TREATMENT OUTCOME IN CLEFT LIP AND PALATE: ISSUES AND PERSPECTIVES

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ABSTRACT: In the last 40 years, great progress has been made toward a better understanding of many aspects of the cleft lip and palate defect, but there is still a long way to go before there is agreement on the optimal treatment procedures. With regard to the primary operations, it can be stated, in a somewhat simplified form, that there are two main schools of thought in cleft treatment. One advocates early closure of the lip and palate, a procedure which imparts a high priority to early speech function. The other recommends delayed closure of the hard palate, thereby according a high priority to the growth of the maxilla. A number of intercenter and multicenter studies have been carried out recently in an effort to elucidate which procedures give the best result, both esthetically and functionally. The results are ambiguous, and this has led a number of researchers to suggest that the randomized clinical trial is the only way to resolve the ambiguity. The fact that it has proved difficult to identify the optimal procedures in the field of cleft lip and palate treatment need not only be due to a less than optimal research design: a contributory factor might also be the great variability in craniofacial morphology and in the response to treatment in patients who have exactly the same cleft lip and palate diagnosis. Intensive research has made it possible to state categorically that clefts occur due to many different factors in an interplay between genetics and environment. Therefore, it is not likely that a single gene can be responsible for clefting. Since scar tissue presents many problems—for instance, impairment of growth—the reduction or prevention of scar formation has long been a desirable goal. The discovery that a fetus can heal without scar formation has led to many animal experiments. The timing of the surgical intervention on fetuses is critical, since late-stage fetuses heal with adult-like scarring. There are still many unsolved problems connected with fetal surgery, and at present prenatal surgery for repair of cleft lip and palate is not ethically defensible in humans. On the other hand, it appears that there are considerable possibilities for the reduction of human scarring after surgery with the introduction of various wound-healing medications.

Key words. Cleft lip and palate, randomized clinical trials, high-volume operators, fetal surgery, wound healing.

Introduction

Despite considerable progress in the treatment of children with non-syndromic cleft lip and palate, there is still no unanimous agreement as to the optimal treatment method. In general, it is agreed that the primary operations as to type and timing are very important for the subsequent growth and development of the palate and face. In brief, it can be stated that there are two main schools of thought as to the timing of cleft lip and palate surgery. One advocates an early closure of both lip and palatal clefts. The claimed advantage is the early re-establishment of speech and chewing function, and early palatal development (Malek et al., 1984). The other school advocates delayed surgical hard palatal closure so that growth of the face is accorded the highest priority. The soft palate is often closed within the first year of life (Hotz and Gnoinski, 1979; Friede et al., 1991; Lilja et al., 1996).

The difficulty in evaluating these two concepts of treatment is that many years must elapse before the results of the treatments can be evaluated with any certainty. Ideally, the patient should be past puberty before any final evaluation of the two treatments can be made. Here too, one is faced with problems that complicate an accurate outcome assessment. For instance, over the years, a long series of operations, orthodontic treatments, prosthetic reconstructions, etc., may also have had a decisive influence on the development and appearance of the face, so that in a patient at the age of 17, it can prove difficult to evaluate the results attributable only to early primary operations.

An additional difficulty is that of evaluating the esthetic results of a lip or a nose operation (Asher-McDade et al., 1992). This means that it is necessary to incorporate many parameters into the evaluation of treatment results. It is also important to be aware of who is evaluating the treatment outcome of a center. Clearly, it should not be staff members from the center involved in the treatment.

In recent years, much attention has been paid to the evaluation of treatment methods and research method-
TABLE 1
Treatment Protocols (Complete Unilateral Cleft Lip and Palate) from the Three Participating Centers in the Eurocleft Study with Good Treatment Outcome

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Presurgical orthopedics</td>
<td>Lip closure (Millard, Skoog)</td>
<td>Lip closure (Millard)</td>
</tr>
<tr>
<td></td>
<td>(Hotz type)</td>
<td>Lip closure (Tennison)</td>
<td>Ant. palate closure (vomerplasty)</td>
</tr>
<tr>
<td>3 months</td>
<td>Lip closure (Von Langenbeck, Perko Wardill, Kriens)</td>
<td>Ant. palate closure (vomerplasty)</td>
<td>Palatal closure (modified von Langenbeck)</td>
</tr>
<tr>
<td>9 months</td>
<td>Soft palate closure</td>
<td>Palatal closure (Wardill pushback)</td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td></td>
<td>Bone grafting</td>
<td>Bone grafting</td>
</tr>
<tr>
<td>22 months</td>
<td></td>
<td>Hard palate closure</td>
<td></td>
</tr>
<tr>
<td>9 years</td>
<td>Bone grafting</td>
<td>Bone grafting</td>
<td>Bone grafting</td>
</tr>
</tbody>
</table>

TABLE 2
Treatment Protocols (Complete Unilateral Cleft Lip and Palate) from the Three Participating Centers in the Eurocleft Study with Poor Treatment Outcome

