A LITERATURE REVIEW OF CONGENITAL CLEFTS OF THE LIP AND PALATE

By

CARL RALPH BULLARD

Bachelor of Science

Central State College

Edmond, Oklahoma

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Thesis Approved:

L. Herbert Bruneau

Thesis Adviser

Bryan K. Cla

J. W. Bragg

Dean of the Graduate School

PREFACE

On June 2, 1963, my third child, Brooks, was born with a bilateral cleft of the lip and palate. At that time three different doctors told me that the deformative was not of a hereditary nature but that they did not know the actual cause. In the two years since that time, I have done considerable library research on the whole broad subject of cleft lip and palate and this report is an outgrowth of that research.

This report has been an attempt to review the literature and to report and discuss some of the more commonly accepted theories and studies dealing with congenital clefts of the lip and palate. It is hoped that the reader sill gain a partial understanding of birth defects in general and cleft lip and palate in specific, and also obtain an appreciation, as I have, for the incredibly large amount of study and research that is being conducted in an effort to eliminate such defects.

Indebtedness is acknowledged to Dr. George Kimball and Dr. Lyndon D. Peer for their assistance in locating current research reports; and to my wife, Starley, for the typing of the manuscript; and to the National Science Foundation and Oklahoma State University for making this year of study possible.

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CHAPTER I

INTRODUCTION

Birth defects have been recorded since the beginning of history. Since early man had no concept of the manner in which birth defects occured, they have always been associated with superstitions. For this reason the belief that impressions of the mother may influence the coming birth has always prevailed without any real proof that maternal impression can in any way affect her child (1). Primitive people, knowing little of scientific biology, have believed that the birth of a defective child was due to various superstitious reasons such as punishment or a result from intercourse between humans and animals.

Cleft lip and cleft palate date back to the beginning of the human race. Dorrance states that the earliest record of cleft palate was reported by Smith and Dawson of London, in their work "Egyptian Mummies". Galen observed cleft lip during the 2nd century A.D. and names it lagocherlos (lip like a hare). Centuries later cleft lip was described by certain Arabian physicians. Ambroise Paie (1510-1590) was familiar with cleft lip and cleft palate and is credited by some writers with the invention of an artificial palate for the improvement of speech (2).

Before 1940, attempts to study cleft lip and palate were mainly restricted to studies of incidence in special populations and among families of probands (affected individuals). Following the announcement in 1940 that congenital malformations had been produced in rats whose mothers had been reared on deficient diets a new era of investigation began (3). From that time until today, there have been earnest attempts to search for environmental agents in the causation of cleft lip and palate.

The following material which has been mainly limited to that which is found in the Oklahoma State University Library, is a partial review of the findings of these recent investigations. Although the amount of current literature related to clefts of all types is volumentous, that which appears in this report is hoped to be fairly representative.

The findings have been attempted to be placed in a logical order and as a result the material is presented under three headings: pathogenesis, incidence, and etiology.

CHAPTER II

PATHOGENESIS

It is probably easier to understand the defective formation of the lip and palate if the normal development is understood first. According to Gilbert:

> "Life begins for each of us at an unfelt, unknown, and unhonored instant when a minute, wriggling sperm plunges headlong into a mature ovum or egg. The quiet ovum, as if electrified by the entrance of this strange creature, reacts with violent agitation, a spurt of activity, and a release of all the man-forming potencies that are inherent in the human egg-cell. It is at this moment of fusion of the sperm and the ovum that a new human being is created. After the ovum has been fertilized, this single egg-cell divides into two cells; soon these two split into four, the four split again to make eight, and it is estimated, forty-four successive divisions take place from the time the ovum is fertilized until the baby is ready to be born. When we realize that between conception and birth the organizm develops from a single cell into a human being composed of trillions of cells which have differentiated to form muscles, bones, nerves and highly specialized organs, we can understand how something can go wrong in the developmental process to cause a child to be born with an abnormality" (4).

Cleft lips and cleft palates seem to result from the persistence of clefts which were normal at certain early stages of development. By the end of the first month of development at the head end of the embryo, there is a wide hole which will become the mouth and a bar below it which will become the lower jaw. During the second month the

face develops rapidly. The lower jaw is formed from the bar which was present earlier and the upper jaw is formed from the tissue which grows forward from the angles of the mouth. The nose also develops at this time and part of this tissue grows downward to form the central part of the upper lip. This central part joins with the parts which grew forward from the angles of the mouth to make the upper lip complete, the union occuring at about the end of the second month. Anything interfering at this time with the union of the middle and side parts of the lip produces a cleft lip.

