CONGENITAL PITS OF THE LOWER LIP WITH CLEFT LIP AND PALATE*

HYMIE GORDON,† M.D., M.R.C.P., F.R.C.P. (EDIN.), DAVID DAVIES, F.R.C.S. AND SHIRLEY FRIEDBERG, B.SOC.SCI.,
From the Comprehensive Medicine Group, Department of Medicine and the Plastic Surgery Unit, Department of Surgery, University of Cape Town

Congenital pits of the lower lip (fistulae labii inferioris congenita, lower-lip sinuses, mucous cysts of the lower lip, etc.) are small depressions in the vermilion part of the lower lip which usually occur in pairs and are situated symmetrically on opposite sides of the midline. Less commonly their relationship to the midline and to the transverse plane of the lip is asymmetrical, and in exceptional cases only one pit is present. The pits may be round, oval, or slit-like, and vary from about 2 mm. to 6 mm. in their greatest diameter. They are usually shallow but may be up to 10 mm. deep. Most commonly the orifice of the pit is flush with the surface of the lip, but sometimes its posterior margin is guarded by a fold of epithelium, and very occasionally it is situated on top of a small cystic papilla. The pits are usually empty, but sometimes they exude a viscid flu'd. Histologically they are found to be lined by a stratified squamous epithelium through which pass the ducts of mucinous glands. Embryologically they are believed to result from the failure of obliteration of the lateral sulci of the mandibular process.[1] The very rare condition of congenital clefts of the lower lip[2] is probably the extreme consequence of the abnormal persistence of these sulci. Cysts of the upper lip have also been described but they are the result of a quite different developmental error.[3]

It is unusual for the secretions from the pits to be so profuse as to constitute a nuisance; stasis and consequent infection are most unusual; and they are seldom so unsightly as to be a serious cosmetic defect. Should it be necessary, however, the operative correction is simple and the result is usually satisfactory. In their own right these lesions would not merit a great deal of attention; their considerable clinical importance is owing to their intimate association with congenital cleft lip and palate.

This association was first recorded in 1845 by Demarquay, an anatomist at the École de Médecine of Paris, when he described the case of young Alexis Pareille.[4] This boy had been brought to the Hôtel-Dieu by his mother because he had a bilateral cleft lip and palate with an anomaly of the lower lip. His mother also had a 'double hare-lip' and the central part of her lower lip was affected with the same anomaly as that of her son, namely 'two depressions ... the external orifices of two cavities which extend a centimetre and a half into the lower lip'. The mother informed Demarquay that her father, her paternal grandfather and several of her siblings had been affected similarly. She had had 7 children, of whom 4 had cleft lips.

Subsequently there were many other reports of such striking familial aggregations of cleft lip and/or cleft palate associated with pits of the lower lip, but it was not until 1943 that Fogh-Andersen of Denmark clearly demonstrated the autosomal-dominant pattern of inheritance in affected families.[5] In reviewing the subject in 1953, Van der Woude referred to 14 previous reports of the familial occurrence of this syndrome and added descriptions of 5 more affected families.[6] Then, in 1967, in a most valuable international study, Cervenka *et al.* brought the subject right up-to-date with a review of 66 families.[7] Of these, no fewer than 23 had been investigated personally by the authors (19 in Prague and 4 in Minnesota); 15 had been investigated by collaborators in Europe and North America; and a further 28 suitably reported families were culled from the literature. Altogether there were 446 cases of lower-lip pits in the 66 families which they analysed.

Their review confirmed the fact that in the majority of cases the syndrome of lower-lip pits with cleft lip and/or palate results from the action of a single mutant autosomal gene with dominant effect. Thus, pedigree analysis frequently showed the appearance of the syndrome in consecutive generations, the sexes were equally affected, and the incidence in the siblings or children of affected individuals was approximately 50%. The incidence in the siblings of the index cases with an affected parent was 49%. The incidence in the 169 siblings of all the 66 index cases was 38%. In the 27 children of the 66 index cases the incidence was 59%. The authors identified 125 'carriers' of the trait, i.e. individuals with at least two affected children, or with one affected child and another affected close relative. Twenty-five (20%) of these 'carriers' were themselves unaffected, indicating that the penetrance of the mutant gene is about 80%. There was considerable variation in phenotypic expression of the gene: lip pits, unilateral or bilateral cleft lip, and cleft palate occurred singly or in every possible combination in different individuals.

