EPIDEMIOLOGICAL ASPECTS OF CLEFT LIP AND CLEFT PALATE IN SOUTH AUSTRALIA 1949-1968 (INCLUSIVE).

CHARLES COURTENAY SPRY B.D.Sc.

DEPARTMENT OF DENTAL HEALTH
THE UNIVERSITY OF ADELAIDE
ADELAIDE, SOUTH AUSTRALIA, 5000

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SUMMARY

With few exceptions, all South Australian children born with a cleft of the primary and/or secondary palate over the last 25 years have been admitted to the Adelaide Children's Hospital for treatment. The hospital case notes of 559 children were examined and details of epidemiological interest were extracted. To supplement this information where possible, interviews were conducted with a parent and the child, at which time, a questionnaire was given to be completed by the mother. A radiographic examination of the child was also arranged in 376 instances so that a cross-sectional analysis of skeletal, facial and dental growth might be completed in a later study.

Findings suggested that the total cleft incidence (1.41 per 1,000 live births) and proportional distribution by type of cleft, sex and laterality of the defect, was essentially similar to other overseas and Australian reports of Caucasoid live births. Variations between this study and others previously reported were generally of a nature and magnitude readily attributable to differences in source of material and related methodology.

Yearly fluctuation in incidence of the major cleft types was appreciable, although the numbers of affected persons were relatively

small. This, together with the seasonal trend noted for combined clefts of the primary and secondary palate [CLCP] and isolated clefts of the secondary palate [CP] was possible evidence of the etiologic significance of unknown environmental influences. Graphical analyses of the reported trends suggested the possibility of rising as against falling incidence.

A family history of cleft of the primary and/or secondary palate among all known relatives, was more often elucidated in cleft primary with or without secondary palate [CL(P)] cases (39.9%) than for patients with CP alone (30.7%). This finding may indicate genetic independence of these cleft groupings. However, limitations on the completeness of family history data precluded detailed study of the genetic factors involved.

The birth weight of specified cases was less than 2.5 kg in 8.8% of CL(P) and 14.1% of CP subjects. No consistent trends towards higher or lower rates of cleft occurrences were recognised in particular maternal age groups with offspring affected with any type of cleft. Only for CP cases was there evidence that increasing paternal age was of etiological importance. A limited birth order analysis suggested that the birth order of CLCP patients was significantly different from that observed in nuptual live births in the general population. A contributing factor was an increased incidence among later birth ranks.

Consistent with other reports was the finding that 23.7% of

CL(P) subjects and 40.9% of CP subjects, for whom these data were available, were affected with one or more (including minor) associated congenital malformations. Overall, males had additional defects more often than females.

This report details basic epidemiological data on a defined population, served by a single treatment facility, and covering a twenty year period. It should be of value to those who would wish to provide the most adequate treatment facilities, as well as aiding in the search for specific genetic and environmental influences on clefts of the orofacial complex.

SIGNED STATEMENT

This project report is submitted in partial fulfilment of the requirements of the Degree of Master of Dental Surgery in The University of Adelaide.

This report contains no material which has been accepted for the award of any other degree or diploma in any University. To the best of my knowledge and belief it contains no material previously published or written by another person except when due reference is made in the text of the report.

CHARLES COURTENAY SPRY

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INTRODUCTION

The total incidence of fairly serious malformations, defined as abnormalities of structure present at birth and attributable to faulty development, has been estimated by CARTER[1] as 2-3% of all births. In their evaluation of data from a number of large and comprehensive studies, LAMY and FREZAL[2] estimated that the overall incidence of malformations visible at birth, and including still-born infants of longer than twenty-eight weeks gestation, was about 1.5%. This figure was reported to increase to between 4% to 5% after a one year observation period, and rose above 5% on inclusion of malformations in embryos, as well as defects not manifested until later. Clefts of the lip and palate have been shown to be one of the most common of all birth defects[3,4]. Unfortunately, however, little is known regarding their etiology.

There are wide variations in the findings of studies related to the occurrence of clefts, and the relationship of cleft etiology to hereditary and environmental factors is conjectural to some extent. It is known that in approximately one third of patients there is a family history of the condition[5,6,7]. Therefore, it seems logical to suggest that these defects are caused more often by environmental factors where there is no known family history. Concordance studies with monozgotic

and dizygotic twins have supported the genetic involvement of cleft lip with or without cleft palate and also indicated a diminished influence of heredity on the formation of cleft palate[5,8,9]. Different teratogenic conditions and substances that have been utilised in the production of experimental cleft palate in animals have been reviewed by GREEN[10]. From such studies it has been hypothesised that environment may have an effect upon the actuation of genetic susceptibility.

As indicated by LAMY and FREZAL[2] in a paper presented at the First International Conference on Congenital Malformations, frequency studies are important because of their theoretical and practical value. These studies are essential to etiologic research and open up new perspectives on the problem of structure and evolution of human populations. Etiologic complexity is such that cleft variations may suggest different clinical entities, or varying combinations of such entities. The factors involved, however, must be identified if the etiology is to be determined. Furthermore, since experimental methods are not possible in research into human maldevelopment, ERHARDT[11] has emphasised that statistical evaluation of large groups of cases may assist in providing the necessary information. Apparent differences in the frequency of occurrence of cleft lip and cleft palate in humans, according to variables such as sex, parental age, birth order, race, geography, season of the year and association with other malformations, may aid in determining etiology.

The aim of the present study was to describe the occurrence of cleft lip and/or palate in children born in South Australia from

1949-1968 and to elucidate associated factors. The findings will be useful in follow-up studies of problems related to the rehabilitation of patients with clefts. In particular, the collection of cephalometric, dental and hand-wrist radiographs for over 300 individuals with clefts of the primary and/or secondary palate will allow cross-sectional study of aspects of facial, dental and skeletal development.

The classification scheme employed in the present report differentiates cleft morphology as follows:-

1.	CL	CLEFT OF PRIMARY PALATE (Cleft lip ± cleft of alveolar process)	Figure 1a
2.	CLCP	CLEFT OF PRIMARY AND SECONDARY PALATE (Cleft lip + cleft palate)	Figure 1b Figure 1c
3.	CL(P)	CLEFT OF PRIMARY PALATE WITH OR WITHOUT A CLEFT OF THE SECONDARY PALATE (Cleft lip ± cleft palate)	
4.	CP	CLEFT OF SECONDARY PALATE (Isolated cleft palate)	Figure 1d

The abbreviations for 1, 2, 3 and 4 will be used throughout this text.

The purpose of the combination of CL and CLCP into one group [CL(P)] is to facilitate analysis of data with respect to probable involvement in these cases of a distinct genetic system to that associated with the etiology of isolated CP[5,7,12,13].

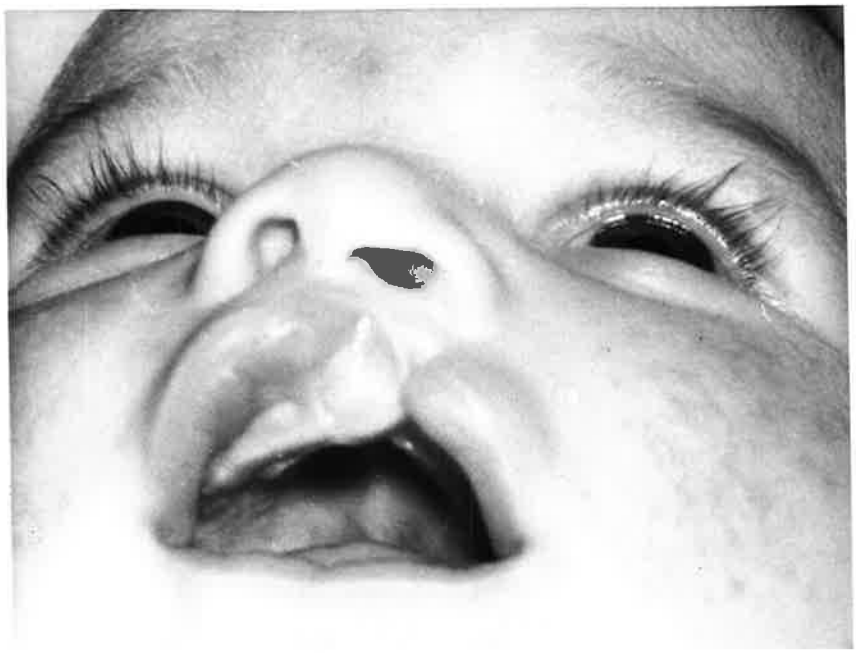

FIGURE 1a Left-sided unilateral incomplete cleft of the primary palate (CL)

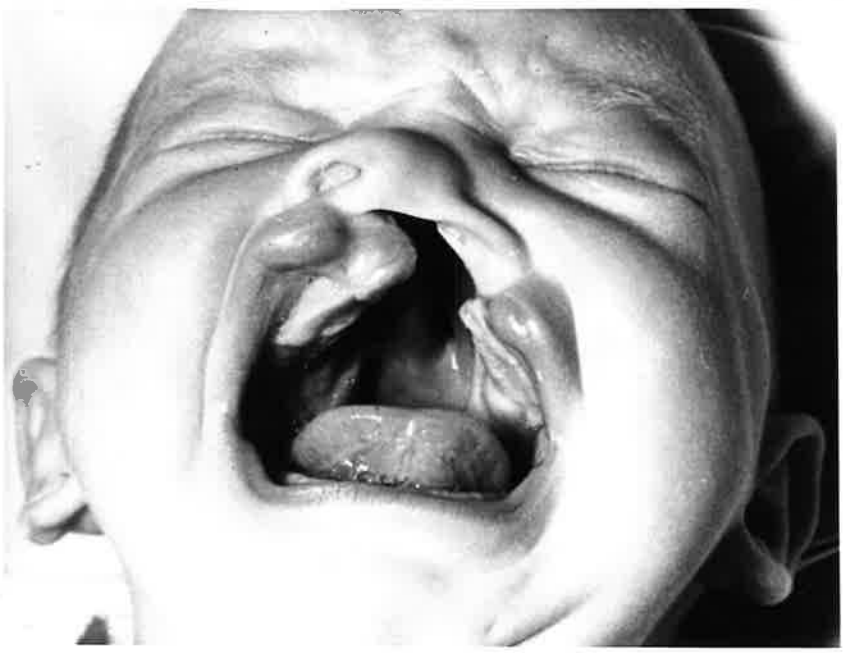

FIGURE 1b Left-sided unilateral complete cleft of the primary and secondary palate (CLCP)

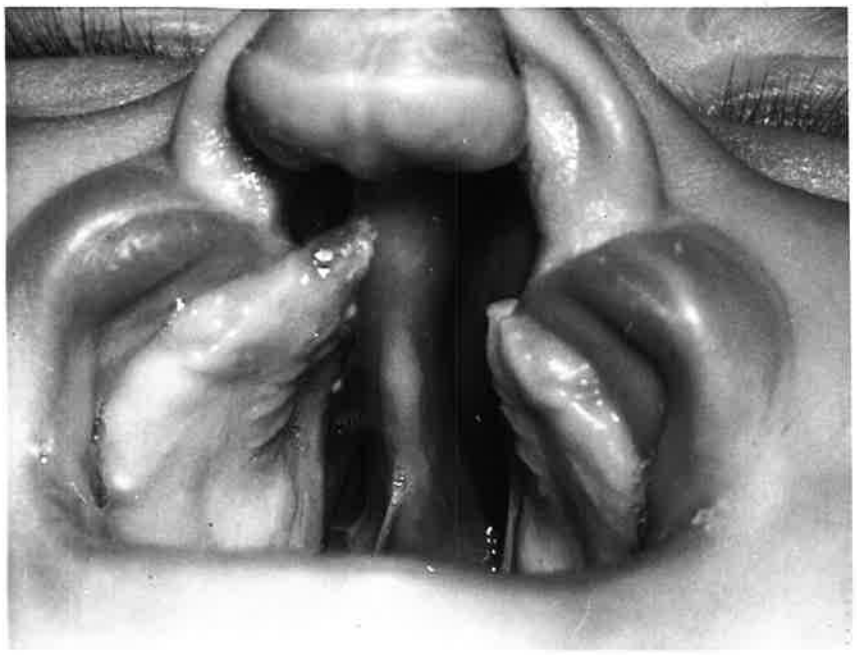

FIGURE 1c Bilateral complete cleft of the primary and secondary palate (CLCP)

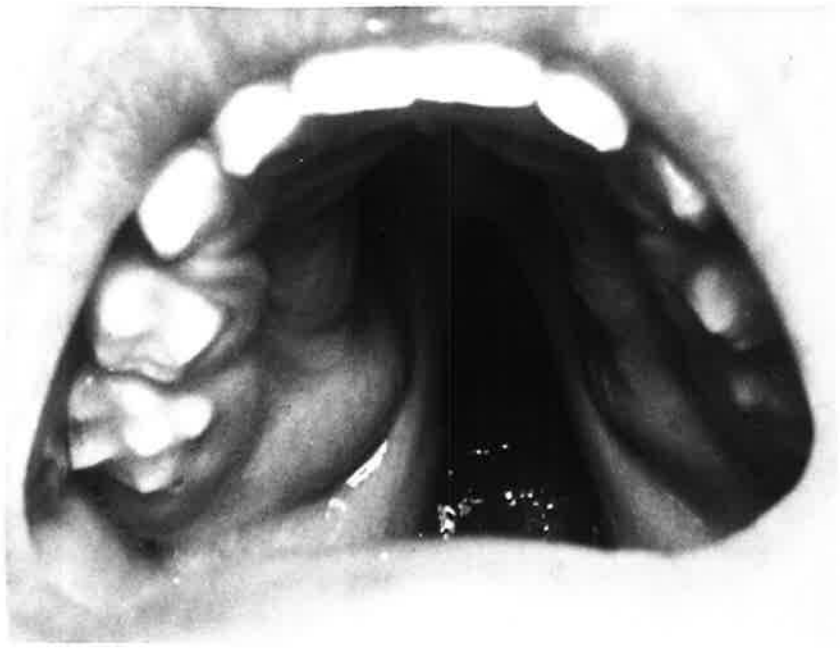

FIGURE 1d Incomplete cleft of the secondary palate (CP)

REVIEW OF THE LITERATURE

INCIDENCE OF CLEFT LIP AND PALATE

The relative occurrence of clefts in relation to other congenital defects is suggested from data compiled by IVY[3,4]. Clefts ranked second only to talipes or club foot in two New York studies in which 7,459 cases were listed in the first series and 9,784 in the second. Other researchers who listed clefts as malformations with relatively high incidence rates are CONWAY and WAGNER[14], and LAMY and FREZAL[2].

In 1942 FOGH-ANDERSEN[5] reviewed the literature and noted that the earliest reference was made by Frobelius who recorded an incidence of 1:1525 in St. Petersburg, Russia during the period 1833-1863. FOGH-ANDERSEN also published a detailed study of the epidemiology of clefts occurring in the Danish population prior to 1941. He reported a frequency of 1.45 per 1,000 live births (1:665) and analysed at length, environmental and hereditary factors in the etiology of these anomalies.

SCHURTER and LETTERMAN[15] examined approximately 150 studies from different countries. A wide range in incidence is seen from the investigations they considered to be the most significant. NEEL[16] has

reported the high total incidence of 2.68 per 1,000 (1:373) in Japanese. The incidence in Negroes, however, is markedly low. ALTEMUS[17] summarised various studies of negro populations in the U.S.A., where the incidence varied from the very low figure 1:4,394 reported by IVY[18] from birth records in Pennsylvania, to 1:1,400 reported by LUTZ and MOOR[19] from hospital records in Los Angeles, California. Differing incidences seem to reflect different racial predispositions but according to FRASER[9], racial variation was more obvious in the incidence of CL(P) than for CP.

Birth certificates, hospital treatment records and maternity records are the main sources of data. The compulsory reporting of congenital malformations on birth certificates is required in many countries. GREEN, VERMILLION, HAY, GIBBENS and KERSCHBAUM[20] gave the following indices for live births in four American States where reporting is mandatory:

Hawaii	1.50/1,000	(1:665)
California	1.24/1,000	(1:808)
Pennsylvania	1.16/1,000	(1:859)
Wisconsin	1.43/1,000	(1:701)

These data were based on 3.5 million birth certificates disclosing 4,451 subjects with a facial cleft. GREEN[10] estimated that over 6,000 such births occurred each year in the United States.

Many studies have been based on birth certificates but IVY[3] has stressed that a number of errors are inherent in this method.

Other studies[14,21,22] have produced evidence of the inaccuracies in the different sources of data and methods of reporting.

Maternity hospital records are thought to comprise one of the more reliable sources for estimates of incidence, according to SCHURTER and LETTERMAN[15]. Research specifically designed to measure the extent of under-reporting of cleft lip and palate was conducted by MILHAM[22] in an analysis of the overlap on birth and death records and hospital records reporting these anomalies. This study, based on data from three hospitals in New York State, included 79,536 births during the period 1950-60. Milham estimated 27.2% would have been missed if birth certificates were used as the sole source of data, while 18.2% would have been missed if only the maternity hospital records were used.

Between 1939 and 1954 a figure of 1.80 per 1,000 live births was reported by GYLLING and SOIVIO[23]. These authors derived their findings from examination of newborns by a pediatrician in the School of Midwifery in Helsinki, who gave special attention to the occurrence of the malformation. This figure was regarded as representative of a true birth incidence and it provided a similar incidence to that derived from the treatment hospital material.

It is recognised, therefore, that investigations on cleft lip and palate are subject to various degrees of under-reporting. However, an indication is given of the extent to which these anomalies occur in various populations. For the purpose of comparison with the present study, a number of reports based on surgical referrals are tabulated in Table 1.

TABLE 1. The incidence of clefts of the primary and/or secondary palate: Investigations in various countries.

AUTHOR AND LOCATION	MATERIAL	NUMBER	INCIDENCE	
HIXON[24] Ontario Canada	S.R. 1943-49	695	1.06*	(1:943)
RANK & THOMSON[6] Tasmania, Australia	C.S.R., M.S. 1954-57	160	1.66**	(1:602)
FOGH-ANDERSEN[25] Denmark	C.S.R. 1953-57	644	1.64*	(1:610)
KNOX & BRAITHWAITE[26] Northumberland & Durham, England	S.R., M.S. 1949-58	574	1.42**	(1:704)
MOLLER[27] Iceland	C.S.R., M.S. 1956-62	64	1.94**	(1:515)
FOGH-ANDERSEN[28] Denmark	C.S.R. 1958-62	712	1.82*	(1:549)
CAMPBELL WILSON[29] S.W. England	C.S.R. 1955-64	683	1.51**	(1:662)

Key to Material:

S.R. Surgical Referrals. C.S.R. Centralised Surgical Referrals.

M.S. Multiple Sources

*Proportion of patients operated upon per 1,000 live births.

**Estimated incidence/1,000 live births.

Although the methods of collecting these data vary, the figures provide an approximate frequency of occurrence in these countries.

In the South West of England CAMPBELL WILSON[29] conducted a survey extending over ten years from 1955 to 1964. A complete appraisal of hospital treatments was assumed because from the start of the National Health Scheme in 1948, the principle was laid down that all children should be referred to the Plastic Surgery Unit in Bristol. From data on 683 subjects a mean annual incidence of 1.51 per 1,000 live births was reported. Excluded from the study were children who did not survive for surgery, or who had moved out of the area pre-operatively. Children who first had surgical treatment after the end of 1966 when they were more than two years old, and eight children whose case notes were not available, were not considered.

All Danish-born children with clefts are reported to a National Institute of Speech Defects and surgical treatment is totally centralised in one hospital in Copenhagen. Between 1953 and 1957, 644 patients had cleft repairs and there were 393,457 live births in Denmark. Therefore, during this period a proportion of 1.64 per 1,000 was operated upon. FOGH-ANDERSEN[25] determined the number of infants reported to the National Institute for Speech Defects who died before surgery, as well as those discharged untreated for various reasons. The probable minimal birth incidence was thus estimated as 1.70 to 1.80 per 1,000 live births. In 1966 Fogh-Andersen[28] upgraded this estimate to 1.82 per 1,000 live births, which was said to correspond to an actual birth incidence of about 2.0 per 1,000. He further stated that

a significant increase in incidence could be demonstrated during the preceding 25 years.

Fogh-Andersen has thus compiled evidence from surgical records which suggested that the incidence of clefts was increasing in Denmark. The reasons for this rise have been related to decreases in infant and operative mortality, steadily improving operating techniques with resulting higher marriage rates and the etiological importance of heredity[25,28]. It should be noted that this author has indicated that a perceptible increase in the incidence of the malformation on a purely genetic basis, may take a considerable number of generations[28,30]. Fogh-Andersen[30] has also suggested that the demonstrated increase could have been due partly to exogenous factors such as the enormous abuse of tablets and pills of all kinds that has taken place in the past few decades.

TÜNTE[31] analysed the incidence figures for different periods and places in Germany over the years 1901-1961. He claimed that during this time the available data showed a definite increase of about 50% in the incidence of cleft primary with or without cleft secondary palate. Tünte discounted the possibility that the increase was due to an improved marriage rate of patients treated by modern methods, and theorised that the observed increase reflected some unknown etiological factor.

Data were also compiled by STEVENSON et al. in 1966 on cleft and other malformations in two Melbourne maternity hospitals as part of a World Health Organisation series of studies on congenital anomalies.

With cleft lip and/or cleft palate only thirteen cases, not associated with other malformations, were reported[33].

CHI and GODFREY[34] in 1970 highlighted the difficulties of reporting from maternity hospitals in New South Wales. The complete birth statistics of 94 hospitals were examined for the years 1964-1966. The estimated incidence of births of infants with a cleft defect was 1.21 per 1,000 or 1:821 live births. The overall figure, including still births and neonatal deaths, was 1.31 per 1,000 or 1:766. These incidence figures were qualified by the authors as approximate only, because it was known that there had been under-reporting from at least three large hospitals outside Sydney which had a total of 10,580 births and only seven infants with a cleft defect recorded in the three years. Three other hospitals could not supply information relating to private-category admissions.

In Tasmania, the majority of babies with clefts are examined and treated at one centre. RANK and THOMSON[6] in 1960 claimed a follow-up of virtually all affected children through cross checking of surgical records with reports from private medical practitioners, hospital case records made for other reasons and from death certificates. Clefts totalled 160 and the authors estimated the incidence in Tasmania during 1945 to 19 7 inclusive, as 1.66 per 1,000 live births (1:602). At that time this relatively high incidence was reported as the highest yet observed in a population of dominantly Caucasoid ancestry.

TYPE OF CLEFT

FOGH-ANDERSEN[5] reported on family patterns of cleft prevalence amongst the relatives of children with clefts. Evidence was provided that clefts involving the primary palate alone, or combined clefts of the primary and secondary palate, were genetically distinct from isolated clefts of the secondary palate. The differing sex ratios for the different genetic entities, the results of concordance studies of twins and the effects of teratogens in animal experiments confirm the need to analyse these data separately according to the type of cleft. There is general agreement with this approach throughout the literature[7,9,13,35,36]. However, RANK and THOMSON[6] and DRILLIEN, INGRAM and WILKINSON[8] have presented data which seemed to refute the above theory of genetic independence of the two cleft entities.

The distribution by type of cleft and sex reported in major studies to date are listed in Tables 2a and 2b. The material and method varies from study to study, and this fact has to be taken into consideration when making comparisons.

TABLE 2a. Cleft morphology: Investigations in countries other than Australia. The percentage distribution* according to type of cleft and sex.

