Oral Clefts in the American Indian

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ORAL CLEFTS vary considerably in incidence among the races (*1–3*). Among the major racial groups the highest frequencies seem to occur among the Mongoloids. Miller (*4*) reported rates for cleft lip and cleft palate in Indians of British Columbia almost identical to those for the Japanese. However, Tretsven (*5*) reported considerably higher rates for Indians born in Montana.

This study, part of a larger program concerned with congenital malformations among American Indians, was undertaken to determine the frequency of occurrence of cleft lip and cleft palate among American Indians born in Public Health Service hospitals.

Source of Data

All births in the Service's Indian hospitals are reported to the Human Genetics Branch of the National Institute of Dental Research. This procedure started on July 1, 1964.

Each report includes the infant's inpatient medical record and some information on prenatal history, delivery, and the newborn's physical examination, course in the hospital, and physical status at discharge. The data cover the period from July 1963 through June 1966. From July 1963 through June 1964 only a discharge summary was available; therefore the information for that year is somewhat less complete than for the last 2 years of this study.

Findings

During the study period, 25,341 births were reported from 46 Indian hospitals. The general locations of the various Indian hospitals within their administrative areas are shown in the map. Medical care is provided through contract with private hospitals for groups not able to use Government facilities. We estimated that approximately one-half of the American Indians born during 1963–66 are included in this study. The incidence of cleft lip and cleft palate found in this study and data for other races are shown in table 1.

Because of the relatively small number of cases available no attempt has been made to examine the data for intertribal variation in the frequency of oral clefts. Such analysis is planned when sufficient data become available. Tabulation by major linguistic groups revealed no significant differences. Because there is considerable evidence to support the hypothesis that cleft lip with or without cleft palate and isolated cleft palate are distinct entities (*6–9*), they are presented separately.

For the cleft lip with or without cleft palate complex the Indian frequency is intermediate between Japanese and Caucasians; however, the Negro frequency is considerably lower than that of the Indian, Japanese, or Caucasian. In contrast, the incidence of isolated cleft palate is almost identical for Indians and Japanese. The Negro and Caucasian series are similar for isolated cleft palate, with an incidence about one-half that of the Mongoloid groups.

Data from two previous studies of cleft lip and cleft palate in the American Indian are

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notable. Although Miller (*4*) did not separate the cleft lip complex from isolated cleft palate, the total frequency he observed among Indians in British Columbia was not significantly different from that found in our study. Among 12,337 births, Miller noted 2.91 combined cases per 1,000 live births.

Tretsven (*5*) reported 27 clefts among 7,461 Indian births during a 7-year period in Montana, an incidence almost two times higher than the figure we observed for Indians born in Public Health Service hospitals throughout the United States. Tretsven's cases were determined as part of a statewide rehabilitation program, and ascertainment was probably nearly complete. Some of the difference between our data and those from Montana may be because in our study a portion of the cases which later came to the attention of a rehabilitation program may not have been detected or recorded on the hospital record for the newborn. This is most likely for the less severe defects; particularly isolated clefts of the soft palate. However, this kind of a difference would be at least partially offset by the inclusion on hospital records of multiply malformed children, with clefts, who do not survive.

In order to make more detailed comparisons of the frequency of oral clefts among Indians born in Public Health Service hospitals in Montana with Indian births for the entire State, we reviewed the Service hospital discharge records for 4,499 births from 1955–61. Fourteen children with oral clefts were recorded. This gave a 7-year incidence in Montana Service hospitals of one in 321 births, a figure somewhat lower than that obtained by Tretsven (*5*) but higher than our U.S. average.

In reviewing copies of the 27 birth certificates of the cleft group reported by Tretsven, for whose cooperation we are grateful, we found that six infants were apparently of the Flathead tribe, a tribe which generally does not obtain medical care from the Public Health