This syndrome has been reported most commonly in Europe,[5] North America[6] and Japan.[8] As there have not yet been any reports from Africa we present an account of two affected families recently seen in Cape Town.

CASE REPORTS

The T Family (Fig. 1: UCT Pedigree 14)

Unless otherwise stated, all the members of this family who were examined by us were generally healthy and had no congenital anomalies other than those described. The Roman and Latin numerals in the square brackets refer to the individual's position in the pedigree chart (Fig. 1).

Index case [III.4]. A.T., a Cape Coloured male, aged 32 years, has a repaired congenital total cleft of the left lip and palate. He had had convulsions in infancy and since early childhood he had been liable to attacks of generalized epilepsy. Clinical examination of the nervous system revealed no abnormality and the electro-encephalogram showed a diffuse dysrhythmia. He has no abnormality of the lower lip. He is married and has 7 children.

Parents. The mother [II.5], 54 years old, has 2 small round pits in the vermilion part of the lower lip. Each pit

*Date received: 14 March 1969.
†Present address: Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55901, USA.

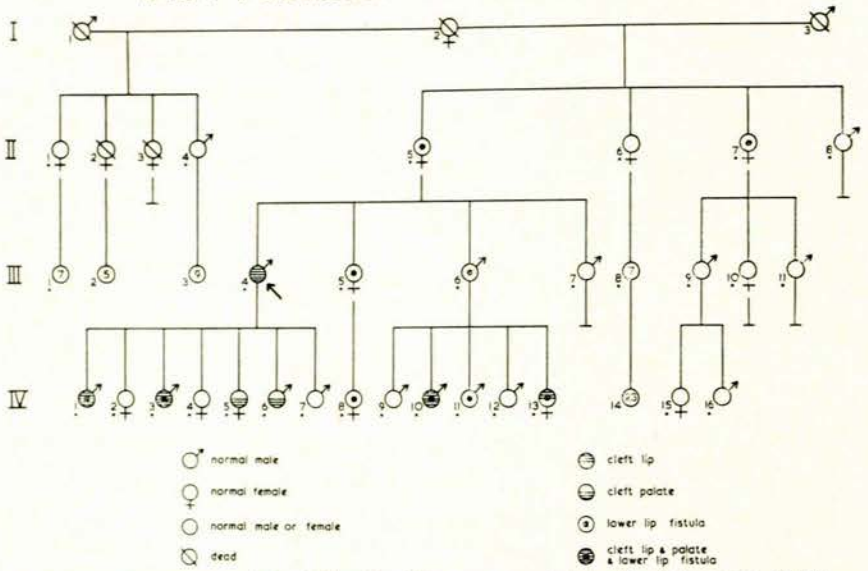

Fig. 1. Pedigree chart of the T family. The arrow points to the index case [III.4]. A dot under a symbol-number means that the individual has been examined by us.

is about 4 mm. in diameter and about 3 mm. deep, and they are symmetrically situated 15 mm. to the right and left of the midline. They contain no secretions. The father, 57 years old, has no anomalies. The parents are not consanguineous.

Siblings. The index case is the oldest of 4. His sister [III.5], 30 years old, has 2 pits in the lower lip, like her mother's. The first brother [III.6], 28 years old, has a single pit on the left side of the lower lip. He has a very high, narrow palate, grooved in the midline, but no cleft. The second brother [III.7], 24 years old, has no anomalies.

Children. The eldest son [IV.1], 9 years old, has a repaired bilateral total cleft lip and palate, with 2 pits symmetrically situated in the lower lip, one on each side of the midline. The pits have caused no symptoms. The 8-year-old daughter [IV.2] has no anomalies. The second son [IV.3], 6 years old (Fig. 2), has a repaired total cleft of the right upper lip and palate. On the lower lip to the left of the midline there is a shallow dimple of about 3 mm. maximal diameter. To the right of the midline and situated rather more anteriorly there is a transverse slit, about 3 mm. long, with a cyst protruding from its anterior margin. This has never produced any discomfort. The 5-year-old daughter [IV.4], has no anomalies, but the youngest daughter [IV.5], 4 years old, has a partial (posterior) cleft of the secondary palate. Her lips are normal. The third son [IV.6], 3 years old, has a submucous cleft of the posterior part of the secondary palate; his lips are unaffected. The youngest son [IV.7], 6 months old, has no anomalies.

