Cleft Lip and Palate in Dogs: A Progress Report

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Over a period of six years a colony of dogs with a variety of types of cleft lip and palate has been maintained at the University of Florida (*3, 4*). The present paper is a report on some genetic aspects of the character in these dogs and observations on drug-induced cleft palate in mongrel dogs.

Methods

In 1959 and 1960 we acquired two newborn English Staffordshire female dogs with clefts of the lip and primary palate. They came from successive matings between two phenotypically-normal purebred dogs with no reported history of malformations in their ancestry. These cleft dogs, both female, were raised to maturity and crossed to both father and to phenotypically-normal litter mates. An American Staffordshire male with an incomplete cleft of the lip and alveolus on the left was acquired and the breeding of phenotypically-cleft males to phenotypically-cleft females carried out. In addition to the Staffordshire dogs and their progeny, we have added Dachshund, Cocker Spaniel, Florida cur, and German Shepherd dogs with a variety of types of cleft lip and palate to the breeding stock.

The general experimental breeding plan that is being carried out includes a) cleft phenotype x cleft phenotype, b) cleft phenotype x mongrel outcross, and c) the testcross of the resultant F_1 hybrid to the cleft strains and to mongrels.

In addition to the genetic studies, preliminary work is being conducted in mongrel dogs in an effort to induce facial clefts by teratogenic agents. Healthy, normal mongrel females in beginning estrus are removed from the newly arrived stock at the dog farm. These dogs are then bred to randomly selected healthy, normal mongrel males in the regular farm stock we are using.

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Findings

In the genetic study there have been a total of 32 matings which have produced 132 viable young. All degrees of expression of cleft lip and palate have been observed in the progeny of these matings: a) phenotypically-normal animals, b) incomplete cleft lip, unilateral (Figure 1), c) complete cleft lip and alveolus, unilateral, d) complete cleft lip and palate, unilateral, e) bilateral cleft lip and primary palate, and f) bilateral complete cleft lip and palate.

In the mating of phenotypically-normal dogs (Figure 2), presumably heterozygous for the character, 7 matings produced 31 young of which 5 were cleft. In 4 matings between a dog with a cleft and a phenotypically-normal litter mate (Figure 3), 13 puppies were produced, of which 4 were cleft. In an F_1 backcross to a cleft dog, 3 of 8 dogs were cleft. Eleven matings between cleft dogs to mongrels (Figure 4), produced 56 dogs in which there was one cleft animal, a female who had a unilateral cleft lip and palate.

In 9 matings of phenotypically-cleft partners (Figure 5), 24 viable young were produced of which 10 were cleft, an expression rate of 41.7%. When the cleft is unilateral, it has been on the left side except in one instance. There have been no sex differences in expression of the character. Of great interest is the fact that the severity of the defect in the parents has not appeared to influence the severity of defect in the offspring. Further, we are now certain that the defect can be passed into a mongrel and retrieved in the backcross of the F_1 heterozygote to the original parent. In matings of the cleft dogs to mongrels, there has been produced one cleft dog in 56 young. This is the single exception within the breeding material which would vitiate the hypothesis that the character is recessive (*7*). It may be that, on occasion, the trait can indeed be expressed in the heterozygote and thus behave as an irregular dominant as postulated by Steiniger (*8*) for mice and Fogh-Andersen (*1*) for humans. On the other hand, it is possible that this mongrel is in fact heterozygous for the trait. Test breedings are planned to determine the validity of this most plausible assumption. Finally, it may be that environmental variables, unknown at the moment and favorable to the expression of cleft lip and palate, played a role. There was nothing unusual in this dog's pregnancy, however, and no medications were given.