Since the face is not formed all in one piece at the start, neither is the roof of the mouth. First the sides of the upper jaw form and at this time there is a cleft between the sides which extend all the way from the front to the back of the mouth. Gradually the sides of the upper jaw grow around until, near the end of the third month; they join in the front of the mouth. The palate then forms from the sides of the upper jaw which grow toward the middle of the mouth. The sides meet first in the front of the mouth where they unite. Gradually this union occurs all along the roof of the mouth until, by the end of the third month, the entire roof of the mouth is completely closed. If something interferes with this fusion of the sides of the jaw when it is starting a cleft will extend throughout the length of the palate. If part of the roof of the mouth has been completed before disturbance occurs then there is

only a partial cleft of the palate (5).

The cleft lip and cleft palate pathogenesis is particularly interesting because it provides the basis for hypothesizing (discussed later in report) that the development of the normal lip and palate differ both in mechanism and in time and that agents which affect one would not necessarily affect the other. In other words, clefts of the lip and palate may have different causative factors (3).

CHAPTER III

INCIDENCE

A study of the incidence of cleft lip and palate is extremely important since almost all studies on the different causative factors are based upon incidence rates. The number of cases of cleft lip and palate reported to occur in the United States or any other country is a gross estimate based on isolated bits of information taken from vital statistics, crippled children's registers, hospital records, private surveys and other sources.

From figures compiled by most researches, one would tend to conclude that cleft cases are occuring more frequently today than formerly. For example, Hixons (3) research shows a wide variation in estimates of cleft lip or cleft palate incidence with a definitely increasing rate over the years (Table I). Possible sources of variation in the data which may explain the apparent increase are case sources, sample size, and decreased perinatal mortality. The data represented in Table I should be viewed primarily as a range of values for cleft lip and palate incidence rather than an indication of any real increase in the case rate.

In a study by Mildam (6), it is reported that there is

TABLE I

ESTIMATES OF THE FREQUENCY OF CLEFT LIP AND CLEFT PALATE *

Year	Location	Number of Cases	Sample Size	Cases per 1000 persons	Study popu-lation per case
1864	St. Petersburg, Russia	118	180,000	0.66	1:1,525
1908	London, England	39	67,945	.57	1:1,742
1918-19	United States	1,466	2,510,791	.53	1:1,880
1926-	Baltimore, Md	24	28,985	.85	1:1,170
	White	17	15,565	1.09	1:915
	Negro	7	12,550	.56	1:1,793
1931	Lubeck, Germany (pop.)	28	34,000	.82	1:1,214
	Birth records	102	102,823	.99	1:1,008
1934	Holland	16	15,270	1.05	1:954
1934	Hamburg, Germany	74	47,200	1.57	1:638
1928-37	Gothenberg, Sweden	28	27,000	1.04	1:964
1910-40	Denmark (All births)	193	128,306	1.50	1:665
	Live births	175	121,102	1.45	1:692
1938-39	Hawaii	35	18,024	1.98	1:550
1942	Pennsylvania	250	202,501	1.23	1:810
1935-44	Wisconsin	736	567,509	1.30	1:770
1942-47	Hawaii	93	47,153	1.97	1:507
1943-49	Ontario, Canada	695	655,322	1.06	1:943
1948-50	Pennsylvania	766	583,690	1.31	1:762
1948-55	New York	1,414	1,242,744	1.14	1:878
1940-50	Birmingham, England	285	218,693	1.30	1:767
1951-55	Pennsylvania (Birth Rec.)	1,269	1,201,976	1.06	1:947
	All Possible sources	1,592	1,201,976	1.32	1:754
1955	California	368	313,164	1.18	1:851
1953-57	Denmark	644	393,457	1.64	1:754

* Greene (3)

usually an under-reporting of incidence of clefts. From 1935-1960 the incidence rate for the United States has ranged from 0.78 per 1000 births to 1.95 per 1000 births. This report shows that there is probably an 18-27% under-reporting when only vital records or hospital records are used. The report gives additional light as to why the wide variation in reported incidence.

An accurate ratio of cleft lip and palate births to all live births is not available for the United States. But most reporters seem to agree fairly well with the Curtis-Fraser-Warburton report figure of 1 per 1000 births (7).

In the study of Rank and Thomson (8) they report that one of every six hundred children born alive in Tasmania, Australia, suffers from cleft lip with or without cleft palate. This is the highest incidence rate that was found in research for this report.