Maternal grandparents. The maternal grandmother [I.2] was born in Richmond, CP, in about 1874. Both her parents were Cape Coloured, but, according to the family, her maternal grandmother was a Scotswoman. She died of a stroke at the age of 68 years. Her sons and daughters are sure that she had no lip pits or cleft. Before marrying the maternal grandfather of the index case, I.2 had had 4 children by a previous husband [I.1]. This man was the son of a Cape Malay woman and an

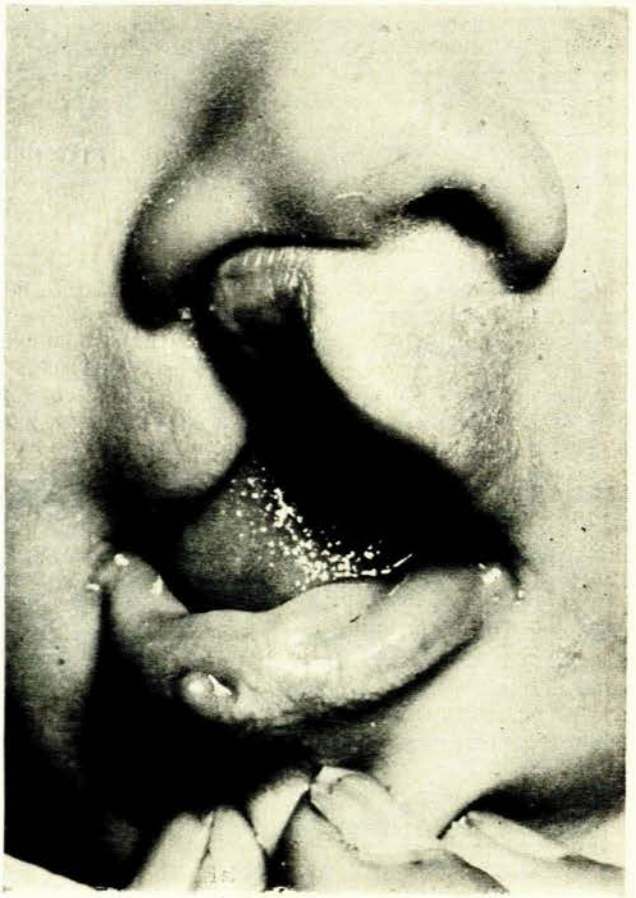

Fig. 2. The third child [IV.3] of the index case of the T family. The photograph, taken at the age of 3 months, shows the right-sided cleft lip and two pits of the lower lip. The left pit is shallow and is situated more posteriorly than the right one. The orifice of the latter is a narrow transverse slit with a cyst protruding from its anterior margin. A total cleft palate is also present, but is not seen in the photograph.

Englishman, his paternal grandfather having been one of the 1820 settlers. Two of their children [II.1 and II.4] are still alive; they have no anomalies, nor have any of their 16 children [III.7 and III.9]. The maternal grandfather [I.3], the second husband of I.2, was a Cape Coloured man. He was born in about 1876 and died at the age of 64 years. The cause of death, according to his son, was 'an enlarged heart', but we have been unable to trace his death certificate. His children are sure that he had no lip pits or clefts. The maternal grandparents were not consanguineous.

Maternal aunts and uncle. A maternal aunt [II.7], 51 years old, has 2 pits in the lower lip; they are equidistant from the midline but the left one is situated more anteriorly (Fig. 3). The other maternal aunt [II.6] and the maternal uncle [II.8] have no anomalies.

Nephews and nieces. A niece [IV.8], 9 years old, has a very high, narrow palate and 2 shallow, symmetrically placed pits of the lower lip. A nephew [IV.9], 10 years old, has no anomalies, and another nephew [IV.10], 7 years old, has a repaired bilateral total cleft lip and palate, with 2 symmetrical pits in the lower lip. A fold of skin overhangs the posterior margin of both pits.