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>D</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Presurgical orthopedics</td>
<td>Presurgical orthopedics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(extra-oral strapping)</td>
<td>(T-traction)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>Lip closure (Variety of methods and timing)</td>
<td>Lip closure (Variety of methods and timing)</td>
<td>Lip closure (Modified Skoog, Tennison-Randall and bone grafting)</td>
</tr>
<tr>
<td>12 months</td>
<td>Palatal closure (Variety of methods and timing)</td>
<td>Palatal closure (Variety of methods and timing)</td>
<td>Palatal closure (Veau-Wardill-Kilner)</td>
</tr>
<tr>
<td>9 years</td>
<td>Bone grafting</td>
<td>Bone grafting</td>
<td>Bone grafting only in cases with failure of primary bone graft</td>
</tr>
</tbody>
</table>

There is general agreement that the diagnosis and management of the complex nature of cleft lip and palate individuals require the expertise of a multidisciplinary team to treat the patients. This has been recommended by the American Cleft Palate Association in a consensus report ("Parameters", 1993) on recommended practices for patients with craniofacial anomalies. Furthermore, a growing body of evidence has shown a close association between the quality of outcome and the availability of high-volume operators in a centralized system (Devlin, 1990; Shaw et al., 1992a,b, Williams et al., 1994, 1996, Rintala and Haapenen, 1995).

Approximately two of every 1000 children are born with a cleft, and this figure covers many cleft subtypes. Successful primary repair of complete clefts requires technical ology in cleft lip and palate. The earlier tendency for journals of plastic and reconstructive surgery to publish a predominance of case reports and few articles with statistical analyses (Velanovich et al., 1987; Roberts et al., 1991; Shprintzen, 1991) is no longer as pronounced.

Even though cleft lip and palate treatment is often carried out in centers, there are great differences in the numbers of patients at the individual centers, and some of these centers have so few patients that sample selection is a problem (Roberts et al., 1991). It is not possible for small centers, within a foreseeable number of years, to obtain a sufficient number of patients with the same cleft diagnosis (Shprintzen, 1991), and the results of studies with disparate samples are not of very great value.

Finally, much attention has been paid in recent years to research methodology in the field of treatment evaluation. Should studies be retrospective or prospective? Are there advantages with intercenter comparisons, or are multicenter comparisons preferable? Many are of the opinion that randomized, prospective clinical trials are the only appropriate study designs (Shaw, 1995). Others consider randomized, prospective clinical trials to be unethical (Berkowitz, 1995).

Issues

Organization and Management of Care

There is general agreement that the diagnosis and management of the complex nature of cleft lip and palate individuals require the expertise of a multidisciplinary team to treat the patients. This has been recommended by the American Cleft Palate Association in a consensus report ("Parameters", 1993) on recommended practices for patients with craniofacial anomalies. Furthermore, a growing body of evidence has shown a close association between the quality of outcome and the availability of high-volume operators in a centralized system (Devlin, 1990; Shaw et al., 1992a,b, Williams et al., 1994, 1996, Rintala and Haapenen, 1995).

Approximately two of every 1000 children are born with a cleft, and this figure covers many cleft subtypes. Successful primary repair of complete clefts requires technical
skills that are unlikely to be achieved with infrequent practice. For instance, a surgeon who receives 40 new cleft cases a year will, on average, repair a complete unilateral cleft once a month and a complete bilateral cleft every three months. Valid threshold numbers can never be calculated precisely, but a steering group from the UK (WC Shaw et al., 1996) has recommended a minimum case load of 30 new cases per operator per year for primary cleft surgery. This applies also to the orthodontic treatment of patients presenting with clefts, where the same steering group recommends that the orthodontic treatment should be performed only by experienced orthodontists with extended cleft lip and palate training and with a minimum intake of 30 new cases per year. At the American Cleft Palate-Craniofacial Association's 49th Annual Meeting in Portland, Oregon, in 1992, it was reported that, of the 237 known craniofacial teams in the world, only 13.4% had admitted more than 100 new patients a year (Strauss, 1992). In a questionnaire study in the UK, Pigott (1992) found that of 71 plastic surgeons treating cleft lip and palate patients, the majority treated fewer than 20 new cleft patients a year.

In 1984, at a symposium in Zürich, Switzerland, representatives of 36 centers from around the world were asked to describe their treatment procedures. The responses were very different. As a clinician, it can be difficult to select an optimal method of treatment, due to the lack of well-documented clinical studies of treatment outcome. That was the background for organizing the European Cleft Lip and Palate Research Group (EUROCLEFT), which was formed in 1986 with the aim of evaluating treatment outcomes at the six participating centers, particularly on treatment outcomes in complete unilateral cleft lip and palate.