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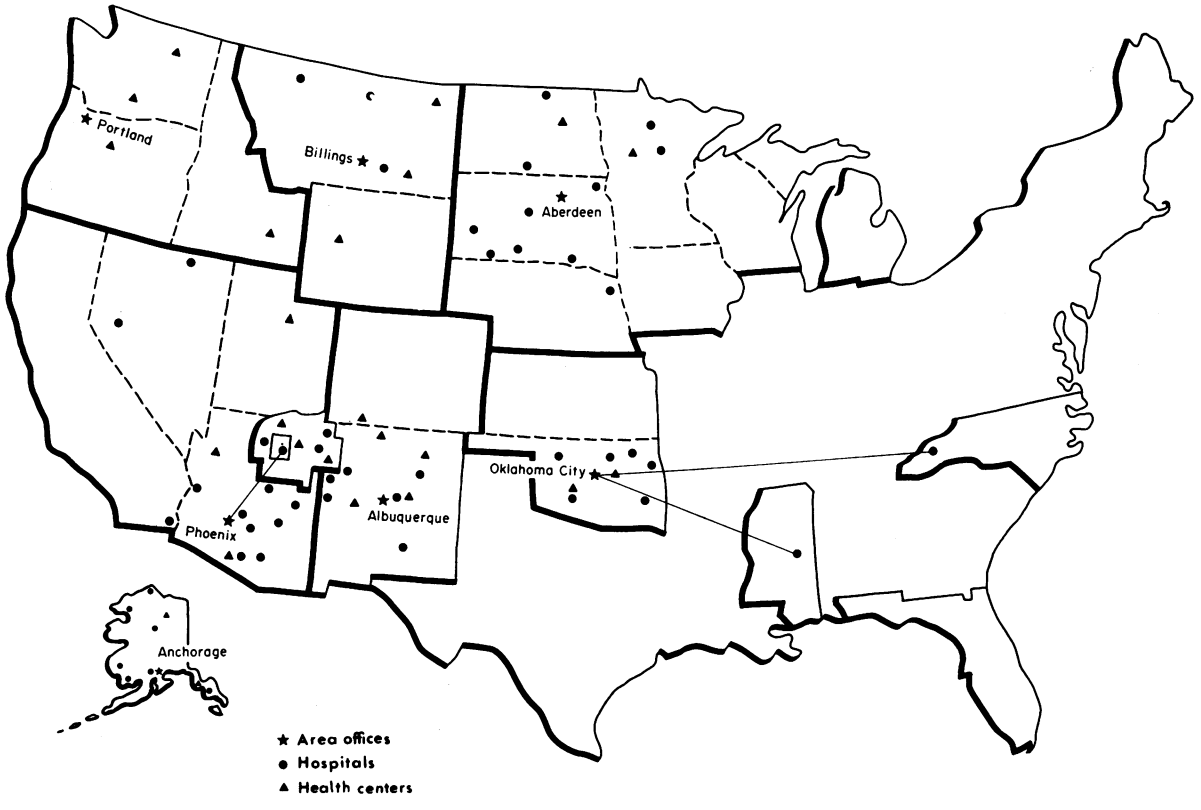

Table 1. Incidence of oral clefts in major racial groups

Racial group and source of data	Number of births	Cleft lip with or without cleft palate		Isolated cleft palate		Combined cases per 1,000 live births
		Number	Cases per 1,000 live births	Number	Cases per 1,000 live births	
Japanese: Neel (*1*)	63, 796	136	2. 13	35	0. 55	2. 68
American Indian [1]	25, 341	35	1. 38	15	. 59	1. 97
Caucasian	204, 341	245	1. 20	68	. 33	1. 53
Fogh-Anderson (*6*)	128, 306	149	1. 16	44	. 34	1. 50
Chung and Myrianthopoulos (*16*)	16, 385	22	1. 34	8	. 49	1. 83
Woolf (*7*)	59, 650	74	1. 24	16	. 27	1. 50
Negro	96, 801	26	. 27	24	. 24	. 52
Altemus (*17*)	79, 842	19	. 24	17	. 21	. 45
Chung and Myrianthopoulos (*16*)	16, 959	7	. 41	7	. 41	. 82

[1] From this study; excludes Alaskan Natives.

Service. According to data obtained from the National Office of Vital Statistics, there were 921 births in the Flathead Agency area during 1955–61, an incidence of oral cleft of one in 154 births for the Flathead tribe. If the Flathead births are removed from Tretsven's data, the incidence for all other Indians in Montana is one in 311, a figure close to that obtained for Service hospitals.

The American Indian is by no means homogeneous genetically and certainly almost all present-day groups contain some Caucasian admixture. Genetic data available regarding the amount of hybridization of reservation Indians is limited. The mother's ABO blood group and Rh type, as well as her statement of her degree of Indian blood, is included on the clinical record for the newborn. Since only two blood-group systems are available and in some cases the samples are small, we did not attempt to present more precise calculations here.