INVESTIGATION		TOTAL CASES	TYPE OF CLEFT CL	CLCP	CL(P)	CP
FOGH-ANDERSEN[5] Denmark 1934-41 C.S.R. 625 subjects	distribution	100%	22.1%	57.6%	79.7%	20.3%
	% male	62.4	65.2	71.4	69.7	33.9
HIXON[24] Ontario Canada 1943-49 S.R. 634 subjects	distribution	100%	30.8%	49.8%	80.6%	19.4%
	% male	60.9	65.0	63.0	63.8	45.0
MacMAHON & McKEOWN[37] Birmingham England 1940-50 M.S. 285 subjects	distribution	100%	23.2%	36.8%	60.0%	40.0%
	% male	52.3	60.6	59.0	59.6	41.2
FRASER & CALNAN[38] Oxford England 1950-59 S.R. 456 subjects	distribution	100%	20.4%	33.3%	53.7%	46.3%
	% male	56.5	65.6	67.8	66.9	44.5
KNOX & BRAITHWAITE[26] Northumberland & Durham Eng. 1949-58 M.S. 574 subjects	distribution	100%	31.5%	35.7%	67.2%	32.8%
	% male	57.3	62.4	67.8	65.3	41.0
GYLLING & SOIVIO[23] Finland 1948-60 C.S.R. 2108 subjects	distribution	100%	11.5%	35.5%	47.0%	53.0%
	% male	47.3	60.4	61.3	61.0	35.2
INGALLS et al.[39] Pennsylvania U.S.A. 1959-61 S.R. 100 subjects	distribution	100%	16.0%	54.0%	70.0%	30.0%
	% male	64.0	62.5	74.1	71.4	46.7
GREEN et al.[20] 4 States U.S.A. 1956-60 L.B.C. 4451 subjects	distribution	100%	27.2%	44.3%	71.5%	28.5%
	% male	59.5	63.0	65.1	64.3	47.5
MOLLER[27] Iceland 1956-62 M.S. 64 subjects	distribution	100%	25.0%	43.7%	68.7%	31.3%
	% male	59.3	68.8	71.4	70.5	35.0
DRILLIEN et al.[8] Edinburgh Scotland 1953-61 S.R. 169 subjects	distribution	100%	16.6%	37.8%	54.4%	45.6%
	% male	56.8	71.4	72.9	71.7	39.0
GILMORE & HOFMAN[40] Wisconsin U.S.A. 1943-62 L.B.C. 2154 subjects	distribution	100%	26.3%	43.7%	70.1%	29.9%
	% male	60.0	64.5	66.7	65.9	46.2
CONWAY & WAGNER[41] New York 1952-62 L.B.C. 1457 subjects	distribution	100%	31.8%	36.1%	67.9%	32.1%
	% male	58.1	63.7	61.7	62.6	48.6

Continued on next page

TABLE 2a. (continued)

INVESTIGATION		TOTAL CASES	TYPE OF CLEFT CL	CLCP	CL(P)	CP
CONWAY et al.[42] New York 1932-65 S.R. 850 subjects	distribution	100%	25.0%	41.0%	66.0%	34.0%
	% male	53.8	51.0	65.0	60.0	42.0
CAMPBELL WILSON[29] South West England 1955-66 C.S.R. 683 subjects	distribution	100%	29.3%	36.7%	66.0%	34.0%
	% male	57.4	61.0	65.7	63.6	45.2

* Where previous investigators have not provided percentage distributions according to type of cleft or sex, these have been calculated from their reported data.

Key: S.R. Surgical Referrals. M.S. Multiple Sources. C.S.R. Centralised Surgical Referrals, L.B.C. Live Birth Certificates. M.H.R. Maternity Hospital Records.

TABLE 2b. Cleft morphology: Australian investigations. The percentage distribution* according to type of cleft and sex.

INVESTIGATION		TOTAL CASES	TYPE OF CLEFT CL	CLCP	CL(P)	CP
RANK & THOMSON[6] Tasmania 1945-57 C.S.R., M.S. 160 subjects	distribution	100%	23.8%	43.1%	66.9%	33.1%
	% male	62.5	63.2	75.4	71.0	45.3
RANK & THOMSON[6] Tasmania 1945-57 + others C.S.R., M.S. 221 subjects	distribution	100%	22.6%	43.9%	66.5%	33.5%
	% male	62.5	64.0	76.3	72.1	43.2
CHI & GODFREY[34] N.S.W. 1964-66 M.H.R. 192 subjects	distribution	100%	24.0%	46.9%	70.8%	29.2%
	% male	57.8	58.7	64.4	62.5	46.4

* Where previous investigators have not provided percentage distributions according to type of cleft or sex, these have been calculated from their reported data.

Key: S.R. Surgical Referrals. M.S. Multiple Sources. C.S.R. Centralised Surgical Referrals, L.B.C. Live Birth Certificates. M.H.R. Maternity Hospital Records.

FOGH-ANDERSEN[5] hypothesised that if all cleft cases in the Danish population were included, the distribution of cleft types would approximate 25% CL, 50% CLCP and 25% CP. However, the distributions from subsequent studies are not in complete accord with his estimation. For this reason BIGGERSTAFF[43] sought a ratio which more accurately described the actual distribution most commonly observed in epidemiological surveys. He felt that the 7:3 ratio (CL(P):CP) was the most appropriate of the five ratios which he tested on data derived from seven major investigations. Biggerstaff stated that the 1:2:1 ratio (CL:CLCP:CP) fitted the observed frequencies from only two of the seven investigations and could not justifiably be adopted to represent the frequency of occurrence of cleft types.

It is noteworthy that in a later report, FOGH-ANDERSEN[30] observed that while the Danish material, as a whole, represented 75% CL(P) and 25% CP, a contrasting distribution of 24% CL(P) and 76% CP was observed for the geographically isolated Faroe Islands and Greenland. Accordingly, he allowed for the possibility of racial differences in genetic susceptibility to types of cleft. The figure reported in Japan by FUJINO, TANAKA and SANUI[44] of 43.9% for CL is further evidence for ethnic differences in the rate of occurrence of the major cleft types.

DONAHUE[45] has indicated the need for caution in interpreting observed racial differences in incidence reports, and stated that observed differences in vital statistics for various racial groups should not be interpreted as necessarily due to inherent racial causes.

He emphasised that race is not independent of other variables and the economic, social and medical circumstances of one racial group may be quite different from those of another. However, he further noted that where optimal socioeconomic factors were apparently related to a higher incidence of cleft palate (CP), the observed difference in incidence seemed to be more dependent upon racial factors than upon economic variables.

Distribution estimates may be biased according to the method used to obtain the data. For example, as pointed out by DRILLIEN et al.[8], studies based on hospital referrals for surgical treatments are unlikely to include still-born infants and those dying in the neonatal period. Studies based on birth certificates may under-report the proportion of primary and secondary clefts; in these circumstances an isolated primary cleft may be reported when actually both the primary and secondary palates are involved.

In Caucasoid populations the usual proportion of clefts involving the primary palate alone (CL) is about one-quarter to one-fifth of the overall incidence. As shown in Table 2a, higher and lower incidences have been reported. KNOX and BRAITHWAITE[26] derived data from hospital referrals and other sources to observe a figure of 31.6% for this defect in the region of Northumberland and Durham in England. In the city of Birmingham, only 200 miles away MacMAHON and McKEOWN[37] employed broadly similar methods and reported that 23.2% of all clefts involved only the primary palate. Knox and Braithwaite[26] also noted yearly fluctuations

in their cleft lip figures, and suggested the existence of a labile determining factor and heterogeneity of aetiology between some cases of cleft lip and other deformities.

DRILLIEN et al.[8] suggested that the North American estimates of isolated clefts of the secondary palate varied between one-quarter to one-third of the total distribution, while the proportion of this type of cleft in Great Britain seemed to be higher. GYLLING and SOIVIO[23] demonstrated a 53.0% isolated secondary cleft contribution to the total incidence in Finland.

Consideration of the literature supports the conclusion that there are true differences in distribution of cleft types in different parts of the world.

TYPE OF CLEFT AND SEX

Populations at large are commonly composed of nearly equal proportions of males and females. In comparison, the overall sex ratio of those affected with cleft lip and/or palate, is seen to favour males[27,34,46]. The samples of eight large studies were combined by GREEN[10] who calculated a male:female ratio of 58:42 from a total of 3,907 subjects. While a male excess is most commonly reported, it may vary with the population and the methods employed in a particular survey. The extent of the variation is apparent from Tables 2a and 2b, in which are listed the percentages of males among all cleft affected persons in various samples.

It is more meaningful to relate the sex ratio to the type of cleft, rather than to give the overall ratio for the combined genetic entities. Tables 2a and 2b demonstrate that CL and CLCP occurred most often in males, and that isolated clefts of the secondary palate were more common in females. From a review of the literature, these trends were consistently confirmed.

In a review of previous studies, HAY[21] noted that the observed sex ratio seemed somewhat dependent on the source of data. Clinical series of CL(P) subjects yielded higher proportions of males than did birth certificates or records of hospital births. Hay related this finding to the possibility that females with CL(P) may be more likely to die shortly after birth and thus excluded to a greater extent than are males, from studies based on clinical data.

While it has been widely observed that CL occurred more commonly in females[5,20,39], DRILLIEN et al.[8] have pointed out that this sex distribution may not apply in samples based on still births and neonatal deaths. HAY[21] further reported that studies of CP based on clinical series tended to have lower proportions of males than studies based on birth records where the proportions of males approached 50%. It was considered that this finding may have indicated that male infants with CP were more severely affected than females and, therefore, more likely to die before they could be included in a clinical or surgical series.

Possibly racial characteristics of the population are important in the relationship between type of cleft and sex ratio. This

hypothesis has been discussed by FRASER[9].

GREEN, VERMILLION and HAY[47] compiled data on a racially heterogeneous sample of 2,162 infants with clefts. These data were gathered from birth certificates by the National Cleft Lip and Palate Intelligence Service from 29 States and two cities in the U.S.A. The reported percentages of 62.3% males (CL), 66.6% males (CLCP) and 43.4% males (CP), for Caucasoid births was significantly different from the percentages of 39.5% males (CL), 47.9% males (CLCP) and 51.9% males (CP) for non-Caucasoid births. In a Japanese study, FUJINO et al.[44] found that, contrary to usual findings for Caucasoids, more females than males (53.5%) were affected with CL. This finding, although possibly reflecting a sample bias because of an increased willingness of females with CL to undergo surgery, supported the report of NEEL[16] who noted that the high incidence of CL(P) in Japan (1.70 per 1,000) appeared to be related to a higher proportion of females with CL.

For clefts involving the primary palate, the excess of males seemed to increase in the more severe defects; that is, the excess was slightly greater for CLCP than for CL[5,20,26,27,38,39,40]. Variation in sex ratio according to severity of CP cases has been recorded by a number of authors[5,6,26,27,48]. The predominance of females with isolated CP was seen to be limited to complete post-alveolar clefts. The sex ratio for less severe clefts of the secondary palate favoured male predominance. MESKIN, PRUZANSKY and GULLEN[49] recorded the extent of secondary palatal clefts from pre-operative casts of 176 patients, and

indicated that 35 of 55 with clefts limited to the soft palate, were males.

TYPE OF CLEFT AND LATERALITY

As noted by OLDFIELD and TATE[50], isolated clefts of the secondary palate tend to be U-shaped and symmetrical. However, the laterality distribution (side of cleft) has been described for both CL and CLCP defects in a number of surveys where these data have been available for analysis.

About three-quarters of all clefts involving the primary palate, that is CL(P), are unilateral. For example, in the series of RANK and THOMSON[6], 77.5% of CL(P) cases were unilateral and according to the material of MOLLER[27], the corresponding figure was 78.9%. When only the primary palate was affected, it was generally demonstrated that an even greater proportion were unilateral rather than bilateral involvements. On the question of bilateral clefts, FRASER[9] has stated that there is an associated cleft palate more often with bilateral (86%) than with unilateral (68%) clefts of the lip. This is consistent with the idea that the cleft palate associated with cleft lip is secondary to the lip defect and hence more likely to occur when the lip defect is more severe.

The numbers of subjects, together with the percentage occurrence of the lateral or bilateral condition reported by a number of previous authors, are presented in Tables 3a and 3b. Not only was the unilateral condition most often reported for CL, but also the left side was

TABLE 3a. Laterality of CL and CLCP: Investigations in countries other than Australia. The percentage distribution* according to type of cleft.

INVESTIGATION		TYPE OF CLEFT											
		CL						CLCP					
		TOTAL CL	Unilateral			Bilateral	Unspec.	TOTAL CLCP	Unilateral			Bilateral	Unspec.
			L	R	Total				L	R	Total		
FOGH-ANDERSEN[5] Denmark 1934-41 C.S.R. 625 subjects	N	138	88	33	121	17	-	360	179	76	255	105	-
	%	100	63.8	23.9	87.7	12.3		100	49.7	21.1	70.8	29.2	
HIXON[24] Ont. Canada 1943-49 S.R. 634 subjects	N	195	99	75	174	21	-	316	130	80	210	106	-
	%	100	50.8	38.4	89.2	10.8		100	41.2	25.3	66.5	33.5	
FRASER & CALNAN[38] Oxf. Eng. 1950-59 S.R. 456 subjects	N	93	48	27	75	18	-	152	82	31	113	39	-
	%	100	51.6	29.0	80.6	19.4		100	53.9	20.4	74.3	25.7	
INGALLS et al.[39] Pa. U.S.A. 1959-61 S.R. 100 subjects	N	16	12	3	15	1	-	54	22	12	34	19	1
	%	100	75.0	18.8	93.8	6.2		100	40.7	22.2	62.9	35.2	1.9
MOLLER[27] Iceland 1956-62 M.S. 64 subjects	N	16	12	3	15	1	-	28	13	5	18	10	-
	%	100	75.0	18.8	93.8	6.2		100	46.4	17.9	64.3	35.7	
DRILLIEN et al.[8] E'burgh Scot. 1953-61 S.R. 169 subjects	N	28	12	15	27	1	-	64	20	19	39	24	1
	%	100	42.8	53.6	96.4	3.6		100	31.2	29.7	60.9	37.5	1.6
CAMPBELL WILSON[29] S.W. Eng. 1955-66 C.S.R. 683 subjects	N	200	123	60	183	17	-	251	124	63	187	64	-
	%	100	61.5	30.0	91.5	8.5		100	49.4	25.1	74.5	25.5	

TABLE 3b. Laterality of CL and CLCP: Australian investigations. The percentage distribution* according to type of cleft.

INVESTIGATION		TYPE OF CLEFT											
		CL						CLCP					
		TOTAL CL	Unilateral			Bilateral	Unspec.	TOTAL CLCP	Unilateral			Bilateral	Unspec.
			L	R	Total				L	R	Total		
RANK & THOMSON[6] Tas. 1945-57 C.S.R. M.S. 160 subjects	N	38	24	10	34	4	-	69	34	16	50	18	1
	%	100	63.2	26.3	89.5	10.5		100	49.3	23.2	72.5	26.1	1.4
RANK & THOMSON[6] Tas. 1945-57 C.S.R. M.S. & other 221 subjects	N	50	34	12	46	4	-	97	48	20	68	25	4
	%	100	68.0	24.0	92.0	8.0		100	49.5	20.6	70.1	25.8	4.1
CHI[51] N.S.W. 1964-66 M.H.R. 192 subjects	N	46	21	10	31	3	12	90	10	12	22	34	34
	%	100	45.7	21.7	67.4	6.5	26.1	100	11.1	13.3	24.4	37.8	37.8

S.R. Surgical Referrals. C.S.R. Centralised Surgical Referrals.
M.H.R. Maternity Hospital Records. M.S. Multiple Sources.

*Where previous investigators have not provided the percentage distribution according to laterality, these have been calculated from their reported data.

involved in the majority of cases. However, the proportional distribution varied: FOGH-ANDERSEN[5] and RANK and THOMSON[6] estimated the ratio for left to right side involvement in CL to be 3:1. In the Edinburgh sample, DRILLIEN et al.[8] found an approximate 1:1 ratio for this distribution.

From a racially heterogeneous sample of 100 cases, SESGIN and STARK[36] observed the distribution, left:right:bilateral for isolated CL to be 1:1:1. In the South West of England, CAMPBELL WILSON[29] reported a relatively high proportion of CL with a distribution of left:right: bilateral of 6:3:1.

In a recent review FRASER[9] stated that in cases of unilateral CL and CLCP, about two-thirds were on the left side for both cleft types. This estimation was confirmed by other investigators. SESGIN and STARK[36] speculated that left-sidedness was due to the turning of the head to the right as the heart develops, which would thus place the left side of the face inferiorly. However, it is very difficult to scientifically confirm this etiologic hypothesis.

TYPE OF CLEFT, LATERALITY AND SEX

KNOX and BRAITHWAITE[26], INGALLS et al.[39] and GREEN et al.[20] were among the authors who found no difference between the sexes in terms of laterality. Others found that the preponderance of males with a CL(P) appeared to increase with increasing severity of the cleft. FOGH-ANDERSEN[5] noted that 65% of patients with isolated cleft lip and

83% with bilateral cleft lip and palate were males. In the Tasmanian study[6], comparable figures were 64% and 76% males. The figures of MOLLER[27] were similar in that 65% of patients with isolated primary clefts and 80% with bilateral primary and secondary clefts were males in his series of 64 subjects from Iceland. However, in the Edinburgh series DRILLIEN et al.[8] stated that 71% of cases of isolated cleft lip were males, but only 62% of bilateral cleft lip and palate cases were males. In the surviving patients in the Edinburgh sample, primary clefts were more severe in extent in females, but in the group of still births/early deaths, more severe defects of the lip were seen in males.

For comparative purposes, the number and percentage distribution of subjects, according to type of cleft, laterality and sex, have been compiled from reports based on varying data and are listed in Tables 4a and 4b.

SEASONAL OCCURRENCE

Many diseases have been analysed for seasonal patterns of occurrence. These analyses have been applied also to congenital malformations such as anencephaly, spina bifida, hydrocephaly, Downs syndrome, congenital dislocation of the hip, and cleft lip and palate. WOOLF, WOOLF and BROADBENT[52] suggested that a seasonal association with incidence would provide evidence of a non-genetic etiological factor. WEHRUNG and HAY[53] have further suggested that if a seasonal trend is demonstrated for a congenital malformation, concomitant trends can be

TABLE 4a. Laterality of CL and CLCP and percentage* of males in particular cleft groupings: Investigations in countries other than Australia.

INVESTIGATION		TYPE OF CLEFT											
		CL						CLCP					
		TOTAL CL	Unilateral			Bilateral	Unspec.	TOTAL CLCP	Unilateral			Bilateral	Unspec.
			L	R	Total				L	R	Total		
FOGH-ANDERSEN[5]	N	138	88	33	121	17	-	360	179	76	255	105	-
Denmark 1934-41	%	100	53.8	23.9	87.7	12.3		100	49.7	21.1	70.8	29.2	
C.S.R. 625 subjects													
	male %	65.2	68.2	54.6	64.5	70.6		71.4	66.5	65.8	66.3	83.3	
INGALLS et al.[39]	N	16	12	3	15	1	-	54	22	12	34	19	-
Pa. U.S.A. 1959-61	%	100	75.0	18.8	93.8	6.2		100	40.7	22.2	62.9	35.2	1.9
S.R. 100 subjects													
	male %	62.5	58.3	100	66.7	0		85.0	72.8	83.3	76.5	68.4	100
MOLLER[27]	N	16	12	3	15	1	-	28	13	5	18	10	-
Iceland 1956-62	%	100	75.0	18.8	93.8	6.2		100	46.4	17.9	64.3	35.7	
M.S. 64 subjects													
	male %	68.8	66.7	66.7	66.7	100		71.4	84.6	17.9	66.7	80.0	
DRILLIEN et al.[8]	N	28	12	15	27	1	-	64	20	19	39	24	1
Edin. Scot. 1953-61	%	100	42.8	53.6	96.4	3.6		100	31.2	29.7	60.9	37.5	1.6
S.R. 169 subjects													
	male %	71.0	75.0	66.7	70.4	100		71.9	85.0	63.2	74.4	66.7	100
CAMPBELL WILSON[29]	N	200	123	60	183	17	-	251	124	63	187	64	-
S.W. England 1955-66	%	100	61.5	30.0	91.5	8.5		100	49.4	25.1	74.5	25.5	
C.S.R. 683 subjects													
	male %	61.0	56.9	66.7	60.1	70.6		65.7	46.5	49.2	59.3	84.3	

TABLE 4b. Laterality of CL and CLCP and percentage* of males in particular cleft groupings: Australian investigations.

INVESTIGATION		TYPE OF CLEFT											
		CL						CLCP					
		TOTAL CL	Unilateral			Bilateral	Unspec.	TOTAL CLCP	Unilateral			Bilateral	Unspec.
			L	R	Total				L	R	Total		
RANK & THOMSON[6]	N	38	24	10	34	4	-	69	34	16	50	18	1
Tas. 1945-57	%	100	63.2	26.3	89.5	10.5		100	49.3	23.2	72.5	26.1	1.4
C.S.R. M.S. 160 subjects													
	male %	53.2	67.7	80.0	58.8	0		75.4	64.7	92.8	74.0	77.8	100
RANK & THOMSON[6]	N	50	34	12	46	4	-	97	48	20	68	25	4
Tas. 1945-57	%	100	68.0	24.0	92.0	8.0		100	49.5	20.6	70.1	25.8	4.1
C.S.R. M.S. & other 221 subjects													
	male %	64.0	64.7	83.3	88.9	0		76.3	66.7	95.0	87.9	86.0	100
CHI[51]	N	46	21	10	31	3	12	90	10	12	22	34	34
N.S.W. 1964-66	%	100	45.7	21.7	67.4	6.5	26.1	100	11.1	13.3	24.4	37.8	37.8
M.H.R. 192 subjects													
	male %	58.7	38.1	50.0	41.9	33.3	66.7	64.4	60.0	58.3	59.1	67.7	64.7

S.R. Surgical Referrals. C.S.R. Centralised Surgical Referrals.
M.H.R. Maternity Hospital Records. M.S. Multiple Sources.

*Where previous investigators have not provided the percentage distribution according to laterality and sex these have been calculated from their reported data.

looked for in other factors such as infectious diseases, availability of certain nutrients, use of chemical pesticides, ingestion of drugs and many other factors.

Although some workers have been able to demonstrate seasonal associations with the occurrence of cleft defects, others have been unable to do so. KNOX and BRAITHWAITE[26] from surgical record data, and GILMORE and HOFMAN[40] from birth certificates, reported no association, although both sets of data were not analysed in relation to seasonal variation in normal births.

WOOLF et al.[52] recorded the month of birth for a total sample of 889 subjects with clefts. Chi-square tests were applied in a search for a significant deviation in seasonal variation between births with cleft defects and normal births, ascertained from vital statistics. No significant seasonal trend was demonstrated for CP or CL(P). From oral surgery records, FUJINO et al.[44] reported on 2,828 cleft cases. Using similar statistical methods to those of Woolf et al.[52] CL(P) births were seen to be decreased among persons born in Japan during winter (from December to February) and were increased among those born in spring (from March to May). The deviation from random expectation was significant at the one percent level in CL and insignificant, although the trend was similar, for CLCP. No seasonal influence could be demonstrated for CP births.

EDWARDS[54] was critical of certain applications of the simple chi-square test to seasonal analyses. He developed what he considered

to be a "more robust" method which applied a chi-square test for the presence of a cyclic trend and fitted a simple harmonic curve to the data. This test is briefly described in APPENDIX D. EDWARDS[55] applied the method outlined in his previous paper to demonstrate a significantly elevated incidence for March births in a Birmingham sample of 113 CL subjects. FRASER and CALNAN[38] using the same method on data derived from surgical reports in Oxford, noted the contrasting finding of no seasonal variation for any type of cleft. CHARLTON[32] and WEHRUNG and HAY[53] also applied the Edwards model after adjustment of monthly rates of cleft births, in relation to the monthly variation seen for births in the general population.

Charlton[32] reported that for CLCP (136 cases) only the Adelaide data showed significant seasonal variation, the highest incidences occurring in June and July. No other types of cleft showed significant seasonal variation in either the Brisbane or Adelaide data.

The establishment of the National Cleft Lip and Palate Intelligence Service enabled Wehrung and Hay[53] to report from birth certificates on approximately 10,000 cases of cleft lip and palate in the U.S.A. A systematic sample consisting of approximately 90,000 birth certificates served as a control group. Adjustments were made for the different number of days in each month and the seasonal variation in normal live births. For the total geographical and climatic area under analysis, only CL(P) was significantly different from the controls. The simple harmonic curve fitted to the data in the Edwards Analysis gave the maximal incidence in March. When data were broken down according to

climatic area of birth, CL(P) occurrence was seasonally significant only in the hot summer - moderate winter region. The maximal incidence occurred in January which preceded the national trend (March) by about two months.