Sex of Child and Type of Cleft

Many large studies are available to provide information on the distribution of cases by sex and by type of cleft deformity. The sources of information and methods of data collection differ in these studies, but, with few exceptions, they agree fairly well on several points; cleft lip and cleft palate occur more frequently together than separately; clefts of the lip with or without associated clefts of the palate are more common in the male than in the female (58:42); cleft palate cases are more common

in the female (59:41); cleft lip cases are more common in males (64:36); cleft lip and palate are more common in males (62:38). This peculiar sex distribution of the types of clefts was devised by Loretz-Westmoreland-Richards (9) (Table II).

The sex distribution of different types of clefts led Fogh-Anderson to hypothesize that cleft lip, with or without cleft palate, may be etiologically distinct from isolated cleft palate (10).

Race

The facial cleft case rates differ between the white and some non-white races so greatly that most researchers have postulated that race might be a significant factor in the occurance of such clefts.

In a study by Lutz and Moor (10) they reported on 303 cleft cases among births in a hospital. By race, the cleft case rates per 1000 live births were: Caucasians, 1.00; Mexican, 1.25; and Negro, 0.71. Many times a person of Mexican ancestry will have Caucasian marked on his hospital record and this makes actual incidence rates hard to determine. Lamy and Fregal (11) reported the incidence rates comparing Caucasians, yellow, and Negro groups as follows: Caucasian, .13%; yellow race, .24%; Negro, .06%. These figures are all within the commonly reported ranges that have been found in the research for this report.

In another interesting aspect of incidence by race,

TABLE II

CLEFT LIP AND CLEFT PALATE BIRTHS BY SEX AND TYPE OF CONDITION IN SELECTED AREAS*

Type of Condition by Area	Number of births	Percent Male	Percent Female
Cleft lip and/or palate, total			
California	368	54	46
Denmark	625	62	38
Ontario	634	60	40
Pennsylvania	751	56	44
Cleft lip and palate			
California	155	58	42
Denmark	360	71	29
Ontario	316	63	37
Pennsylvania	278	54	46
Cleft lip only			
California	102	60	40
Denmark	138	65	35
Ontario	195	65	35
Pennsylvania	292	67	33
Cleft Palate only			
California	111	44	56
Denmark	127	34	66
Ontario	123	45	55
Pennsylvania	181	41	59

*Loretz-Westmoreland-Richards (9)

Krantz and Henderson (13) studied the frequency of cleft cases in relation to maternal ancestry. This study demonstrated lower rates among offspring of mothers of "unmixed" ancestry than among children born of mothers of "blended" ancestry. They found that children of Filipino mothers who are a blend of black, brown, yellow, and white races have an attack rate significantly higher (3.50 per 1000 live births) than children born to Caucasian mothers (0.5 per 1000 live births).

Although most of these studies of racial factors consist of limited observations made on selected populations, they strongly suggest that there are differences in attack rates among the races. The rates are lower for Negroes than for whites, and the rates are higher for "blended" races than for whites.

Age of Mother

Green (3) reports several studies which show a disproportionately large number of babies with clefts born to mothers more than 35 years of age. These studies demonstrated a positive relationship between older parental age and the incidence of cleft lip and cleft palate combined. But several other studies have shown that there is not any relationship between the age of the mother and clefts in children. If an association does exist between maternal age and the incidence of clefts, the association is not very pronounced, because the literature contains a number

of studies which deny the association and a number which support it.

CHAPTER IV

ETIOLOGY

The apparent differences in he frecuency of occurance of cleft lip and cleft palate cases according to sex, race, and parental age serve as clues to discover the causes of cleft lip and palate. According to Dr. Rustin McIntosh, the ultimate hope of all scientific investigation is that sufficient understanding of causes may develop to permit prevention.

Heredity, nutrition, stress, parental age, infectious diseases, and x-radiation have been indicated as possible etiological factors. In this report the author limited the study to two areas: (1) Hereditary and (2) Environmental consisting of parental age and nutrition.

Heredity

The role of heredity in the etiology of cleft lip and cleft palate has been investigated extensively and the evidence clearly shows heredity to be one of the causative factors. Rank and Thomson (8), in their Tasmania report, believed so strongly in the hereditary nature of clefts that they recommended that migrant families known to carry the trait for cleft lip or cleft palate should not be

freely admitted to the community.

Clefts are dependent, in part, on the baby's genes, but the genetic basis for the defect may be different in different cases. There is a rather rare type of cleft lip associated with little pits on the lower lip, which are the openings of extra salivary glands in the lip. The extra salivary glands are caused by a dominant gene, and about 1/2 the people who inherit the gene have a cleft lip and/or palate as well as the extra glands. So in this type of cleft, the genetic basis is fairly clear-cut, and one can predict that each child of a person with the defect has one chance in two of inheriting the gene, and therefore one chance in four of having a cleft lip and/or cleft palate (1).