Table 2 shows the frequency of B or AB and Rh-negative phenotypes of the mothers of infants reported by the hospital where the birth occurred and the percentage of mothers who claimed less than three-fourths Indian ancestry. The particular hospitals listed were chosen only because they were the ones for which the most blood-typing data were available. Collectively, they account for more than 70 percent of the births reported here. The first column lists the tribal affiliation of the obstetrical patients. The rather sizable amount of genetic admixture and the variation between facilities can readily be seen. It is apparent that a large proportion of the admixture has been Caucasian since the increase in Rh-negative genes is relatively greater than the addition of group B genes. Rh-negative is more common in Caucasian populations than in Negro, while the reverse is true for group B. Both antigens are almost nonexistent among pure Indians.

Discussion

Even though American Indians and Japanese are more closely related to each other than to Caucasians, they nevertheless have been genetically isolated for a considerable period of time. Differences between the two groups have had ample time to arise from a variety of sources, with genetic drift being perhaps one of the most important. It is of interest, however, to examine our data under the assumptions that the two populations are similar with respect to the genetic factors underlying oral clefts and that if appreciable differences in gene frequencies have arisen in subgroups, through drift, the mean frequencies have remained similar.

As presented, our data emphasize that the frequency of cleft lip with or without cleft palate in American Indians approaches the frequency in Caucasian populations more closely than it does another Mongoloid population, specifically the Japanese. Interestingly,

the frequency of isolated cleft palate in Indians is nearly identical to that in the Japanese and approximately twice that in Caucasian and Negro populations. These observations can be explained in part by a consideration of what is known of the genetic basis of oral clefts and the documented racial admixture which characterizes the American Indian.

A number of lines of evidence support the hypothesis that genetic factors are of greater importance in the cleft lip with or without cleft palate complex than in isolated cleft palate. In human beings the evidence comes primarily from data on twins (*9*, *10*). Thus, heritability estimates are approximately 0.40 for cleft lip with or without cleft palate in contrast to 0.006 for isolated cleft palate. Pedigree analyses also tend to indicate a lower genetic component in isolated cleft palate (*10*, *11*). Several authors have documented the occurrence of simple dominant inheritance in some cases of isolated cleft palate (*6*, *12*). In light of the twin and pedigree studies it is apparent that dominant genes, although present, cannot account for a very large portion of the defect.

Studies of the cleft lip with or without cleft palate complex have, however, pointed to a more important genetic component. Fogh-Anderson (*6*) suggested that cleft lip with or without cleft palate was inherited as an "incomplete" recessive, while Cox and associates (*10*) concluded that at least two independent recessive loci were involved. Reed (*13*) concluded that cleft lip in the A strain of the house mouse is probably due to the cumulative action of several recessive genes with environmental modification. It has not been possible to confirm a simple mode of inheritance for cleft lip with or without cleft palate in human beings; however, multiple recessive genes as suggested for the house mouse provides a tenable working hypothesis.

Assuming that the genetic basis of the defect is identical in the two parent populations and the pre-Columbian mean gene frequencies were similar, genetic miscegenation will result in in-

Table 2. Frequency of blood groups B or AB and Rh negative and maternal degree of Indian ancestry, by area and facility

Area and facility	Tribe [1]	Percent with <¾ Indian ancestry	Percent B or AB	Percent Rh negative
Aberdeen:				
Red Lake	Chippewa	23	3	0
Pine Ridge	Sioux	30	0	5
Eagle Butte	do	37	3	2
Belcourt	Chippewa	98	12	7
Albuquerque:				
Shiprock	Navajo	0	0	1
Zuni	Zuni, Navajo	1	7	2
Fort Defiance	Navajo	3	0	0
Tuba City	do	3	0	0
Gallup	do	4	1	3
Billings:				
Browning	Blackfoot	53	2	5
Crow Agency	Crow, Cheyenne	26	2	2
Phoenix:				
San Carlos	Apache	1	0	0
Sells	Papago	2	0	0
Sacaton	Papago, Pima	5	0	0
Schurz	Paiute, Shoshone	24	3	2
Oklahoma:				
Philadelphia, Miss	Choctaw	0	0	0
Lawton	Choctaw, Kiowa, Comanche	19	4	3
Pawnee	Ponca	24	4	6
Talihina	Choctaw	28	3	2
Claremore	Creek, Cherokee	30	7	1
Tahlequah	Cherokee	44	7	5
Cherokee	do	47	4	4

[1] Only tribes constituting more than 10 percent of hospital population are listed.

termediate frequencies in the hybrid in the absence of heterosis. Considering the amount of Caucasian admixture present in the American Indian, the observed similarity between Caucasians and American Indians is, in the case of cleft lip with or without cleft palate, compatable with a relatively simple genetic model.

