishing a colony for the study of chromosomal aneuploidy (*23*).

Despite these studies, karyotypes from animals with malformations are under reported. For example, for eugenic reasons one interesting familial cluster of multiple malformations in Pekingese dogs was lost to further study (Fig. 3) (*24*). Perhaps cytogenetic laboratories should encourage veterinarians to submit specimens. A difficulty which must be tactfully overcome is the reluctance of owners and breeders to allow study of their defective animals. Most owners prefer euthanasia of their animals rather than permit scientific study in order to protect the breeder's reputation.

Chimerism

A mosaic individual has multiple cell lines derived from one zygote, while a chimera has multiple cell lines from more than one zygote (*25*). The chimera, long known to mythology, first found biologic importance when freemartin cattle were described (*26*). The origin of the syndrome has been better

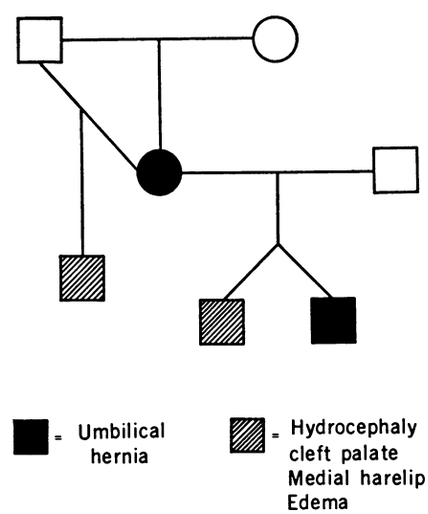

Fig. 3. Familial syndrome of congenital malformations in Pekingese dogs. Euthanasia prevented further study (*18*). Squares represent males, circles represent females.

understood with current cytogenetic analysis. Recognizable as a sterile female, the freemartin results from the intrauterine cross-circulation of blood from a male twin via vascular anastomoses in the placenta. Evidence sustains equally the hypotheses that excessive testosterone from the male sterilizes the female, or that the twins exchange gonadal or blood stem cells which become established in the partners. That the latter event of chimerism sometimes occurs is supported by finding in each twin cells that can be distinguished by histochemical staining, by red cell antigens, or by karyotypes (*27*). Although it is presumed that the placental vascular anomaly occurs less frequently in man than in cattle, at least eight sets of human chimeric twins have been found; thus, chimerism must be considered as an alternate explanation to mosaicism when a patient has two or more cell types. Chimerism, a concept of practical importance in organ transplantation and in the diagnosis of anomalous sexual development, deserves continued study; perhaps one of the best models is the original one—the sterile heifer.

Single Gene Defects

In domestic animals, the number of traits clearly caused by single gene defects is far smaller than would be expected from experience in man. The purist may never accept homology in comparative pathology: the argument can always be advanced that a defective gene is expressed over the background of all other genes, some of which are unique to the species. Yet, some spontaneously occurring animal diseases have been sufficiently studied so as to deserve the claim of homology. Two examples are the Ehlers-Danlos syndrome, inherited as a dominant trait, and the recessive Chediak-Higashi syndrome.

Recently, a heritable disorder of connective tissue in mink and dog was described that resembles the Ehlers-Danlos syndrome in man (*28*). The clinical findings in the animals were lax and hyperextensible joints and skin that was easily stretched, bruised, and scarred. Selective matings and short gestations facilitated the prompt demonstration of an autosomal dominant mode of inheritance. Measurements of the tensile strength and collagen content of the skin suggested a basic defect in the intramolecular cross-linking of collagen, similar to that widely considered responsible for the human condition. Histologically, in both man and the animals, the collagen bundles of the dermis are irregularly smaller and haphazardly ordered with frequent whorl formations. Yet, the elastic fibers in the dog and mink appeared normal in number and appearance—an observation contrasting with the popular notion that elastic fibers are more numerous and abnormal in Ehlers-Danlos syndrome of man (*29*). It is noteworthy that more recent studies in man suggest the abnormal elastic fibers are secondary to the basic collagen defect (*30*). With this new model in mink, dogs, and perhaps in pigs and cattle (*31*) and renewed interest in collagen research, great strides can be anticipated in the understanding of Ehlers-Danlos syndrome, long stagnant from a lack of methods and subjects.