In the teratogenic study 19 gravid mongrel dogs were studied. Chlorzyclizine hydrocholoride has been extensively studied by King and his colleagues (*5, 6*) at the National Institute of Dental Research. In doses akin to those used in this study, this compound has been found to be highly effective in producing cleft palate, microstoma, micrognathia, and skeletal deformities in Sprague-Dawley rats. Seven dogs treated with chlorcyclizine (up to 50 mgm/kg body weight daily on days 22 through 28) produced 25 normal young. No abnormalities were observed grossly

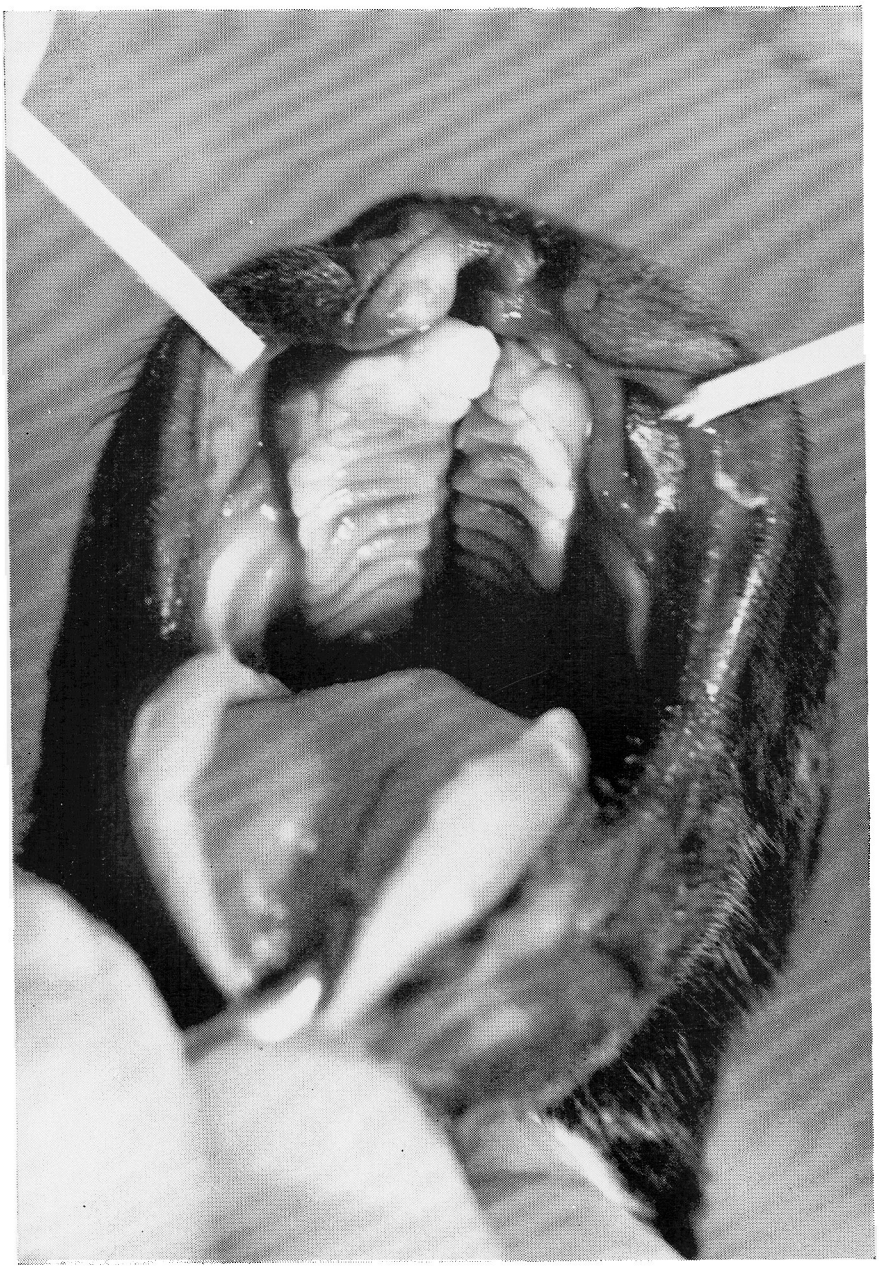

FIGURE 1. Incomplete cleft lip, unilateral, as an example of the hereditary malformations seen in the colony of dogs.