FAMILY HISTORY

For many years it has been recognised that genetic predisposition plays a significant role in the etiology of clefting. However, the exact mechanisms remain unclear[9,10,12].

From early years pedigree studies have been conducted on families with children born with clefts. FOGH-ANDERSEN[5] cited Trew, who reported in the mid-eighteenth century on the occurrence of clefts in a family pedigree over four generations. Rischbieth was cited by DRILLIEN et al.[8] to have estimated that one in five children with clefts of the primary and secondary palate had relatives with this type of defect. The family histories of affected children have been recorded by many subsequent researchers. The results of some of these investigations are listed in Table 5.

Because of differences in material, method and, in particular, the extent to which the pedigree has been investigated, only limited comparison is possible between one study and another. The importance of this restriction was demonstrated by FOGH-ANDERSEN[5]. This investigator quoted Sanders who found that 45% of his sample had a family history of clefting when relatives as far distant as "17th degree cousins" were

TABLE 5. Studies detailing the proportions of probands with a family history of clefts*

INVESTIGATION	RELATIVES	TYPE OF CLEFT					
		CL(P)		CP		TOTAL	
		No.	%F.H.+ve.**	No.	%F.H.+ve.	No.	%F.H.+ve.
FOGH-ANDERSEN[5]	7 nearest groups same cleft type	498	36.7%	205	19.0%	703	31.6%
BEDER et al.[56]	all known	275	27.3%	98	13.3%	373	23.6%+
PEER et al.[57]	all known	283	22.6%	117	25.6%	400	23.5%
	4 nearest groups	283	4.6%	117	8.5%	400	5.8%
RANK & THOMSON[6]	all known	107	37.4%	53	22.6%	160	32.5%
	7 nearest groups						23.1%
SPRIESTERSBACH et al.[58]	all known	84	45.0%	27	37.0%	111	43.0%
WOOLF et al.[7]	7 nearest groups	418	43.1%	135	24.4%	553	38.5%
DRILLIEN et al.[8]	all known	92	42.4%	77	32.5%	169	37.9%
	5 nearest groups		22.8%		19.5%		21.3%

*Where previous investigators have not provided the percentages of probands with a family history of clefts, these have been calculated from their reported data.

**F.H.+ve. Family History positive.

+Inaccurate calculation in publication.

included. Fogh-Andersen estimated that every individual could expect to have 35 relatives with clefts if more than 30,000 relatives to the 17th degree were listed. For this reason, he limited consideration of the history to near relatives and restricted the term "familial disposition" to:

1. Patients with isolated clefts of the secondary palate reporting relatives with this type of cleft.
2. Patients with primary with or without secondary palatal clefts, having relatives with either of these defects.

As previously stated, Fogh-Andersen considered that two mutually independent malformations with no genetic connection were involved. He restricted his pedigree examination to the seven nearest groups of relatives. These were: parents, siblings, grandparents, aunts and uncles, cousins, nephews and nieces. WOOLF et al.[7] followed the same system.

DRILLIEN et al.[8], SPRIESTERSBACH, SPRIESTERSBACH and MOLL[58] and NISWANDER and ADAMS[59] are among those who examined pedigrees for relatives in the five nearest groups (excluding children, nephews and nieces) affected with any type of cleft. RANK and THOMSON[6] and also DRILLIEN et al.[8] extended their studies to include affected relatives of a more distant, but known relation to the proband than the "near relative" group. The majority of researchers in this field appear to have followed the latter approach. Rank and Thomson[6] and Drillien et al.[8] have also applied the term "family history positive" irrespective

of the relative's type of cleft in relation to the proband. Both RANK and THOMSON[6] and KNOX[60] have emphasised that the distinction between the two major genetic entities is not completely clear-cut. Rank and Thomson felt that it was a prejudgement to accept a family history as positive only in instances when the relative's cleft was of the same type as the proband's.

Table 5 summarizes the findings of studies and outlines methodology. The numbers and calculated percentages are given of positive family histories for subjects affected with each cleft entity, both separately and combined. It can be seen that CL(P) probands more often have a positive family history than do CP probands. An exception is the report of PEER, STREAN, WALKER, BERNHARD and PECK[57] which analysed data from 400 completed questionnaires. Since this response resulted from 1,000 postal questionnaires, the possibility of sample bias must be taken into account. These investigators noted that cases with CP more often had a positive family history than cases of CL(P). Drillien et al.[8] have suggested that CL(P) probands were more likely to be included in the family history positive group because of a cleft reported in a distant relative only, than were cases with isolated cleft palate.

Interpretation of familial association may be subject to error from two main sources, as described by RANK and THOMSON[6]. Firstly, the amount of information available about any family is dependent upon the number in the sibship and the knowledge provided by the relatives

interviewed. Secondly, there is no way of distinguishing between coincidental sporadic cases appearing together in a genealogy and genetically controlled familial occurrences, when the latter are in the minority and the defect is common in the general population.

It is advantageous to record a pedigree for each proband so that a count may be taken of the number of relatives with clefts in relation to the total number of known relatives. SPRIESTERSBACH et al.[58] stated that it was quite possible that cultural differences between samples of "families" might introduce a systematic bias. This bias would be related to differences in the number of relatives that were reported from one sample to another.

Analysis of the number of counted relatives in comparison with a control group is also helpful. Spriestersbach et al. recorded pedigrees for a control group specifically matched to their sample of patients with clefts. A semi-standardised interview technique was employed and a 17% positive family history was found in the control group.

Family history in relation to type of cleft and sex.

It has been widely observed[5,7,27,39] that when affected relatives are grouped according to type of cleft, there is an increase among the relatives of CL(P) propositi of this same type of cleft. At the same time relatives with cleft type CP occur at a frequency expected in the general population. Among the relatives of the CP propositi, there is an increase of the same type of cleft but no increase in the number of

CL(P) clefts.

The frequency of the trait in near relatives, especially those of first and second degree, seemed to be higher when the patient was of the sex less often affected. It has been shown that this was the case for CL(P)[8,61,62,63] and also for CP[8,9].

Thus for CL(P) where males were more likely to be affected, the recurrence risk was higher for the siblings of females and the reverse was true for CP. For more distant relatives, it was more difficult to demonstrate this type of association[63]. Such evidence supports the hypothesis that CL(P), in particular, is of multifactorial, polygenetic etiology and of threshold character[9,12,62,65]. However, genetic research would be assisted by additional material involving high-risk families, twin pairs and syndromic occurrences.

BIRTH WEIGHT

Previous authors have established that the birth weight of children with congenital abnormalities was below average. A high proportion of infants with low birth weight was observed for nearly every listed category of malformation in almost every ethnic group in a report by ERHARDT and NELSON[66], based on 4,986 birth certificates completed for malformed infants in 1958-1959 in New York City.

A birth weight of 2.5 kg (5.5 lbs) has been chosen by the American Academy of Pediatrics as an objective index of prematurity[67].

Birth weight may also be assessed in relation to length of gestation period. However, a time-based index of prematurity has limitations in respect to uncertainty of exact gestational period of study populations and scarcity of adequate control data. As available data in the present study was limited to birth weight, this review will be concerned primarily with this aspect.

The association of birth weight and orofacial cleft conditions has been investigated by a number of authors. From a birth certificate study LORETZ, WESTMORE and RICHARDS[68] found that 7.2% of live births in California in 1955 were less than 2.5 kg at birth, while 19.0% of 368 cleft cases were premature. The differences were reported as highly significant. Based on birth certificates also, GREEN et al.[20] classified 14.0% of single births with clefts as premature in comparison with 6.0% for single birth controls. BARNADOUVE[69] similarly found in Montana that 14.7% of 312 subjects were premature as against 7.5% for control live births over the same period.

FRASER and CALNAN[38] reported that in an English sample compiled from 456 surgical reports, the birth weight was lower for infants with clefts. DRILLIEN et al.[8] noted from a similarly derived sample that of the affected infants, 9.5% had birth weights of less than 2.5 kg while the comparable figure for the general population was 6.5%. From 1,088 surgical cases in Finland, RINTALA and GYLLING[70] observed that 7.4% of cleft affected births were premature, as against 3.4% for the control group. CAMPBELL WILSON[29] found that in surgical cases for which data

were available, the incidence of prematurity among cleft affected births was 8.5%.

The proportion of premature births is seen to vary according to type of cleft. This variation was found to be insignificant by BARNADOUVE[69], while RINTALA and GYLLING[70], in observing a percentage of prematurity of 7.3% for CL, 6.7% for CP and 8.4% for CLCP, reported that birth weight seemed to be correlated with severity of the anomaly. MOLLER[27] noted that the lowest average birth weight was observed in CLCP cases. CHI and GODFREY[34] stated that in their maternity hospital survey 11.4% of CL, 18.9% of CP and 19.1% of CLCP cases were premature, as judged from the weight of the infant at birth.

A preponderance of low birth weight subjects with CLCP was not, however, a constant finding. FRASER and CALNAN[38] found a predominance of premature births in the CP group and stated that their findings agreed with those of LUTZ[71]. DRILLIEN et al.[8] reported similarly from data, also based on surgical referrals, while the proportions described by GREEN et al.[20] from birth certificates were 8.0% for CL, 18.0% for CP and 15.0% for CLCP.

The association of prematurity and sex of the infant has been described by various authors, among whom several have found that lower birth weight was most markedly associated with females with CP[8,38,71]. In the Edinburgh sample all but one of the nine low weight babies with CP were females[8]. It is generally accepted that females are more likely to survive complications of intrauterine development and birth, but it

has been indicated that in studies of intrauterine growth retardation, based on samples of both live and still-born infants, there was a marked prevalence of females so affected[67]. Whether the association of low birth weight with female sex reflected the female ability to survive, or actually indicated a true association between growth retardation and sex, is an interesting question. At this stage it may be said that the exact significance of association between live premature births and sex is unclear.

MATERNAL AGE

It is known that the occurrence of certain human malformations is more common at increased maternal age[72]. The precise mechanism of the maternal age effect remains to be explained. This age effect seems strongest for mongolism, a defect which involves a chromosomal aneuploidy[47]. However, in a number of conditions with normal karyotype, a maternal age effect on incidence has been demonstrated. These conditions include hydrocephalus, cleft lip, with or without cleft palate[38], and achondroplasia[38,73]. Possibly, a maternal age effect is related to spontaneous genetic mutation[73]. Even so, the association between incidence and parental age provides strong presumptive evidence of environmental influence[74].

From examination of the literature it is apparent that the nature of the maternal age association with cleft lip and palate has been a controversial point. Many investigators have reported a positive

relationship between advanced maternal age and occurrence of clefts[20,29,46,60,68,69,75], while other investigators have been unable to demonstrate this association[5,39,57,76,77].

GREEN[10] criticized the statistical methodology of some studies and stressed the need to base data on age specific attack rates. This involved a comparison of the number of mothers in a specific age group with cleft affected children, and the number of mothers in the general population in the same age group. Green considered that it was not sufficient to compare the mean age of mothers of children with clefts with the mean age of mothers in the general population. Data grouped in this way could mask existing associations unless these associations were very marked.

ERHARDT and NELSON[66], AZAZ and KOYOUMDJISKY-KAYE[78] and ALTEMUS[17] have suggested that clefts may be relatively more common among issue of young mothers. However, the latter two investigations were based on relatively small samples. In contrast, WOOLF et al.[52] suggested that among issue of younger mothers there were fewer CL(P) cases. BARNADOUVE[69] supported this theory, but only in relation to CP. MESKIN[79] suggested that a relationship existed between maternal age and the extent of the cleft.

A number of authors have reported maternal age associations, especially in relation to type of cleft. MacMAHON and McKEOWN[37] recorded maternal age for 248 subjects with clefts and 1,105 controls.

These authors showed that the incidence of CL(P) increased with maternal age from 0.37 per 1,000 total births at ages under 23, to 1.41 per 1,000 at ages 38 and over. The incidence of CP appeared to be independent of maternal age. FRASER and CALNAN[38] demonstrated a significantly increased mean maternal age for CLCP but not for CL or CP subjects. WOOLF et al.[52] concluded that a statistically significant positive relationship existed between maternal age and CL(P) occurrence, but no such relation was seen for the occurrence of CP. GREEN et al.[20] found that the discrepancies between ages of mothers of 4,448 children with facial clefts and children in the control group, became greater with increasing age. This relationship was most evident for infants with CLCP and was only slightly less evident for those with CP. No relationship was shown for CL.

According to a further study by GREEN et al.[47], utilising birth certificate data from 29 States and two cities in the U.S.A., the paternal, rather than the maternal age effect, was most important for CLCP. A study by HAY[80] based on age specific occurrence rates of clefts in 6,698 infants, reported that when cleft of the primary palate was noted as a single malformation, no relationship with maternal age was seen. However, the other types of cleft, CP and CLCP, showed an increase with increasing age of the mother. For clefts occurring with one or more additional malformations, there was an increase with increasing parental age for all types of cleft, including cleft of the primary palate occurring alone.

In the Australian studies, CHI and GODFREY[34] found that only

isolated cleft lip was significantly related to maternal age, while RANK and THOMSON[6] reported no significant differences between mean maternal ages for any of the cleft sub-groupings and normal children. This finding agreed with a similar analysis of families reporting a familial disposition to the trait.

In conclusion, from the preceding review it appears that occurrence of clefts may increase with advancing maternal age, particularly in relation to CL(P). An association with CP was demonstrated less frequently.

PATERNAL AGE

Numerous authors have concluded that the age of the father has little significance[39,48,49,52,57,76]. It has been shown in other studies that paternal age appeared to be of etiologic importance[20,38,47,80].

FRASER and CALNAN[38] noted that paternal age appeared to be significantly raised in CLCP and to a lesser extent in CP. In further analysis, the paternal age effect could not be correlated with the patient's sex, or with the site of the defect. WOOLF[81] determined whether the parental age effect observed in 411 CL(P) propositi was of maternal or paternal origin. The findings indicated that paternal age was important in the etiology of this cleft group. GREEN et al.[20] in a study of four American States showed that the paternal age discrepancy between cleft and control groups became greater with advancing age of the father and mother. This relationship was most evident for CLCP and

CP. Only for fathers over 50 was an appreciable increase seen for infants with CL. These researchers also examined the paternal age effect when the mother's age was held constant. It was found that when the father was more than ten years older than the mother, the risk of producing a child with a facial cleft was increased. Further research by GREEN et al.[47] suggested that for CLCP it was the father's age, regardless of the age of the mother, which was of significance. For CP, however, both maternal and paternal age seemed to show an effect on the frequency of reported cases.

The high correlation of the mother's age with the age of the father was also acknowledged by HAY[80], who studied the relationship of paternal age to maternal age, holding maternal age constant and vice-versa. The findings were that even with more than 6,000 cases there was still the problem of very small frequencies for some of the more critical age combinations. Nevertheless, the results tended to confirm the independent etiological significance of increasing paternal age. For clefts occurring with one or more additional malformations, there was an increase with increasing paternal age for all types of cleft. When CL was reported as a single malformation, no relationship was observed. However, for CLCP and CP the incidence was seen to increase among children of older fathers.

No particular explanation was postulated for the observation that increased parental age seemed to be related more to clefts occurring with other malformations, than to those occurring as a single

entity. However, it was considered that some clefts, particularly those involving the lip and occurring as a single malformation, may have had a different etiology from those occurring with other malformations.

In summary, it appears that although many investigators have reported no relationship, more recent and larger studies have shown a slight paternal age effect on occurrence of clefts.

BIRTH ORDER

According to BETHMANN[82] some authors considered that the incidence of offspring with anomalies was greatest after the fourth birth, possibly because the uterine mucous membrane became exhausted after three births. The likelihood of subsequent congenital deformities was thus increased. The precise mechanisms responsible are, however, conjectural at the present time.

HAY and BARBANO[83] stated that an epidemiologic investigation of congenital malformations should include an analysis of maternal age and birth order. Indirect evidence for environmental causes might be provided by an association of the occurrence of malformations with either of these two variables. Hay and Barbano noted that few investigations have been made of populations large enough for analysis of the independent effects of these interrelated variables.

MacMAHON and McKEOWN[37] studied the relative incidence of affected children with CL(P) and CP, of the same birth rank and maternal

age. Their evidence suggested that CL and CLCP were unrelated to birth order but increased with maternal age. The incidence of CP was seen to be independent of both maternal age and birth order.

A relationship between birth rank and the probability of the birth of children with clefts was reported by MAZAHERI[48]. The difference between the distribution of defective children by birth rank and a purely random order was found to be statistically significant. Mazaheri noted also a tendency for the probability of the birth of a child with a cleft lip and/or cleft palate, to increase with increased age of the mother. A comparison of cleft affected first births in young mothers, as compared with older mothers, showed that associations with birth rank and maternal age were not merely different aspects of the same phenomenon. The first births of older mothers were defective twice as frequently as the first births of younger mothers, and the differences were statistically significant.

GREEN[10] considered that the relationships demonstrated by Mazaheri remained open to question because the birth of a defective child may have discouraged further pregnancies, and also the representativeness of the sample, based on chance reporting of cases for treatment, was questioned. Birth order, computed with the age of the mother held constant, was examined by GREEN et al.[20] for any difference between the observed and the expected number of babies born with facial clefts. No consistent trend was observed.

Another method of testing the effect of birth order and parental

age on the occurrence of clefts was proposed by BARKER and RECORD[84] who reported that this correlation was best described by a related frequency method. This method requires knowledge of the sibship size and is most meaningful when sibships in which birth rank is terminal, are excluded. WOOLF[64] also used this method and found that the excess of propositi in the later birth ranks was correlated with parental age and not with birth order.

In a recent report by HAY and BARBANO[83], malformation incidence rates, specific for age and parity groups, were calculated per 100,000 live births. Data on over 10,000 persons with clefts were compared with corresponding data from a control group derived from a 1% systematic sample of over eight million registered births. No readily available birth order trends were observed for CL, CLCP or CP.

BETHMANN[82] examined the surgical records of 4,365 cleft affected German patients to determine if there was any relationship between this anomaly and the ordinal number of birth. No relationship was demonstrated for all clefts combined, or separately, for different types of clefts. Other investigators have failed to demonstrate an association with birth order[5,8,38,52,60].

A number of authors have presented contrary findings suggesting that there is an association with parity for all cleft types combined[6,39,40,46] and for CL and CP only[39]. However, the weight of evidence seems to support the contention that birth order is unrelated to incidence of clefts.

ASSOCIATED MALFORMATIONS

The overall incidence of all malformations reported from birth certificates varies around 1%[85]. A common estimate of occurrence of congenital malformations is 4% to 5%[2], but this proportion may still be an underestimation. SALZMANN[86] quoted Lederberg who stated that up to fifteen out of every 100 births may later in life show some form of inherited disorder.

The frequency with which clefts have occurred with other malformations, has been of particular interest to previous investigators, as have the types of malformations which are commonly associated with clefts. The most severe spectra of defects frequently result from chromosomal abberations. BHATIA[12] considered chromosomal groups D and E to be most commonly involved. The proportion of cases in which defects result from chromosomal abberations is, however, small. In the study reported by DRILLIEN et al.[8] only four subjects had defective chromosomes out of 37 cases in which the cleft was associated with other malformations.

A number of specific syndromes appear to be etiologically related to particular mutations affecting single genes. For example, a dominant gene has been identified for the syndrome which, when complete, includes clefts of the primary with or without cleft secondary palate, fistulae of the lower lip and syndactyly. This was first described by VAN DER WOUDE[87]. The gene was also segregated in at least seven out of 142 families by WOOLF, WOOLF and BROADBENT[88] which is a higher incidence

than the 0.05% postulated by Van Der Woude. In the sample selected for cleft in parent and child, reported by Woolf et al., clefts of either the primary or secondary palate appeared in conjunction with lip pits. These workers observed that there was likely to be more than one syndrome involving facial clefts and lip pits. The Pierre Robin syndrome in which a hypoplastic mandible is usually associated with a cleft of the secondary palate, is another example of the manner in which a cleft may be part of a recognised syndrome. FRASER and CALNAN[38] stated that the gene concerned may account for a large proportion of CP cases. Out of 28 patients with CP and associated abnormalities, nineteen clefts occurred with micrognathia.

FRASER[9] has indicated that there may be about 50 specific syndromes in which clefts of the primary and/or secondary palate occur with other defects; CZEIZEL and TUSNADI[89] observed that although such syndromes were rare, they possibly included a considerable proportion of all multiple defects. According to GREEN et al.[20], the majority of cases in which the cleft was one of a number of defects were not syndromic, and the defects appeared to occur in a haphazard and totally unpredictable way. In a recent publication, HAY[90] stated that the majority of infants with multiple malformations appeared to represent the outcome of random disorganisation of fetal development.

Samples based on referral of infants for surgical treatment should show a lower incidence of associated defects than those based on all live births, or live and still births. Infants with other defects have been

shown to be less likely to survive the early neonatal period[37]. HAY and WEHRUNG[85] have suggested that some malformations, for example, heart defects, are not diagnosed at birth. Associations between clefts and such malformations are therefore, probably grossly underestimated when reporting is limited to birth certificates and other neonatal records.

FOGH-ANDERSEN[5] thought it possible that most of the patients with associated malformations had a greater chance of being treated in the large clinics from which publications emanated. GREEN et al.[47] also reported the possibility of an increased index of suspicion resulting from the observation of any single malformation.

As reported by DRILLIEN et al.[8], the incidence of other defects was likely to be lower if data obtained from hospital records were compiled for other purposes. For example, FRASER and CALNAN[38] noted that in their surgical series the incidence would be expected to be lower than in the series of MacMAHON and McKEOWN[37], since in the former sample early death would have excluded all gross malformations. In another investigation[58] where patients with clefts were personally examined for the detection of other abnormalities, the incidence of associated defects was relatively high (23.4%). Furthermore, the incidence of other defects is known to be associated with the age of the patient at the time of examination.

CZEIZEL and TUSNADI[89] analysed various epidemiologic characteristics of a Hungarian population by dividing CL(P) and CP affected individuals into two further groups, according to whether or not multiple

malformations were involved. However, differences in definition of "malformation" and difficulty in the recognition of syndromes, limit meaningful analyses of associated anomalies with clefts. Thus, because of possible variability in criteria from one study to another, it is difficult to make direct interstudy comparisons.

The reasons for variation that have been outlined should be considered when interpreting published reports. From maternity hospital records of 163 subjects, FOGH-ANDERSEN[5] noted that more than 10.0% of cleft affected children had other severe defects; most of these children were still-born or died shortly after birth. LUTZ and MOOR[19] reported that 25.7% of the 70 subjects whose hospital birth records were reviewed had some associated defect. In a control group of 152 births, the corresponding proportion was 3.9%. In the same study, 50 out of 315 (16.5%) surgical patients had associated defects. DRILLIEN et al.[8] excluded patients in whom other defects became apparent at a later age than that of the hospital follow-up. They reported that 61 of 159 subjects (38.4%) had associated malformations. MacMAHON and McKEOWN[37] attempted to include in their sample all live and still-born infants with cleft defects in Birmingham over a ten year period. In this sample the percentage of associated malformations exhibited by affected subjects was 15.8%. A figure of 16.5% was given by GREEN et al.[47] from birth certificate data documenting 2,003 infants with clefts, while DONAHUE[75], from a large sample derived from birth certificates, reported 10.0% with associated defects as against 3.8% with congenital malformations for a control group. KRAUS, KITAMURA and OOE[91] reported that 61.7% of 60

aborted embryos and fetuses with cleft lip and/or cleft palate, had other deformities.

Associated malformations by type of cleft.

Various investigators have reported on the percentage of associated malformations for combined cleft types. For the purpose of close comparison, however, the relevant figures for individual cleft types reported from a number of studies, based mainly on surgical referrals, are summarised in Table 6. The observation that isolated palatal clefts were most often associated with other defects is consistently confirmed from surgical records, and other sources of data such as birth certificates and hospital births[5,14,20,34].