A 6-year-old nephew [IV.11] has 2 shallow pits in the lower lip, symmetrically situated on opposite sides of the midline, and a nephew [IV.12] of 2 years has no anomaly. A niece [IV.13] was born in 1967 while this investigation was in progress. She has a severe bilateral cleft lip with a protruding central maxillary mass. There are also 2 relatively large pits on the vermilion part of the lower lip, situated close to the midline. The pits are about 7 mm. across their maximal diameter, and their posterior margins are connected by a transverse skin fold (Fig. 4). Her palate is normal.

None of the 10 maternal first cousins [III.7 - 11] was found to have any congenital anomaly. We have examined only 2 of the 25 maternal first cousins-once-removed [IV.15 and 16]; neither is affected. The remaining 23 [IV.14] are all said to be unaffected.

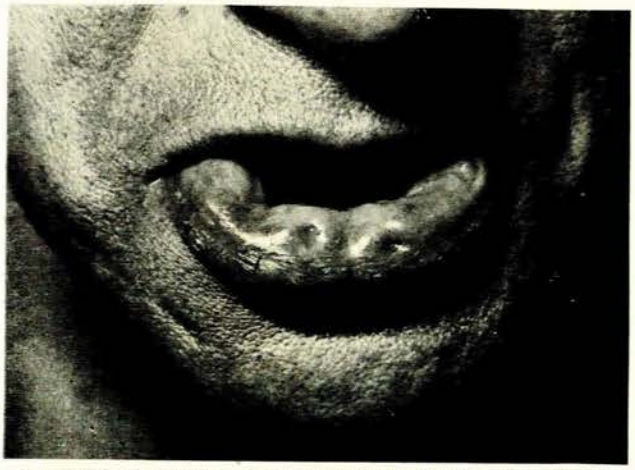

Fig. 3. The lower lip of a maternal aunt [II.7] of the index case of the T family. There are 2 pits, equidistant from the midline, the left one being more anteriorly situated. There is no cleft lip or palate.

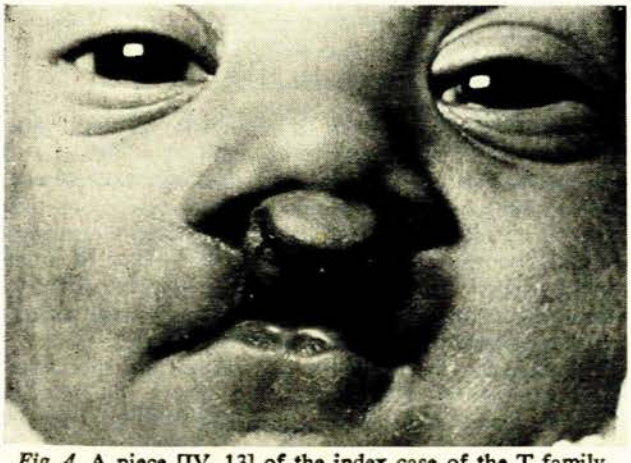

Fig. 4. A niece [IV. 13] of the index case of the T family. The photograph, taken at the age of 1 month, shows a bilateral cleft lip with protruding central maxillary mass and 2 pits of the lower lip. The posterior margins of the pits are connected by a transverse skinfold. There is no cleft palate.

The A Family (Fig. 5: UCT Pedigree 67)

We have far less information about the A family, in which we have identified only one individual—the index case—with lower lip pits.

Index case [III.5]. L.A., a Cape Coloured female, 5 years old, has an unrepaired congenital partial cleft of the posterior part of the secondary palate. She also has 2 cup-shaped, oval pits, each about 5 mm. × 3 mm., situated symmetrically on opposite sides of the midline of the lower lip. The posterior margin of each pit is elevated (Fig. 6). There is no secretion from the pits. She has no other anomalies.

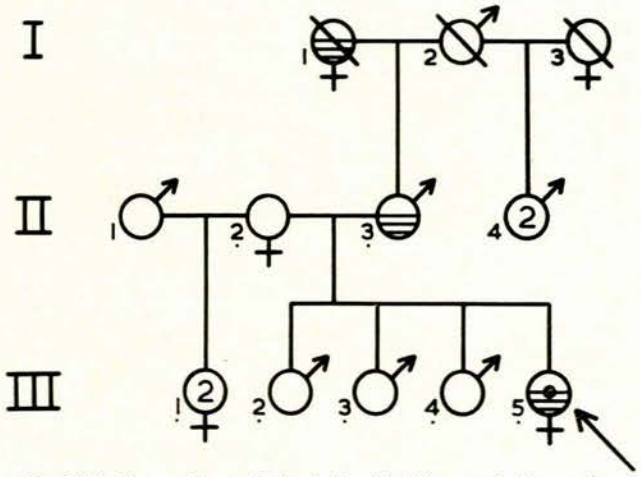

Fig. 5. Pedigree chart of the A family. The symbols are the same as in Fig. 1.

