Incidence of Clefts and Parental Age

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Clefts of the lip and palate are among the most frequent of serious congenital malformations, affecting about one in every seven hundred babies born in the United States. While evidence exists for both hereditary and environmental etiologies, the actual cause or causes of these defects remains a mystery in spite of considerable research.

About three years ago the Epidemiology Branch of the Division of Dental Health established the National Cleft Lip and Palate Intelligence Service (NIS) designed to encompass a number of types of research projects centering on the study of clefts. The present report is concerned with one facet of one of these projects.

This project is based on all birth certificates from 29 states and from two cities (New York City and Baltimore) on which a congenital malformation of any kind is recorded and on a control or contrast group composed of a one percent sample of birth certificates on which no malformation is recorded (Figure 1). The mention of birth certificates for medical research may provoke an immediate and negative response among some persons. Nevertheless, birth certificates do provide large numbers of cases of congenital malformations, and if the investigator is aware of their limitations as well as their advantages, they can be a valuable source of data for epidemiologic studies.

For this analysis of data on clefts and parental age, only white single live births which occurred during the years 1962 through 1964 were selected. White single births comprise 83% of the controls and 91% of the cleft cases reported on birth certificates during those years (Table 1).

Many investigators who have used an adequate control group have reported a positive correlation between the incidence of clefts and parental age. For example, MacMahon and McKeown in England (*4*), and Woolf and associates in Utah (*5*) found a relationship between maternal age and cleft lip and cleft lip with cleft palate, but not cleft palate alone. In two studies previously published, we reported a relationship between increasing age of father as well as of mother and the frequency of cleft lip with cleft palate and of cleft palate, but not cleft lip alone (*2*, *3*). These findings supported earlier work of Fraser and Calnan (*1*). Es-

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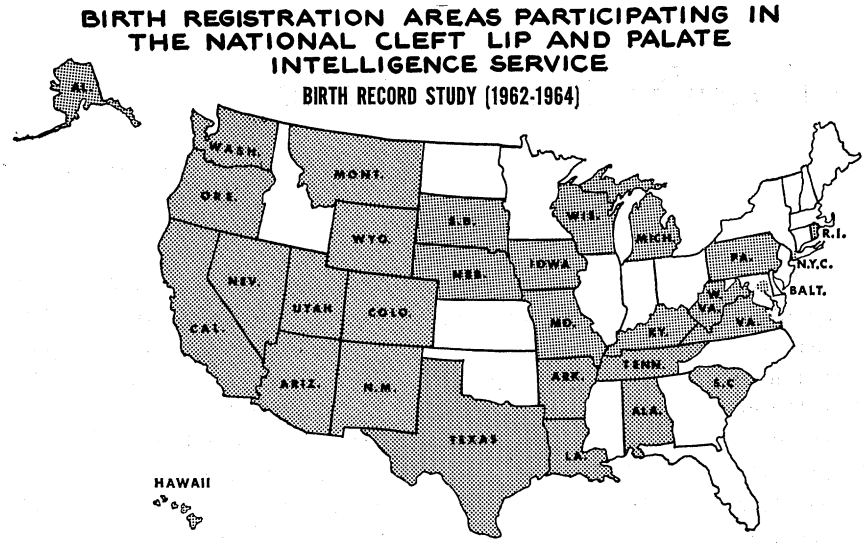

FIGURE 1.

sentially the same relationship is found in the present study. Tables 2 and 3 show present data regarding incidence of clefts according to age of mother and to age of father. The number of observed cases are those actually reported on birth certificates. The ratio of observed to expected cases is the number of observed cases divided by the number of cases expected if the parental age distribution was the same as it was among the non-malformed controls. Thus ratios less than 1.00 represent fewer than the expected number of cases, and ratios greater than 1.00 represent an excess over what was expected.

When the cleft cases were separated into two groups, those with no other malformations and those with one or more additional malformations, and then analyzed separately by parental age, an interesting difference was identified. When cleft lip is reported as a single malformation, no relationship to maternal age is seen, but the other types of clefts show an increase with increasing age of mother (Table 4). The

TABLE 1. Distribution of cleft and normal births by race and plurality of birth (NIS, 1962–64).

	number of births								
	white			*nonwhite*			*total*		
	single births	*plural births*	*total*	*single births*	*plural births*	*total*	*single births*	*plural births*	*total*
normals	56436	1061	57497	10481	275	10756	66917	1336	68253
clefts	6700	114	6814	549	18	567	7249	132	7381

TABLE 2. Number of births with a cleft and ratio of observed to expected cases among white single births, by type of cleft and by age of mother (NIS, 1962–64). Two births are excluded in the all ages category: age of mother was unknown.

