Hereditary and Genetic Studies on Harelip and Cleft Palate

The first report

1 Clinical Investigation
2 Heredo-familial Study

附設醫院外科主任 王 世 祿

Up to the present very little has been definitely known of the actual cause of these and other anomalies found at birth. The subject may be broadly divided into two factors--heredity and environment -- and there is growing evidence that each may play a part in the cleft lip and cleft palate deformity.

,For the case of heredity, Fogh-Anderson,s studies in Den-mark, first published in 1942, and more recently reiterated (1957), point to the following conclusions, quoted in part:Within the groups of cleft lip alone and cleft lip plus cleft palate a familial disposition can be demonstrated in 27% and 41% respectively, but only in 19% of the case of isolated cleft palate. Robert H.Ivy had the experience of this factor in 20.6% of case of cleft lip alone, in 25.5% of case of cleft lip plus cleft palate, and 17.6% of case of cleft palate alone From these statistical findings it is apparently that inheritance has become one of the main factors to elicited the presence of cleft lip and cleft palate.

For the purpose of clinical investigation and further study of these anomalies we started to find and call on patients around Taichung. It is too difficult to meet our expectations owing to the preservative nature and ignorance of medicine in the country, we can not excellently get the cooperation of patients and their relatives. However, we will goahead steadily and extend this troublesome job to the utmost of our ability. Clinical investigation is performed in our recent 61 cases besides the heredo-familial study, while the genetic study will be considered later.

Clinical Investigaiion

A lot of papers about the incidence of these anomalies have been made already. Fogh-Anderson of Denmark drew the conclusion that these anomalies occur singling or together in only 0.14% (1:665) of the country's population. Statistics in Table 1 lump together all cases of cleft lip and cleft palate occurring singly and together. Our data which were collected from six excellent hospitals are further shown as Table 2.

Table 1 THE INCIDENCE OF CLEFT LIP AND/OR CLEFT PALATE

Year	Investigator	Place	Ratio	Incidence
1950-54	Douglas	Tennessee		1:1694
1955	Lending et al.	New York City		1:1342
1960	Sezgin and Stark	N.Y.City	21:27087	1:1289
1965-67	S.L.Wang(author)	Taiwan	13 : 12618	1 : 971

Table 2 INCIDENCE OF FISSURE PATIENT IN OUR SERIES

Year	Hospital	Ratio	Incidence
1965-67	The Third Army General H.	1:2700	1:2700
〃	Taichung Airforce H.	1:1080	1:1080
〃	Provincial Taipei H.	2:1757	1:878
〃	Provincial Taichung H.	1:1050	1:1050
〃	Provincial Chiayi H.	3:3520	1:1173
〃	The Second Army General H.	5:2511	1:502
Average		13:12618	1:978

In all of our 61 cases, there are 35 males (57.3%) and 26 females (42.7%), while in 26 cases in which cleft lip occ-urred only, 15 males (57.7%) and 11 females (42.3%) are noticed. Tyeh are 57.1% (20cases) and 42.9% (15cases) of male and female respe-ctively in the cases of cleft lip plus cleft palate and cleft palate alone in which only one case is discovered. The comparison of incidence about sex of our series with that of Fogh-Anderson and Rosenthal is shown as Table 3.

Table 3 SEX AND HEREDITARY INCIDENCE

Sex (%)	Male			Female		
Type	our series	F.-A.	Rosenthal	O.S.	F.-A.	R.
Cleft lip	57.7(15)	65.2		42.3(11)	34.8	
C.1.and/or C.P.	57.1(20)	71.4		42.9(15)	28.6	
Total	57.3(35)	58.05		42.7(26)		41.95
Hereditary condition	14.8(9)			16.4(10)		

Although it was noticed apparently in the Fogh-Anderson's study that the age of the parents and the order of birth in the "mother" series of pregnancies seem to be without any influence what-ever. In our 67 cases included 61 patients and 6 siblings, it seems that the incidence of the first and the second children, 27% (18cases) and 24% (16cases) respectively, are much more increase than that of the others. This means that the younger the parent the higher the inciderence of these anomalies. This finding is evidenced in Table 4.