However, MacMAHON and McKEOWN[37] reported a sample from multiple sources comprising 86.0% live births and 14.0% still births and neonatal deaths. This sample differed from others in that combined clefts of primary and secondary palate were more often associated with other defects, than were other cleft types. As DRILLIEN et al.[8] suggested, this finding may be due to the inclusion of still births in the sample. CZEIZEL and TUSNADI[89], on the other hand, derived Hungarian data from multiple sources including still births, and reported a 28.9% proportion of multiple defects in the CP group and 10.5% in the CL(P) group.

Associated malformations: type of cleft and sex.

CZEIZEL and TUSNADI[89] recently confirmed previous genetic

TABLE 6. Studies (based mainly on surgical referrals) detailing the proportions of cleft cases with associated malformation.

AUTHOR	CL			CLCP			CL(P)			CP			TOTAL		
	No.	A.M.*	%	No.	A.M.	%	No.	A.M.	%	No.	A.M.	%	No.	A.M.	%
LUTZ & MOOR[19]													303	50	16.5
BEDER et al.[56]	54	4	7.4	255	31	12.2	309	35	11.3	114	28	24.6	423	63	14.9
PEER et al.[57]													400	40	10.0
RANK & THOMSON[6]	38	1	2.6	69	5	7.2	107	6	5.6	53	16	30.2	160	22	13.8
CURTIS & WALKER 1960**							424	21	5.0	157	29	18.5	581	50	8.6
FRASER & CALNAN[38]	93	1	1.1	152	3	2.0	245	4	1.6	211	28	13.3	456	32	7.0
KEYS SMITH[92]	90	4	4.4	224	14	6.3	314	18	5.7	45	4	8.9	359	22	6.1
SPRIESTERSBACH et al.[58]							134	21	15.7	37	19	51.4	171	40	23.4
INGALLS et al.[39]	16	2	12.2	54	5	9.3	70	7	10.0	30	15	50.0	100	22	22.0
DRILLIEN et al.[8]	21	7	33.3	64	19	29.7	85	26	30.6	74	35	47.3	159	61	38.4
CONWAY et al.[42]													850	170	20.0
CAMPBELL WILSON[29]	200	15	7.5	251	27	10.8	451	42	9.3	232	39	16.8	683	81	11.9

*A.M. = associated malformations
**Cited by DRILLIEN et al.[8]

In those studies where the proportions of subjects with other malformations have not been specified for particular cleft groups, these data have been calculated from the reported data.

evidence[64,88] that clefts occurring with other malformations were etiologically distinct from clefts occurring as isolated defects. This evidence was based partly on the fact that while a significant excess of males could be observed in all CL(P) cases (63.4%), the sex ratio for CL(P) with other defects (51.6% male), was very similar to the male proportion of 51.7% cited for the newborn population at large. However, in the W.H.O. sample[33], in CL(P) with other defects, the percentage of males (78.0%) was an even higher proportion than that observed when the cleft occurred as the sole malformation. In the Hungarian study[89] fewer males than females (41.4% male), were found with isolated CP, but in CP with other defects, the sex ratio (48.5% male) was essentially the same as the control value. Similar findings were reported in the W.H.O. series in that for CP, 41.0% were male, while for CP with other defects, eighteen of 37 cases were male (48.7%).

From another perspective, MESKIN and PRUZANSKY[93] showed that, independent of cleft type, females more often had additional malformations than males. For CL, 4.2% of males and 8.3% of females had additional defects. For CLCP the proportions affected were 8.1% of males and 15.0% of females, and for CP, 14.3% of males and 20.2% of females. Meskin and Pruzansky cited Rumler and Peter who reported similar findings from a German population and concluded that females were able to survive with more malformations than were males. GREEN et al.[20] also reported that of 4,451 live-born infants with clefts, girls had more associated malformations than boys. Not all workers have reported data in agreement with the studies cited above. DRILLIEN et al.[8]

found little difference in the incidence of associated defects in males and females in any of the cleft type sub-groups. CONWAY and WAGNER[41] noted that males in all cleft categories demonstrated associated malformations more often than females, while PANNBACKER[94] made this observation only for CLCP and CP. For all cleft groups combined, IVY[4] found males to be affected more often than females.

From the above, there appears to be little agreement as to the nature of the sex distribution within the major cleft classes when the cleft is associated with other malformations. However, there is some evidence that both CL(P) and CP with other defects, should be considered as anomalies of different etiological origin from clefts unassociated with other defects.

In summary, the literature contains numerous varying and often conflicting epidemiologic reports relating to the incidence of clefts by sex and site, in secular and seasonal patterns of occurrence, in family history and in associations with birth weight, parental age, parity and associated malformations. While the above aspects are among those that have received most attention, many other associations have been investigated. These include geographic, socio-economic, emotional and dietary factors, exposure to radiation, viral infections, and specific chemical and other teratogenic agents.

In spite of the extensive search for etiologic understanding, knowledge of genetic and environmental aspects is limited. While a multifactorial, polygenetic theory is currently favoured, specific

environmental agents remain unidentified although they are assumed to be operative. Because of the difficulty of specifying the basis for the occurrence of either CL, CL(P) or CP, there is a need for basic information from populations not previously studied.

MATERIAL AND METHOD

THE SAMPLE STUDIED

An exceptional opportunity exists in South Australia for the study of epidemiological aspects of cleft lip and cleft palate. With very few exceptions, all cases are referred to the Adelaide Children's Hospital for treatment. The reasons for this are that feeding difficulties and other postnatal problems in the care of cleft affected children require specialist nursing training and facilities. In addition, the plastic surgeons who carry out early surgical repairs are concentrated in the city of Adelaide.

Under these circumstances, where a defined population is served by a single medical facility, it is advantageous to combine two recognized methods of case selection for an analytic epidemiologic survey, as outlined by MacMAHON, PUGH and IPSEN[95]. The first method is the inclusion of all cases of the disease seen between specified dates at a medical care facility; the second is the inclusion of all cases of the anomaly occurring between specified dates in a limited or defined population.

The Records Department of the Adelaide Children's Hospital

maintains an index based on the medical condition responsible for all admissions. Admissions with multiple anomalies and with an oral or facial cleft as a secondary condition also were listed over the years under study. The pertinent records were collected and the name and hospital record number were noted over the period January 1949 to June 1968, inclusive. In addition, the records were examined from July 1968 to December 1971, in order to include children born prior to December 1968, who were admitted for surgery over the following three year period.

The hospital case notes of the listed admissions were recorded on a year to year basis, and the subjects were included for further study when the following conditions were fulfilled:-

The case note was located.

The subject was born between January 1949 and December 1968, inclusive.

The subject was born within the State of South Australia.

All subjects included for further study were listed alphabetically by surname, and given a study number. Perusal of hospital case notes yielded data of varying degrees of completeness for individual subjects. In spite of this limitation, basic epidemiological data were abstracted from the case notes of all subjects and recorded on forms ACH 1 (Appendix A 1) and ACH 2 (Appendix A 2).

Tracing these subjects was necessary to allow confirmation and expansion of case history data and also to obtain a series of radiographs of the skull, jaws and hand-wrist. A subsequent cross-sectional study

is planned of the facial, dental and skeletal development of the population under study.

The subjects were recognised as differing by type of cleft and sex over a wide age range, and accordingly a large sample was required. However, for the reasons listed below, the following subjects were excluded from the study.

Deceased.	24
Family now interstate.	10
Extremely severe congenital deformities and/ or under the care of a special institution.	3
Unknown or insufficient address.	3
TOTAL	40

The Adelaide Children's Hospital Admissions Index lists over 650 children with clefts of the orofacial complex. As 559 of these fulfilled the study requirements of being born in South Australia over the years 1949 - 1968 inclusive, they were given a study number.

With the exclusion of the 40 subjects listed above, the remaining 519 were sent a letter requesting participation in the project. The envelope included an explanatory letter (Appendix B 1) and an appointment to enable parental interview and subject examination, as well as a reply slip in a post-paid envelope. There were two forms of this general letter. Letter 1G a (Appendix B 1, B 2, B 3) was sent to the parents or guardians of children seventeen years of age or younger. Letter 1G b (Appendix B 4, B 5, B 3) which was a modification of Letter 1G a, was

sent direct to subjects seventeen years of age or older.

The first general letter produced a response from 317 patients, so that 61.1% responded by attending the first appointment, by telephoning or by returning the reply-paid appointment slip to arrange another appointment. A total of 202 patients failed to respond.

A number of letters were returned by the post office marked "address unknown". If there was no response to the first letter, a second identical letter was sent to the original address. Some subjects responded to the second letter, but again some were returned by the post office. Lists were compiled of names and last recorded addresses of 98 subjects who were known to be no longer resident at the original address. The State Electoral Office was able to locate a new address for 41 of these individuals.

A list was compiled also of the names and last recorded addresses of 52 of the subjects who had failed to respond to the second letter, but whose letters were not returned by the Post Office. The Electoral Office was unable to locate 57 subjects. The names of 109 subjects not traced so far were supplied to the plastic surgeons and orthodontists in South Australia, who were asked to search their files for further information. In this way, current addresses of 23 more patients were obtained, making a total of 64 new addresses located through the efforts of the Electoral Office, the plastic surgeons and the orthodontists. The original general letter was sent to the 64 new addresses and, if necessary, a second identical letter. Contact was eventually established

with 47 of these families.

A more urgent letter was sent to 62 patients in a final attempt to establish contact. This letter, Letter 2 G (Appendix B 6, B 3) resulted in contacting a further 25 subjects. Personal contact was established with an additional 25 families. Many had had recent surgical or orthodontic treatment and had been attending the Royal Adelaide Hospital and Adelaide University Clinics.

From the original list of 519 subjects, contact was established with 414 subjects or their families, that is 79.8%. This result compares favourably with responses obtained by CAMPBELL WILSON[29] and by KNOX[60]. Campbell Wilson reported a positive response from 61.3% of the 612 families with whom contact was sought. Knox obtained an overall reply rate of 66.0%.

The initial appointment with the subject and parents, or guardians, was designed to accomplish four objectives. The first aims were to confirm the nature of the cleft and to interview the parent. Data Sheets ACH 1 and ACH 2 (Appendix A 1 and A 2) were available and the examination and questions were directed towards expanding and confirming the data. The third aim was to explain a questionnaire, relating mainly to maternal history, before asking the parent to complete it, either immediately, or to return it at a later date in a reply paid envelope. This questionnaire (Appendix C) was slightly modified from that developed by the St. Luke's Hospital, New York City and reproduced by STARK[96]. This basic format was used although it was recognised that the use of a retrospective questionnaire relating to minor events in the

course of pregnancy occurring many years previously, has severe limitations[10,95]. Finally an appointment was arranged for a radiographic examination to include left lateral head, postero-anterior head, left hand-wrist and panoramic radiographic films of the jaws. The radiographs were for later analysis.

In the early stages of the study, the interviews and examinations were conducted at the Adelaide Children's Hospital. It was then necessary for the subject to attend the Dental Department of the Royal Adelaide Hospital for the radiographic examination. The taxi fare was paid from research funds where necessary. This arrangement was often inconvenient and for the latter stages, the interviews and examinations were conducted in the Orthodontic Section of the Dental Department at the Royal Adelaide Hospital.

For a variety of reasons, some subjects did not present for radiographic examination as previously arranged, or the parents did not return a questionnaire. In such instances, specific letters were sent requesting continued co-operation. [Letter 3a (Appendix B 7); Letter 3 b (Appendix B 8) and Letter 3 c (Appendix B 9).]

The results of the follow-up investigations are summarised below:

Interviews Although contact was established with the parents, guardians, or the subjects themselves in 414 instances, only 372 parents or guardians attended an interview. Co-operation in this respect was refused by seventeen families; in six instances, financial difficulties

precluded attendance; seven families had moved interstate; one subject had been permanently institutionalised; five failed to attend following two special letters seeking to arrange an interview, and the remaining six interviews were pending when the present figures were compiled. Once contact had been established, the co-operation level was 89.4%. Interviews were obtained with persons other than the mother, e.g. father, sister or aunt in sixteen instances. In three of these cases, mothers were deceased, two mothers had been committed to institutions, and eleven mothers could not attend for various domestic reasons.

Examination of individual Subjects : A total of 376 subjects representing a level of 90.8% co-operation were examined essentially for the purpose of confirming the site and extent of the original cleft. Examinations were impossible for 38 subjects because thirteen refused co-operation, six were unable to attend because of the considerable distances involved, nine were resident in another state, one had been permanently institutionalised, and nine subjects had agreed to participate but were unable to attend during the study period.

Questionnaire : Of the 376 parents given or sent a questionnaire, 331 (88.0%) co-operated by completing and returning it. Questionnaires were completed by a person other than the natural mother or father in five instances. Three mothers refused to return the questionnaire and a further 41 failed to do so, even though a second questionnaire and covering Letter 3 c (Appendix B 9) had been sent to 32 of them. One questionnaire was returned incomplete.

Radiographic Examination : Five of the 376 subjects who attended the general examination and were given an appointment in the Dental Radiography Department, did not attend for radiographs. One subject refused to co-operate for any of the radiographs and in another instance, because of severe congenital deformities, radiographs were unobtainable. Three subjects failed to attend after a second letter had been sent specifically requesting co-operation - Letter 3 b (Appendix B 8). The full series of four radiographs was obtained for 315 subjects. In three cases no hand-wrist film was obtained, and in eleven cases, no lateral head or postero-anterior head film was taken because of consistent lack of co-operation from some young patients. In 51 cases panoramic radiographs of the jaws were impossible because the machine had not been installed in the Dental Radiography Department until after the study had started.

COLLATION AND ANALYSIS OF EPIDEMIOLOGICAL DATA.

The data were transferred from form ACH 1 (Appendix A 1), which incorporated an abstract of the hospital case note, and from the questionnaire (Appendix C) on to a data analysis form, designed to allow ready transferral to punched cards, prior to computer analysis.

In consultation with Mr. P.I. Leppard of the Department of Statistics, the University of Adelaide, programmes were devised to present, in summary, findings from all aspects of the study and to statistically describe certain findings of epidemiological interest. In

particular, the following aspects were analysed in greater detail:

Incidence of clefts.

Incidence by type of cleft and sex.

Secular variation in incidence.

Seasonal variation in incidence.

Family history of clefts.

Birth weight.

Maternal age.

Paternal age.

Birth order.

Associated abnormalities.

CLEFT CLASSIFICATION

HARKINS, BERLIN, HARDING, LONGACRE and SNODGRASSE[97] have stated that while the anatomy and severity of the defect constitutes the basis for classification, the detail to which subdivision is carried depends upon the aim of the observer in any given situation. The classification scheme proposed by KERNAHAN and STARK[98] was based on anatomic principles. According to these principles, the incisive foramen and not the alveolus, demarcates the primary from the secondary palate. This classification corresponds to the main types of facial clefts described by FOGH-ANDERSEN[5] and to the suggestion for classification advanced by Harkins et al. Although the scheme of Kernahan and Stark was adopted in principle, the present study was concerned with the common types of

cleft. More rare types such as median cleft of the lips or oblique clefts of the face were not included.

Accordingly, clefts were divided into the three anatomical groups:

CL	CLEFT OF PRIMARY PALATE (Cleft lip ± cleft of alveolar process)
CP	CLEFT OF SECONDARY PALATE (Isolated cleft palate)
CLCP	CLEFT OF PRIMARY AND SECONDARY PALATE (Cleft lip + cleft palate)

It has been recognised that retrospective review of hospital records and patient examination many years following a repair, presents difficulties in ascertaining the original anatomical extent of the defect. For this reason, analysis of completeness or severity of the cleft conditions was not attempted. However, the laterality distribution was included for analysis.

RESULTS

Incidence

A total of 552 subjects born in South Australia from 1949-1968, inclusive, with clefts of the orofacial complex, were included for study. The cleft site was specified as involving the primary and/or secondary palate and thus classified as CL, CLCP or CP.

The registered number* of live births occurring in South Australia during the years 1949-1968 was 392,228. An incidence rate for specified cases of 1.41 per 1,000 (1:711) live births was therefore calculated.

Type of Cleft

Clefts of the primary palate made up 29.7% of the total, clefts of the secondary palate 33.3%, and combined clefts of the primary and secondary palate contributed 37.0% to the total South Australian incidence. Table 7 gives the number of clefts of each type, the corresponding incidence per 1,000 live births and the percentage

*Data supplied by the Adelaide Office of the Commonwealth Bureau of Census and Statistics. This figure includes additional late registrations of births occurring during 1949-1968 and received by 1972.

distribution by type of cleft. Clefts involving the primary with or without the secondary palate were twice the number involving the secondary palate alone.

TABLE 7. Incidence and cleft morphology distribution in South Australia (1949-1968)*

SUBJECTS	TYPE OF CLEFT				
	CL	CLCP	CL(P)	CP	TOTAL CLEFTS
Number	164	204	368	184	552
Incidence per 1,000 live births	0.42	0.52	0.94	0.47	1.41
% distribution	29.7	37.0	66.7	33.3	100

*Subjects with unspecified cleft type or rare facial clefts were excluded from calculation (seven cases).

Sex ratio

There were more males than females with clefts involving the primary palate, while the majority of cases with isolated cleft secondary palate were females. The sex ratios or percentages of males in the major cleft groupings are given in Table 8 and Figure 2. Of live births registered** in South Australia over the study period, 51.3% were male.

**Data supplied by the Adelaide Office of the Commonwealth Bureau of Census and Statistics. Live birth registrations may differ slightly in sex ratio from live birth occurrences.

TABLE 8. The cleft morphology distribution and percentage of males in particular cleft groupings South Australia (1949-1968).

SUBJECTS	TYPE OF CLEFT				
	CL	CLCP	CL(P)	CP	TOTAL CLEFTS
Males	107	135	242	73	315
Females	57	69	126	111	237
Males + Females	164	204	368	184	552
% male	65.2	66.2	65.8	39.7	57.1
X^2 - value on 1 d.f.	12.80	18.02	30.78	9.96	7.33
Probability	<0.01	<0.01	<0.01	<0.01	<0.01

$P \quad (X_1^2 \geq 6.64) = 0.01$

The chi-square test (Appendix E) was used to evaluate the significance of deviation of observed to expected occurrence by sex within the major cleft classes. Table 8 shows that significantly more males than females were found for CL, CLCP, CL(P) and all clefts groups combined, while significantly more females than males had CP ($P<0.01$).

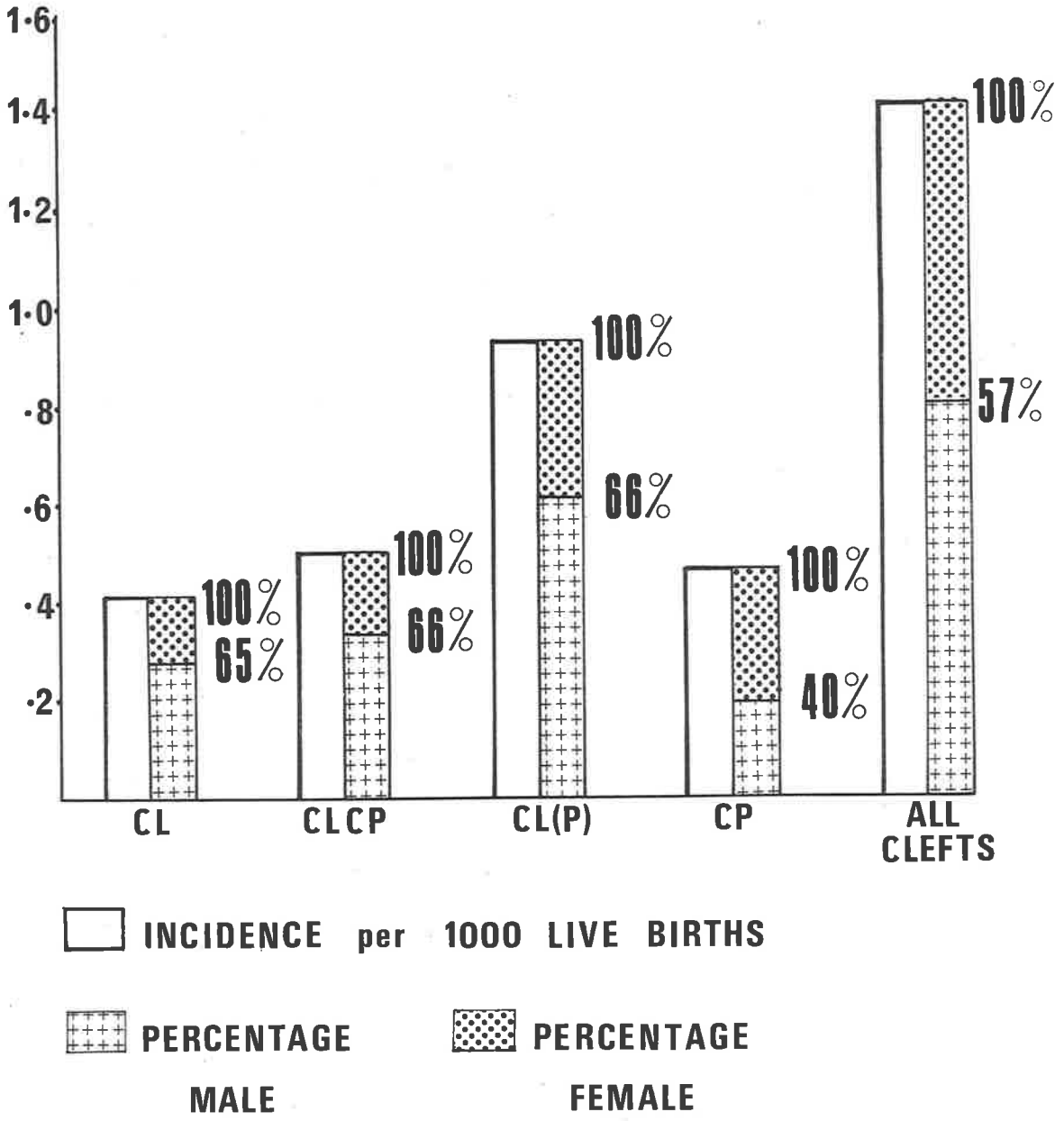

FIGURE 2. The incidence per 1000 live births and the percentage of males in particular cleft groupings in S.A. (1949-68).

Laterality

The number and percentage distribution of laterality is given for cleft types CL and CLCP in Table 9. For thirteen (7.9%) CL cases the laterality was unspecified. Of specified cases, the left-sided, unilateral defect was almost twice as common as right-sided unilateral cleft, and unilateral CL defects outnumbered bilateral CL in a ratio of approximately 7:1. Six cases (2.9%) of CLCP were unspecified as to side of cleft; for specified CLCP cases, left-sided unilateral clefts were almost half as common again as right-sided defects. Unilateral CLCP was nearly three times as common as the more severe bilateral CLCP.

TABLE 9. The laterality distributions of CL and CLCP in South Australia (1949-1968).

SUBJECTS		LATERALITY OF CLEFT					
		ALL CASES	UNILATERAL			BI-LATERAL	UNSPECIFIED
			L.	R.	TOTAL		
CL	Number	164	84	48	132	19	13
	Distribution	100%	51.2%	29.3%	80.5%	11.6%	7.9%
CLCP	Number	204	86	59	145	53	6
	Distribution	100%	42.5%	28.2%	71.1%	26.0%	2.9%

Laterality and Sex

Table 10 gives the distribution by laterality of the defect with males and females considered separately. Also described is the sex ratio for cleft types CL and CLCP by laterality. For both cleft types CL and CLCP, little difference was seen between the sex ratios of either the left, right or bilateral sub-group and that previously described in Table 8 for the major cleft grouping.

TABLE 10. The laterality distributions for CL and CLCP and the percentage of males in particular cleft groupings in South Australia (1949-1968).