Parents. The mother [II.2], 39 years old, has no anomalies, and the father [II.3], 47 years old, has an unrepaired congenital partial cleft affecting the posterior part of the secondary palate. He has no lip or other anomalies. The parents are not consanguineous.

Siblings. The 3 older brothers of the index case [III.2 - 4] are all unaffected. There are also 2 maternal half-sisters, neither of whom is affected.

Grandparents. The paternal grandparents are both dead. The paternal grandmother [I.1] is reported by her son to have had a cleft palate, but he was separated from his mother at an early age and does not know whether she had lower-lip pits or not. The paternal grandfather [I.2] is reported to have been unaffected. The maternal grandparents were not examined by us; they were reported to be unaffected. There was no consanguinity between either pair of grandparents.

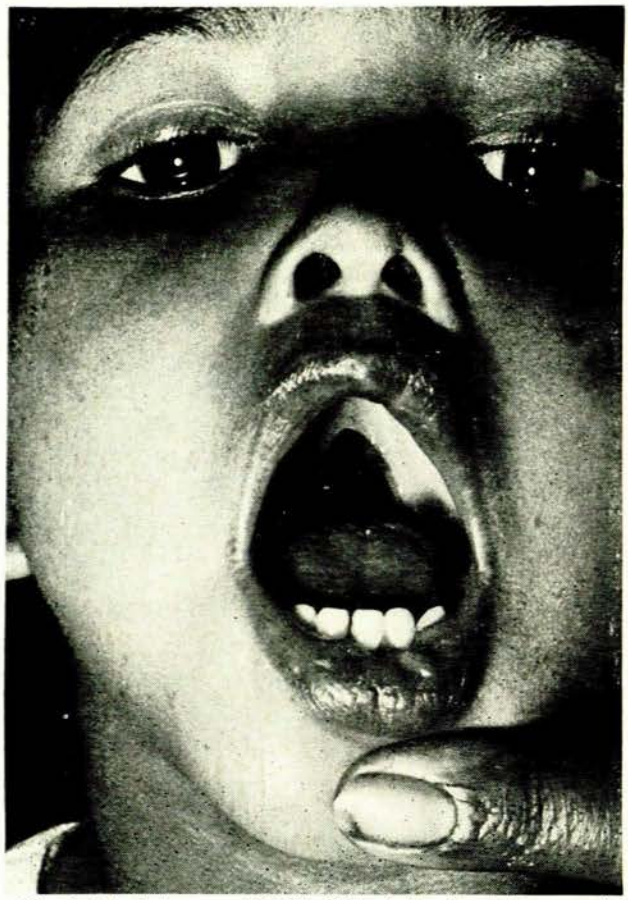

Fig. 6. The index case [III.5] of the A family at the age of 5 years, showing 2 pits of the lower lip and an unrepaired cleft of the posterior part of the secondary palate.

There are 5 maternal uncles, 5 maternal aunts and 45 maternal first cousins, none of whom is known to have a cleft or lip pits. They have not been examined by us. The paternal half-uncles [II.4] are both reported to be unaffected.

DISCUSSION

Family T illustrates well the typical genetical characteristics of the syndrome of congenital pits of the lower lip with cleft lip and palate. There are 13 affected individuals in 3 consecutive generations. The sexes are almost equally represented, 7 males and 6 females being affected. There are 20 children who are the offspring of affected individuals; of these, 11—approximately 50%—are also affected. Father-to-son transmission has occurred 5 times. These features are the hallmarks of the autosomal-dominant pattern of inheritance.

We have been unable to trace the syndrome back beyond generation II because all the members of generation I are dead. However, none of the children of the marriage of I.2 and I.1 is affected, but 2 of the 4 children of the marriage of I.2 and I.3 are affected. The syndrome, therefore, appears to derive from I.3. He is not known to have been affected, and if our information is correct it may be presumed that the gene responsible for the syndrome arose as a new mutation in his germinal epithelium.