Table 4 ORDER OF BIRTH (RELATION TO HEREDITY)

Order of birth	Ist	2nd	3rd	4th	5th	6th	Total
clinical cases	18	16	10	6	10	3	67
Hereditary condition	5	6	2	4	2		19

Stark and his co-worker (1954,1958) have proposed a new classification of clefts of the lip and palate based on our more recent knowledge of the embryology of the region involved. Some of the older classification take the alveolar ridge as the critical structure for type dteermination. Kernahan and Stark (1958) use the incisive foramen as the criterion, on the basis that hard and soft tissue structures anterior to this point --designated primary palate-- are formed by the seventh week of embryonic life, while the tissues posterior to the incisive foramen-- secondary palate--fuse later, between the eighth and twelfth weeks of intrauterine life. Accor-ding to this of classification, all clefts involving the lip and alveolar process wold belong to "primary" palate anomalies, while the cleft of the hard and soft palate without involvement of the

lip and alveolar process would be in the category of "secondary" palate clefts.

According to Kernahan and Stark's criterion which are described as following: 1. Unilateral subtotal cleft of primary palate 2. Unilateral total cleft of primary palate. 3. Bilateral total cleft of primary palate. 4. Sutotal cleft of secondary palate. 5. Total cleft of secondary palate. 6. Unilateral subtotal cleft of primary and secondary palate, 7. unilateral total cleft of primary and secondary palate, and 8. Bilateral total cleft of primary and secondary palate. Most of our cases are though as unilateral, total clefts primary and secondary palates (45%), followed by unilateral, subtotal cleft of primary palate (25%) and unilateral total cleft of primary palate (20x%). In Table 5 our series is shown of 65 cases are taken into the consideration included 6 cases of sibling, but two of which are lack of information.

Table 5 CLASSIFICATION

Classification	Primary		Se con.				P.andS.		Total
	1	2	3	4	5	6	7	8	
Cases	16	13	1	1	0	1	29	4	65
%	25	20					45		

Heredo- Familjal Studies

Only eight cases of our patients (13%) as shown in Figure I have the history of familial anomalies of cleft lip and/or palate, either in father side or in mother side. As it is diffcult to get the patient's cooperation, we are certain that the true figure might be higher than that we have alredy kept. In consideration of five families (8.2%) as shown in Fig. II contained over two abnormal siblings without any hereditary charactors, cleft lip alone canbe traced in two or which, cleft lip plus cleft palate in other two, while one cleft lip and the other cleft palate in another family. According to Fogh-Anderson's statistics, If two normal pareants have a cleflip child, there is a 4.5% chance of their having another such child. Although it looks like a lower incidence of inheritance in our series, the comparison of sibling and that of relative (31%) which is the total members of familial influence included 8 inheritances and 11 siblings are quite near that of another authorities. (Table 6)

Table 6 FAMILY INFLUENCE

	Our series	F.Anderson	J.Gabka	R.H.Ivy.
Inheritance	13%(8)		26.2%	
Sibling	8.2%(5)*	4.5%(cleft lip)		
Relative	31%(19)	19-41%	17.6-20.6%	

..... indicate household.

In the classification of these 8 inheritary cases, we find 2 patients have cleft lip alone, The incidence of inheritance is 7% (2 cases in 30 patients). Five patients with hereditary cleft lip plus palate in 34 cases (15%) are noted ' While in the case of

cleft palate, only one case is detected (100%), which is a female and has the herditary history, The relation between inheritance and classification is shown in Ta-ble 7.

Table 7 RELATION BETWEEN INHERITANCE AND CLASSIFICATION

	Our series	F.-Aneerson	R.H.Ivy.
Cleft lip	7%(2)	27%	20.6%
Cleft liptpalate	15%(5)	41%	25.5%
Cleft palate alone	100% (1)	19%	17.6%

In the count of anomalous ancient, there are 5 aunt, 3 uncle, 2 father and 1 grandfather. It is great fun that 4 members are found in both mother line and father line shown as Table 8.