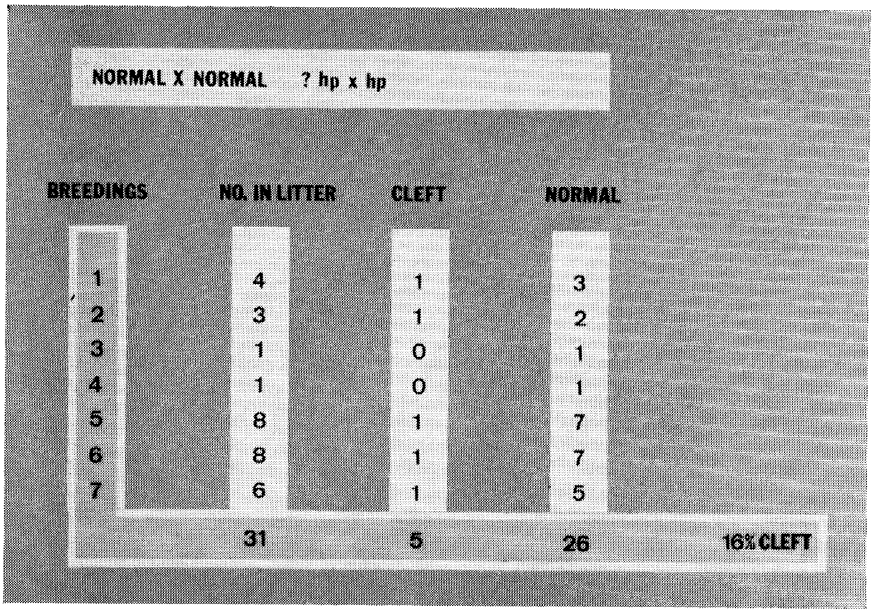

FIGURE 2. Breeding record of phenotypically normal dogs, presumably heterozygous for the character.

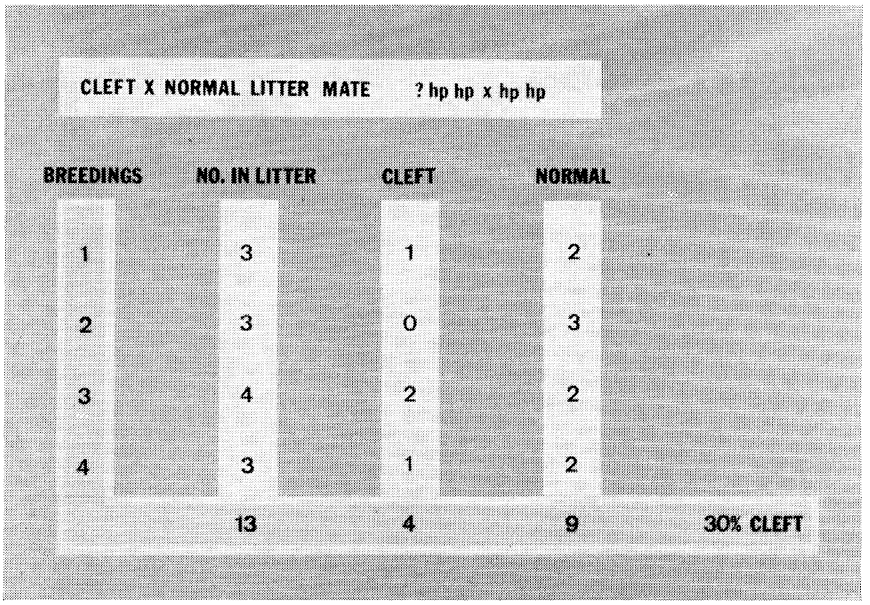

FIGURE 3. Breeding record of cleft to phenotypically-normal litter mates.