age of mother	*type of cleft*							
	lip		*lip and palate*		*palate*		*total*	
	N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
all ages	1785	1.00	2869	1.00	2044	1.00	6698	1.00
under 20	202	.78	352	.85	252	.86	806	.83
20–24	667	1.03	1067	1.02	739	1.00	2473	1.02
25–29	468	1.04	690	.96	478	.93	1636	.97
30–34	268	1.05	409	1.00	305	1.04	982	1.03
35–39	138	1.02	235	1.08	205	1.32	578	1.14
40 and over	42	1.07	116	1.84	65	1.44	223	1.51

TABLE 3. Number of births with a cleft and ratio of observed to expected cases among white single births, by type of cleft and by age of father (NIS, 1962–64). One hundred eighty-seven births were excluded in all ages category: age of father was unknown.

age of father	*type of cleft*							
	lip		*lip and palate*		*palate*		*total*	
	N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
all ages	1738	1.00	2788	1.00	1987	1.00	6513	1.00
under 20	47	.73	99	.96	57	.78	203	.84
20–24	439	.92	705	.92	492	.90	1636	.92
25–29	524	1.03	806	.98	575	.98	1905	.99
30–34	344	1.00	538	.97	389	.99	1271	.99
35–39	224	1.10	348	1.07	256	1.10	828	1.09
40–44	105	1.12	170	1.13	135	1.26	410	1.17
45 and over	55	1.17	122	1.62	83	1.55	260	1.48

same is true of paternal age (Table 5). For clefts occurring with one or more additional malformations (Tables 6 and 7), there is an increase with increasing parental age for all three type of clefts, including cleft lip. For cleft lip and palate, the parental age relationship is even stronger than that shown for the single malformation group.

Because age of mother is highly correlated with age of father, it seems essential to study the relationship of clefts to maternal age, holding paternal age constant, and vice versa. Unfortunately, even with more than 6,000 cases, there still is the problem of very small frequencies in some of the more critical age combinations. Tables 8 and 9 and Figures

TABLE 4. Number of births with a cleft reported as a single malformation and ratio of observed to expected cases among white single births, by type of cleft and age of mother (NIS, 1962–64). Two births are excluded: age of mother was unknown.

age of mother	*type of cleft*							
	lip		*lip and palate*		*palate*		*total*	
	N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
all ages	1651	1.00	2528	1.00	1502	1.00	5679	1.00
under 20	191	.80	308	.84	188	.86	687	.83
20–24	613	1.02	950	1.04	543	1.00	2106	1.02
25–29	436	1.05	633	1.00	362	.96	1431	1.00
30–34	253	1.07	353	.98	219	1.02	825	1.02
35–39	122	.97	198	1.03	143	1.25	463	1.07
40 and over	36	.99	84	1.51	47	1.42	167	1.34

TABLE 5. Number of births with a cleft reported as a single malformation and ratio of observed to expected cases among white single births, by type of cleft, by age of father (NIS, 1962–64).One hundred fifty three births are excluded: age of father was unknown.

age of father	*type of cleft*							
	lip		*lip and palate*		*palate*		*total*	
	N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
all ages	1606	1.00	2457	1.00	1465	1.00	5528	1.00
under 20	43	.72	88	.97	43	.79	174	.85
20–24	422	.96	621	.92	365	.91	1408	.93
25–29	474	1.00	731	1.01	425	.99	1630	1.00
30–34	321	1.01	479	.98	282	.97	1082	.99
35–39	204	1.09	305	1.06	189	1.10	698	1.08
40–44	94	1.08	131	.99	100	1.26	325	1.09
45 and over	48	1.11	102	1.54	61	1.54	211	1.41

2 and 3 are therefore a compromise, showing the ratios of observed to expected cases of clefts for combinations of four parental age groups: mothers under 35, and 35 and over; fathers under 40, and 40 and over. Ratios for three other congenital malformations are included for comparison.

For single malformations (Table 8 and Figure 2), there are some apparent deviations from the expected age distributions of cleft cases. Based on the Chi-square test, differences this great might be expected to occur by chance one in twenty times for cleft lip and palate and less than one in a thousand times for cleft palate. The observed differences for cleft lip,

TABLE 6. Number of births with a cleft reported with additional malformations and ratio of observed to expected cases among white single births, by type of cleft, by age of mother (NIS, 1962–64).

age of mother	*type of cleft*							
	lip		*lip and palate*		*palate*		*total*	
	N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
all ages	134	1.00	343	1.00	542	1.00	1019	1.00
under 20	11	.57	44	.89	64	.81	119	.81
20–24	54	1.11	117	.94	196	1.00	367	.99
25–29	32	.95	57	.66	116	.85	205	.80
30–34	15	.78	56	1.14	86	1.11	157	1.08
35–39	16	1.57	37	1.42	62	1.50	115	1.51
40 and over	6	2.07	32	4.27	18	1.51	56	2.50