Table 8 INHERIT FROM FORMER GENERATION

Mother	0 cese
Father	2
Aunt	5
Uncle	3
Grand-fathher	1
Grand-mother	0
Mother line	4 Case
Father line	4

When we pay attention to the sex of these 19 patients, we find 9 of these are male (14.8%) and 10 female (16.4%) as shown in Table 3. It is possible still from this result that the difference of hereditary incidence between male and female are very few.

If we talk about the relation between order of birth and heredity, there are something worthy to say e.g.the first and second children have more hereditary character than the subsequent children. In our series 5 first children 6 second, 2 third, 4 fourth and 2 fifth are found.(table 4)

DISCUSSION

Although the cases are too few to establish a more detail statistical result in heredity, we are sure that the percentage is not 13% only. However, we find in our limited materials something worth mentioning.

Fogh-Anderson concluded that cleft palate alone is due to a simple dominant gene with sex limitation to the female. In our series only one patient is discovered, who ot only is just a female but has strangly the heredofamilial history. (As shown in Table 5 and Fig. I,Case 5)

We have noticed in our 8 hereditary families that 4 families, which contain cleft lip plus palate, have abnormal parents with cleft lip. In the other one, both abnormal parents with cleft lip plus cleft palate, and cleft lip-offspring are found. It is embryological theory which emphasizes that cleft lip and cleft palate occur at he different period.If a cleft palate or a cleft lip is produced, genetic and envirnmental-fctors must come into playing before these shelves fuse or before mesoderm penerate

the epithelial wall. In cn-sideration of these five cases, parental anomalies with cleft lip may be transmitted to their offspring with cleft lip plus palate. While the parents with cleft lip plus cleft palate may be also transmitted to cleft-lip-offspring. Although it may be true that the hereditary factor is not two but one only, the reasons why many quite different type of offspring occur are so many exogenic factors take part in the function that the end effect of hereditary factor are changed at the different period. This idea we will take much consideration and further studies in our latergen eic study.

As there are not so many cases in our series, we can not certain whether the higher incidence in first and second children is true or not. But we believe that after further investigation and study we can make it sure, The relationship between incidence and parental age, and the nature of the exogenic factors will be recognized also.

It is adopted currently that cleft palate and other congenital deformities are determined mainly by endogenic factor such as heredity e.g. the arrangement of gene and chromosome and exogenic influence such as environmental agents which presumably act by affecting directly the developing embryo or indirectly by interfering with normal maternal fetal relationship. Attempting to find what influences--endogenic or exogenic --cause cleft formation, J. Gabka found in 1,300 patients with fissure from the department for Kiefer-Gesichtschirurgie of the Rudolph Virchow-Kroankenhaus, Berlin the interesting statistics in which influencing factors such as inheritance (26.20%), causes on dysplasmatic state (11.40%), phaenocopies 30.40%) and psychotraumatic causes (17.20%) are described. Then I will discussed about the hereditary factor and explain to remaining exogenic factors in following also.

Owing to get negative cooperation of patients and their relatives inheritance of our series is 13% only. If the siblings are taken together with this e.g. the incidence of relative, then the result will be raised to 31% as shn whoin Table 6. In the other word, the true incidence of inheritance in our series is just the same as that of Joachim Gabka above.

Referring to the exogenic factors, so call "Stress" may be the most important elicited cause. It is Cortison which formed the main product immediately after stress occurring at the critical periord. Fraser (1950) have prod uced a high incideence of cleft palate deformity in the offspring of pregnant mice which were given cortison. Any psychological stress which can stimulate the adrenal gland and produch much amount of cortison are considered as a causative agent of cleft palate deformity. These have been investigated by Lyndon A. Peer, by Warkany and by others.