SUBJECTS		LATERALITY OF CLEFT					
		ALL CASES	UNILATERAL			BI-LATERAL	UNSPECI-FIED
			L.	R.	TOTAL		
CL	No. Males	107	54	32	86	12	9
	Distribution	100%	50.5%	29.9%	80.4%	11.2%	8.4%
CL	No. Females	57	30	16	46	7	4
	Distribution	100%	52.6%	28.1%	80.7%	12.3%	7.0%
CL	No. Males & Females	164	84	48	132	19	13
CL	% Male	65.2%	64.3%	66.7%	65.2%	63.2%	69.2%
CLCP	No. Males	135	56	37	93	37	5
	Distribution	100%	41.5%	27.4%	68.9%	27.4%	3.7%
CLCP	No. Females	69	30	22	52	16	1
	Distribution	100%	43.5%	31.9%	75.4%	23.2%	1.4%
CLCP	Number Males & Females	204	86	59	145	53	6
CLCP	% Male	66.2%	65.1%	62.7%	64.1%	69.8%	83.3%

Secular Variation in Incidence

As seen in Table 11 and in Figure 3, the yearly variation in incidence was quite marked for various cleft types. The incidence for CL(P) ranged from 0.52 per 1,000 in 1950 and 1951, to 1.42 per 1,000 in 1967. For CP the incidence ranged from 0.29 per 1,000 in 1951 to 0.82 per 1,000 in 1965.

Since the data included almost the entire population with these types of congenital malformations, the present study is a parallel to that reported by HAY and WEHRUNG[35] in describing congenital malformations in twins. Similarly, it was concluded that descriptive statistics alone provided an adequate characterisation of the population and thus no statistical tests of significance were performed. Table 12 sets out the mean yearly occurrences of the major types of cleft, together with the ranges and calculated standard deviations of the distributions.

TABLE 11. The yearly occurrence and incidence of clefts per 1,000 live births in South Australia (1949-1968).

YEAR	TYPE OF CLEFT				TOTAL CLEFTS	TOTAL LIVE BIRTHS	RATIO (Clefts to total)
	CL	CLCP	CL(P)	CP			
1949	3 .19	6 .37	9 .56	6 .37	15 .93	16,204	1:1080
1950	3 .17	6 .35	9 .52	7 .40	16 .92	17,322	1:1083
1951	5 .29	4 .23	9 .52	5 .29	14 .81	17,319	1:1237
1952	9 .50	10 .56	19 1.06	6 .34	25 1.40	17,904	1:716
1953	5 .27	9 .49	14 .77	6 .33	20 1.10	18,184	1:909
1954	8 .44	7 .38	15 .82	8 .44	23 1.25	18,359	1:798
1955	9 .49	12 .65	21 1.14	8 .44	29 1.58	18,386	1:634
1956	9 .46	6 .31	15 .77	10 .52	25 1.29	19,359	1:774
1957	11 .56	9 .46	20 1.01	9 .46	29 1.47	19,706	1:680
1958	8 .40	11 .55	19 .95	6 .30	25 1.26	19,909	1:796
1959	17 .81	12 .57	29 1.39	9 .43	38 1.82	20,892	1:550
1960	9 .43	4 .19	13 .61	10 .47	23 1.09	21,157	1:920
1961	10 .47	8 .37	18 .84	11 .51	29 1.36	21,392	1:738
1962	3 .14	15 .70	18 .84	14 .66	32 1.50	21,340	1:667
1963	5 .24	23 1.08	28 1.32	14 .66	42 1.98	21,205	1:505
1964	6 .29	12 .58	18 .86	11 .53	29 1.39	20,830	1:718
1965	6 .29	10 .48	16 .77	17 .82	33 1.59	20,792	1:630
1966	12 .59	13 .64	25 1.23	12 .59	37 1.82	20,314	1:549
1967	13 .64	16 .78	29 1.42	6 .29	35 1.71	20,442	1:584
1968	13 .61	11 .52	24 1.13	9 .42	33 1.56	21,212	1:643
Total	164 .42	204 .52	368 .94	184 .47	552 1.41	392,228	1:771

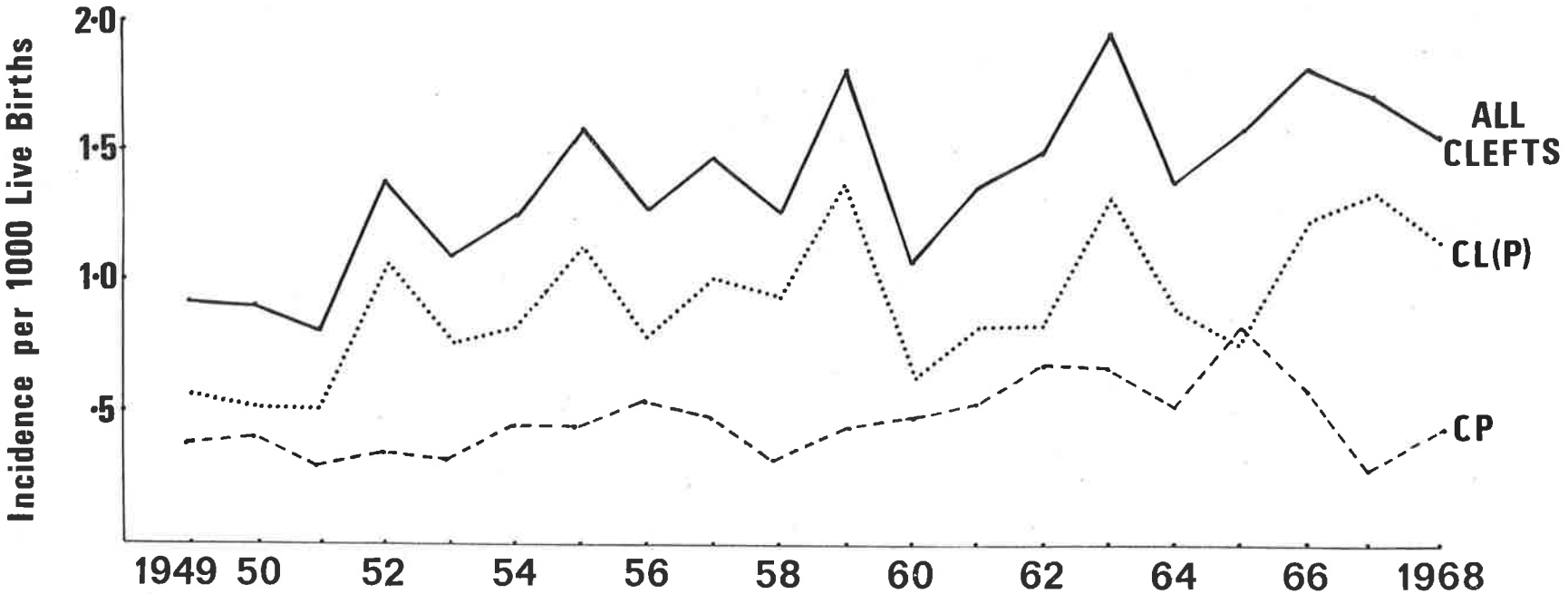

FIGURE 3. The yearly incidence per 1000 live births of CL(P), CP and all clefts combined in S.A. (1949-68).

TABLE 12. Summary statistics of total and average yearly cleft occurrences in South Australia 1949-1968.

SUBJECTS	TYPE OF CLEFT				
	CL	CLCP	CL(P)	CP	TOTAL CLEFTS
Total No.	164	204	368	184	552
Mean incidence/1,000	0.42	0.52	0.94	0.47	1.41
Mean yearly occurrence	8.2	10.2	18.4	9.2	27.6
Range of yearly occurrence	3-17	4-23	9-29	5-17	14-42
S.D. of yearly occurrence	3.79	4.51	6.26	3.24	7.76

Seasonal Variation in Incidence

The distribution by month of birth for both normal children and children with clefts is shown in Table 13. Using the method of EDWARDS[54] for detection of cyclic trends, it was found that there was a significant seasonal variation for normal births with a maximal frequency occurring in August. For this reason, the monthly totals for each cleft type were converted to the proportions of all births occurring per month. These adjusted totals are also listed in Table 13. Subsequently, adjusted monthly totals were subjected to the Edwards analysis as applied by CHARLTON[32] and WEHRUNG and HAY[53].

In order to portray cyclic trends and percentage variations in the monthly distribution, the ratio of frequency of malformation to average monthly frequency by month of birth was calculated. These ratios, referred to for convenience as ratio of observed to expected cleft affected births, are listed in Table 13 and plotted for those cleft types showing significant seasonal variations in Figures 4 and 5. The Edwards fitted simple harmonic curves are also graphed in Figures 4 and 5. Both CLCP and CP showed significant seasonal variation ($P<0.05$), while no such significance could be attached to the seasonal variation in occurrence of CL(P) and CL. The months of maximal birth incidence were calculated for CLCP and CP as occurring in May and in March respectively.

TABLE 13. The average monthly occurrence of clefts in South Australia (1949-1968).

MONTH OF BIRTH	TOTAL LIVE BIRTHS[f]	TYPE OF CLEFT											
		CL			CLCP[d]			CL(P)			CP[d]		
		Obs.[a]	Adj.[b]	Ratio[c]	Obs.	Adj.	Ratio	Obs.	Adj.	Ratio	Obs.	Adj.	Ratio
January	32,449	11	11.12	0.81	28	28.11	1.65	38	38.39	1.25	20	20.11	1.31
February	30,213	9	9.77	0.71	8	8.63	0.51	17	18.44	0.60	17	18.36	1.20
March	33,525	7	6.85	0.50	18	17.49	1.03	25	24.44	0.80	19[e]	18.49	1.21
April	32,121	14	14.30	1.05	23	23.32	1.37	37	37.76	1.23	16	16.25	1.06
May	33,214	15	14.82	1.08	21[e]	20.60	1.21	36	35.53	1.16	24	23.57	1.54
June	32,126	11	11.24	0.82	15	15.23	0.90	26	26.53	0.87	11	11.17	0.73
July	33,194	13	12.85	0.94	27	26.50	1.56	40[e]	39.50	1.29	11	10.80	0.70
August	33,643[e]	19	18.53	1.36	18	17.43	1.03	37	36.05	1.18	14	13.58	0.89
September	33,956	14	13.53	0.99	13	12.47	0.73	27	26.06	0.85	11	10.57	0.69
October	34,103	23[e]	22.13	1.62	9	8.60	0.51	32	30.76	1.00	13	12.44	0.81
November	31,500	14	14.58	1.07	12	12.41	0.73	26	27.05	0.88	12	12.43	0.81
December	32,184	14	14.27	1.04	13	13.16	0.77	27	27.50	0.90	16	16.22	1.06

a Observed number of cleft affected births per month.
b Adjusted number of cleft affected births per month in relation to the monthly variation in normal births.
c Ratio of adjusted to average monthly cleft affected births.
d Significant ($P<0.05$) variation in seasonal incidence.
e Month of peak seasonal occurrence derived from Edwards' analysis.
f Registered number of live births occurring in S.A. 1949-1968 and registered by 1972.

Data supplied by the Adelaide Office of the Commonwealth Bureau of Census and Statistics.

FIGURE 4. Graphic representation of the average monthly incidence of CLCP in S.A. (1949-68) and the fitted simple harmonic curve derived from Edwards' seasonal analysis.

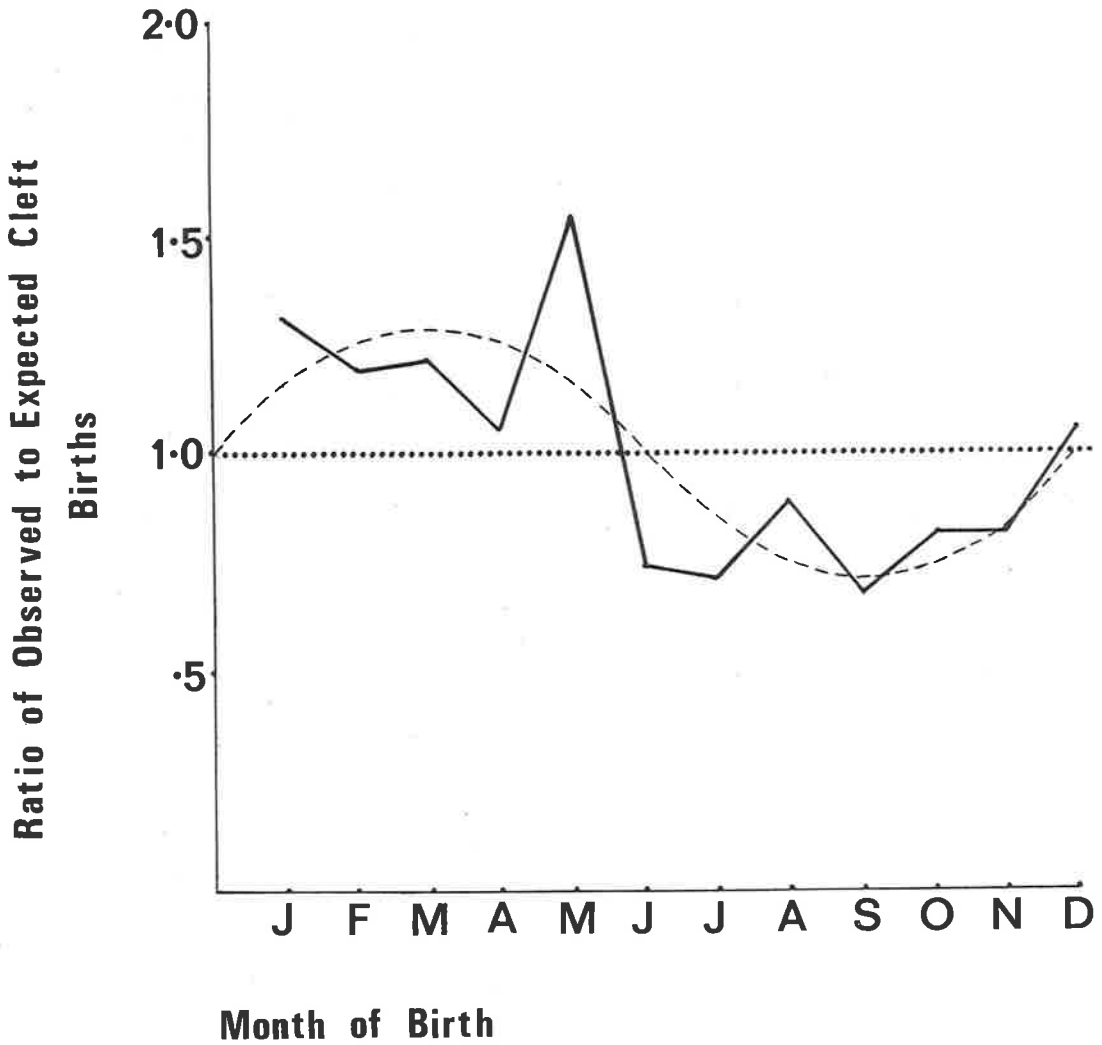

FIGURE 5. Graphic representation of the average monthly incidence of CP in S.A. (1949-68) and the fitted simple harmonic curve derived from Edwards' seasonal analysis.

Family history.

No information on family history of clefts was available for 119 of the 552 subjects. Table 14 gives the number of probands in each cleft group with a specified family history and the number and percentage of probands with known affected "near" relatives and also "all known" affected relatives. The "near" relative group included the five nearest sets of relatives (siblings, parents, aunts and uncles, grandparents and first cousins). The "all known" relative group included near relatives and others of a more distant yet known relationship to the cleft affected proband.

TABLE 14. The proportions of probands with a family history of clefts among near and all known relatives in South Australia (1949-1968)*.

TYPE OF CLEFT	SUBJECTS with specified F.H.	F.H. + ve.** near relatives.		F.H. + ve.** all known relatives.	
	No.	No.	%	No.	%
CL	126	25	19.8	46	36.5
CLCP	167	32	19.2	71	42.5
CL(P)	293	57	19.5	117	39.9
CP	140	26	18.6	43	30.7
ALL CLEFTS	433	83	19.2	160	37.0

* Family history was unspecified for 119 cases.

** F.H.+ve. Family history positive.

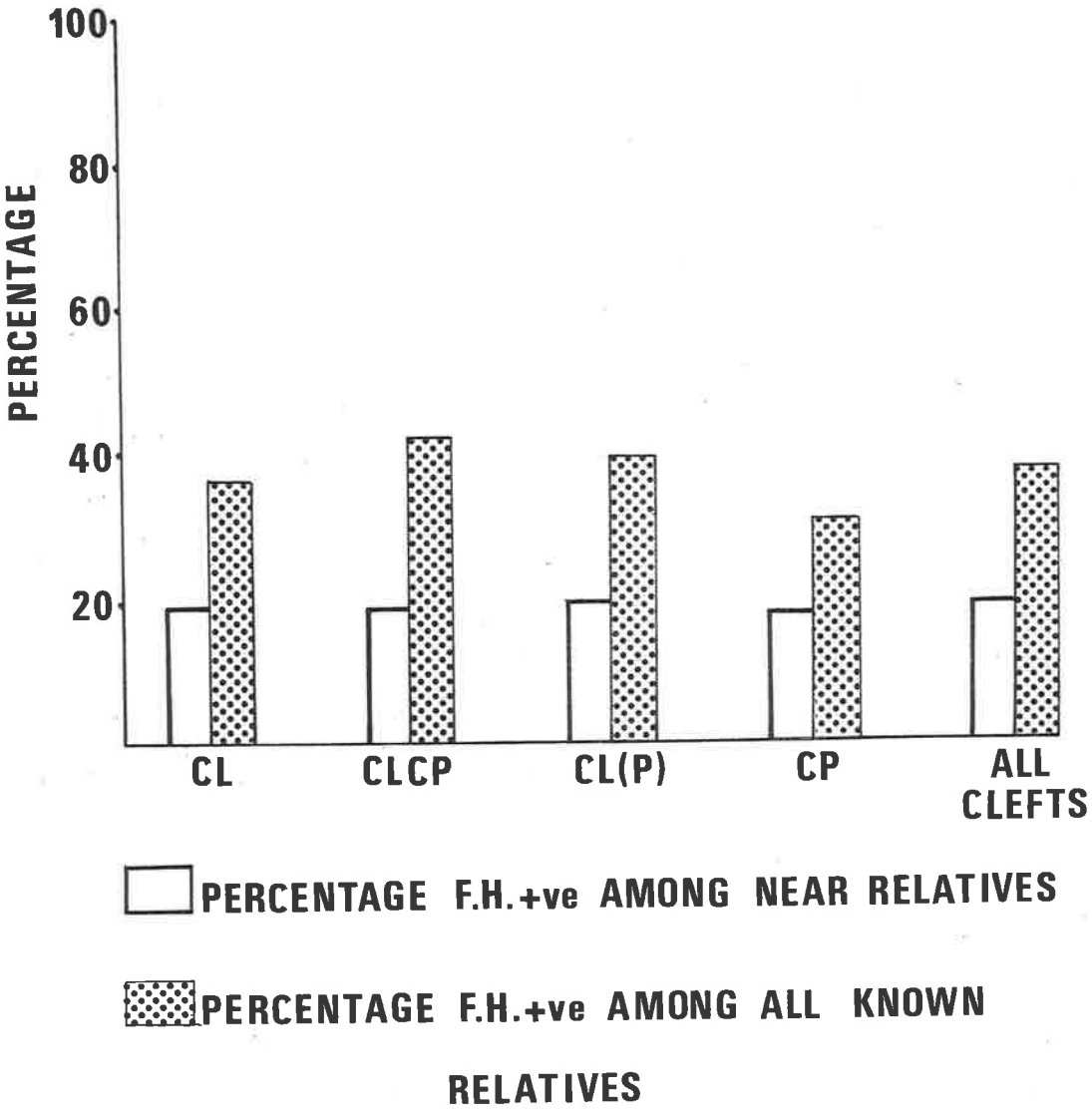

FIGURE 6. The percentage of cleft cases with family history of clefts among near and all known relatives in S.A. (1949-68).

It is apparent from Table 14 that 19.2% of subjects in the group of all clefts types combined, had affected near relatives. This percentage was increased to 37.0% on inclusion of all known relatives.

Also from Table 14 and from Figure 6, it is seen that there was very little difference between cleft types in the proportions of probands with affected near relatives. A positive family history among near relatives was found in 19.5% of CL(P), and in 18.6% of CP cases. However, when all known relatives were included, 39.9% of CL(P) and 30.7% of CP cases were family history positive.

Table 15 arranges the data according to major cleft entity, sex and familial disposition, for all known relatives and also for near relatives.

TABLE 15. The proportions of male and female probands with a family history of clefts among near and all known relatives South Australia (1949-1968)*.

TYPE OF CLEFT	MALE SUBJECTS				FEMALE SUBJECTS			
	F.H.+ve.[a]		F.H.-ve.[b]	All males with specified F.H.	F.H.+ve.[a]		F.H.-ve.[b]	All females with specified F.H.
	No.	%	No.		No.	%	No.	
Near relatives								
CL(P)	33	(17.4%)	157	190	24	(23.3%)	81	103
CP	9	(16.1%)	47	56	17	(20.2%)	77	84
All known relatives								
CL(P)	75	(39.5%)	115	190	42	(40.8%)	61	103
CP	17	(30.4%)	39	56	26	(31.0%)	68	84

* Family history was unspecified for 119 cases.

a. F.H.+ve. Family history positive.

b. F.H.-ve. Family history negative.

Table 15 shows that females had a higher proportion of positive family histories among near relatives than males in the CL(P) and CP groups. The all known relative group was characterised by little difference between the sexes in proportions of affected subjects with a positive family history.

Birth Weight

Mean birth weights in kilograms are given by sex within the various cleft groupings in Table 16.

TABLE 16. The average birth weight in kilograms, of male and female infants with clefts in South Australia (1949-1968).*

CLEFT TYPE	MALE SUBJECTS	FEMALE SUBJECTS	TOTAL CASES
CL	3.522	3.235	3.242
CLCP	3.242	3.196	3.226
CL(P)	3.363	3.213	3.311
CP	3.352	3.233	3.284
ALL	3.360	3.222	3.302

* Birth weight was unspecified for 66 cases

The mean birth weight of males was slightly higher than that of females for all cleft types. However, no control data were available for South Australia to allow statistical testing of the observed birth weight distribution by sex in relation to normal values. For the purpose of comparison with other reports, the proportions of specified cases according to cleft type and sex with birth weight of 2.5 kg or less, are recorded in Table 17. Of all subjects, 10.5% were premature by this criterion. Those with CP were most often of low birth weight (14.1%), followed by CLCP (10.7%), CL(P) (8.8%) and CL (6.3%). Within all cleft classes, females were more severely affected than males, and this phenomenon was most marked in CP cases; of all female births with CP, 17.8% were premature. The lowest prematurity rate was for CL males (3.2%).

TABLE 17. Birth weights of the total sample and the proportions of infants of birth weight less than 2.5 kg. in South Australia (1949-1968).

BIRTH WEIGHT*	CL			CLCP			CL(P)			CP			ALL CASES		
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL
Unspecified	14	7	21	13	4	17	27	11	38	7	21	28	34	32	66
1-2 kg	1	1	2	2	1	3	3	2	5	3	3	6	6	5	11
2-2.5 kg	2	5	7	8	9	17	10	14	24	3	13	16	13	27	40
2.5-3 kg	10	12	22	34	14	48	44	26	70	12	13	25	56	39	95
3-4 kg	66	28	94	70	37	107	136	65	201	39	54	93	175	119	294
4-5 kg	14	4	18	8	4	12	22	8	30	9	6	15	31	14	45
5-6 kg	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1
Total	107	57	164	135	69	204	242	126	368	73	111	184	315	238	552
Total specified	93	50	143	122	65	187	215	115	330	66	90	156	281	205	486
Total < 2.5 kg	3	6	9	10	10	20	13	16	29	6	16	22	19	32	51
Percentage < 2.5 kg	3.2%	12.0%	6.3%	8.2%	15.4%	10.7%	6.0%	13.9%	8.8%	9.1%	17.8%	14.1%	6.8%	15.6%	10.5%

* includes upper boundary

Maternal Age

Maternal age at birth (Table 18) was recorded for 59.1% of the total sample. Maternal age at confinement was available only for the years 1955-1968, inclusive, for the total South Australian population.* There were 439 cleft affected subjects born during this period and maternal age at birth was recorded in 280 instances (63.8%). To facilitate comparisons between maternal age groupings and cleft types, the age specific birth rate for specified cases was calculated from these data and expressed as the rate per 1,000 live births. From Table 18, it is difficult to recognize any consistent trends towards higher or lower rates of cleft occurrences in any particular maternal age groups for any type of cleft.