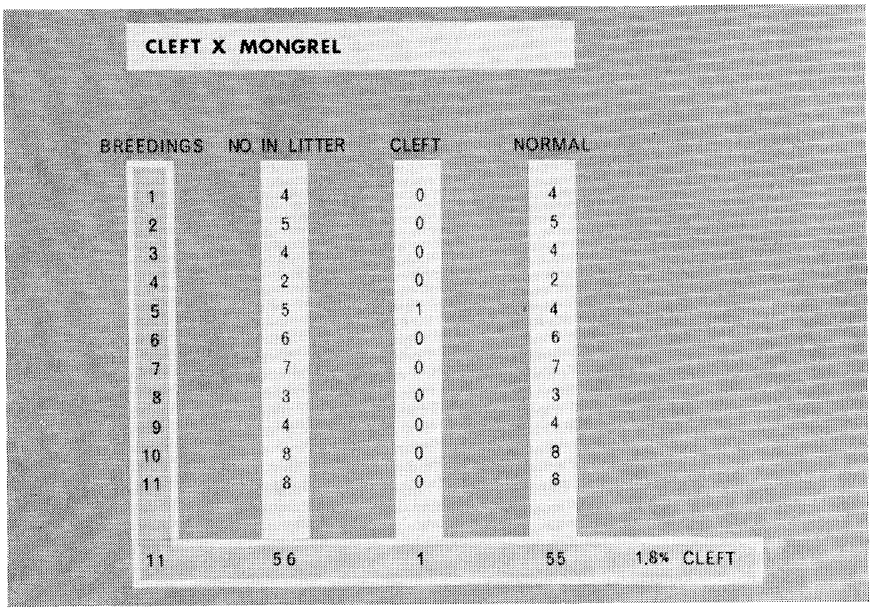

FIGURE 4. Breeding record of cleft dogs to mongrels.

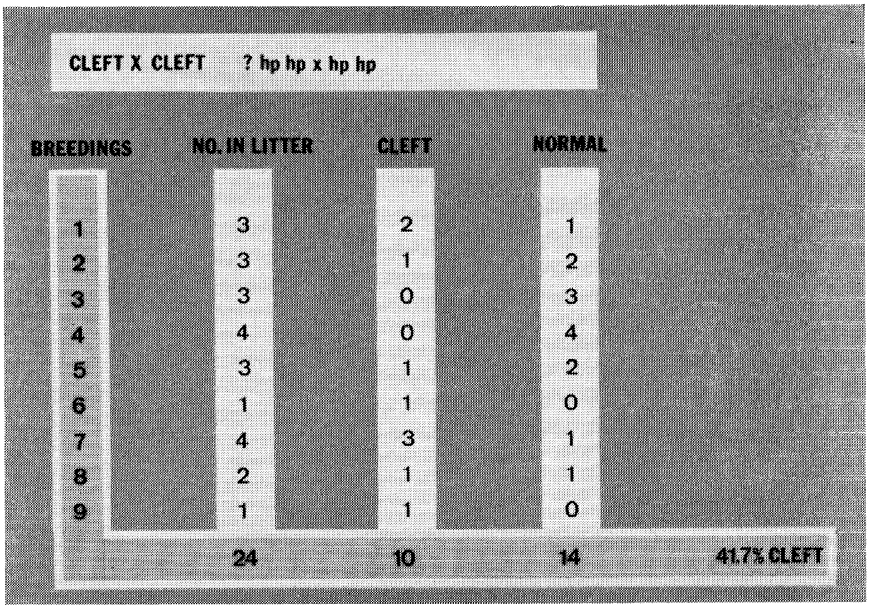

FIGURE 5. Breeding record of cleft dogs.

at hysterotomy on days 50 to 58, nor were any noted at subsequent autopsy. No fetal deaths were noted.

Eight dogs were given 0.15 mgm/kg 6-Diazo-5-oxo-L-Norleucine (DON) on days 19, 20, and 21 of gestation. DON is a competitive inhibitor of glutamine essential for the contribution of amide groups in the synthesis of purine base in DNA. All of the progeny of 7 of the 8 dogs (36 fetuses in all) were found as necrotic resorption sites in the uterine horns, indicating early fetal death. The remaining dog gave premature birth on the 43rd day to 5 pups without gross abnormalities, save for the immaturity.

Treatment days were then changed to days 25 through 28 of gestation; dose and route of administration were kept the same. In 2 dogs so treated there were 3 fetal deaths, 4 normal feti, and 3 with limb deformities. In a third dog, there were 2 viable pups which had complete clefts of the secondary palate, micrognathia, club foot, and syndactyly (Figure 6). Friedman (*2*) has observed similar defects in a dog treated with 0.15 mgm/kg DON on days 19 through 21. Thus, there is confirmation that DON is capable of producing cleft palate in the dog. Dose and timing appear to be extremely critical. In our study, when the compound was