One of our 61 cases is a premature infant. In cases inducing drugs were administered by their mothers at the time of pregnancy for attempt to abortion. While in another, x-ray irradiation were frequently given to his mother due to pulmonary tuberculosis,

Evidence that dieary deficiency might be causal factors in the production of cleft palate deformities was first reported in Germany, Strauss (1914) who studies the congenital anomalies of animals in the Berlin Zoo, observed that inadequate nutrition may be associated with the production of cleft palate.

Since Vitamin B6 is a coenzyme necessary for amino acid metabolism and Folic acid is required for the metabolism of purine, dit may be possible that the palatal process

cannot properly fuse when these coenzymes are not present or physiologically functioning during the critical period of palatal growth.

Then the economic condition might be an important problem. All of our patients are so poor that they unfortunately get not only nutritional disturbance but much psychological stress which are frequently induced by bad environment. The etiological factors in our series are shown in Table 9.

Table 9 ETIOLOGICAL FACTORS IN OUR SERIES

1. Hereditary factor	31% (19cases)
2. Environmental factors	
Twin pyegcannr	1 case
Attempt to abortion (chemical)	3 〃
Allergic diathesis	2 〃
Premature	1 〃
X-ray irradiation (T.B.)	1 〃
Poor economy	more than 90%
Others	

It seems mainy author ty agrees with this view, but so far we still can not make sure, why the incidence of anomalies in non-hereditary families which have two siblings a-re so high (8.2%) It might be that when the mother whose first child is in anoma get gestation again, some particular physiological stress which was eliciated due to app rehension of the first experience present The same finding has been obtained in Fraser Robert's information.If an afetdcref child is born to nomal parents and there is no affected first-degree relative,the chance against a further child being affected are about ecighty to one and twenty to one in cleft palate alone and harelip with or without clefe palat espectively. While if there is also an affected first degree relative, the chance of cleft palate alone are ten to one(10%).In the cases of harelip with or without cleft palate if one parent is affected, the chance against any child being affected are fifty to one, while if there is also an affected child the risk to subsequent children is about one to ten.

We have not found any other associated anomalies accompanied with our patients except in a family with 6 siblings, anomalies of lip and palate are noticed in 3 elder chidren and the eldest and the next one sadly have deafmute too. (Fig.II-Case 5,Table10)

Table 10 ASSOCIATED ANOMALIES

Two cases of "Deafmute " found is siblings.

(67 materials)

Finally dicuss the mortality rate herein. As shown in table 11, four cases of the patients are died (6%) in 67 total cases under four year of age.

Table 11 MORTALITY RATE

Four cases of the patients are died (6%) in 67 total cases under four years of age.

Summay

These anomalies occur singly or together in 0.1% (1 : 971) in the average of the six excellent hospitals.

In our series 61 cases who live around Taichung city are investigated and studied The incidence in both sex are pretty nearly the same. Although the order of birth in the " mother " series of pregnance had been report seemly to be without any influence. we bind the order of first andsecond are more than others. The incidence of sex and order of birth have the same finding both in the hereditary and non-hereditary cases.

According to the classification of Kernahan and Stark, most of our cases are the unilateral, total cleft of primary and secondary palate, followed by the unilateral subtotal cleft of primary palate and unilateral total cleft of primary palate. Only one case who is a female is suffered from the secondary cleft palate alone.

Owing to get negative cooperation of patients and their relatives, hereditary condition in our fissure patientso isonly 13%. But the relative incidence (31%) is just the sameas that of other authorities. If two normal parents have a cleft child, there is in our series a 8.2% chance of their having subsequently such children.

Heredita-ry factors and enviromental influences are adopted currently as the most important causative elements of these anomalies. In our series the former is in 31%. In the conside-ration of exogenic factors, the economic condition seems to be the most important problem. Over 90% of our Patients are poor in economy which freg uently elicited the precipitaing factors, the nutritional disturbances and psychological stress.

No any other associated anomalies can be found except deaf-mute in two siblings. 6% of mortality rate can be traced also.

It is certain that at the next time we will much extent our investiga-tion and study, and the genetic study included the importance of chromosome will be also taken into the consideration.