Apparently the most common type of research to determine possible genetic factors has been to study the family ancestry of an affected child to determine the possibility of hereditary factors in a family group. In a study by Curtis-Fraser-Warburton (7); they report that although most of the clefts do show a familial tendency, they do not conform to any simple Mendelian pattern of inheritance. The study took information from three comparable family studies, combined the results and derived some "risk figures" for genetic counseling. The risk figures were derived from 1583 families which had a child with a cleft lip with or without cleft palate. (Table III).

They found the frequency of defect in the general population to be 0.1%. In the situation where one of the

TABLE III

COUNSELING RISKS FOR CLEFT LIP WITH OR WITHOUT CLEFT PALATE (CL±CP) AND CLEFT PALATE (CP) FOR VARIOUS FAMILY SITUATIONS*

	Proband has (CL±CP)	(CP)
I. Frequency of defect in the general population.	.1%	.04%
II. My spouse and I are unaffected		
A. We have one affected child What is the probability that our next baby will have the same condition if:		
(1) We have no affected relatives:	4%	2%
(2) There is an affected relative:	4%	7%
(3) Our affected child also has another malformation:	2%	2%
(4) My spouse and I are related	4%	2%
What is the probability that our next child will have some other sort of malformation?	Same as general population.	
B. We have two affected children What is the probability that our next baby will have the same condition:	9%	1%
III. I am affected (or my spouse is)		
A. We have no affected children What is the probability that our next baby will be affected	4%	6%
B. We have an affected child What is the probability that our next baby will be affected?	17%	15%

*Fishbein (1)

parents is affected, the probability that their child will be affected is 4% as compared to normal parents probability of 0.1%. But if the couple in which one of the members is affected should have one affected child, then the probability of their next child being affected goes up to 17%.

In another study based on a 40% return of questionnaires sent to one thousand mothers of children with repaired clefts, it was found that 23% of the children has positive family histories (3). This data may not be too reliable since only 40% of the mothers responded to the questionnaire and they could differ widly from the other 60%.

Further evidence that cleft lip and/or cleft palate is of a hereditary nature comes from twins. When the twins are monozygotic, they both have exactly the same genes, and if one has a cleft lip, the other is likely to have one too--specifically in about 40% of such pairs. If the twins are dizygotic, they are genetically different, and they are alike for cleft lip and/or cleft palate only about 5% of the time. This comparison clearly shows that the genes must have something to do with deciding whether a baby will be born with some type of cleft (1).

By working with different strains of mice and injecting the pregnant females with cortisone (cortisone usually induces cleft palates), Loevy (12) was able to determine which strains were susceptible and which ones were resistive to cleft palates. Then by crossing resistive female strains with resistive male strains, there were marked reductions

of number of induced clefts. He also found the opposite to be true when crossing susceptible strains together. This type of experiment gives additional evidence that there is genetic factor involved in clefts.

There are many different theories offered to explain the possible mode of inheritance. It would be out of the scope of this report to discuss all of the available theories, but a few of the more commonly reported ones will be summarized.

Rank and Thomson (8) suggest that at least two main genetic complexes are involved in cleft lip and cleft palate; and that one or more dominant autosomal genes of reduced manifestation probability are responsible in each case. Another theory is that the genetic factors occur both as dominant and recessive and that the abnormality may skip a generation because of varible expressivity or reduced pentrance (3).

In a study by Loevy (12) he reports that Reed and Snell, working with house mice, have presented evidence to show that cleft lip, with or without cleft palate, is a result of multiple genetic factors interacting with environmental ones. According to their findings, Loevy says that it is probably that cleft lip results when a smaller number of cumulative genes are present in the homozygous condition.

Green (3) reports that Fogh-Anderson suggested that cleft lip and cleft palate are two genetically independent malformations; and that in the case of cleft lip and cleft

the responsible gene generally is recessive, but under favorable conditions the defect is also manifested in heterozygotes. Also that cleft palate is genetically determinal in only a small number of cases and that the manner of inheritance is that of simple dominance with low penetrance.

Another theory of inheritance is that more than one or two genes are factors in producing cleft lip and palate; that there is at least one autosomal gene and one partially sex-linked gene, and that they are probably recessive (3).