TABLE 7. Number of births with a cleft reported with additional malformations and ratio of observed to expected cases among white single births, by type of cleft, by age of father (NIS, 1962–64). Thirty-four cases are excluded: age of father was unknown.

age of father	*type of cleft*							
	lip		*lip and palate*		*palate*		*total*	
	N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
all ages	132	1.00	331	1.00	522	1.00	985	1.00
under 20	4	.82	11	.90	14	.73	29	.80
20–24	17	.42	84	.93	127	.89	228	.84
25–29	50	1.29	75	.77	150	.98	275	.95
30–34	23	.88	59	.90	107	1.03	189	.97
35–39	20	1.30	43	1.11	67	1.10	130	1.13
40–44	11	1.55	39	2.18	35	1.24	85	1.60
45 and over	7	1.94	20	2.25	22	1.56	49	1.84

spina bifida, and polydactyly are not significantly different from those expected. Down's Syndrome, or mongolism, shows by contrast a dramatic and highly significant increase with increased maternal age.

In Table 9 and Figure 3, the same types of malformations, occurring with one or more other congenital anomalies of any type, are distributed among the same four parental age groups.

Both spina bifida and polydactyly show an increased incidence only in the age group in which both parents are older. The Chi-squares are significant at the 5% level for the former and at the .1% level for the latter. Though the exact etiology of spina bifida has not been estab-

TABLE 8. Number of births with a cleft and other selected congenital malformations reported as single malformations and ratio of observed to expected cases among white single births, by parental age groups (NIS, 1962–64). One hundred fifty-five clefts, fifty-four spina bifida, eighty-five polydactyly, and forty-four Down's Syndrome cases are excluded: age of parents was unknown.

type of congenital malformation	*total cases*	*mother under 35 years*				*mother 35 years and over*			
		father under 40		*father 40 and over*		*father under 40*		*father 40 and over*	
		N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
total clefts	5526	4710	.98	198	1.24	280	1.06	338	1.18
lip	1606	1395	1.00	56	1.20	69	.89	86	1.03
lip and palate	2455	2093	.98	87	1.22	129	1.10	146	1.14
palate	1465	1222	.96	55	1.29	82	1.17	106	1.39
spina bifida	2123	1833	.99	62	1.01	100	.98	128	1.16
polydactyly	2119	1857	1.01	71	1.15	101	.99	90	.82
Down's syndrome	2308	1064	.53	50	.75	393	3.55	801	6.67

TABLE 9. Number of births with a cleft and other selected congenital malformations reported with additional malformations and ratio of observed to expected cases among white single births, by parental age groups (NIS, 1962–64). Thirty-four clefts, forty-three spina bifida, thirteen polydactyly, and fourteen Down's Syndrome cases are excluded: age of parents was unknown.

type of congenital malformation	*total cases*	*mother under 35 years*				*mother 35 years and over*			
		father under 40		*father 40 and over*		*father under 40*		*father 40 and over*	
		N	*ratio*	*N*	*ratio*	*N*	*ratio*	*N*	*ratio*
total clefts	985	788	.92	28	.98	63	1.33	106	2.07
lip	132	107	.93	3	.79	7	1.11	15	2.17
lip and palate	331	254	.88	8	.83	18	1.13	51	2.97
palate	522	427	.94	17	1.13	38	1.51	40	1.48
spina bifida	1415	1230	1.00	34	.83	58	.85	93	1.26
polydactyly	399	324	.93	12	1.03	18	.94	45	2.17
Down's syndrome	341	201	.68	8	.81	44	2.68	88	4.97

lished, it is generally agreed that polydactyly is a hereditary trait, transmitted by a dominant gene. A purely genetic trait should not be related to parental age, as the potential genetic contribution to the next generation is determined at the time of conception of the parents themselves, fresh mutations excepted. Thus it may be that while the majority