Acknowledgements

The auther is particularly greatful to Dr. K.T. Kitahara, the professor of public health, Kagoshima university, and Dr. K.P. Chen, the professor of public health, Taiwan university, for their precious direcious directions.

The authtr is much indebted to Dr. C. S. Liao, the super - intedent of Zun-Aie general hospital, hospital, Taichung, for his kindly supplying materials.

The autheres thank are due to assistant K.T.Liao and Dr. T.L. Liao for their much help. This study was supported by the Third Army general hospital, Taichung Airforce hospital, Provincial- Taipei hospital, Taichung hospital, Chiayi hospital and The Second Army general hospital. They are kindly supplied statistical data for analysis.

Reference

1.A.B.Wallance: Transactions of the international society of plastic surgeons. 1959
2.Stark: Plastic surgery. 1962
3.Lemesurier: Harelips and their treatment 1962
4. C.A. Clarke: Genetics for the clinician 1964

摘　要

有關新生兒兎唇及口蓋破裂之發生率，從1965年到1967年，來自6所大醫院的資料，我們得到一平均數值約爲0.1%，即1：971。

我們醫院更將居住於臺中市的61位病人，作進一步的調查與研究，很明顯地，這種發生率在性別上幾乎沒有差異。雖然曾經有人報告過，胎兒的先後次序，對於這種異常的發生率並沒有多大影響，但在這些病例中，我們却發現第一胎及第二胎比其他以後的胎兒有較大的發生率，而且，不論病人有無遺傳關係，而這種性別及胎序與發生率之關係，都得到相似之結果。

根據 Kernahan 及 Stark 之一類法，在我們的病例中，最多屬於原發性及繼發性之單側完全口蓋破裂。其次爲原發性單側不完全口蓋破裂，及原發性單側完全口蓋破裂。至於繼發性口蓋破裂者，只有一個病例，而且是女性病人。

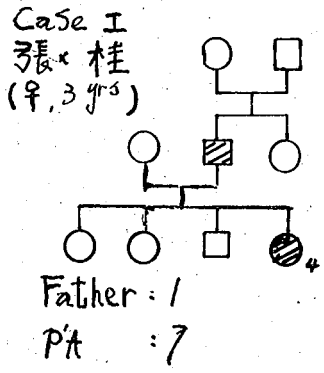
由於不能得到病人及其家屬之充分合作，在我們的病例中，有遺傳關係病人的發生率僅爲13%，但如果加上有遺傳關係之兄弟，而成爲親屬遺傳之發生率（31%）時，其結果即與其他學者所報告的相同。如果兩位正常夫婦生了一位兎唇或口蓋破裂缺陷的小孩，那麼他們再生出這種不正常小孩發生率則爲8.2%。

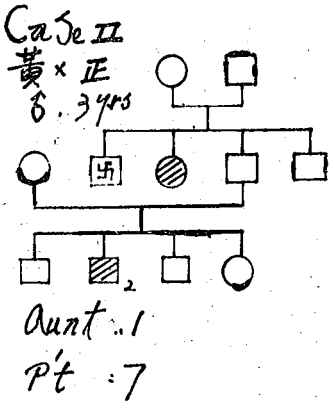
有關這種異常的原因，目前被認爲最重要的有遺傳因子，及環境的影響。在我們的61個病例中，前者佔31%，至於外在的環境因素，則以經濟條件最爲重要，在我們這些病人中，90%以上都屬於貧困的家庭。而經濟貧困不僅會引起營養不良，亦可導致心理上的壓迫，這就是口蓋破裂及兎唇發生的主要誘因。

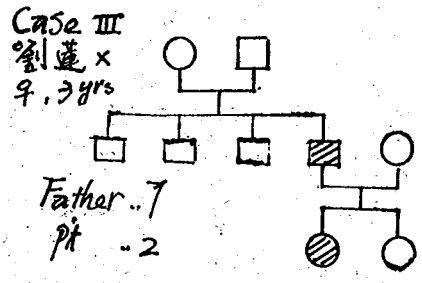
除了兩位兄弟有啞聾外，在我們的病例中，不再發現有其他併發違常，至於死亡率則爲6%。