EUROCLEFT published its first results in 1992 (Asher-McDade et al., 1992; Mars et al., 1992; Mølsted et al., 1992; Shaw et al., 1992a,b; Grundwell, 1993). These authors pointed out that it was important to evaluate treatment outcomes in a multifaceted way. In their studies, the following aspects were evaluated: craniofacial morphology, dental arch relationships, nasolabial appearance, and speech. The results from the EUROCLEFT study revealed that three centers emerged with almost equally good results for patients at nine years of age. Their treatment protocols are listed in Table 1. Three centers had inadequate treatment outcomes; their treatment protocols are listed in Table 2.

It is apparent that different treatment protocols can achieve equally good results. Two of the centers in Table 1 practiced closure of the lip and the most anterior part of the palate in patients at age three months, while the rest of the palate was closed in patients at age 18-22 months (centers B and E). The third center (A) did not close the hard palate until the patient was nine years of age. The treatment outcome at the other three centers in the study was evaluated as poor in all aspects studied except for speech outcome, where there were no differences among the centers (Grundwell, 1993). In two of the three (C and D), the surgical management varied, and many different surgeons were involved in the primary procedures. In the third center (F), the surgical timing was very similar to that of two of the centers with a good outcome (B and E). The main difference between the center with poor treatment outcome (F) and the other two centers was that center F practiced presurgical orthopedics and primary bone grafting, procedures which that center has now abandoned.

Figs. 1 and 2 show the shape of the palate and the occlusion of two patients operated on at centers A and F.
respectively. The two cases have been chosen for illustrative purposes because they are typical for their respective centers. There is a distinct difference in the amount of scar tissue in the two patients, and their occlusion also differs markedly. The impeded maxillary growth seen in the patients from center F resulted in a large number of mandibular overjets in that group (Mars et al., 1992).

It must be pointed out that, so far, results have been published from only the first part of the study, when the patients were nine years old. The patients have been followed for eight years at five of the centers, and the results of the new evaluations were presented at the 8th International Congress on Cleft Palate and Related Craniofacial Anomalies in Singapore in 1997. The same ranking of centers as described for patients at nine years of age still applied for patients at the age of 17 years (Shaw, 1997).

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Iowa Non-recession (n = 8)</th>
<th>Iowa Recession (N = 1.5)</th>
<th>Oslo (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary protrusion angle</td>
<td>79.1</td>
<td>75.0</td>
<td>77.5</td>
</tr>
</tbody>
</table>

*BCLP = Bilateral cleft lip and palate; s = sella turcica; n = nasion; ss = subspinale (A point). Recession group: surgical setback of the premaxilla.

Bardach et al. (1992) evaluated their treatment outcome in bilateral cleft lip and palate with a multidisciplinary approach. The evaluation was made by a plastic surgeon, an orthodontist, an otolaryngologist, and a speech pathologist. Unfortunately, there were few children in the test group; however, this is the first reported attempt at a multidisciplinary evaluation of a center's treatment management of complete bilateral cleft lip and palate with no associated malformations. A comparison of the craniofacial morphology of patients treated by the Oslo team (Semb, 1991) and the Iowa team is shown in Table 3. The treatment procedures are listed in Table 4. The surgical setback of the premaxilla in one of the Iowa groups (Recession group) resulted in a retrognathic maxilla. The Iowa non-recession group seemed to have good maxillary development, but there were very few patients in that group. The Iowa team lacked a defined treatment protocol, and it is therefore difficult to draw any conclusions as to which treatment procedure is the best.

Other multicenter studies have been conducted in recent years (Ross, 1987; Friede et al., 1991; Brattström et al., 1992; Enemark et al., 1993). Preliminary results from the Scandinavian multicenter study of children born with complete unilateral cleft lip and palate (Friede et al., 1991; Enemark et al., 1993) indicated that delayed closure of the hard palate at the time of secondary bone grafting, usually at nine years of age, seemed to reduce the risk of impaired maxillary growth compared with earlier palatal closure. Model analysis, with a modified Glosion Yardstick procedure, an index for registrations of malocclusion, was used in the study (Friede et al., 1991). Unfortunately, there was no mention of any method error analysis, nor was it stated whether the test was a blinded one. This is a critical point because of the potential bias that therapists from the individual centers may have had in evaluating their own results objectively. It has been stated (Dorf and Curtin, 1982) that good speech requires palatal closure in infants between six and nine years of age.
TABLE 4

<table>
<thead>
<tr>
<th>Treatment Protocol (Bilateral Cleft Lip and Palate) for the Iowa Team and the Oslo Team</th>
<th>Oslo</th>
<th>Iowa</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>Lip closure:</td>
<td>Lip closure:</td>
</tr>
<tr>
<td></td>
<td>Two-stage straight line</td>
<td>Triangular flap</td>
</tr>
<tr>
<td></td>
<td>Ant. palate closure:</td>
<td>Millard repair</td>
</tr>
<tr>
<td></td>
<td>Vomerplasty</td>
<td>Straight line closure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Veau repair</td>
</tr>
<tr>
<td>18 months</td>
<td>Palatal closure:</td>
<td>Palatal closure:</td>
</tr>
<tr>
<td></td>
<td>Von Langenbeck</td>
<td>Two-flap palatoplasty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Four-flap Wardill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kilner</td>
</tr>
<tr>
<td>5 years</td>
<td>'Surgical repositioning with bone grafting when premaxilla is severely displaced.</td>
<td></td>
</tr>
<tr>
<td>9 years</td>
<td>Bone grafting</td>
<td>Bone grafting</td>
</tr>
<tr>
<td>9 years and older</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Fifteen out of 23 patients in the Iowa group had a premaxillary reposition with bilateral bone grafting.