The pedigree of family T is also a good illustration of the very varied phenotypic expression of this gene: there are 6 individuals with lip pits only; 1 with pits and bilateral cleft lip; 2 with pits, bilateral cleft lip and palate; 1 with pits, unilateral cleft lip and palate; 1 with unilateral cleft lip and palate (no pits); and 2 with cleft palate only. The index case of family A has another variant: she has lower-lip pits and cleft palate but no cleft lip. The information about family A is incomplete but is also consistent with the autosomal-dominant pattern of inheritance.

The most important fact about the presence of lower-lip pits is their significance in genetical counselling. The parents of a child with cleft lip and/or cleft palate frequently ask about the risk of the anomaly recurring in subsequent children. In the usual case of cleft lip and/or cleft palate, the recurrence risk is low—about 3 - 6%. However, if the cleft is associated with lower-lip pits, or if there are near relatives with lower-lip pits, the risk of its recurrence is greatly increased; depending on the circumstances it may be from 20 to 50%.[7] Table I summarizes the empirical risks of recurrence of these anomalies in different circumstances and combinations. It will be clear that it is essential to look for the presence of lower-lip pits in the patient and to ask about their presence in other relatives before making a genetical prognosis in respect of cleft lip and cleft palate. It is our practice, when counselling in these cases, to show the parents a photograph of lower-lip pits and to ask whether they have observed these in any other relative.

TABLE I. RISK OF CLEFT LIP AND/OR CLEFT PALATE AND/OR LIP PITS IN CHILDREN OF AFFECTED PARENTS

	Percentage of children affected with:	
Lesion in parents	*Lip pits and/or cleft*	*Cleft with or without lip pits*
Cleft lip ± cleft palate	—	3
Cleft palate only	—	6
Lip pits only[7]	46	22
Lip pits and cleft[7]	60	39
Cleft only but lip pits in other first-degree relative[7]	48	30

The two families who are the subject of this report were found during the course of a survey of 398 cases of cleft lip and/or palate in Cape Town.[6] Altogether this series included 5 individuals with lower-lip pits as well as clefts; hence 1 in 80 cases (1·2%) of clefts of the lip and/or palate were associated with lower-lip pits. This is rather higher than the incidence calculated by Cervenka *et al.* from an analysis of 6 series totalling 8,524 cleft

patients: 57 of these had lower-lip pits, giving an incidence of 1 in 150 (0·66%).[7] However, in these 6 series the care with which the presence of lip pits was recorded was very variable: in some the data were derived from routine hospital notes; others were specifically examined by the investigators. It is not surprising, therefore, that the incidence of pits varied in the 6 series from 0·37 to 1·81/100 patients with clefts. Accordingly, our estimate of 1·2% can be taken as a reasonable reflection of the true incidence of lower-lip pits in patients with clefts.

In Cape Town, the incidence of cleft lip and/or palate is much the same as in Europe and North America, namely 1·6/1,000 births, or 1 in 625 births.[10] Hence we can estimate the incidence of lower-lip pits accompanying cleft lip and/or palate to be about 1 : 625 × 1 : 80, which is about 1 in 50,000 births. However, 20 - 30% of cases of lower-lip pits are not associated with clefts,[7] and so the over-all incidence of these pits (with or without clefts) is greater and may be about 1 in 35 - 40,000 births.

In the aetiology of the usual kinds of cleft lip and palate (i.e. without lower-lip pits) complex hereditary influences are involved, but there is no doubt about the importance of environmental factors as well. In the special case of the syndrome of clefts with lower-lip pits the hereditary factor is of greatest importance, while environmental factors are significant as a possible explanation of the striking differences in phenotypic expression observed even within a single family. These differences could be due to the interaction of the mutant gene with other genes, or they could be due to modifying environmental influences. In this connection, a pair of probably monozygotic twin girls reported by Cervenka *et al.* are most instructive.[7] Both had lip pits, but only one had a cleft lip. If the syndrome were entirely due to genetical factors, then these genetically identical girls should have been phenotypically identical; only the effect of exogenous influences during early foetal life can account for the difference between these 2 girls. If similar partial discordance for the syndrome can be shown in other pairs of monozygotic twins, valuable insight will be obtained into the interplay of inherent and exogenous factors in the pathogenesis of cleft lip and cleft palate.