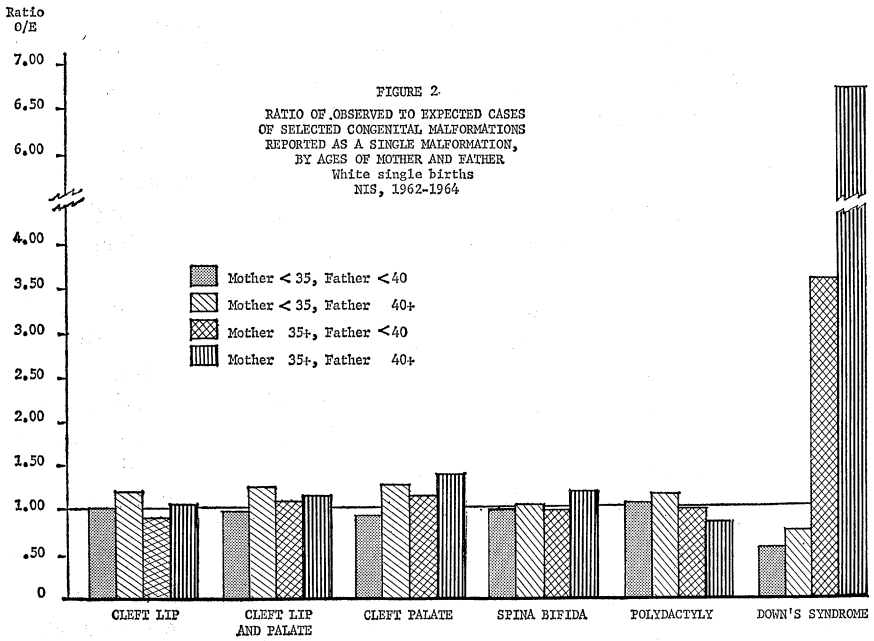

FIGURE 2.

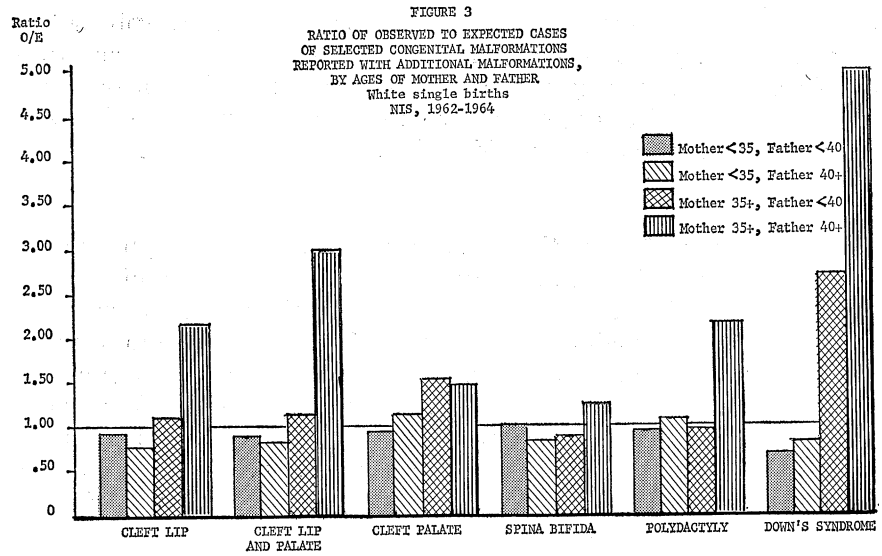

FIGURE 3.

of cases of polydactyly are transmitted genetically, some cases occurring in conjunction with other defects have some other etiology.

Down's Syndrome shows a remarkable and highly significant increase with increased maternal age among the multiple malformation

cases as well as among those in which it was the only anomaly reported. The relationship between maternal age and the non-disjunctive type of Down's Syndrome, which represents the great majority of cases, is well known. A small proportion of cases of Down's Syndrome are caused by another type of chromosomal aberration—a translocation—and this type, being unrelated to maternal age, can result in a young mother having an affected child. Down's Syndrome is thus an example of a single congenital disease entity known to have two quite different, though related, etiologies.

For clefts occurring with additional malformations, cleft palate shows an increase over expectancy among older mothers regardless of the age of the fathers. Cleft lip and palate as well as cleft lip alone show a substantial increase over the expected values only when both parents are older. This increase is particularly striking when compared to clefts occurring as single malformations. The probabilities that these deviations from the expected age distributions might have occurred by chance are one in fifty for cleft lip, less than one in a thousand for cleft lip and palate, and one in a hundred for cleft palate.

No particular explanation is postulated for this observation that increased parental age seems to be related more to clefts occurring with other malformations than those occurring as a single malformation. It is impossible to do more than make the observation in the present study. However, it may be that some clefts, particularly those involving the lip and occurring as a single malformation, may have a different etiology from those occurring with other malformations, which may themselves have more than one cause. This may be an approach well worth following with more definitive field studies.

Summary

From a study of more than 6,000 cases of cleft lip and palate reported on birth certificates, the incidence of cleft palate and of cleft lip and palate was found to be increased among older parents when the clefts were the only malformation reported. This relationship to parental age did not appear for cleft lip without involvement of the palate. For clefts occurring in conjunction with other congenital malformations, the relationship to older parental age was shown not only for cleft lip and palate and for cleft palate but also for cleft lip. These results were suggested to be possible further evidence for multiple causation of these particular congenital anomalies.

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