months of age. Speech evaluation of the patients in the Göteborg group (Lohmander-Agerskov et al., 1997) revealed some speech problems, but the lack of a control group of children with early closure of the hard palate makes it difficult to interpret the speech results.

The Zürich Approach (Hotz et al., 1986) has a long tradition of practicing delayed closure of the hard palate. Adherents prefer to leave the hard palate open until the child reaches the age of five years. An important objection to delayed palatal closure has been that the residual cleft could cause the patient considerable problems: In addition to speech problems, these children could also experience food regurgitation. The potential impact of having a residual cleft that was not closed until the age of five years was studied by means of a questionnaire (Gnoinski and Stäger, 1997). Ten percent of the parents considered the residual cleft as a considerable discomfort to their children.

It has been stated that a significant amount of spontaneous narrowing of the hard palate cleft occurs in children up to five years of age (Hotz et al., 1986). The change in the residual cleft in the hard palate after repair of the soft palate was studied by the analysis of dental casts, post-operatively, from children ages 1 1/2 to seven years (Owman-Mall et al., 1997). The conclusion was that it is not possible, at present, to predict how the residual cleft will change. Accordingly, it is difficult to have a standard surgical program for closing the residual palatal cleft, since there are great individual variations in the size of the residual cleft and in the associated problems, even in children with the same primary cleft diagnosis.

A controversial article in the Cleft Palate Craniofacial Journal in 1996, dealing with cleft palate closure in the neonate (Denk and Magee, 1996), will be briefly discussed here. The purpose of closing the cleft of the lip and palate shortly after birth is, according to the authors, based on the wish to "normalize muscular development and to improve speech". The aim of the study was not, as might be expected, to document better speech development, but merely to determine if the procedure is "relatively safe for the child". Since the center concerned has practiced this surgical procedure since 1991, the least one would expect is that the center could present some early speech results as well as an evaluation of palatal shape and size by analyzing casts to provide an early indication as to whether such a radical procedure impairs growth. Justified criticism of this study has also been raised by, for example, Berkowitz (1996a), who points out that this is yet another undocumented paper stating that this new method is a better way to close the palatal cleft. According to Berkowitz, history is full of examples of such "hit-and-miss approaches to a complex biological problem".

A search of all issues of the Cleft Palate Craniofacial Journal from 1994 to October, 1997, revealed that there were 21 clinical trials published during this period (Table 5). Thirteen of the studies were single-center studies with, for the most part, very small test groups. Only two of the clinical studies investigated more than one aspect of treatment outcome. This review also showed that the main emphasis was on cephalometric studies (Table 6).

It is still disappointing that so few intercenter and multicenter studies are being conducted, because they are extremely valuable in assessing the outcome of primary surgery together with the other major components

| TABLE 5 |
| Clinical Trials Reported in the Cleft Palate Craniofacial Journal from 1994-1997 (November, 1997, not included) |
|---|---|---|
| | Retrospective | Prospective | RCCT* |
| Single center | 12 | 1 | - |
| Intercenter | 8 | - | - |
| Multicenter | - | - | - |

* RCCT = Randomized controlled clinical trials.
TABLE 6
Clinical Trials Reported in the Cleft Palate-Craniofacial Journal from 1994-1997 (November, 1997, not included)*

<table>
<thead>
<tr>
<th></th>
<th>Cephalometry</th>
<th>Dental Casts</th>
<th>Photo/video</th>
<th>Phonetics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single center</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Intercenter</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Multicenter</td>
<td>-</td>
<td>-</td>
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</table>

*Only two of the above-listed clinical trials evaluated more than one aspect.

of the treatment program at the respective centers, provided that the entry procedures for the study are equivalent in all the participating centers. There will always be some limitations in multicenter studies, though. It will be difficult to single out one key factor as the reason for a center's good treatment outcome, just as it will be difficult to single out a key factor as the reason for a center's lack of success in treatment outcome (Mølsted et al., 1993a).