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*Confinements, nuptual and exnuptial, resulting in one or more live births by age of mother (1955-1968). Data supplied by the Adelaide Office of the Commonwealth Bureau of Census and Statistics.

TABLE 18. The maternal age distribution of the total sample (1949-1968) and maternal age specific rates of occurrence in South Australia (1955-1968).

TYPE OF CLEFT		MATERNAL AGE (Years) <20	20-24	25-29	30-34	35-39	>40	un-spec.	TOTAL
CL	1949-68	6	24	26	25	5	4	74	164
	1955-68	6	22	20	24	3	3	53	131
rate/1,000	1955-68	0.256	0.244	0.238	0.466	0.112	0.359		
CLCP	1949-68	9	37	40	23	21	1	73	204
	1955-68	9	30	33	20	18	1	51	162
rate/1,000	1955-68	0.384	0.333	0.393	0.388	0.673	0.120		
CL(P)	1949-68	15	61	66	48	26	5	147	368
	1955-68	15	52	53	44	21	4	104	293
rate/1,000	1955-68	0.639	0.578	0.631	0.855	0.785	0.479		
CP	1949-68	8	30	31	21	13	2	79	184
	1955-68	6	27	25	20	11	2	55	146
rate/1,000	1955-68	0.256	0.300	0.298	0.388	0.411	0.239		
ALL LIVE BIRTHS S.A. 1955-1968		23,461	89,987	83,961	51,491	26,751	8,359		284,010

The chi-square test was used to estimate the significance of the deviation between observed and expected numbers of age specific occurrences. These data are given in Table 19. No cleft type showed a significant deviation from the expected maternal age distribution.

TABLE 19. The observed and expected maternal age distribution of cleft affected infants in South Australia (1955-1968).*

MATERNAL AGE (Years)	TYPE OF CLEFT							
	CL		CLCP		CL(P)		CP	
	obs.	exp.	obs.	exp.	obs.	exp.	obs.	exp.
-20	6	6.4	9	9.2	15	15.6	6	7.5
20-24	22	24.7	30	35.2	52	59.9	27	28.8
25-29	20	23.1	33	32.8	53	55.9	25	26.9
30-34	24	14.4	20	20.1	44	34.3	20	16.5
35-39	3	7.3	18	10.5	21	17.8	11	8.6
40-	3	2.3	1	3.3	4	5.6	2	2.7
Total	78		111		189		91	
X^2 - value on 5 d.f.	10.44		7.73		4.99		2.13	
Probability	>0.05		>0.05		>0.05		>0.05	

P $(X^2_5 \geq 11.07) = 0.05$

* Maternal age was unspecified for 159 cases; CL(53), CLCP(51), CP(55).

Paternal age

Paternal age at the birth of the child (Table 20) was recorded for 58.3% of the total sample. Paternal age at the time of the mother's confinement was available only for the years 1962-1968 for the total South Australian population.* Of the 241 children born with clefts during this period, the father's age at birth was recorded for 148 (61.4%). From these data, the age specific birth rate for specified cases was calculated and expressed as the rate per 1,000 live births. These data, presented in Table 20, suggested the existence of no definite trend towards increased occurrences of any cleft type with advancing paternal age.

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* Confinements, nuptual and exnuptial, resulting in one or more live births by age of father (1962-1968). Data supplied by the Adelaide Office of the Commonwealth Bureau of Census and Statistics.

TABLE 20. The Paternal age distribution of the total sample (1949-1968) and paternal age specific rates of cleft occurrence in South Australia (1962-1968).

TYPE OF CLEFT		PATERNAL AGE (Years) <20	20-24	25-29	30-34	35-39	>40	un-spec.	TOTAL
CL	1949-68	1	11	32	29	7	10	74	164
	1962-68	1	5	13	7	2	1	29	58
rate/1,000	1962-68	0.449	0.189	0.295	0.219	0.103	0.083		
CLCP	1949-68	2	21	41	31	23	11	75	204
	1962-68	0	14	21	14	12	5	34	100
rate/1,000	1962-68	-	0.530	0.477	0.439	0.617	0.415		
CL(P)	1949-68	3	32	73	60	30	21	149	368
	1962-68	1	19	34	21	14	6	63	158
rate/1,000	1962-68	0.449	0.719	0.772	0.658	0.720	0.498		
CP	1949-68	0	21	26	26	16	14	81	184
	1962-68	0	14	9	10	8	12	30	83
rate/1,000	1962-68	-	0.530	0.204	0.313	0.411	0.996		
ALL LIVE BIRTHS S.A. 1962-1968		2,225	26,416	44,044	31,898	19,448	12,050		136,081

The significance of the difference between observed and expected age specific cleft occurrences was established with the chi-square test (Table 21). Only cleft type CP showed a significant deviation ($P<0.01$) from the expected paternal age distribution. The deviation was especially evident when the father's age was 40 years or over.

TABLE 21. The observed and expected paternal age distribution of cleft affected infants in South Australia (1962-1968).*

PATERNAL AGE (Years)	TYPE OF CLEFT							
	CL		CLCP		CL(P)		CP	
	obs.	exp.	obs.	exp.	obs.	exp.	obs.	exp.
<20	1	0.5	0	1.1	1	1.6	0	0.9
20-24	5	5.6	14	12.8	19	18.4	14	10.3
25-29	13	9.4	21	21.4	34	30.8	9	17.2
30-34	7	6.8	14	15.5	21	22.3	10	12.4
35-39	2	4.1	12	9.4	14	13.6	8	7.6
>40	1	2.6	5	5.8	6	8.4	12	4.7
Total	29		66		95		53	
X^2 - value on 5 d.f.	4.01		2.20		1.36		17.07	
Probability	>0.05		>0.05		>0.05		<0.01	

$P \quad (X^2_5 \geq 11.07) = 0.05$

$P \quad (X^2_5 \geq 15.09) = 0.01$

* Paternal age was unspecified for 93 cases; CL(29), CLCP(34), CP(30).

Birth Order

Analysis of birth order is best related to maternal age[83,84]. Accordingly, the birth order distribution by maternal age for cleft types CL(P) and CP is given in Tables 22a and 22b, respectively, for the total sample and for the years in which corresponding data on the South Australian population were available.* Birth order data were available for 177 (85.1%) of the CL(P) cases born during this period, but for only 115 (55.3%) of these 208 subjects, was maternal age also known. Birth order data were available for 85 (84.2%) of the CP cases born during 1949-1955, 1964-1968, but for only 52 (51.5%) of these 101 subjects, was maternal age also known. The birth order and maternal age specific rates of occurrence per 1,000 live births for specified cases were calculated. However, with such small numbers, only guarded conclusions are possible regarding the effect of birth order on incidence in a particular maternal age group.

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* Nuptual confinements by maternal age and birth order resulting in one or more live births, South Australia (1949-1955, 1964-1968). Data supplied by the Adelaide Office of the Commonwealth Bureau of Census and Statistics.

TABLE 22a. The maternal age and birth order specific rates of CL(P) occurrence in South Australia (1949-1955) and (1964-1968).

BIRTH ORDER		MATERNAL AGE (Years) <20	20-24	25-29	30-34	35-39	>40	sub-total	un-spec.	TOTAL
First	CL(P)	5	13	12	4	-	1	35	15	50
	S.A.	10,905	35,766	18,478	6,144	2,613	764	74,670		
	Rate/1,000	0.459	0.363	0.649	0.651	-	1.309	0.469		
Second	CL(P)	3	15	9	6	3	-	36	19	55
	S.A.	2,184	21,414	24,689	10,164	3,591	787	62,829		
	Rate/1,000	1.374	0.700	0.365	0.590	0.835		0.573		
Third	CL(P)	0	2	7	7	3	1	20	13	33
	S.A.	201	6,750	16,047	10,869	4,672	1,072	39,611		
	Rate/1,000	-	0.296	0.436	0.644	0.642	0.933	0.505		
Fourth	CL(P)	-	1	5	4	3	-	13	3	16
	S.A.	19	1,649	6,299	6,703	3,995	1,063	19,728		
	Rate/1,000	-	0.606	0.794	0.597	0.751	-	0.659		
Fifth and later	CL(P)	-	-	2	4	4	1	11	12	23
	S.A.	2	445	3,324	5,501	5,560	2,534	17,366		
	Rate/1,000	-	-	0.602	0.727	0.719	0.395	0.633		
Sub-Totals	CL(P)	8	31	35	25	13	3	115	62	177
	S.A.	13,311	66,024	68,837	39,681	20,431	6,220	214,504		
	Rate/1,000	0.601	0.470	0.508	0.630	0.636	0.482	0.536		
Unspecified	CL(P)	-	-	-	-	1	-	1	30	31
Total	CL(P)	8	31	35	25	14	3	116	92	208

TABLE 22b. The maternal age and birth order specific rates of CP occurrence in South Australia (1949-1955) and (1964-1968).

BIRTH ORDER		MATERNAL AGE (Years) <20	20-24	25-29	30-34	35-39	>40	sub-total	un-spec.	TOTAL
First	CP	2	11	3	1	1	-	18	10	28
	S.A.	10,905	35,766	18,478	6,144	2,613	764	74,670		
	Rate/1,000	0.183	0.308	0.162	0.163	0.383	-	0.241		
Second	CP	2	6	8	-	2	-	18	9	27
	S.A.	2,184	21,414	24,689	10,164	3,591	787	62,829		
	Rate/1,000	0.916	0.280	0.324	-	0.557		0.286		
Third	CP	-	2	4	1	1	-	8	7	15
	S.A.	201	6,750	16,047	10,869	4,672	1,072	39,611		
	Rate/1,000		0.296	0.249	0.092	0.214	-	0.202		
Fourth	CP	-	-	1	1	3	-	5	4	9
	S.A.	19	1,649	6,299	6,703	3,995	1,063	19,728		
	Rate/1,000	-	-	0.159	0.149	0.751	-	0.253		
Fifth and later	CP	-	-	1	-	2	-	3	3	6
	S.A.	2	445	3,324	5,501	5,560	2,534	17,366		
	Rate/1,000	-	-	0.301	-	0.360	-	0.173		
Sub-Totals	CP	4	19	17	3	9	-	52	33	85
	S.A.	13,311	66,024	68,837	39,681	20,431	6,220	214,504		
	Rate/1,000	0.301	0.288	0.247	0.076	0.441	-	0.242		
Unspecified	CP	-	-	-	-	-	-	-	16	16
TOTAL	CP	4	19	17	3	9	0	52	49	101

The association of the incidence of particular cleft types with birth order was therefore examined without regard to maternal age, according to the method of MacMAHON and McKEOWN[37] and WOOLF et al[52]. Table 23 shows that birth order data were obtained for 262 (84.8%) of the 309 cleft affected infants born during the years 1949-1955 and 1964-1968. Although the corresponding birth order statistics for South Australia were available only for nuptual births, the birth order specific rate of occurrence for specified cases was still calculated as an aid to interpretation of these data.

TABLE 23. The birth order distribution of the total sample (1949-1968) and the birth order specific rates of cleft occurrence in South Australia (1949-1955) and (1964-1968).

TYPE OF CLEFT		BIRTH ORDER 1	2	3	4	5	6	7	>8	Un-spec.	TOTAL
CL	1949-1968	33	42	33	13	9	3	2	1	28	164
	1949-55, 1964-68	17	25	20	7	3	1	0	0	19	92
	rate/1000 1949-55, 1964-68	0.228	0.398	0.505	0.355	0.338	0.238	-	-		
CLCP	1949-1968	51	59	28	19	15	8	1	4	19	204
	1949-55, 1964-68	33	30	13	9	10	6	0	3	12	116
	rate/1000 1949-55, 1964-68	0.442	0.477	0.328	0.456	1.126	1.426	-	1.216		
CL(P)	1949-1968	84	101	61	32	24	11	3	5	47	368
	1949-55, 1964-68	50	55	33	16	13	7	0	3	31	208
	rate/1000 1949-55, 1964-68	0.670	0.875	0.833	0.811	1.464	1.663	-	1.216		
CP	1949-1968	46	51	29	20	6	5	1	3	23	184
	1949-55, 1964-68	28	27	15	9	3	2	0	1	16	101
	rate/1000 1949-55, 1964-68	0.375	0.430	0.379	0.456	0.338	0.475	-	0.405		
ALL LIVE BIRTHS (nuptual) S.A. 1949-55, 1964-68		74,670	62,829	39,611	19,728	8,882	4,209	2,108	2,467		214,504

The significance of the observed birth order in comparison to the normal distribution, was calculated by the chi-square method. These data are shown in Table 24.

Only for cleft type CLCP was the observed distribution significantly different from the expected ($P<0.01$). There was a markedly greater than expected number of cleft cases born in the fifth and later birth ranks.

TABLE 24. The observed and expected birth order distribution of cleft affected infants in South Australia (1949-1955) and (1964-1968).*

BIRTH ORDER	TYPE OF CLEFT							
	CL		CLCP		CL(P)		CP	
	obs.	exp.	obs.	exp.	obs.	exp.	obs.	exp.
First	17	25.4	33	36.2	50	61.6	28	29.6
Second	25	21.4	30	30.5	55	51.8	27	24.9
Third	20	13.5	13	19.2	33	32.7	15	15.7
Fourth	7	6.7	9	9.6	16	16.3	9	7.8
Fifth & later	4	6.0	19	8.6	23	14.6	6	7.0
Total	73		104		177		85	
X^2 - value on 4 d.f.	7.20		14.91		7.22		0.62	
Probability	>0.05		<0.01		>0.05		>0.05	

$P \quad (X^2_4 \geq 9.49) = 0.05$

$P \quad (X^2_4 \geq 13.28) = 0.01$

* Birth order was unspecified for 47 cases; CL(19), CLCP(12), CP(16).

Associated Malformations

In order to gain an appreciation of the nature and extent of the occurrence of associated malformations with cleft defects, all anomalies found in conjunction with the cleft were recorded and categorised according to the scheme given in Table 25. This scheme broadly covers a full range of possible defects and also makes particular reference to specific abnormalities commonly found in conjunction with clefts of the primary and/or secondary palate.

Table 25 lists in order of frequency of occurrence, the numbers of subjects, by sex, for whom it was found that the cleft was not the only congenital defect.

TABLE 25. The number of subjects with one or more associated congenital malformations according to malformation category and sex in South Australia (1949-1968).

Type of Associated Malformation	Subjects		
	Male	Female	TOTAL
Micrognathia: including any reference to Pierre Robin syndrome or hypoplasia of mandible.	16	14	30
Eye defects: including any reference to conditions of anophthalmos, microphthalmos, congenital cataracts, glaucoma, corneal opacity and other defects of globe of eye. Extra-ocular eye defects including nystagmus, muscle defects, strabismus or other specified defects.	14	15	29
Central nervous system defects: including any reference to anencephaly, hydrocephaly, microcephaly, spina bifida, encephalocele, meningocele, cephalomeningocele.	13	15	28
Skeletal defects: including any reference to defects of the skull, vertebra, ribs, trunk, reduction and other deformities of the extremities, multiple or generalised skeletal defects and congenital dislocations and any skeletal defect not elsewhere classified.	12	12	24
Ear defects: including any reference to conditions of anotia, microtia, atresia of auditory canal, absence of any part of external ear, low set ears, tags (auricular, preauricular). Other defects of shape, size or position and conditions of deafness which were not superficially due to infections and were of likely congenital origin.	11	13	24
Positional foot defects: including any reference to conditions of club foot, talipes, flexion defects.	9	10	19

(continued over)

TABLE 25 - continued

Type of Associated Malformation	Subjects Male	Female	TOTAL
Cardio-vascular system defects: including any reference to conditions of structural or functional abnormality of the heart and peripheral vascular defects.	10	7	17
Genito-urinary system defects: including any reference to conditions of structural or functional abnormality of the male or female genital organs or of the urinary system.	15	2	17
Gastro-intestinal system defects: including any reference to conditions of structural or functional abnormality of the abdominal cavity, of the abdominal musculature (except umbilical hernia) or of the digestive system.	9	0	9
Hypertelorism:	3	1	4
Syndactyly: of hands, feet or hand and feet or of unspecified site.	2	2	4
Polydactyly: of fingers, thumbs, toes or of unspecified site.	1	1	2
Other defects: malformations of lung, larynx, trachea, skin, blood, endocrine, tumors, metabolic disturbances and a number of minor defects.	21	13	34

It is more meaningful to describe associated malformations according to the type of cleft defect.

These data are given in Table 26 together with the percentage of male, female and combined sexes in each cleft group with or without one or more associated malformations.

TABLE 26. The proportions of male and female subjects with one or more associated malformations and the percentage of males in particular cleft groupings in South Australia (1949-1968).

SUBJECTS	TYPE OF CLEFT														
	CL			CLCP			CL(P)			CP			TOTAL CLEFTS		
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL
TOTAL	107	57	164	135	69	204	242	126	368	73	111	184	315	237	552
Specified for A.M.	84	48	132	120	64	184	104	112	316	63	96	159	267	208	475
No A.M.	66	40	106	88	47	135	154	87	241	29	65	94	183	152	335
% of specified with no A.M.	78.6	83.3	80.3	73.3	73.4	73.4	75.5	77.7	76.3	46.0	67.7	59.1	68.5	73.1	70.5
% male			62.3			65.2			63.9			30.9			54.6
X^2 - value on 1 d.f.			5.08*			10.38**			15.35**			15.70**			1.48
One or more A.M.	18	8	26	32	17	49	50	25	75	34	31	65	84	56	140
% of specified with A.M.	21.4	16.7	19.7	26.7	26.6	26.6	24.5	22.3	23.7	54.0	32.3	40.9	31.5	26.9	29.5
% male			69.2			65.3			66.7			52.3			60.0
X^2 - value on 1 d.f.			3.40			3.89*			7.06*			0.03			4.25*

P $(X_1^2 \geq 3.84) = 0.05$. P $(X_1^2 \geq 6.64) = 0.01$

Presence of other malformations was unspecified for 77 cases; CL(32), CLCP(20), CP(25).

*Significant deviation (P<0.05) from the percentage of males (51.3%) among all live birth registrations in S.A. (1949-1968).

**Significant deviation (P<0.01) from the percentage of males (51.3%) among all live birth registrations in S.A. (1949-1968).

A.M. Associated malformations.

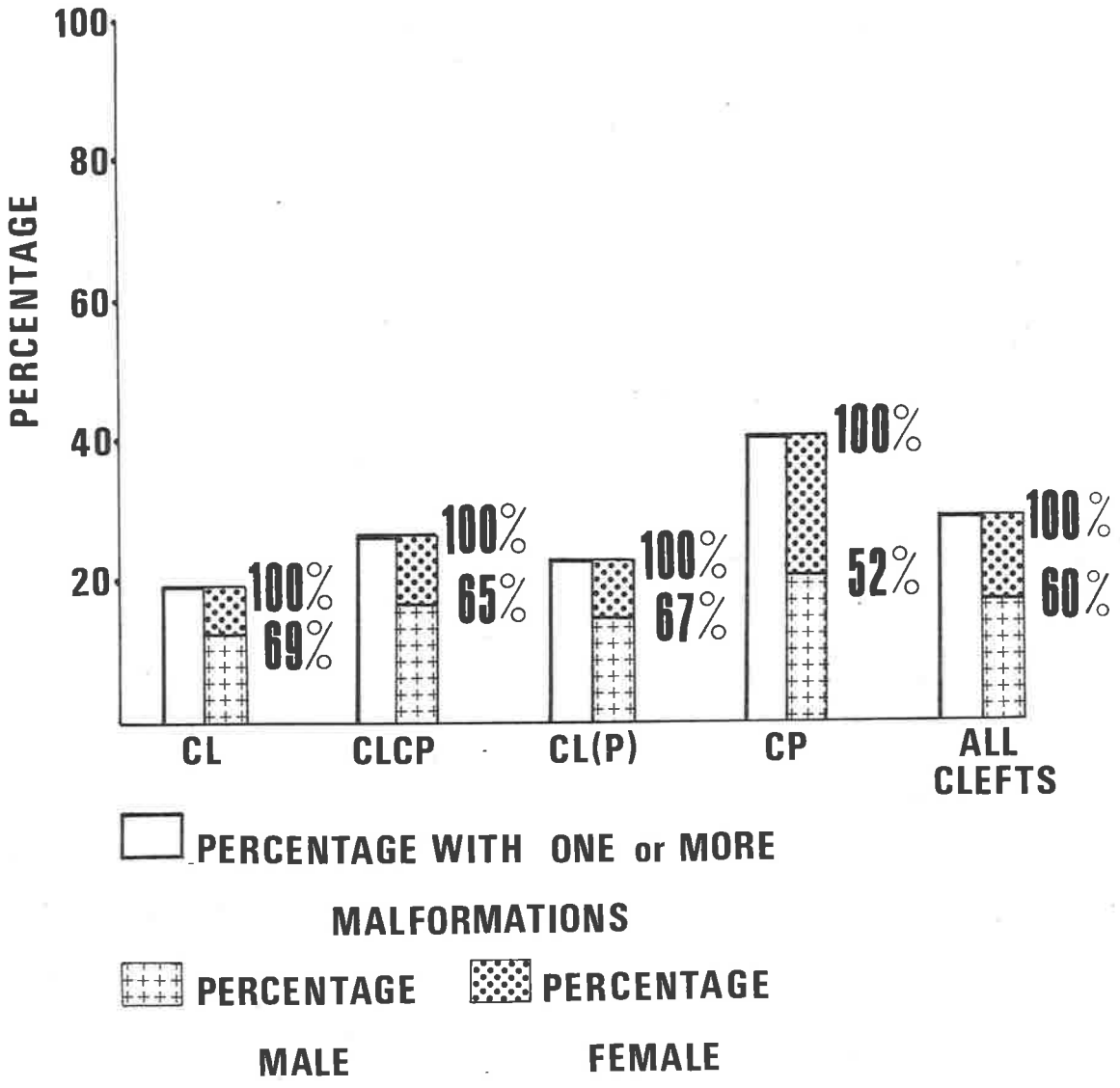

FIGURE 7. The percentage of cleft cases with one or more malformations and the percentage of males in particular cleft groupings in S.A. (1949-68).

Of all specified cases 19.5% had one or more associated malformations. Patients with isolated CP were most frequently affected with other abnormalities while those with CL were least frequently affected. The total percentages of subjects with one or more associated malformations were 19.7% of CL, 26.6% of CLCP, 23.7% CL(P) and 40.9% of CP cases. The percentage of males having additional defects was higher than the percentage of females in all cleft groups, although only marginally so for CLCP. The tendency towards a higher percentage of males to have multiple defects was most marked for isolated CP cases, where 54.0% of males and 32.3% of females had one or more associated malformations.

The proportions of males in the various cleft groups, with and without other defects, are also detailed in Table 26. Figure 7 diagrammatically illustrates the proportions of males in the various groups of subjects with clefts and associated malformations. Moreover, it can be seen from Table 26 that the difference between the percentage of males in the CP group with no associated defects (30.9% male) and the percentage of males in the general population (51.3% male), was highly significant ($P<0.01$). However, the sex ratio pertaining to the group of CP cases with associated malformations (52.3% male) was very similar to that observed in the general population. This observation was not true of the other cleft groups. A significantly different sex ratio in comparison with the general population was observed for the other individual cleft groupings with no other defects. However, the sex

ratio for the cleft groups CLCP, CL(P) and total clefts with defects was significantly different from that observed in the general population. The trend was similar, although insignificant, for cleft type CL with associated defects.