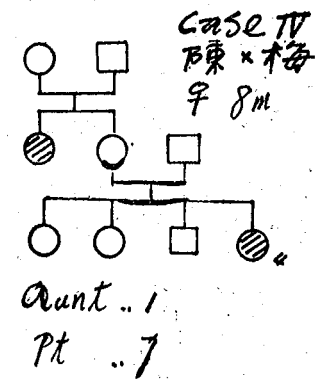
最後，我們下定決心將再作更廣泛與更深入的調查與研究。使得下回報告的內容更充實更完善，其他有關發生學與染色體的研究，亦將於下回的報告中提出。

附：同學們若有現發此種病例，請向附屬醫院報告。

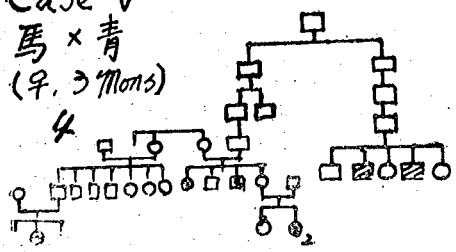




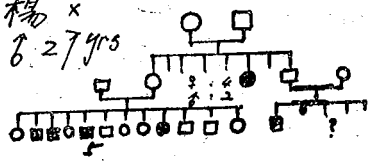




Case V
馬 × 青
(♀, 3 Mons)

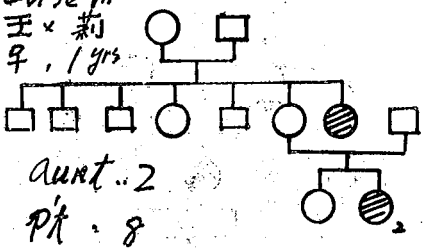


Case VI
楊 ×
♂ 27 yrs



Aunt..?
Pt : 2

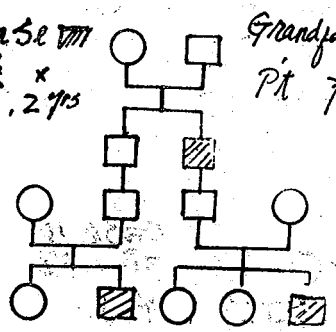
Case VII
王 × 莉
♀, 1 yrs



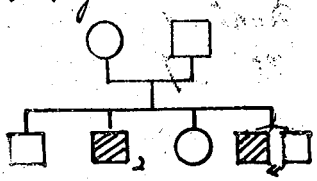
Aunt..2
Pt : 8

Case VIII
吳 ×
♂, 2 yrs

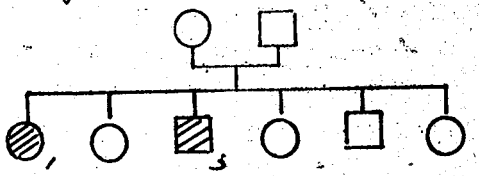
Grandfather
Pt ♂ : ??



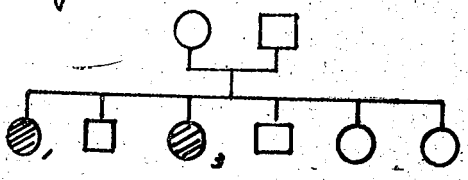
Case I, (2)
賴 × 土 (♂, 64)
: 1
Sibling (4) : 1



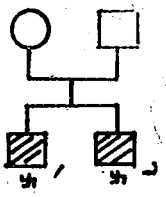
Case II (1)
張 × 嬌 (♀, 23y)
Sibling (3) : 2



Case III (1)
陳 × 青 (♀ 30 yrs)
: 7
Sibling (3) : 7



Case IV
黃 × (♂, die in 3 yrs)
Sibling (2) : (♂ in abortion about 7 mons.)



Case V (1)
陳 × 陳 (♂, 15 y, deaf-mute) : 1
Sibling (4) (♀, 7y, deaf-mute) : 1
Sibling (5) (♀, 5y) : 1