Randomized Prospective Clinical Trials

Definition: Experiment in which individuals are randomly allocated to receive or not receive an experimental preventive, therapeutic, or diagnostic procedure and then followed to determine the effect of the intervention. (Haynes et al., 1996)

There has been considerable debate in clinical research circles about randomized prospective clinical trials. Again, there has been no agreement as to what path to take. For progress to be made, it has been stated (Roberts et al., 1991; Shaw, 1995) that the only way to find the optimal surgical procedures has been via randomized controlled clinical trials, and that retrospective studies have not been suitable for identifying the optimal surgical procedures. Berkowitz (1995) remarked that the concept of prospective randomized clinical trials is unethical for a number of reasons. In a randomized clinical trial, the surgeon is forced to disregard the great variability within the same cleft type and perform a standard surgical treatment on all cleft patients based on the assumption that all individuals, even with diverse craniofacial morphology and facial growth patterns, regardless of size, shape, and degree of osteogenic deficiency, will react in the same manner to a standard operation. Furthermore, differences in surgical skill constitute another significant variable, even in a prospective clinical trial study, since one cannot expect all surgeons to be equally skilled in all procedures. The surgeon may be forced to perform a procedure he/she does not favor or finds unjustified. This is unethical if he/she favors another procedure and fails to tell the patient. Schulz et al. (1995) and Schulz (1996) have pointed out that there have been problems with randomization in prospective clinical trials. They assessed the quality of randomization of 250 controlled trials and found that trials in which the allocation sequence had been inadequately concealed yielded larger estimates of treatment effects than trials in which the authors reported adequate concealment. The authors attempt to explain the abovementioned phenomenon, which has also been reported by others (Chalmers et al., 1983), by stating that investigators intellectually grasp the need for randomization in a clinical trial, but they are subject to many conflicting interests that could lead to bias in the outcome measures in the course of the trial. Perhaps they "know" the more effective treatment, so they may want certain patients to benefit, or they may want the results of the study to reveal what they believe to be valid. The empiric evidence that many inadequately implemented randomized controlled clinical trials are biased has led to new guidelines (CONSORT Group, 1996). The purpose of the guidelines is to improve the quality of reporting of randomized controlled trials.

The ethical problems associated with prospective randomized or non-randomized clinical trials have not yet been resolved. Palter (1996) argues that the modern clinical trial is a form of human experimentation. There is a long history of disregard for the individual rights of patients in this context, and special attention must be paid to the ethical guidelines for these studies. There are also unresolved problems connected with the participation of newborns in randomized clinical trials (Field, 1997). Furthermore, an unresolved problem with randomized controlled trials is that many patients refuse to participate in trials in which the treatment is decided by drawing lots. This has caused Zelen (1979) to propose an alternative design for randomized controlled trials. The proposal, pre-randomization, which has also been referred to in an editorial in The Lancet (Editorial, 1995), involves, in brief, that formal written consent must first be obtained after randomization, and only from patients randomized to receive extraordinary treatment, and not those receiving conventional treatment. This proposal is itself not without ethical problems, because the patients would be randomized without their or their parents' permission (Post, 1979; Horton, 1994; Meran, 1995; Field, 1997). Whether parents should be informed of a trend or of preliminary results in the study in which they or their children are asked to participate is yet another ethical issue, which emphasizes the crucial difference between...
randomized clinical trials and ordinary treatment decisions (Meran, 1995).

In conclusion, it appears to be premature to advocate or prescribe a specific surgical protocol as being superior to all others. There are probably many ways of achieving a good result, and the question is whether it is realistic to aim, in the future, for a single concept of treatment, taking the great variability in cleft lip and palate treatment into account.

Variability in Clefts

Even in children born with the same type of cleft and treated by identical treatment procedures, the treatment outcome can differ very considerably, because a great variability in craniofacial form and cleft form is observed in persons born with a cleft lip and palate.

The causes of this variability may lie in the origin of cleft lip and palate, which probably arises in different ways. Spranger et al. (1982) classified errors of morphogenesis into five categories (Fig. 3). In this system, clefts of the lip and palate are classified as a malformation. The malformation is defined as a morphologic defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process. Intrinsic means that the developmental potential of the organ—its anlage (primordium)—was abnormal. According to this definition, cleft lip and palate arise as a result of a primary insufficiency of tissue involved in the formative facial development.

A disruption is defined as a morphological defect of an organ, part of an organ, or a larger region of the body, resulting from the extrinsic breakdown of or interference with an originally normal developmental process. This means that the development is normal in the beginning, but is disturbed at a critical point—for instance, by an external insult. A sporadically occurring cleft lip and palate probably have a stronger element of environmental factors, and, accordingly, some of the sporadic clefts could be classified as disruptions. Even though a disruption is not hereditary, it is possible that inherited factors can predispose to it.

It is conceivable that a cleft arising as a result of an intrinsically abnormal developmental process may be difficult to treat because of the primary tissue insufficiency. A cleft that has arisen as a result of extrinsic breakdown or interference with an originally normal developmental process will probably not exhibit the same tissue insufficiency.

The factors determining the variability in cleft lip and palate can be classified under the following three main headings: intrinsic, adaptive, and induced.