DISCUSSION

Incidence, type of cleft, sex and laterality

Comparisons of incidence should be made with those series having a case source parallel to the present study which utilized surgical referrals to a centralised treatment facility. Accordingly, it may be seen that the South Australian incidence of 1.41 per 1,000 live births was similar to that reported by KNOX and BRAITHWAITE[26] of 1.42 per 1,000 in Northumberland and Durham, England, and also to the incidence of 1.51 per 1,000 reported for the South-west region of England by CAMPBELL WILSON[29]. The consistently higher incidence reported by FOGH-ANDERSEN[25,28] for Danish births suggested more complete reporting or a higher occurrence in Denmark.

When related to other Australian studies, the South Australian incidence was below the 1.66 per 1,000 reported by RANK and THOMSON[6] for Tasmania. Their data were obtained from multiple sources and included death certificates. The incidence of 1.21 per 1,000 live births reported by CHI and GODFREY[34] for New South Wales was slightly lower. However, this study differed from the present one in that maternity hospital records only were utilised as a case source.

It must be recognised that all incidence studies suffer to some degree from under-reporting. The present investigation can be no exception and the material was not entirely unselected. Cases lost to the study included still births and infants who died very soon after birth, before referral was possible to the Adelaide Children's Hospital for management.

The South Australian distribution according to cleft type, 29.7% (CL), 37.0% (CLCP), 66.7% (CL(P)), 33.3% (CP), may be compared with corresponding distributions reported from other countries, Table 2a, and other Australian States, Table 2b. The English studies of KNOX and BRAITHWAITE[26], and particularly that of CAMPBELL WILSON[29], were in very close agreement with the local data. Both English series were also based on surgical referrals. Close similarity in proportion of cleft type was also apparent in comparison with data from birth certificates[41]. The South Australian data differed slightly from the 7:3 ratio for CL(P):P described by BIGGERSTAFF[43] and differed appreciably from the 1:2:1 ratio for CL:CLCP:CP, suggested by FOGH-ANDERSEN[5].

Comparison with the two other major Australian surveys (Table 2b) was also of interest. The proportional contribution of CP was similar to the Tasmanian estimate[6], and slightly higher than that reported for New South Wales[34]. In both of these studies CLCP was relatively more common, and CL less common than seemed to be the case in South Australia. No explanation is readily apparent for the differences. The site of cleft was confirmed for 68.1% of the present series, while the Tasmanian

sample, although smaller, was completely confirmed. Subjects were not examined for the purpose of confirmation of cleft type in the New South Wales series, because the intrinsically different methodology did not allow personal follow-up of subjects.

The findings relating to sex distribution (Table 8) were in general accord with the findings of other overseas investigators (Table 2a). It was observed that the female predominance in sex ratio for CP was even more marked in the South Australian sample (39.7% male) than in those from New South Wales or Tasmania (Table 2b). Also, the Tasmanian sample was characterised by a greater excess of males with CLCP and CL(P) than was observed locally (CLCP 66.2% male, CL(P) 65.8% male), while in New South Wales the male predominance in CL was less marked than that seen in South Australia (65.2% male).

In regard to laterality of the defects, for unilateral CL left-sided involvement was about twice as common as right-sided involvement, and left-sided CLCP was half as common again as right-sided CLCP when the defects were unilateral. While a trend of this nature has been widely reported[9], it was informative to compare the South Australian sample with the other Australian studies (Table 4b). In Tasmania, there was a stronger tendency for left-sided involvement in both CL and CLCP. In New South Wales CL was most often left-sided; however, for CLCP, the right side was most often involved. However, good reasons were given to suggest that this contrary finding was only an apparent one[34].

It can also be seen from Table 9 that about three-quarters of all bilateral defects in the present sample extended into the secondary palate (53 out of 72 cases). This finding supported the contention that when a cleft of the secondary palate occurs with a cleft of the primary palate, it is secondary to the primary palatal cleft and hence more likely to occur with increased severity of the primary palatal defect[5,9].

There was general agreement concerning laterality and sex (Table 10) with the findings of KNOX and BRAITHWAITE[26], INGALLS et al.[39] and GREEN et al.[20] that there was no real difference in distribution by laterality between male and female probands for either CL or CLCP. Further comparisons are possible with the studies summarised in Tables 4a and 4b. For example, although the reports of FOGH-ANDERSEN[5] and RANK and THOMSON[6] may have indicated that as the defect increased in severity from unilateral CL to bilateral CLCP, the sex ratio increasingly favoured males; the present investigation only weakly supported such a contention. As seen in Table 10, 65.2% of unilateral CL cases were male, and the percentage was less for bilateral CL (63.2%). For CLCP the percentage of males increased form 64.1% for unilateral to 69.8% for bilateral cases.

In general, observed sex ratios of lateral or bilateral conditions did not differ markedly from those previously reported.

Secular and seasonal variation in incidence

The degree of yearly fluctuation in incidence of the various cleft

types raised questions concerning the environmental aspects of etiology. Although the small sample size limited conclusions when data were broken down for yearly occurrences of the major genetic entities, that is CL(P) and CP, consideration was given to the nature of the distributions over the years under study (Figure 2). As the data represented almost the total affected population, it would seem that these results were evidence for labile determining factors of environmental origin.

In the birth certificate study of GILMORE and HOFMAN[40], data were collected covering a period similar to the present study. These investigators also noted that the yearly variations in incidence for the various cleft types were not always proportional to the variations in numbers of total live births. Whether the present data truly reflected a rise in incidence is not known. There is a possibility that an increasing number of persons, especially with minor clefts, are presenting for treatment. If this is the case, it may have accounted for the slight rise in incidence that was graphically apparent (Figure 2).

The Edwards analysis of seasonal effect on incidence indicated that cleft types CLCP and CP showed significant seasonal variation. The finding in relation to CLCP was similar to that of CHARLTON[32] who noted a significant June increase in this type of cleft in his South Australian data spanning 15 years. A review of the literature revealed no report where isolated CP had been shown to demonstrate a significant seasonal pattern of occurrence, as was present in South Australia. The

present analysis could not statistically confirm the findings of WEHRUNG and HAY[53] or FUJINO et al.[44] of a seasonal pattern for CL(P). However, the simple harmonic curve fitted to the South Australian data was in agreement with the finding that the incidence was highest for spring conceptions. EDWARDS[55] reported a significantly increased incidence of CL centred around March for Birmingham data. March births in South Australia with this defect were seen to be at the base of the trough of the fitted simple harmonic curve. If an opposite seasonal effect in each hemisphere is allowed for, these results might be compatible.

As WEHRUNG and HAY[53] have pointed out, the Edwards analysis for seasonal trends has limitations, because the model also detects by means of its chi-square test, other types of trend which are neither in the simple harmonic category nor in the more general cyclic category (Appendix D). For this reason, a graphic representation of observations was also helpful in analysing the nature of the seasonal patterns of occurrence. It was apparent from Figure 3 that although the peak seasonal occurrence for CP was centred in March, by far the highest rate of clefting of the secondary palate occurred in May births.

Family History

Table 14 showed that there was little variation by type of cleft in the proportion of probands with positive family history in the near relative group. Nevertheless, previously reported trends were confirmed in that in the all known relative group, the CL(P) subjects were more

often (39.9%) family history positive than the CP subjects (30.7%). The South Australian data were in agreement with the report of DRILLIEN et al.[8] who also noted, as ascertained from near relatives, little variation in the proportion of family history positive cases among different cleft types. However, when all known affected relatives were counted in the Edinburgh sample, an increase was observed from 22.8% positive family history for CL(P) and 19.5% for CP among near relatives, to 42.4% for CL(P) and 32.5% CP, respectively. The findings of the present study also confirmed the contention of Drillien and co-workers that CL(P) probands were more likely to be included in the family history positive group because of a cleft reported in a distant relative only, than were probands with CP.

In comparison with the other Australian study where this aspect was also investigated, it was seen that a similar proportion of CL(P) subjects (37.4%) was recorded as having a positive family history, when all known relatives were included[6]. A lower figure of 22.6% was given in this Tasmanian study as against 30.7% for South Australia, as the proportion of CP cases with familial disposition.

When the family history data for male subjects were analysed separately from the corresponding data for female subjects, it was apparent that particularly for CL(P), females tended to have a slightly increased proportion of near relatives reported to be family history positive than did males. There was almost no difference according to sex of proband in the proportion of all known affected relatives for either

CL(P) or CP (Table 15). In considering all known relatives, this result differed from the findings of DRILLIEN et al.[8]. These workers reported that more than twice the proportion of males with CP reported a positive family history than was reported by the corresponding group of females; nearly one and a half times as many females with CL(P) were family history positive, than were the corresponding proportion of males.

In considering near relatives of propositi, the finding that CL(P) female probands more often had a positive family history may be compared with that of WOOLF[64]. He failed to demonstrate an increase of CL(P) in near relatives (siblings excluded) of females with CL(P) over similarly affected males. According to FRASER[9], the recurrence risk for CL(P) seems to be higher for the siblings of females. Therefore, the inclusion in the present analysis of siblings in the near relative group might have accounted for the slight increase of CL(P) female probands with affected relatives in this sample. It might also explain why the finding seemed to be at slight variance with that of WOOLF[64].

In general terms, the present findings concerning sex of probands with CL(P) were in accord with the currently held view that female CL(P) probands should have a higher percentage of affected near relatives. There is some evidence that as the above is true for CL(P), the reverse should apply for CP probands. That is, that males with CP should have an increased proportion of affected relatives, if it is assumed that this type of cleft is also a quasi-continuous variant, or threshold character of multifactorial and polygenetic etiology[9,12,61]. The

present finding that CP males had a lower proportion of affected near relatives than CP females was at variance with the above.

A comprehensive genetic study requires a more complete analysis of data according to the specific degree relationship of affected relatives, than is provided in the present study. For instance, first, second, third, or more distant degree relationships, should be studied in regard to the type of defect involved, both in proband and relative. When collecting the present material, it was found that limitations inherent in such retrospective research were considerable. The quality of the family history data was questionable in many cases. For this reason, and also because of the difficulty of obtaining adequate control data, analyses of family history of cleft affected subjects were not extended further.

Birth weight and prematurity.

The reported prematurity figure of 10.4% for all cleft cases in this study was imilar to that described by other investigators using similar material[8,29,70]. The percentage was also considerably higher than that ascertained for control populations by the same investigators. It is interesting that the birth certificate based studies of LORETZ et al.[68] and BARNADOUVE[69] reported slightly higher incidences for prematurity among both cleft affected births and controls, as was reported by GREEN et al.[20] for cleft affected births only. In New South Wales, CHI and GODFREY[34] reported that 17.1% of 181 children with clefts

weighed less than 2.5 kg at birth. This study was different again in that hospital birth records were the source of material.

The proportional excess of premature infants with isolated clefts of the secondary palate seen in the present study was also observed in surgical patients by DRILLIEN et al.[8], FRASER and CALNAN[38] and in live birth certificate data by GREEN et al.[20]. This finding did not support statements by MOLLER[27] and RINTALA and GYLLING[70] suggesting that lower birth weight was related to the extent of the cleft defect.

A notable feature of the birth weight distribution by type of cleft according to sex, was that for all classifications of cleft type, the percentage of premature females was greater than the percentage of premature males. The proportion of females was highest for CP cases and lowest for those with CL. This result was in agreement with findings by other investigators[8,38,71,89]. As previously indicated, this finding may indicate that affected females are more able to survive, but it may also point to a real association between sex and conditions of poor intrauterine growth. It was also recognised that CP is more often associated with major congenital defects, and infants with severe congenital anomalies, and especially multiple defects, were more likely to be of low birth weight than normal infants[67].

Maternal age, paternal age and birth order

It was concluded from the present data that there was no significant evidence for a maternal age association with the occurrence

of any type of cleft. However, it must be borne in mind that the observed maternal age distribution was not necessarily similar to that which would be described if maternal age data had been available for every cleft case.

The findings of the other two Australian studies were confirmed, except that in New South Wales, isolated CL was found to be significantly related to maternal age. The present data were contrary to the findings of a number of overseas investigators that maternal age was significantly related to the occurrence of various types of cleft[20,45,46,60,68].

The present study tended to confirm previous reports that the age of the father is of etiological significance in CP[20,47,80]. However, no relationship was demonstrated between paternal age and any other type of cleft. As paternal age data were available for 61.4% of the 1962-1968 cleft affected births, the data may not have been truly representative of the cleft population. Furthermore, the relatively small sample size was a limitation to possible conclusions with regard to this factor. No analysis of paternal age, whilst holding maternal age constant, or vice versa, was attempted because of the small numbers which would have been available when these related variables were analysed for individual types of cleft.

The limitation of birth order analysis have been discussed by McKEOWN and RECORD[74] and BARKER and RECORD[84]. According to the latter investigators, it is possible that the control group method (calculation of the relative or absolute incidence of a disease in each birth rank)

may show changes in incidence with fraternity size and thus it is usual to compare fertility in the control and affected groups. In the present analysis fraternity size was not available for the control data and therefore was not considered. For this reason, caution must be exercised in interpreting the result of the chi-square analysis which suggested that the birth order distribution of patients with CLCP alone was significantly different ($P<0.01$) from that observed of births in the general population during the corresponding period. The major contribution towards such a result was seen in Table 24 to come from the large number of cases (19 as against an expected number of 8.6) that were fifth and later births. This result for CLCP was similar to that reported by CZEIZEL and TUSNADI[89] and FUJINO et al.[44]. However, in both of these investigations a significantly greater occurrence for CL and CP among later birth ranks was also observed.

Other recent research has indicated that birth rank was probably unrelated to incidence of clefts. However, the segregation of the effects of birth order, fertility and maternal age, requires a large sample size, appropriate data from both a cleft and a control group and a suitable method of analysis. This type of analysis was beyond the scope of the present report.

Associated malformations

In comparison with previous surveys, the proportion of all subjects with associated malformations was relatively high (29.5% with

one or more other defects). The investigations based on surgical referrals listed in Table 6, show that only DRILLIEN et al.[8] reported an appreciably higher percentage (38.4%). However, the proportions given by SPRIESTERSBACH et al.[58], INGALLS[39] and CONWAY et al.[42] were 20%, or greater. The finding for the present sample may be explained by the fact that children are treated at the Adelaide Children's Hospital until the age of fourteen years, and the hospital records were examined to include all children born over a 20 year period. In this way, malformations not normally discovered until late in childhood would have been recorded for a large proportion of the subjects. Also pertinent, was the fact that relatively minor defects occurring, for example, in the ears or eyes were included as associated malformations. In comparison with other surveys, ear and eye defects were reported to have a higher order of occurrence.

Micrognathia occurred with CP in 23 cases and in seven instances with CLCP. Pierre Robin syndrome is only diagnosed for isolated clefts of the secondary palate[38,65], although micrognathia may occur with CLCP[89]. It is not suggested that all 30 instances of "micrognathia" were examples of the Pierre Robin syndrome. It may have been that in cases of both CLCP and CP an examining physician was more likely to comment on a smaller than usual mandible and it seemed likely that some of these cases were included.

As expected from previous reports[6,8,29,38,39,56,58], a substantially higher percentage of CP subjects (40.9%) had additional malformations than CL(P) subjects (23.7%). The tendency towards a

higher proportion of cleft affected males to have other defects confirmed the trends noted by IVY[4], CONWAY and WAGNER[41], and PANNBACKER[94], and was in contrast to the findings of MESKIN and PRUZANSKY[93] that females more often had additional malformations than males. It may be pertinent that in the present study and others[41,94] which indicate male predominance with other defects, the reported proportions of patients with cleft plus other defects, were higher than those reported by Meskin and Pruzansky.

The present data favoured male predominance in sex ratio to a greater extent for CL(P) with other defects (66.7% male) than it did for all CL(P) cases (65.8% male) or for CL(P) cases without other defects (63.9% male). In this, the findings were similar to those reported in the W.H.O. series[33]. In disagreement with the report of CZEIZEL and TUSNADI[89], the sex ratio of CL(P) with other defects was found to be significantly different from the new-born population.

In general agreement with both the Hungarian[89] and W.H.O.[33] samples, the sex ratio altered from marked female predominance for all CP cases (39.7% male) and for CP cases without other defects (30.9% male) to almost equal proportions of male and female subjects with CP with other defects (52.3% male)

Corroborative evidence was thus supplied that CP in particular, when it occurs with other defects, should be segregated on subsequent analysis because it is of different etiologic origin from CP occurring alone. It may be that CL(P) occurring with other abnormalities, should

also be regarded as distinct from the isolated defect. However, supporting evidence was not apparent from the present data.

SUMMARY AND CONCLUSION

Among the factors investigated for the different types of clefts, a number of trends were evident. In particular, differences according to types of cleft, sex ratios, yearly and seasonal incidence fluctuation, familial association, and association with other congenital deformities, were seen as possible evidence for the independence of etiology of CL and CLCP, as compared with CP. The involvement of genetic predisposition was exemplified by the proportion of subjects with a family history of these defects. However, the demonstrated seasonal effect and the fact that other defects of widely separated structures were present in a considerable proportion of subjects, were considered as indicators of environmental teratogenic conditions and/or agents.

The present study was essentially an incidence report and limitations of sample size and availability of data were not apparent until much of the material had been recorded. For this reason, although numerous trends were reported, some findings remained inconclusive. Improved data collection and recording will enable further studies to provide more information on the interaction of environmental and genetic aspects of orofacial clefting and other congenital malformations.

To this end, the implementation of a compulsory congenital malformations registration system would be of great assistance. Routine use of a detailed and unambiguous system of classification of cleft type and extent, and detailed recording of the genealogy of affected persons are also desirable. The potential of the Cleft Lip and Palate Clinic at the Adelaide Children's Hospital, to gather necessary data as part of its routine operation, is recognised as a valuable avenue of furthering research into cleft conditions.

The results of the investigation can be summarised as follows:-

1. The mean incidence of clefts of the primary and/or secondary palate among live births in South Australia during the years 1949-1968 was a minimum of 1.41 per 1,000 or 1:711.

2. Of the total sample of affected subjects, 29.7% presented with CL, 37.0% with CLCP and 33.3% with CP.

3. Of CL cases 65.2% were male, 66.2% of CLCP were male, and of these two classes combined, CL(P) 65.8% were male. Males comprised 39.7% of CP cases. In all classes the observed sex distribution was significantly different, ($P<0.01$) from that of all live births.

4. More CL cases were unilateral (80.5%) than bilateral (11.6%) and twice as many unilateral defects were left-sided as against right-sided involvements. More CLCP cases were unilateral (71.1%) than bilateral (26.0%) and 59.3% of these occurred on the left side.

5. Of unilateral CL cases, 65.2% were male and 63.2% of bilateral

CL cases were male. 64.1% of unilateral CLCP cases were male and 69.8% bilateral CLCP cases were male.

6. Yearly fluctuation in incidence was quite marked for all individual cleft types. In combining all cleft types, a range of between 14 and 42 clefts occurred in a single year (mean = 27.6; S.D. = 7.76).

7. Analysis for seasonal effect suggested that cleft types CLCP and CP showed significant deviation from expected occurrence ($P<0.05$) with peak seasonal trends being observed in May and March respectively.

8. Of all cleft cases, 37.0% had a family history of some type of cleft among all known relatives. A greater proportion of CL(P) probands (39.9%) had a family history than did CP probands (30.7%). In subjects affected with either CL(P) or CP, there were almost equal proportions of males and females with a positive family history.

9. Prematurity, that is, a birth weight of 2.5 kg or less, occurred in 10.5% of all specified subjects. CP patients were most often of low birth weight (14.1%). Within all cleft classes females were more severely affected than males.

10. No significant relationship was demonstrated with maternal age for subjects with any type of cleft. However, paternal age of CP cases was significantly different ($P<0.01$) from the expected distribution. A greater than expected number of fathers were 40 years of age or older.

11. A significant relationship with parity ($P<0.01$) was observed only

for CLCP subjects when analysed without regard to related variables. A greater than expected number were of fifth birth order or later.

12. A total of 29.5% of cleft affected children were found to have one or more associated congenital malformations which were more often associated with CP (40.9%) than with CL(P) (23.7%). These associated defects occurred slightly more often among males.

THE ADELAIDE CHILDREN'S HOSPITAL (INC.)

Circle All Positive Squares

C L E F T A B N O R M A L I T I E S

GENERAL INFORMATION

NAME : _____ PARENTS' INITIALS : _____

ADDRESS AT BIRTH : _____

LAST RECORDED ADDRESS : _____ TELEPHONE NO : _____

PARENTS' OCCUPATION AT BIRTH : _____

REFERRING DR. & ADDRESS : _____

SURGEON : _____

RECORD NO : [1 ... 7] BIRTH DATE : [8 ... 13] (d d m m y y) SEX : [14] Male 1, Female 2 BORN AT : _____

PRIVATE PATIENT : [15] Yes 1, No 2 TWIN : [16] Yes 1, No 2 SEASON : [17] Winter 1 (1st June), Spring 2 (1st Sep.), Summer 3 (1st Dec.), Autumn 4 (1st Mar.) BIRTH RANK : [18] _____

SEX & NUMBER OF SIBLINGS : Male [19 20] Female [21 22]

TYPE OF CLEFT : [23 24]

(L) P Complete	01
(R) P Complete	02
(L) P Incomplete	03
(R) P Incomplete	04
(L) Unilateral P & S	05
(R) Unilateral P & S	06
Bilateral complete P & S	07
Bilateral Incomplete P & Complete S	08
Bilateral Complete P & Incomplete S	09
Bilateral Incomplete P & S	10
Complete S	11
Incomplete S	12
Submucous Bony	13
Submucous Muscular	14
Congenital Short Palate	15
P. Robin	16
Other (Specify)	17

GRADING OF SEVERITY : [25]

Severe (or complete)	1
Less severe	2

REMARKS : _____

PREGNANCY AND BIRTH DATA

HOSPITAL : _____ BIRTH WEIGHT : [26 ... 28] Kg

DELIVERY : [29]

Full Term	1
Premature	2
Caesarian	3
Other	4

BLOOD GROUP :

	Mother [30]	Child [31]
A	1	1
B	2	2
AB	3	3
O	4	4
RH+	5	5
RH-	6	6

PREGNANCY : [32]

Normal	1
Medical Illness	2
Infective Illness	3
Mental Illness	4
Other Illness	5
Allergy	6
Threatened Abortion	7
Drugs	8

FEEDING PROBLEMS : [33] Yes 1, No 2

ASSOCIATED DEFECTS : [34 35]

Club foot	01
CNS	02
CVS	03
Ear Defect	04
Eye Defect	05
Syndactyly	06
Polydactyly	07
Hypertelorism	08
Spina Bifida	09
Skeletal	10
Hip Dislocation	11
Micronathia	12
C.V.	13
G.I.	14
Other (Specify)	15
Multiple	16

DEFECTS TREATED : [36]

Adelaide Child. Hospital	1
Other S.A. Hospital (Specify)	2
Interstate	3

TIMING OF ILLNESS OR DRUG : [37]

1st Trimester	1
2nd Trimester	2
3rd Trimester	3

HEREDITARY HISTORY

OTHER DEFECTS : [38]

Nil	1
Sibling	2
Parent	3
Grandparent	4
Aunts, Uncles	5
1st Cousins	6
2nd Cousins	7
Vague Reference	8

SEX RELATIVE AFFECTED : [39]

Male	1
Female	2

MATERNAL or PATERNAL SIDE : [40]

Maternal side	1
Paternal Side	2

REMARKS : _____

HEREDITARY DEFECT INVOLVED : [41 42]

Club foot	01
CNS	02
CVS	03
Ear Defect	04
Eye Defect	05
Syndactyly	06
Polydactyly	07
Hypertelorism	08
Spina Bifida	09
Skeletal	10
Hip Dislocation	11
Micronathia	12
C.V.	13
G.I.	14
Other (Specify)	15
Multiple	16

HEREDITARY HISTORY CLEFTS : [43]

Nil	1
Sibling	2
Parent	3
Grandparent	4
Aunts, Uncles	5
1st Cousins	6
2nd Cousins	7
Vague Reference	8

SEX RELATIVE AFFECTED : [47]

Male	1
Female	2

MATERNAL/PATERNAL SIDE : [52]

Maternal Side	1
Paternal Side	2

TYPE OF CLEFT INVOLVED : [44 45]

(L) P Complete	01
(R) P Complete	02
(L) P Incomplete	03
(R) P Incomplete	04
(L) Unilateral P & S	05
(R) Unilateral P & S	06
Bilateral Complete P & S	07
Bilat. Incomplete P & CompS	08
Bilat. Comp. P & Incomp. S	09
Bilateral Incomplete P & S	10
Complete S	11
Incomplete S	12
Submucous Bony	13
Submucous Muscular	14
Congenital Short Palate	15
P. Robin	16
Other (Specify)	17

PREVIOUS BIRTHS : [46]

Normal	1
Still birth	2
Miscarriage	3
Abortion	4

NO. DEFECTIVE CONCEPTIONS : Before [48] After [51]

TIMING REL. PRESENT BIRTH : [53]

Adjacent	1
Non-Adjacent	2

REMARKS : _____ [80] [1]

THE ADELAIDE CHILDREN'S HOSPITAL (INC.)