The almost identical frequencies of isolated cleft palate in American Indians and Japanese are difficult to explain with classic genetic models. One might speculate that the racial differences observed in the frequency of isolated cleft palate result not from differing frequencies of a specific gene or genes but rather from a complex genetic predisposition. A predisposition involving nonspecific multiple homozygosis with expression depending largely on environmental factors, as suggested by Neel (*1*), might be reasonable. Until such complex systems are better understood, it is impossible to predict with certainty the results of racial mixture.

The high frequency of oral clefts among the Flathead Indians suggests that a major gene has reached high frequency as a result of genetic drift in a small isolate. An autosomal dominant gene responsible for cleft lip and cleft palate has been reported by Van der Woude (*14*). She found that in Michigan this gene accounted for only 0.5 percent of the cleft cases, but she suggested that its true frequency might be higher. At least one other example of an isolate with a high frequency of oral clefts is known. Studies among the Haliwa Indians of North Carolina, a triracial isolate numbering approximately 3,700 persons, have revealed 50 cases of cleft lip or palate (*15*). Clinical and genetic studies indicate that this defect is apparently due to a single autosomal gene and is probably the same syndrome reported by Van der Woude (*14*). Although fistulae of the lower lip were present, this was an inconstant finding. We examined 34 of the Haliwa patients and noted only two with fistulae of the lower lip. Pedigree analysis of this highly endogamous group indicates a common genetic basis for at least 30 of the patients.

We suggest that the unusual frequency of oral clefts in Montana may have been due to a similar situation, namely, the presence of a usually rare major gene at high frequency among the Flathead tribe. The general high frequency of clefts in Montana perhaps represents recent diffusion of this gene into other tribes in the area.

Conclusions

The overall frequency of cleft lip with or without cleft palate in American Indian infants born in Public Health Service hospitals is intermediate between the incidence in Mongoloid and Caucasian populations. Considering the documented admixture of Caucasian genes, the present-day Indian frequency approximates what might be expected if the genetic basis for this congenital malformation is relatively simple. Isolated cleft palate does not follow this pattern, and it is unlikely that simple genetic mechanisms contribute materially to the observed cases.

Reports of unusually high frequencies of oral clefts in small isolated Indian populations are probably the consequence of random genetic drift. Documentation of the full extent and degree of variation in the frequency of oral clefts which exists among present-day tribes of North American Indians must await accumulation of additional data.

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Research Grant for Alcoholism Studies

The newly established National Center for Prevention and Control of Alcoholism of the Public Health Service's National Institute of Mental Health is awarding its first grant, $248,961, for alcoholism research and research training to Washington University in St. Louis, Mo. NIMH plans to provide a total of $1,107,787 for the project over 5 years.

Funds will be used for conducting research and a research training program designed to prepare young investigators for their own independent careers in alcoholism research.

Projects planned cover a broad spectrum of research dealing with alcohol and alcoholism. Clinical-sociological investigations will include family studies, criminality, suicide, psychiatric illness, and alcohol usage patterns in alcoholics. The investigators hope these projects will yield important information in causes of early chronic alcoholism, the most effective methods of therapy for different personality types, the therapeutic effect of immediate hospitalization of an alcoholic after loss of a loved one as a suicide prevention measure, and other related aspects of alcoholism.

A psychological study is planned, based on the theory that responses learned in a drugged condition may not transfer to the nondrugged condition, or vice versa. This investigation could produce an explanation for the difference in the relative efficacies of various treatment modalities.

Neurophysiological research will be concerned with studying alcoholics and their hallucinations, and in the awake, inebriated, and withdrawal phases. Brain chemistry in alcoholism will be the focus of neurochemical studies, with emphasis on the metabolism of alcohol in both alcoholics and nonalcoholics.