An Epidemiologic Investigation of Factors Related to the Extent of Facial Clefts. I. Sex of Patient

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Previous investigations have indicated that the incidence of facial clefts is not equal for males and females. Differences between the two sexes have been noted which appear dependent on the type of cleft (isolated cleft lip, cleft lip in combination with cleft palate, or isolated cleft palate) (*2, 3*). Furthermore, it must be noted that within the three qualitative cleft types there are quantitative gradations. For example, not all clefts of the lip are complete and not all palatal clefts involve the entire hard and soft palate. Indeed, it is possible to have an extremely large number of quantitative assessments of the facial cleft process.

Little is known about the sex distribution for the severity spectrum of isolated cleft lip and cleft lip-cleft palate combinations. However, there are data concerning this aspect for isolated cleft palate. Knox and Braithwaite (*5*) divided palatal clefts into two groups: a) complete postalveolar clefts, and b) submucous clefts of soft palate and minor hard palate. Their results were based on 104 cases of isolated cleft palate and indicate that, for all clefts of the palate, without regard to extent, the female-to-male ratio was 1.5:1. When these clefts were analyzed according to the two anatomic divisions, the sex ratios were found to be 2.1:1 and 0.94:1 respectively. The reversal in sex ratio for the less severe clefts is quite evident.

Two other studies yield data which lend themselves to similar comparisons. Fogh-Andersen (*1*) divided palatal cleft into two groups: large and small clefts. The so-called large clefts involved both hard and soft palates, while the small-cleft group involved the soft palate

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TABLE 1. Data from three studies regarding the relationship between sex distribution and anteroposterior extent of cleft palate.

extent of cleft	*Knox and Braithwaite (5)*			*Fogh-Andersen (1)*			*Mazaheri (6)*			*all studies*		
	f	*m*	*f/m ratio*	*f*	*m*	*f/m ratio*	*f*	*m*	*f/m ratio*	*f*	*m*	*f/m ratio*
complete.....	72	34	2.1/1	65	21	3.1/1	96	64	1.5/1	233	119	2.0/1
partial.....	32	34	0.94/1	68	51	1.33/1	43	39	1.1/1	124	124	1.2/1
total.....	104	68	1.5/1	133	72	1.8/1	139	103	1.3/1	376	243	1.5/1

only. His results demonstrated a similar phenomenon. The ratio of females to males for palatal clefts of all types was 1.8:1; for complete hard and soft palate clefts, 3.1:1; and for clefts of the soft palate only, 1.3:1. The study of Mazaheri (*6*) employing Veau's classification, illustrated the same phenomenon. The results of all three studies are summarized in Table 1.

The present study was designed to investigate in detail the sex-severity relationships not only with regard to isolated cleft palate, but also isolated cleft lip and cleft lip in combination with cleft palate.

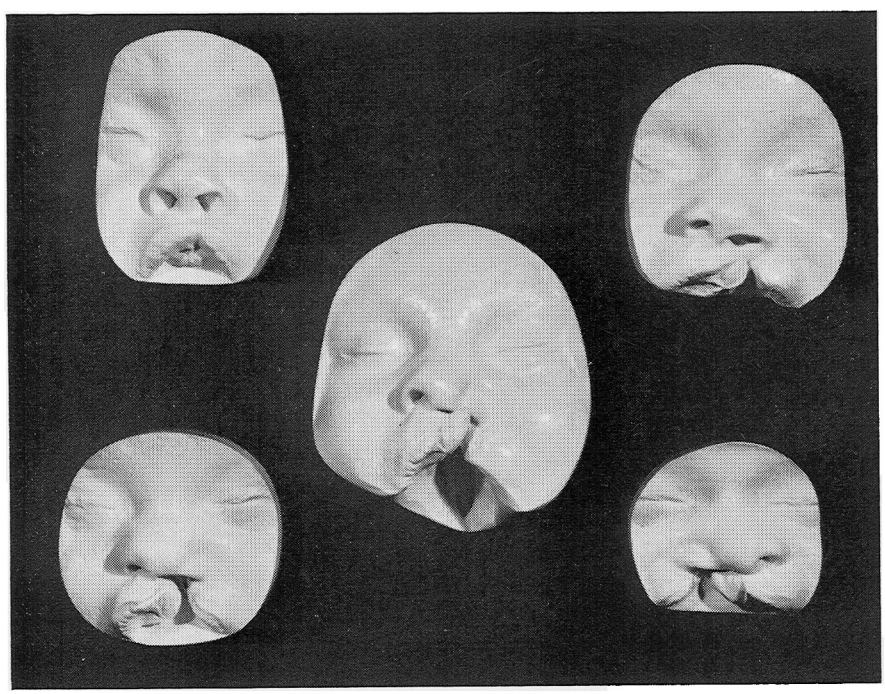

FIGURE 1. Facial mask of unoperated unilateral cleft lips demonstrating a range of variation from a notch extending to the vermillion border through complete clefts of the nose with variable relation to the alveolar segment.