Circle all Positive Squares

CLEFT ABNORMALITIES

BASIC TREATMENT

RECORD NO : 1 7

AGE 1ST LIP REPAIR : 8 10 mths

NO. SECONDARY LIP REPAIRS: 13 14

AGE 1ST PALATE REPAIR : 16 17 Years

NUMBER SECONDARY PALATE REPAIRS : 20 21

COMPLICATIONS PALATE REPAIRS: 22

Yes	1
No	2

ORTHODONTIC TREATMENT: STARTED (AGE) 25 27 Years

FINISHED (AGE): 28 30 Years

TYPE OF ORTHODONTIC TREATMENT : 31

Removal	1
Fixed	2
Both	3
Consultive only	4

HAMULI FRACTURE : 11

Yes	1
No	2

TYPE SECONDARY LIP REPAIR: 15

Trim	1
Abbe	2
Z-Plasty	3
Vermilion Correction	4
Others	5

TYPE PRIMARY PALATE REPAIR: 18

Push Back	1
Langenbach	2
Pharyngoplasty	3
Bone Graft	4
Simple	5
Others	6

RESIDUAL FISTULA : 23

Yes	1
No	2

PRE-SURGICAL ORTHOPAEDICS: 32

Yes	1
No	2

TYPE OF PRIMARY REPAIR (LIP) 12

B-M	1
Le. M	2
Rose	3
Simple	4
Z-Plasty	5
Others	6
Millard	7
Lip & Palate	8

TYPE SECONDARY PALATE REPAIR: 19

Simple	1
Closure of fistula	2
Pharyngoplasty	3
Bone Graft	4
Other	5

SPECIFIC NASAL COSMETIC OPERATIONS: 24

Yes	1
No	2

DENTAL DATA : 33

Extract. Perm. Teeth	1
Missing Teeth(Cong)	2
Supernumerery Teeth	3
Hypoplasia	4
High Caries Rate	5
Prosthetic Denture	6
Prosthetic Obturator	7
Prosthetic Retainer	8

REMARKS : _____

_____

_____

SPEECH THERAPY STARTED (AGE) : 34 35 Yrs

SPEECH THERAPY DURATION : 36 37 Yrs.

APPROXIMATE FREQUENCY THERAPY: 38 39 Mths

ADENOIDECTOMY : 40

Yes	1
No	2

EFFECT OF ADENOIDECTOMY ON SPEECH: 41

Improvement	1
Worsening	2
Nil Noted	3
Temporary Worsening	4
Temporary Improvement	5
Nil	6
Other	7

SUMMARY COSMETIC RESULT: 42

Normal	1
Excellent (Appr. Normal)	2
Good	3
Fair	4
Poor	5

SUMMARY SPEECH RESULT : 43

Normal	1
Excellent (appr.normal)	2
Good	3
Fair	4
Poor	5

REMARKS : _____

_____

_____

_____

SUMMARY ORTHODONTIC RESULT: 44

Normal	1
Excellent (Appr. normal)	2
Good	3
Fair	4
Poor	5

OTHER SURGICAL TREATMENT: (Specify type and Hospital)

_____

_____

_____

_____

E.N.T. TREATMENT : 45

Ear Surgery	1
Drainage only	2
Cosmetic Ear Surgery	3
Drugs only	4
Hearing Loss	5
Tonsils	6
Other	7

INTELLIGENCE ASSESSMENT : 46

Very Superior	1
Superior	2
High Average	3
Average	4
Low Average	5
Borderline Defective	6
Mentally Defective	7

SOCIAL ASSESSMENT : 47

Working	1
Office	2
Professional	3
Social Worker Cons. needed	4

RECORDS AVAILABLE : 48

Photographs	1
Speech	2
Orthodontic	3
Cosmetic	4
X-ray	5
Other	6

FOLLOW-UP QUESTIONNAIRE : 49

Yes	1
No	2

REMARKS : _____ 80

_____ 2

_____

_____

The Adelaide Children's Hospital (Incorporated)

Telephone: 67 2351

72 King William Road
North Adelaide S.A. 5006

A very important investigation is about to be carried out in South Australia to try to help solve the problem of cleft lip and palate. In order to do this satisfactorily we wish to interview as many children and parents of children with cleft lip and palate as possible. We have obtained the full permission of the surgeon who was in charge of your case to do this investigation, and we would be very grateful for your co-operation.

It will be necessary for you to attend the Adelaide Children's Hospital for one short interview, and on the same occasion to have x-rays taken to study the jaw growth of your child. This investigation will involve no expense to yourself, either for the attendance or for the x-ray.

We earnestly request you to take part in this investigation as it will most certainly be of great value in helping children who may be born in the future with this defect, and at the same time could very possibly aid in the further treatment of your own child.

Yours sincerely,

D.N. ROBINSON,
M.B., B.S., F.R.C.S.(Eng.),
F.R.A.C.S. Plastic Surgery.

Visiting Plastic Surgeon,
Adelaide Children's Hospital.

M.A.C. NUGENT,
B.D.Sc.(Qld.), M.S.(Roch.),
D.Orth.R.C.S., F.A.C.D.S.

Orthodontist,
Adelaide Children's Hospital.

THE UNIVERSITY OF ADELAIDE

ADELAIDE, SOUTH AUSTRALIA, 5001

D.D.H.

Ph. 230-230 extn. 8007.

Dear

In anticipation of your help in the conducting of this Survey, an appointment for an interview and x-rays has been arranged for you and your child on

At this appointment we would like to interview both the mother and child. Should this time be inconvenient, we will be interviewing through on Wednesday mornings. If necessary, would you please return the enclosed slip in the post-paid envelope to indicate a more suitable date. The appointment time will be altered accordingly.

We wish to make use of an x-ray machine especially designed for this project, which is housed in the Dental Department of the ROYAL ADELAIDE HOSPITAL in Frome Road, Adelaide. For this reason we will conduct the interviews in the Orthodontic Clinic on the 4th floor of the above Dental Department.

Thank you for your consideration of this matter.

Yours sincerely,

CHARLES C. SPRY, B.D.Sc.,
CLEFT RESEARCH CO-ORDINATOR.

APPENDIX B 3 Appointment Confirmation included in LETTER 1 G a, b and LETTER 2 G

I,_____NAME

OF_____PRESENT ADDRESS

_____

_____

will be able to attend the Dental Dept. Royal Adelaide Hospital on :

_____/_____/ 72
(date most suitable)

NO POSTAGE STAMP REQUIRED IF POSTED IN AUSTRALIA

BUSINESS REPLY POST
PERMIT No. 1137 ISSUED AT ADELAIDE

Postage and fee will be paid on delivery to:

THE UNIVERSITY OF ADELAIDE

BOX 498 D, G.P.O., ADELAIDE
SOUTH AUSTRALIA 5001.

UA 22/64

The Adelaide Children's Hospital (Incorporated)

Telephone: 67 2351

72 King William Road
North Adelaide S.A. 5006

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It will be necessary for you to attend the Adelaide Children's Hospital for one short interview, and on the same occasion to have x-rays taken to enable us to make an assessment of your facial development. This investigation will involve no expense to yourself, either for the attendance or for the x-ray.

We earnestly request you to take part in this investigation as it will most certainly be of great value in helping children who may be born in the future with this defect, and at the same time could very possibly aid in your further treatment.

It will be of great advantage if at least one of your parents could attend with you.

Yours sincerely,

D.N. ROBINSON,
M.B., B.S., F.R.C.S.,(Eng.),
F.R.A.C.S. Plastic Surgery.

Visiting Plastic Surgeon,
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CLEFT RESEARCH CO-ORDINATOR.

THE UNIVERSITY OF ADELAIDE

ADELAIDE, SOUTH AUSTRALIA, 5001

D.D.H.

Ph. 230-230 extn. 8007.

Dear

A letter was previously sent to you requesting that you take part in the Cleft Lip and Palate research project. We realise that it may have been inconvenient to attend for an interview at that time.

A considerable volume of information has now been collected. However, for a project of this nature, it is imperative that we include in the study all persons in the State who have been affected. We anticipate that you would like to contribute to the success of the project as the collected information will help in future treatment. Accordingly, another appointment has been arranged to interview Mrs. and to obtain x-rays of on

Should this time be inconvenient, we will be interviewing through on Wednesday mornings. If necessary, would you please return the enclosed slip in the post-paid envelope to indicate a more suitable date. The appointment time will be altered accordingly.

An x-ray machine, especially designed for this work is housed in the Dental Department of the Royal Adelaide Hospital in Frome Road, Adelaide. For this reason, we will conduct the interviews in the Orthodontic section of the above Department. (4th floor).

Thank you for your consideration of this matter.

Yours sincerely,

CHARLES C. SPRY, B.D.Sc.,
CLEFT RESEARCH CO-ORDINATOR.

THE UNIVERSITY OF ADELAIDE

ADELAIDE, SOUTH AUSTRALIA, 5001

D.D.H.

Ph. 230-230 Extn. 8007.

Dear

I would be very grateful if you could present for X-Rays and return the Questionnaire in connection with the Cleft Lip and Palate Research Project.

A considerable amount of data has been collected, but it is imperative that we obtain X-Rays of every child who is to take part in the Study.

As you will remember, the X-Rays are to be taken at the Dental Department of the Royal Adelaide Hospital on Frome Road, Adelaide. Wednesday afternoons between 2.00 and 4.00 p.m. and Friday afternoons between 2.00 and 3.30 p.m. are the most suitable times. Should you be unable to attend during these periods you might arrange a more suitable time by ringing 230-230 extn. 269.

I am assuming that you may have misplaced the Questionnaire or do not know where to send it. Accordingly, I am enclosing another Questionnaire and reply paid envelope for your convenience.

Thank you once again for your help in the conducting of this project.

Yours sincerely,

CHARLES C. SPRY, B.D.Sc.
CLEFT RESEARCH CO-ORDINATOR.

THE UNIVERSITY OF ADELAIDE

ADELAIDE, SOUTH AUSTRALIA, 5001

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Thank you once again for your contribution to the success of this project.

Yours sincerely,

CHARLES C. SPRY, B.D.Sc.
CLEFT RESEARCH CO-ORDINATOR.

THE UNIVERSITY OF ADELAIDE

ADELAIDE, SOUTH AUSTRALIA, 5001

D.D.H.

Ph. 230-23 ; extn. 8007.

Dear

At the time of our interview concerning the Cleft Lip and Palate Research Project, I asked you to return a questionnaire, relating mainly to your medical history during your pregnancy with

I am assuming that you may have misplaced the questionnaire, or do not know where to send it. Accordingly, I am enclosing another copy of the questionnaire and a reply paid envelope for your convenience.

Thank you once again for your help in the conducting of this project.

Yours sincerely,

CHARLES C. SPRY, B.D.Sc.
Cleft Research Co-ordinator.

CCS:pb

QUESTIONNAIRE

Patient's Name: _____

Date of Birth: _____ Sex_____ Tel.No._____

Address: _____

Father's name: _____ Race_____

Mother's name: _____ Race_____

Questionnaire completed by:_____ Date _____

FAMILY

Q. Are you Single / Married / Separated / Divorced ? _____

Is your husband the father of this child ? _____

Is the father of this child a cousin or a relation to you ? _____

If so, what relation is he to you ?_____

GEOGRAPHICAL NATIVITY

Q. In what country were you born ?_____

In what country were your parents born ?_____

In what country was the father of this child born ?_____

In what country were the parents of the father of this child born ?_____

PARENTAL AGE

Q. How old are you?_____ How old is the father of this child?_____

How old were you when this child was born ?_____

How old was the father of this when it was born?_____

HISTORY OF MORTALITY AND PERIODS OF RELATIVE INFERTILITY

Q. In what year were you married?_____How many children have you?_____

Have you had any miscarriages or unsuccessful pregnancies?_____

Have any of your children been born dead?_____

Have any of your children died after they were born?_____

If so, what did they die of?_____

HISTORY OF MORTALITY AND PERIODS OF RELATIVE INFERTILITY (Contd.....)

How long was your pregnancy with this baby?_____

How much did your baby weigh at birth?_____

List the names of all your children and the years they were born :

NAME	YEAR	NAME OF FATHER

List all the miscarriages you have had and the year they occurred :

Miscarriage	Year

HEREDITARY HISTORY

Q. Did anyone in your family have the same condition as your baby? _____

Who ? _____

Has anyone in your family or in the family of the father of this child had any of the following ?

	What relation to you ?
Hare lip	
Too many fingers	
Too many toes	
Club feet	
Cleft palate (hole in the roof of mouth)	
Mental retardation	
Fingers that are stuck together (webbed)	
Toes that are stuck together (web toes)	

HEREDITARY HISTORY (Contd.....)

What relation to you ?

Deformed ears _____

Bumps or holes in front of the ears _____

Heart murmur _____

Heart deformity _____

Birth marks on the face-what colour _____

Tumors or growths of any kind _____

Undescended testicles _____

Any other deformity _____

_____

HEALTH OF PARENT AT THE TIME OF CONCEPTION

Q. Were you well at the time you became pregnant?_____

Was the father of the child well at the time you became pregnant?_____

If you or the father were not well, what was the matter ?

_____

Were you sick just before you knew you were pregnant?_____

How many months before you became pregnant did you get sick?_____

Describe how you felt_____

What kind of medicine did you take?_____

How long were you sick?_____

VOMITING

Q. Did you have any vomiting during your pregnancy?_____

What months of pregnancy did you vomit?_____

What meals made you sick?_____

Did you lose any weight the first 3 months?_____How much?_____

Did the doctor give you pills to stop vomiting?_____

What was the name of the pills?_____

WORK

Q. Did you work while you were pregnant?_____

What kind of work were you doing?_____

What months of pregnancy did you work?_____

Was it light or heavy work?_____

ANAEMIA

Q. Have you ever had anaemia?_____low blood_____ weak blood_____

Did you have it when you were pregnant with this baby?_____

Did the doctor give you pills for it?_____

What was the name of the pills?_____

What months of pregnancy did you take the medicine?_____

BLEEDING

Q. Did you have any bleeding (vaginal) during this pregnancy?_____

Did you have any spotting (vaginal) during this pregnancy?_____

Did you bleed in month 1-2-3?_____ which month?_____

Did you have to be a patient in the hospital because of the bleeding?_____

How much bleeding did you have? (pads per day) _____

Were you given any medicine for the bleeding?_____

What?_____

CONTRACTIONS:

Q. Did you feel any contractions in your first three months of pregnancy?

_____

Pressure pains or cramps?_____

What month did you feel them?_____

HYPOXIA

Q. Did you have any operations while you were pregnant with this baby?_____

If so, what was the operation?_____

Did you have the operation in the first 3 months you were pregnant?_____

Did you feel dizzy in the beginning of your pregnancy?_____

Did you faint in month 1-2-3? _____

IRRADIATION

Q. Did you have an X-ray of your chest taken while you were pregnant?_____

What month of pregnancy?_____

Did you have an X-ray of your stomach taken while you were pregnant?_____

What month of pregnancy?_____

Did you have any other X-rays while you were pregnant with this baby?

_____

IRRADIATION (Contd.....)

What were the X-rays of ?_____

What month of pregnancy were they taken?_____

INFECTIONS AND DISEASES

Q. Did you have a cold in the first 3 months of pregnancy?_____

Did you take any pills for the cold? _____ What pills?_____

Did you have a fever with this cold?_____

_____

When you were pregnant were you ever exposed to German Measles?_____

Did you ever have them in the first 3 months of pregnancy?_____

Did you ever have any of these illnesses in the first 3 months of pregnancy with this child?

Whooping cough _____

Regular Measles _____

Mumps _____

Smallpox _____

Encephalitis _____

Chicken pox _____

Flu _____

Do you have diabetes (sugar in the blood)?_____

Do you take anything for it?_____

How long have you had it?_____

Have you ever had any thyroid condition?_____

Was your thyroid over-active or under-active?_____

Do you take medicine for it? _____

Did you take medicine for it when you were pregnant with this baby?_____

Do you know whether your blood is Rh Negative or Rh Positive?_____

Did you have high blood pressure when you were pregnant?_____

What month of pregnancy?_____

Have you ever had rheumatic fever?_____

What operations have you had and when ?_____

Did you get many headaches in early pregnancy?_____

What did you take for them?_____

INJECTIONS

Q. During the first 3 months of pregnancy were you given any injections of :

Gamma globulin _____

Cortisone _____

ACTH _____

Did you receive any flu shots in the first 3 months of pregnancy?_____

Did you receive any polio shots in the first 3 months of pregnancy?_____

Did you have any smallpox vaccinations in the first 3 months of pregnancy?_____

Did you have any Asian flu shots in the first 3 months of pregnancy?_____

DIET

Q. Did you eat meat, vegetables & potatoes regularly when you were pregnant?

_____

How many months were you pregnant?_____

Did you lose any weight while you were pregnant?_____

If so, how much?_____

Does your religion cause you to eat any special foods or fast for any long period of time ?_____

ALCOHOL

Q. Do you drink anything alcoholic?_____

Does your husband?_____ Or the father of this child?_____

How many drinks a day do you have ?_____

How many drinks a day does the father of this child have?_____

VITAMINS

Q. When did you start taking vitamins during your pregnancy?_____

What kind do you take?_____

Did you take the vitamins regularly or only occasionally?_____

Did you ever take more than you were supposed to during your pregnancy?

_____

ALLERGIES

Q. Do you have an allergy?_____ to what?_____

Penicillin_____ Hay fever _____

Tomatoes _____ Sea food _____

Soap _____ Dogs,cats,bees_____

Were you allergic during your pregnancy?_____

Did you take any medicine for it?_____ If so,what?_____

Did you have an allergy reaction when you were pregnant?_____

During what month?_____

Describe how you felt_____

Were you sick just before you got pregnant?_____

Describe the illness_____

EMOTIONAL STRESS

Q. Were you upset or nervous during your pregnancy?_____

If so, what was the matter?_____

When during your pregnancy did this occur?_____

Do you consider yourself to be a nervous person or a calm person?_____

_____

If you were unhappy, nervous, or tense during your pregnancy, were you :

Slightly upset_____Very upset?_____Extremely_____

Do you have headaches when you are upset?_____

Does your stomach hurt when you are upset?_____

Do you get a rash or diarrhea when you are upset?_____

PSYCHIATRIC

Q. Have you ever been to see a psychiatrist?_____

Did you see one while you were pregnant?_____

For what reason were you seeing the psychiatrist?_____

_____

Have you ever had a nervous breakdown or have you ever been put in the hospital for your nerves?_____Year_____

MISCELLANEOUS

Q. What does the father of this child do for a living?_____

How long has he worked there?_____What is his job?_____

What does he have to do?_____

Do you smoke?_____Did you smoke when you were pregnant?_____

How many cigarettes a day?_____

Did you take any pills or medicines to bring on your period just before you realized you were pregnant?_____

If so, what was the name of the pills?_____

At what month did you take them? _____

Did you take any sleeping pills in the first 3 months of pregnancy?_____

If so, what was the name of the pills?_____

Did you take any pills for your nerves when you were pregnant?_____

What month did you take them?_____

What is the name of them?_____

Did you have any infections in the uterus?_____When?_____

Did you have a kidney infection while you were pregnant?_____

Did you have a kidney X-ray (IVP)?_____What month of pregnancy?_____

_____

PLEASE ADD ANY FURTHER INFORMATION YOU THINK WOULD BE USEFUL

_____

_____

_____

_____

_____

_____

_____

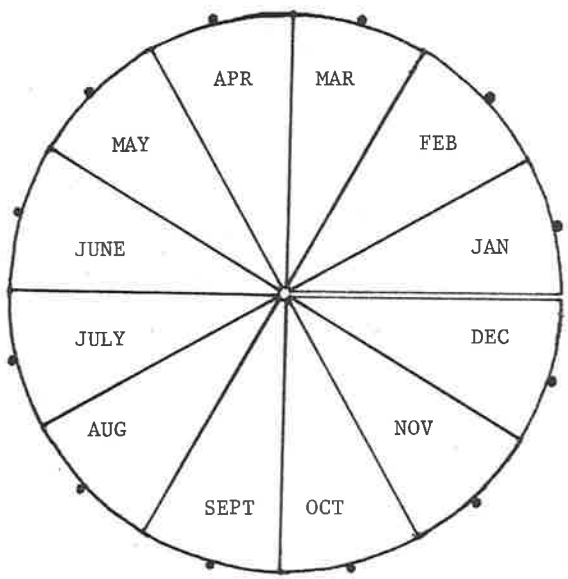
_____

SUMMARY OUTLINE OF THE EDWARDS SEASONAL ANALYSIS REPRODUCED FROM WEHRUNG and HAY[53].

Briefly, the Edwards' model divides a circle into 12 equal sectors, each centred at angle

$$\theta_i = \frac{2\pi i}{12} - \frac{1}{2}\left(\frac{2\pi}{12}\right) \quad (i=1,2,.....,12)$$

from a fixed starting line as in diagram below. The months of the year are assigned consecutively to these sectors starting with January in sector 1.



A weight consisting of a square root transformation of the observed frequency of a malformation, Ni, for month i is then placed on the rim of the circle at angle θ. At this point it is assumed that the expected monthly frequencies, $E(\sqrt{Ni})$, are proportional to the simple harmonic curve, $1 + \alpha \sin(\theta_i + \phi)$, where $0 \leq \alpha \leq 1$ allows a variable amplitude and $0 \leq \phi \leq 2\pi$ is the angle corresponding to the date of maximum incidence on the fitted curve. Both α and ϕ are to be estimated in this procedure.

Under the null hypothesis, $\alpha = 0$ and the expected monthly frequencies are equal. Intuitively this would place the centre of mass of the above weighted circle at the origin. A significant deviation of the computed centre of mass from the origin would then give reason for rejecting the null hypothesis and accepting an alternative hypothesis that $\alpha > 0$. The square of this deviation can be shown to have a chi-square distribution with two degrees of freedom under the null hypothesis and this is the basis for testing the null hypothesis versus the alternative hypothesis.

Empirically the Edwards' model has been successful in detecting cyclic trend of the simple harmonic type. Unfortunately, the model also detects by means of its chi-square test other types of trend which are neither in the simple harmonic category nor in the more general cyclic category. A hypothetical example illustrates this point.

Month of Birth	*Jan.*	*Feb.*	*Mar.*	*Apr.*	*May*	*June*
Observed Frequency	20	20	20	20	20	20
Month of Birth	*July*	*Aug.*	*Sep.*	*Oct.*	*Nov.*	*Dec.*
Observed Frequency	60	20	20	20	20	20

$Z^2 = 7.41$ (probability level 0.025)
$= 195^{\circ}$ (July)

THE CHI-SQUARE TEST

$$X^2_{k-1} = \sum_{i=1}^{k} \frac{\left(f_i - Np_i\right)^2}{Np_i}$$

where X^2 = chi-square value

N = sample size

k = number of classes

f_i = number in ith classes

P_i = probability belonging to ith class

$$\sum_{i=1}^{k} P_i = 1$$

and all P_1 P_2 - - - P_k are specified

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