- Intrinsic factors include the circumstances leading to the formation of the cleft in the early embryonic period.
- Adaptive factors arise in connection with clefts: Once the cleft is there, subsequent growth will continue to be affected by it.
- Induced factors include the sequelae of cleft treatment, with surgery as the dominant factor.

**Intrinsic aberrations**

The evidence for the existence of intrinsic morphological aberrations is still uncertain. The cranial base is broader and more obtusely angled in infants with complete clefts of lip and palate (Fig. 4) (Mølsted et al., 1995). It has also been pointed out that the spheno-occipital synchondrosis in newborns with complete clefts is broader than in newborns with a minor, incomplete cleft lip (Mølsted et al., 1993b). Since the spheno-occipital synchondrosis is all that remains of the early chondrocranium in a newborn, and since the cranial base is developed from the early chondrocranium (Fig. 5), the altered cranial base in newborns with complete clefts might be an example of an intrinsic aberration. However, to clarify the role of intrinsic factors in facial morphogenesis, further embryological studies of fetal development, in particular of cleft lip and palate fetuses, are necessary.

**Growth adaptation**

Asymmetry of the anterior part of the maxilla with an upward tilt of the premaxillary region and a distortion of the nasal septum are constant findings in patients with complete unilateral cleft lip and palate (Mølsted and Dahl, 1990). This asymmetry is seen in newborns with complete unilateral cleft lip and palate even before the primary operations. Fig. 6 shows a newborn with complete unilateral cleft lip and palate. The Fig. depicts the deviation of the nasal septum and that of the entire premaxilla toward the non-cleft side. Growth adaptation has been suggested as a possible explanation for this deviant growth pattern, which continues postnatally (Latham, 1969; Chierici et al., 1973a,b).

**Induced aberrations**

The induced aberrations are the only ones we can affect at present. Surgery is the induced aberration that has attracted the most attention in the literature and is also the main topic of this article. When the initial surgical treatment is planned, greater emphasis should be placed on an individually based course of treatment instead of using standard procedures as is being done at present. This calls for considerable knowledge of each individual's craniofacial growth and development, and should be a target area for research in coming years.

**Perspectives**

**Genetic factors—Environmental factors**

Twin studies have indicated that genetic factors play a major role in the etiology of both cleft lip/cleft palate and

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**Figure 5.** A schematic illustration of the bones in the cranial base that are derived from the early chondrocranium (i.e., the ethmoid, the body of the sphenoid, the lesser and greater wings of the sphenoid, the base of the occipital bone and otic capsule, and the petrous portion of the temporal bone). (top) Sagittal plane; (bottom) axial plane.
cleft palate alone, but environmental influences cannot be ruled out (Christensen and Fogh-Andersen, 1993a,b; Bailey et al., 1995; Christensen et al., 1996). Christensen et al. (1996) have shown that changing location of residence did not decrease the frequency of recurrence of facial clefts in later-born sibs. But change of partner significantly reduced the risk of recurrence. Environmental factors, however, also play a decisive role. There is, for instance, considerable evidence that maternal smoking is a contributing factor in the etiology of a substantial number of cleft cases (e.g., Ericson et al., 1979; Khoury et al., 1989; Werler et al., 1990; GM Shaw et al., 1996; Källén, 1997). Furthermore, if both parents smoke, risks are generally greater than if only the mother smokes. Two- to three-fold higher risks for cleft lip ± cleft palate and isolated cleft palate were observed when both parents smoked ≥ 20 cigarettes a day (GM Shaw et al., 1996). But even if the evidence suggests that a connection between cleft lip/palate and smoking exists, this association may not be directly causative and could be due to confounding factors. Since a positive correlation between smoking and drinking may exist, alcohol could be a confounding factor of particular interest. Two studies have investigated this association between smoking and drinking, and neither study changed the calculated odds ratios for maternal smoking (Khoury et al., 1989; Werler et al., 1990).

Transforming growth factor alpha (TGFα) is a secretory, protein-binding epidermal growth factor receptor, and it has been localized to palatal epithelium prior to and during palatal closure (Dixon et al., 1991). Non-population-based genetic studies have identified a two- to five-fold increased risk for cleft lip and palate among individuals with the uncommon allele for TGFα (Shiang et al., 1993). Infants with clefts have been examined to test for associations between maternal exposures such as drug use and cigarette smoking, genetic markers and clefts (Hwang et al., 1995; GM Shaw et al., 1996). Both studies showed that genetic factors in the developing fetus and environmental factors due to maternal smoking may act jointly to increase an individual's risk of clefting. Cigarette smoking may influence embryonic development, inter alia, via embryonic hypoxia. Two common

Figure 6. Frontal radiograph of a newborn child with complete unilateral cleft lip and palate (left). Note the displacement of the maxilla toward the non-cleft side (arrow). On the right is a frontal radiograph of a newborn child with a minor incomplete cleft of the lip. No asymmetry is seen.
agents from cigarette smoke, carbon monoxide and nicotine, can produce hypoxia (Longo, 1982), and hypoxia has experimentally been shown to induce clefts (Bronsky et al., 1986; Johnston and Bronsky, 1995).