Similar research models may be offered by mink, cattle, and mice which have a condition resembling Chediak-Higashi syndrome (*32*). In 1943, children were described who had white streaks in their hair, photophobia, pale eyes, and most strikingly, a marked proclivity to contract bacterial infections causing death by 7 years of age. Their leukocytes showed abnormally large granules in the cytoplasm. In 1941, a strain of mink, designated Aleutian, arose with unusually light coat color, photophobia, pale eyes, and a tendency to develop infections. The breed was propagated (in an autosomal recessive pattern) for its coat, but not until the early 1960's was the resemblance recognized between the leukocyte granules of the Aleutian mink and those of patients with Chediak-Higashi syndrome. This identity prompted studies in a unique herd of partially albino, photophobic Hereford cows. Again, the large, pale lysosomes and autosomal recessive inheritance were obvious. Although the clinical severity of the disease differs in the three species, the basic defect may be failure of lysosomes to rupture following phagocytosis of bacteria. These findings in domestic animals led Bennett *et al.* (*33*) to discover an autosomal recessive trait in the beige laboratory mouse consisting of pigmentary dilution and giant lysosomes in leukocytes. But the murine condition is a less satisfactory model than that of cattle and mink, for there is no diathesis for infection.

The almost simultaneous discovery of three diverse species manifesting a "new," rare disease points out the likelihood of finding animal homologs to many human diseases caused by single genes. People with diseases of single gene etiology are individually rare and present limited research opportunities. Further understanding of their traits seems worthwhile in order to relieve a disproportionate amount of suffering and to advance general biomedical knowledge that has applications far beyond the few affected individuals. It appears at present that domestic animals deserve wider exploitation.

Genes Linked on the X Chromosome

Comparative study of traits borne on the X chromosome enjoys a theoretical advantage over studies of autosomal traits, namely, the remarkable stability of the genetic content of that chromosome during mammalian evolution (*34*). A constant 5 percent of the nuclear DNA in each mammalian cell seems to be located on the X chromosome. Moreover, the X chromosomes of man and other mammals surely bear homologous genes, thereby providing landmarks for mapping other genes. Comparable genes include those responsible for hemophilias A and B, glucose-6-phosphate dehydrogenase, and cystinuria (*35*). Animals with these traits are useful for understanding clinical and molecular aspects of the human conditions.

Even more valuable might be the use of animals in analyzing gene linkage groups. Linkage analyses in man are tedious because of small families and long generation time. It can take years to prove a loose linkage. Often only the more common protein polymorphisms can be studied in humans. Matings of appropriate animals could quickly reveal linkage groups. If these groups included a locus for a homologous human trait, then a new human linkage group could be suggested. While direct extrapolation back to man is hazardous, hypotheses suggested by studies in animals can be promptly tested in man. For example, the locus for glucose-6-phosphate dehydrogenase has been linked in pigs to

the "H" locus (*36*). If confirmed, this fact should promote a search for the comparable human locus. The efficiency of using animals for linkage analysis has been shown by Hines *et al.* (*37*) in a study of 17 polymorphic loci in 6545 mother-daughter cattle pairs. Four linkage groups, including one triplet, were demonstrated. Hines *et al.* emphasized, in particular, the excellent breeding records which expedited their work.

Polygenic Inheritance

The bulk of human disease that has any significant genetic basis cannot be attributed to a single gene, but to many interacting genes, no one of which is dominant. Such inheritance is known as polygenic or multifactorial. Two common human birth defects, one of the heart and the other the hip, seem to be polygenic traits. Comparative aspects of these diseases are strikingly similar in man and dog (*38–40*). For both species, the overall incidence rate of each defect is two to seven per thousand (*41*). Both defects occur more commonly in purebred dogs and in some breeds the high incidence of heart defects is caused by a single type of malformation which might be considered breed specific (Fig. 4). For example, poodles tend to have patent ductus arteriosus, while German shepherds have a persistent right aortic arch. Increased risk of hip dysplasia is partly a function of larger adult size; thus, St. Bernards have 50 times the risk of miniature or toy poodles, which have twice the risk of mongrels.

Advantages of Domestic Animals

Every species used for research, including man, is a compromise from both theoretical and practical considerations. Animals other than man, however, offer the advantages of experimental control and reproducibility. Their breeding—and inbreeding, to a certain extent—can be regulated. The killing of pregnant animals at specific intervals can quickly clarify the embryogenesis of birth defects.

Domestic animals are not a research panacea. Their size alone might prohibit their use at some institutions, especially if breeding experiments were planned. Compared to laboratory rodents, gestations are longer and litter sizes are smaller; sometimes only one or two offspring are produced per cycle. Equally important is the lack of readily available data on ultrastructural and radiologic anatomy, physiology, and pathology of species or breeds.