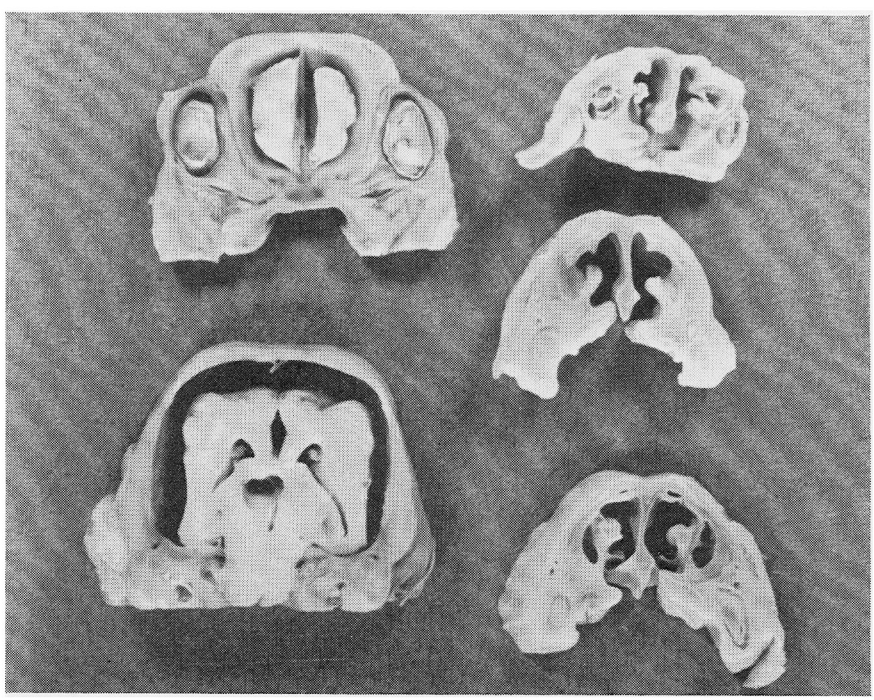

FIGURE 6. Serial sections of the head of a cleft pup which had received 6-Diazo 5-oxo-L-norleucine (DON).

given early there was wholesale fetal death. The discrepancy between our study and Friedman's is due almost surely to the difficulty of determining when conception actually occurs.

It is our general purpose to establish time and dosage in the mongrel of various known teratogens. Once established, the compounds in doses subteratogenic for the mongrel can be studied in the genetic colony of animals.

Summary

A colony of dogs has been established to study the genesis of clefts of the lip and palate. All varieties of cleft lip and palate have been seen in these dogs from incomplete clefts of the lip to bilateral complete clefts of the lip and palate. Data are not sufficient to warrant solid conclusions on the gross Mendelian characteristics of the trait. The data neither confirm or deny the hypothesis that cleft lip and palate is recessive with expression controlled by environmental or possibly genetic modifiers. Chlorcyclizine hydrochloride is not teratogenic when given to gravid mongrel dogs within the conditions of this study. 6-Diazo-5-oxo-L-norleucine can produce cleft palate, micrognathia and limb deformities in the mongrel dog.

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References

1. Fogh-Andersen, P., Inheritance of Harelip and Cleft Palate. Copenhagen, Denmark: Ejnar Munksgaard, 1943.
2. Friedman, M., cited by M. Lois Murphy, Congential Malformations. Boston: Ciba Foundation Symposium, Little-Brown Company, 1961.
3. Jurkiewicz, M. J., A study of cleft lip and palate in dogs. *Surgical Forum, 15,* 457–458, 1964.
4. Jurkiewicz, M. J., A genetic study of cleft lip and palate in dogs. *Surgical Forum, 16,* 472–473, 1965.
5. King, C. R. G., Teratogenic effects of meclizine hydrochloride on the rat. *Science, 141,* 353–355, 1963.
6. King, C. R. G., Weaver, S. A. and Nanod, S. A., Antihistamines and teratogenicity in the rat. *Pharmacol. exp. Ther., 147,* 391–398, 1965.
7. Reed, S. C., Harelip in the house mouse II. *Genetics, 21,* 361–374, 1936.
8. Steiniger, F., Neu Beobacktungen an der erblichen Hasencharte der Maus, *Zeitschrift fur Menschliche Verebungsund Konstitutions, 23,* 427–462, 1939.