Several studies have discussed the possibility of reducing the recurrence of clefts by prophylactic intake of multivitamins, including folic acid. Tolarova and Harris (1995) have linked a reduced recurrence of clefts after peri-conceptional multivitamin and folic acid supplementation. The strongest effect was found in probands with unilateral clefts. This conflicts with Hayes et al. (1996), who could not demonstrate a protective association between the peri-conceptional use of folic acid supplement and the risk of clefts.

**Gene Therapy**

Generally speaking, gene therapy holds great promise. This may not be the case in cleft lip and palate because of the complex interplay between many genes and environmental factors (Melnick, 1992).

It has been mentioned that a distinction should be made between corrective genetic therapies and molecular diagnosis (Wagner, 1997). While it is true that molecular diagnosis is capable of being utilized for eugenic purposes (Albin, 1996), this cannot be said to apply to corrective genetic therapies. This might be considered as a natural evolution in pharmaceutical technology, although there are important differences between traditional drug development and gene therapy development. Gene therapy as a drug cannot be considered from a eugenic viewpoint, because the intention of a gene therapy is basically to help a patient who has a disease trait.

There are several ethical problems involved in gene therapy, problems which have been highlighted with China’s Maternal and Infant Health Care Law. There, people diagnosed with a genetic disease of a serious nature are asked to use long-term contraceptive measures or be sterilized (Eugenic Law, 1995; Editorial, 1997).

Albin (1996) foresees that the temptation to ensure a child’s optimum “genetic health” will prove irresistible to many, that is why it is important to start a debate now so that these fundamental ethical decisions are not left to a handful of individuals.

**Fetal Surgery—“Scar-free” Wound Healing**

The first part of this paper has focused on different surgical procedures and their timing. It has been shown that, in some cleft lip and palate centers, speech is accorded a high priority that leads to an early closure of both the hard and soft palates. Other centers give a higher priority to growth and postpone closure of the hard palate to avoid growth impairment of the maxilla as a result of scar tissue formation. It is obviously difficult to decide on priorities because there are differing opinions on what is most important: speech or appearance? For obvious reasons, there has been much research in recent years into how to avoid formation of scar tissue.

Open fetal surgery in humans is now a reality, and reports indicate that fetal surgery is safe for the mother and that the procedure does not adversely affect subsequent pregnancies. Consequently, it was stated by Harrison et al. (1990) and Longaker et al. (1991) that the intrauterine repair of congenital anatomic lesions might potentially be expanded to include facial clefts. Fetal wounds heal with markedly reduced or no scarring (Longaker and Adzick, 1991). The advantage of fetal wound healing is that, with “scar-free” healing, secondary maxillary growth restrictions would not occur. Several animal models have been developed to test this hypothesis (Hallock, 1985; Sullivan, 1989; Adzick and Longaker, 1991; Kaban et al., 1993). The animal models can be divided into two principal groups: Animals with a generally short gestation period—such as rats, mice, and rabbits—have the disadvantage that fetal manipulation has to be carried out late in gestation, when the postoperative intra-uterine period is short and often after the period of “scar-free” healing has passed. The other group consists of animals with a longer gestation, such as sheep and monkeys, who have a long postoperative intra-uterine period for continued growth and development during the period after lip repair (Hedrick et al., 1996). It must be emphasized that these animal models involve surgically created clefts, because no practical, intrinsic model exists today. In other words, when an artificial cleft is made in a fetus with otherwise normal facial growth potential, one must be cautious in drawing conclusions about the test animal’s postnatal growth after fetal surgery.

Even if it were possible to conduct successful fetal surgery in human cleft fetuses, one would only be affecting the induced factors; the intrinsic factors would not be affected, and the adaptive factors only to a certain extent. The critical developmental period for the primary palate spans the fifth to the seventh weeks of gestational age, whereas the critical developmental period for the secondary palate extends from the end of the sixth week to the eighth week of gestational age (Kjaer, 1989; Kjaer et al., 1993). If one were to affect the adaptive growth factors to prevent secondary growth deformities, the fetal repair would have to be undertaken soon after the development of the primary palate, i.e., at about 10-12 weeks’ gestational age. A correlation exists between the extent of tissue damage and the gestational age at which one has to operate to obtain “scar-free” healing. The greater the extent of tissue damage, the earlier in development one has to operate to obtain “scar-free” healing.