What, then, are the advantages of using domestic breeds rather than the usual laboratory animals? First and most important is the fact that their diseases occur spontaneously. Spontaneity indicates only that the condition was not induced experimentally by an exogenous agent; it does not imply that the trait appeared unexpectedly or without genetic manipulation. For example, the classic laboratory model of diabetes mellitus requires the administration of alloxan, while the disease appears spontaneously (but not unexpectedly) in man as well as cattle, cats, and dogs (*42*). Traits that have some aspects of diabetes (such as obesity) appear in mice and rats, but no rodent mimics the human condition exactly because of differences in pathophysiology or genetics (*43*). Intensive breeding solely for laboratory use may artificially maintain not only genes for the pathologic trait but also other linked genes whose effects might be subtle but significant. Random use of farm animals with a sporadic disease would thwart this hazard. The second advantage is that domestic animals are comprised of a greater variety of species and families than are the usual laboratory animals and they are frequently more closely related to *Homo sapiens* phylogenetically. Third, men and domestic animals share similar environments, with the same atmospheric toxins and water pollutants, while laboratory species are protected from these potential teratogens and mutagens. Fourth, the size and docility of domestic animals facilitate repeated measurements and observations of a broad range of parameters, such as blood chemicals, tissue biopsies, placentas, and fetal physiology (*44*). Fifth, the genetic background on which diseases caused by single genes are expressed can be modified. On the one hand, a random genetic background, as would be present in mongrel dogs, would be desirable in studying a single mutant gene. On the other hand, a largely shared gene pool, as in purebreds, would be used for reliably producing traits of polygenic inheritance: for example, congenital defects of the heart and hip are most common in purebred dogs. The fact that inbreeding among domestic animals usually fails would deter their use in fields requiring identical genotypes, such as transplantation research. Sixth, individual breeds can have numerous pathologic traits offering a variety of experimental models in a single breed.

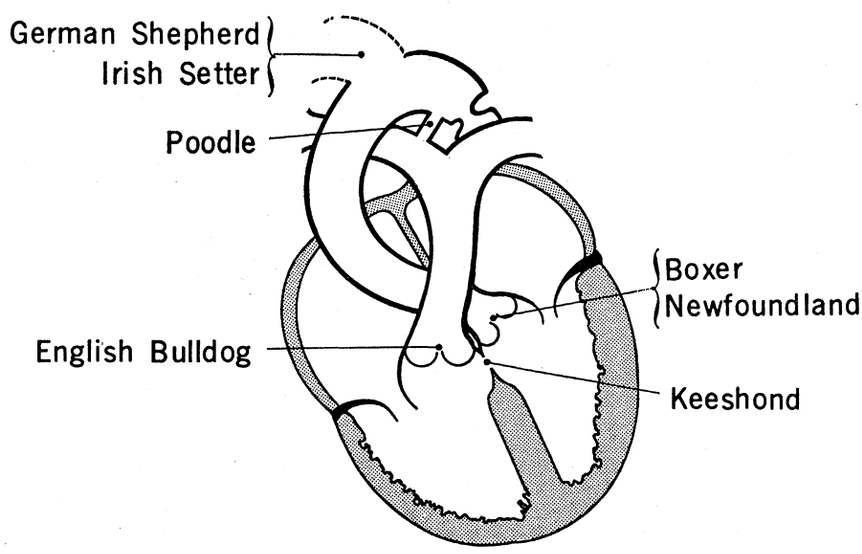

Fig. 4. Breed-specific congenital heart defects in dogs at the School of Veterinary Medicine, University of Pennsylvania, 1958–1965 (*40*). Certain breeds of dogs have significant excesses of specific heart defects ($P < .01$, except English bulldog where $P < .05$). For example, Keeshonds had an excess frequency of ventricular septal defects (as part of tetralogy of Flofallot). Persistence of the right aortic arch was common in German shepherd dogs and Irish setters.

Summary and Recommendations

A large number of experimental models exists throughout the nation in barnyards, kennels, and homes, as well as in clinics of veterinary medical schools. Spontaneously occurring congenital defects in these animals can give life-saving clues to new environmental teratogens of importance to man, such as methylmercury. Their genetic disorders, whether of chromosomal, single gene, or polygenic etiology, provide research opportunities that are often unavailable in the usual laboratory species. The Klinefelter, Ehlers-Danlos, and Chediak-Higashi syndromes, chimerism, congenital heart disease, and congenital hip dysplasia are some human conditions that can be studied in domestic animals. In the past, comparative research on these conditions has been sporadic and fortuitous. While serendipitous discoveries may be of great value, a systematic approach would be more effective.

In order to promote this systematic approach, several programs are now under way:

1) Documentation of the frequency of disease in a defined population of animals (*39, 45*).

2) Simultaneous surveillance of a human and animal population to identify outbreaks of congenital defects that might be caused by a teratogen (*14, 46*).

3) Formal training programs in comparative pathology (*47*).

4) A national exchange of information on animal models (*48*).

Besides these systematic programs, other efforts are equally desirable, but harder to define: (i) establishment of biologic (including radiologic, immunologic, and endocrinologic) standards in each species and breed; (ii) greater awareness of the veterinary literature by biomedical researchers, a state which can be achieved by reading *Current Contents* (*49*) and through library subscriptions to standard veterinary periodicals; and (iii) greater cooperation between animal owners and veterinary scientists, so that potential models are not killed before they are adequately studied.

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49. The Institute for Scientific Information, Philadelphia, publishes weekly issues in one annual volume for each of five scientific fields.

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