Pits of the lower lip occur occasionally in 2 other rare hereditary syndromes. Thus, Gorlin and Psaume have recorded their presence in a single case of the oral-facial-digital syndrome.[11] This syndrome is probably caused by an X-linked gene with dominant effect, and the common manifestations are hyperplasia of the frenula, cleft palate and cleft tongue, hypoplastic nasal and malar bones, brachydactyly, syndactyly, and mental subnormality. There is no resemblance genetically or morphologically between this syndrome and the one which we are reporting. Lower-lip pits have been found consistently in the even rarer popliteal-web syndrome.[12] This is probably the manifestation of an autosomal gene with dominant effect, and the important features are cleft lip and palate, oral webbing, popliteal webbing, toenail dysplasia and variable anomalies of the extremities and genitalia. The presence of these non-oral manifestations clearly distinguishes the popliteal-web syndrome from the relatively less complex syndrome of lower-lip pits with cleft lip and/or palate.

Finally we have to consider the pathogenesis of the lip pits, cleft lip and/or palate syndrome. According to the hypothesis of Warbrick *et al.*,[1] lower-lip pits are the result of a failure of obliteration of the lateral mandibular sulci before the 12-mm. embryonic stage: that is, during the fifth and sixth week of foetal life. This is about the same time that fusion of the lateral maxillary processes and the medial nasal processes should occur, and it is the failure of the fusion of these processes which results in cleft lip. However, fusion of the maxillary palatal processes which form the palate takes place rather later: usually after the eighth week. If there is already a cleft lip, failure of palatal closure could be explained as a simple mechanical consequence of this; but it does not explain those cases of cleft palate without cleft lip, nor those cases of isolated cleft palate which occur in the absence of both lower-lip pits and cleft lip (e.g. cases IV.5 and IV.6 of family T). We can only speculate that the production of these 3 anomalies is the result of a defect in the embryonic organizer system concerned with the development of the lips and palate and that this defect, in turn, is the result of a mutation in one of the autosomal genes concerned in the regulation of that organizer system. The phenotypic expression of the trait will presumably depend on exogenous factors in the early foetal environment which influence the activity of that organizer system.

SUMMARY

The syndrome of congenital pits of the lower lip with cleft lip and/or cleft palate is the manifestation of an autosomal mutant gene with dominant effect, a high degree of penetrance, and variable phenotypic expression. If a person has a cleft lip and/or cleft palate accompanied by congenital pits of the lower lip, or with a history of such pits in a near relative, the risk of having a child with an oral cleft may be as high as 40%. This is in striking contrast to the situation in the usual case of cleft lip and/or palate without lower-lip pits, where the risk of having a similarly affected child is only 3 - 6%. Two pedigrees of Cape Coloured families are presented to illustrate the clinical and genetical features of this syndrome.

The work of the Comprehensive Medicine Group is supported by a grant from the National Institutes of Health of the US Public Health Service (HE 06267). Additional funds for the present investigation were provided by a University of Cape Town Staff Research Grant (C. L. Herman Bequest).

REFERENCES

1. Warbrick, J. G., McIntyre, J. R. and Ferguson, A. G. (1952): Brit. J. Plast. Surg., **4**, 254.
2. Abramson, P. D. (1952): Surgery, **31**, 761.
3. Radcliffe, W. (1940): Brit. J. Surg., **28**, 329.
4. Demarquay, J. N. (1845): Gaz. méd. Paris, **13**, 52.
5. Fogh-Andersen, P. (1943): Tandlaegebladet, **47**, 411.
6. Van der Woude, A. (1954): Amer. J. Hum. Genet., **6**, 244.
7. Cervenka, J., Gorlin, R. J. and Anderson, V. E. (1967): *Ibid.*, **19**, 416.
8. Watanabe, Y., Hakushi, I., Otake, M. and Tomida, K. (1951): Oral Surg., **4**, 709.
9. Gordon, H., Davies, D., Friedberg, S. and Botha, V. (1969): S. Afr. Med. J., **43**, 1267.
10. Horner, R. and Lanzkowsky, P. (1966): *Ibid.*, **40**, 171.
11. Gorlin, R. J. and Psaume, J. (1962): J. Pediat., **61**, 520.
12. Hecht, F. and Jarvinen, J. M. (1967): *Ibid.*, **70**, 927.