Methods and Materials

The study group consisted of 477 Caucasian facial cleft patients who were treated at the University of Illinois Cleft Palate Clinic during the period of 1950 through 1964. For each of these subjects there exists a set of preoperative dental casts (Figures 1 and 2). These casts were examined and graded according to extent of cleft, using criteria proposed by the American Cleft Palate Association and reported by Harkins and associates (*4*).

Although these criteria proved to be satisfactory for initial categorization, the extremely large number of observed combinations made it necessary to regroup the subjects into different categories, as follows.

1. Isolated cleft palate (176 patients)
   a. Complete cleft of hard and soft palate
   b. Incomplete cleft of hard palate and complete cleft of soft palate
   c. Complete cleft of soft palate only
   d. Incomplete cleft of soft palate
2. Isolated cleft lip (56 patients)
   a. Complete bilateral or unilateral cleft lip
   b. Incomplete bilateral or unilateral cleft lip

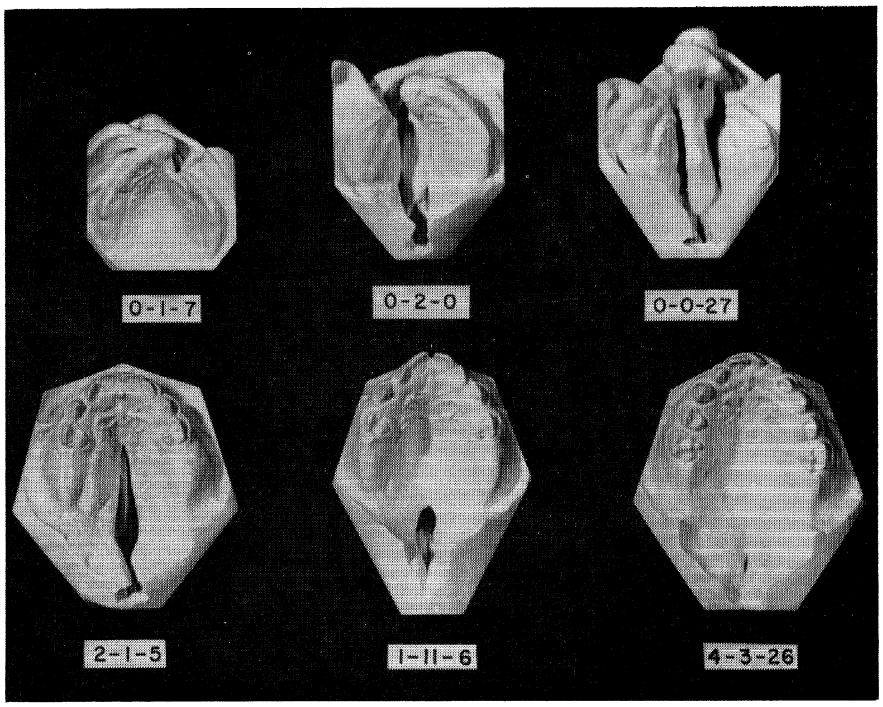

FIGURE 2. Casts of various types of unoperated clefts of the lip and/or palate.

3. Combination of cleft lip and cleft palate (245 patients)
   a. Complete bilateral or unilateral cleft lip and cleft palate
   b. Incomplete bilateral or unilateral cleft lip and cleft palate

The resulting information was used to test the null hypothesis that there is no relationship between extent of cleft and sex of patient. Under this hypothesis, it would be expected that the sex distribution of facial cleft patients would be essentially the same for each of the three groups and for each of the subgroups within each group. The null hypothesis was tested using the chi-square test.

Results

Table 2 indicates that females represented 62% of all patients in the isolated cleft palate sample. The subcategories, however, displayed considerable variation from this percentage with the highest proportion of females noted in the more severe cleft categories. The chi-square analysis yielded a highly significant result.

As shown in Tables 3 and 4, the female with a cleft lip with or without a cleft palate has a greater likelihood of having a complete cleft than has her male counterpart. This phenomenon is illustrated further by the fact that of patients with isolated cleft lip, 32% of the females and only 9% of the males had a complete cleft. Similarly, among patients with combined clefts of lip and palate, 68% of the females had complete clefts as contrasted with 58% of the males.

Discussion

Among the number of hypotheses that can be entertained to explain the results noted in this investigation, the one which we will discuss considers a hypothetical model based on palatal development. This model assumes that at a given gestational moment in time, male embryos as a group are more advanced or retarded in palatal morphogenesis than females. Another assumption is that the mechanism that produces the defect must operate at an as yet unknown but fixed gestational time.