Environment

As discussed earlier in the chapter dealing with incidence, many researchers believe that parental age is one of the causative factors in the development of cleft lip and/or cleft palate. The risk of producing a child with a cleft lip with or without cleft palate is said to be decreased in younger parents and increased in older parents. One of the theories, as to why, proposes that this is due to differential gametic selection with advancing parental age. As the parental age increases, there is a relaxation of selection against those gametes containing a possible genetic or chromosomal mechanism predisposing the cleft lip and palate (13).

Langman recently reported on interesting work on the influence of teratogenic (malformation producing) agents on serum proteins (3). He found that a number of environ-

mental teratogenic factors which caused congenital malformations in animals were accomplished by a disturbance in maternal serum proteins. He studied protein metabolism, the risk of abnormally ending a pregnancy was increased. This indicates that clefts may result from some unknown factor which interferes with the metabolic processes in the mother; the factor may possibly be related either to the mother's dietary intake or to a genetic factor.

Some of the most recent research into environmental causes of clefts is being conducted on vitamin deficiency. The Peer-Walker group of East Orange, New Jersey, is one group doing this type of research (4). They now have a total of 211 births recorded from vitamin treated pregnancies in women who previously delivered cleft lip or cleft palate children. After deleting cases who took vitamins but became nauseated and discontinued them and women, who on careful questioning took their vitamins too late (after 2 1/2 months of pregnancy), they found that out of their total series of 211 birth they had only 2 cleft palate births and no cleft lips. This amounts to about 2% compared to the generally accepted 5% expected to occur in a control group of women who had given birth to cleft lip or cleft palate children, became pregnant again and do not take supplemental vitamins during the early months of pregnancy.

Since the 5% in the control group series were collected by questionnaire forms, it was possible that some small

clefts in the lips were omitted by the mothers answering the questionnaires. That would bring the probable expectance of cleft lip and cleft palate births in untreated mothers to about 7% which is the figure that Dr. Peer says Shelden Reed, a noted genetic counsellor, accepts.

Dr. Peer also states the findings of a Hopkins Group in humans that the administration of vitamin D (which is toxic in excess) to pregnant women resulted in deformed children indicates that an excess of vitamin A or D or a deficiency in A, D or the B vitamins may be causative factors in producing birth deformities in humans.

The current literature is filled with many studies dealing with possible environmental factors in the development of cleft lip and palate. Some of the more commonly reported factors, in addition to those mentioned in the report, are stress, infectious diseases, and radiation.

CHAPTER V

SUMMARY AND CONCLUSIONS

The purpose of the report was to review the literature in an attempt to gain understanding as to the development, incidence, and cause of cleft lip and palate. Before 1940 there was little scientific investigation dealing with actual causes. The literature contains conflicting reports of wide variations in incidence by sex, parental age, and race. Although, there is partial agreement that the white and yellow races have a higher incidence rate than do Negroes; and that cleft lip with or without cleft palate is more common in males than females and cleft palate is more common in females than in males. The data on which many of these reports rest their conclusions are not completely adequate.

Though there is strong evidence that both genetic and environmental forces are involved in cleft formation, the genetic mechanism is not clearly understood and the specific environmental agents have not been identified. The theories based on environment alone or on genetics alone do not fully explain the varied data found in the literature. There seems to be a quite complex interaction between genetic mechanisms and environmental factors in the development of

clefts.

Some of the more perplexing questions which remain unanswered are as follows: Are some cases of cleft lip and palate purely genetically determined and others purely environmentally determined? Are there inherited modifiers of genetic and environmental teratogenic forces? Are there environmental modifiers of genetic forces? The fact that investigators are now able to raise more intelligent questions about the roles of hereditary and environment in cleft formation attests to the progress that has been made toward understanding the mechanisms involved.

CHAPTER VI

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VITA

Carl Ralph Bullard

Candidate for the Degree of

Master of Science

Report: A LITERATURE REVIEW OF CONGENITAL CLEFTS OF THE LIP AND PALATE

Major Field: Natural Science

Biographical:

Personal Data: Born in Britton, Oklahoma, November 21, 1937, the son of Harold and Vaughn Bullard.

Education: Attended grade school in Edmond, Oklahoma; graduated from Edmond High School in 1956; attended Bacone College 1956-57; received the Bachelor of Science degree from Central State College, with a major in Physical Education, in May, 1960; did graduate study in Ecology at Oklahoma University, summer, 1964; completed requirements for the Master of Science degree in August, 1965.

Professional experience: Taught and coached at Casady School, Oklahoma City from 1960 to 1962; taught biology and coached athletics at Edmond High School from 1962 to 1964.