The accuracy of intra-uterine cleft diagnosis is of
major importance before fetal repair of clefts can be considered. A prenatal diagnosis of a cleft was first reported in 1981 by Christ and Meininger, who diagnosed a bilateral cleft lip and palate in a fetus at 28 weeks of gestation. Benacerraf and Mulliken (1993) found, in a retrospective analysis of 32 fetuses diagnosed by ultrasonographic examination as having cleft lip and palate, that the clefts were accurately diagnosed after 16 weeks of gestation as far as complete clefts were concerned. Incomplete cleft lip was not as easy to visualize before the beginning of the third trimester, and cleft lip was identified more easily than cleft palate. Benacerraf and Mulliken (1993) stressed the importance of a careful sonographic examination to identify those fetuses who have isolated cleft lip and palate with no associated malformations. Seventeen of the 32 fetuses had other sonographically detected anomalies, and one fetus, which was thought to have isolated unilateral complete cleft lip, also had vertebral/rib anomalies and died shortly after birth. Stoll et al. (1995), in an evaluation of routine prenatal diagnoses, reported a low detection rate for cleft lip.

Ross and Johnston (1972) have calculated that perhaps one-third of all embryos developing clefts of the primary palate are lost through spontaneous abortion. A striking feature of these abortions is the very high frequency of associated malformations, which means that one should be very cautious not to introduce fetal surgery in the treatment of facial clefts unless there is a very accurate prenatal diagnosis. Furthermore, it must be noted that, basically, one cannot judge the results of cleft repair only by the presence or absence of a scar. Minimizing scarring may be a minor consideration compared with the other stigmata of the cleft deformity. Also, preterm labor in operated fetuses is a major problem (Estes et al., 1992), and it appears, therefore, that it will be a long time before it is ethically defensible to practice fetal repair of clefts in humans (Strauss and Davis, 1990).

In the many experiments involving fetal wound healing, several factors of great importance in the healing mechanism have been reported. Modulation of the growth factor profile of the wound site seems to be a critical therapeutic factor in controlling scarring. For instance, various strategies to reduce the activity of transforming growth factor α (TGF-α), at the wound site have all proved to have anti-scarring effects (Whitby and Ferguson, 1991a,b; Armstrong and Ferguson, 1995). The possibility of the therapeutic reduction of human scarring after surgery is extremely promising (Ferguson et al., 1996). This will also reduce the number of secondary operations due to “scar-related” complications.

Other methods to reduce wound contraction and scar formation have been tried. Most surgical repairs of a cleft in the palate leave areas of denuded bone in the lateral region of the palate. These areas are left open to heal by secondary intention. During the wound-healing process, wound contraction and continuous scar contraction are seen. Wound contraction is considered to be one of the factors causing disturbance in maxillary growth (Kremenak, 1984; Berkowitz, 1999). In both periodontology and dental implantology, various biocompatible membranes have long been used in the oral cavity. The reason for using membranes in connection with the primary cleft palate operations on children is that by implanting a membrane into the denuded areas, it would be possible to obtain a temporary barrier that could prevent scar tissue from attaching to the underlying bone (de Braeck et al., 1995; Fujioka and Fujii, 1997). An important requirement is that the membrane used must be biodegradable, since it would be unacceptable to have to remove the membrane surgically with the risk of causing new scar formation. With the biodegradable membrane, one is faced with another problem, namely, that such membranes are resorbed too quickly. Therefore, further clinical experiments on animals are needed before the effects of these membranes in primary palatal surgery can be evaluated.

**Distraction Osteogenesis**

Distraction osteogenesis is the regeneration of bone between vascularized bone surfaces that are separated by gradual distraction (Aronson, 1994). In craniofacial surgery, distraction osteogenesis has been used in the mandible with good results. The method is technique-sensitive but easily carried out. There is no need for prolonged hospitalization and bone grafting. The complication rate seems to be low, and there may be minimal relapse after treatment (McCarthy et al., 1992).

Hung et al. (1997) have treated 10 patients, aged 7 to 10 years, with cleft lip and palate and severe midface retrusion with distraction osteogenesis. A palatal split was fabricated and attached to the upper jaw. A Le Fort I osteotomy was performed, and the protraction was done by means of a face mask. Advancement of the maxillary segment from 7 to 12 mm could be achieved, but the long-term effect of the early distraction is not yet known.

One of the disadvantages of distraction osteogenesis has been that the expansion devices have been large and external. A variety of new craniofacial devices that are simpler and smaller is currently under development, and it appears that distraction osteogenesis will be used more frequently in the midface and the cranium.

**Concluding Remarks**

It may never be possible to find the optimal treatment method for cleft lip and palate. There is great variability
in craniofacial morphology and in tissue response to treatment, even in children with the same type of cleft. Most likely, there are many ways of obtaining a good treatment result.

Intercenter and multicenter studies are useful methods for evaluating treatment outcome, provided that the inclusion criteria are the same, and that the results are assessed from several perspectives, including craniofacial morphology, occlusion, facial appearance, and speech.

All of the surgical methods used result in the formation of scar tissue, which, to various degrees, inhibits growth in the entire maxillary complex. With the expected advantage of significant reduction in scar formation by utilizing agents presently under investigation, the adverse effects on growth are expected to be significantly reduced. Timing of various surgical procedures would then be dictated more by function and esthetics than by growth considerations.

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