TABLE 2. Sex distribution of patients with isolated clefts of the secondary palate, according to extent of cleft.

extent of cleft	*males*		*females*		*total*
	N	%	*N*	%	
complete hard and soft palate cleft	13	31	29	69	42
incomplete hard complete soft palate cleft	23	29	56	71	79
complete soft palate cleft	14	42	19	58	33
incomplete soft palate cleft	17	77	5	23	22
total	67	38	109	62	176
chi square	17.95				

TABLE 3. Sex distribution of patients with isolated clefts of the lip, according to extent of cleft. The chi-square was corrected with the Yate's correction factor; before correction, the value was 4.85.

extent of cleft	*males*		*females*		*total*
	N	%	*N*	%	
complete bilateral or unilateral isolated cleft lip	3	30	7	70	10
incomplete bilateral or unilateral isolated cleft lip	31	67	15	33	46
total	34	61	22	39	56
chi-square	3.41				

TABLE 4. Sex distribution of patients with clefts of lip and palate, according to extent of cleft. The chi-square was corrected with the Yate's correction factor; before correction, the value was 2.06.

extent of cleft	*males*		*females*		*total*
	N	%	*N*	%	
complete bilateral or unilateral cleft lip and cleft palate	99	66	51	34	150
incomplete bilateral or unilateral cleft lip and cleft palate	71	75	24	25	95
total	170	69	75	31	245
chi-square	1.68				

The hypothetical results of this model, as applied to facial clefts, are depicted in Figures 3 and 4 which describe the developmental distribution of male and female embryos at a given moment in time, during which the teratogen can operate. For purposes of the hypothesis, development of the palate is divided into ten arbitrary stages. Stage I through III and VII through X are not susceptible to the action of the teratogen. It should be borne in mind that the stages of development represent successive degrees of closure of the embryonic palatal structures and that teratogenic action at a lower stage of development will result in a cleft of greater extent than will such action at a higher stage of development.

Utilizing this model and assuming that males are more advanced in regard to primary and secondary palate formation than females and that males and females in the susceptible stages of development will demonstrate a facial cleft of some magnitude, the following predictions can be formulated.

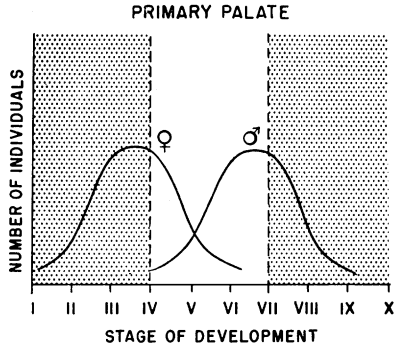

FIGURE 3. A hypothetical distribution of Caucasian embryos according to stage of development and sex during the teratogenic period.

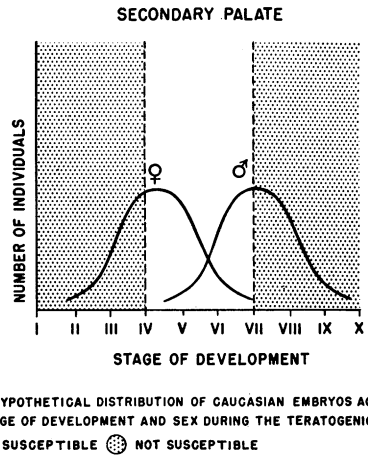

FIGURE 4. A hypothetical distribution of Caucasian embryos according to stage of development and sex during the teratogenic period.

a) According to Figure 3, it would be expected that since the area under the curve for males in the "susceptible zone" is greater than the area under the curve for females in the "susceptible zone," more males than females would have primary palatal clefts of all extents. This is in accordance with the actual sex distribution noted in the literature for isolated clefts of the lip. However, if a random sample of patients was selected from a pool of patients with lip clefts of all magnitudes, the female should have a greater likelihood than the male of having a more complete cleft. This results from the fact that, at the time of action of the teratogen, the females proportionately are at an earlier stage of development of the primary palate than are the males.

b) Similar reasoning can be applied to clefts of the secondary palate (Figure 4). In this situation, one would predict that females would predominate in both extent and absolute numbers since both relevant areas under the curve for females are greater, absolutely and relatively, than the corresponding areas under the curve for males.

It must be pointed out that, although the results presented earlier and those predicted in Figures 3 and 4 are consistent, this in no way affirms our hypothetical model since the model was derived from data yielded in this study. However, it is demonstrated that a plausible hypothesis relating sex and severity of clefting can be advanced based on the assumption of differential rates of palatal development for the two sexes. The plausibility of this hypothesis must be tempered at this time by the realization that the data on which the model is based results from a sample which may or may not be representative of the universe of facial clefts in utero. The true test of this model will require further, more definitive studies in which the hypotheses can be tested in an a priori fashion.

Conclusion

Preoperative dental casts of 477 Caucasian facial cleft patients were examined and graded according to extent of cleft process. The criteria for grading was a modified form of that advocated by the American Cleft Palate Association. This information was then used to test the null hypothesis that there was no relationship between extent of cleft and sex of patient. The results of this analysis indicated that, independent of major cleft type, the female with a facial cleft appears to have a greater likelihood of demonstrating a complete cleft than does her male counterpart. A model based on the assumption of differential palatal development of the sexes was advanced to explain these findings.

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