The aetiology and pathogenesis of craniofacial deformity

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Summary

Craniofacial malformations have been recorded since time immemorial. While observational studies have assisted in the recognition of syndromes, little light has been shed on the causal mechanisms which interfere with craniofacial development. Animal studies in which malformations occur spontaneously or have been induced by teratogenic agents have permitted step-by-step investigation of such common deformities as cleft lip and palate. The role of the ectomesenchymal cells of the neural crest and the possible phenomenon of disorganized spontaneous cell death are described in relation to lip clefts. The factors associated with isolated cleft palate, Pierre Robin syndrome and submucous clefts are described by reference to animal models.

The haemorrhagic accident preceding the onset of craniofacial microsomia is discussed as is the distinctly different phenomenon of disturbance to the migration or differentiation of neural crest cells in the pathogenesis of Treacher Collins syndrome. The more severe anomalies of the calvarium such as plagiocephaly, Crouzon and Apert syndrome still defy explanation; in the absence of an appropriate animal system to study; some thoughts on the likely mechanism of abnormal sutural fusions are discussed.

Key words: craniofacial deformity, facial clefts, microsomia, dysostosis, craniosynostosis.

Introduction

In the developing embryo there occur critical morphogenetic events which involve the migration of cell masses, the fusion of facial processes and the differentiation of tissues. Based on a genetically determined plan, growth processes lead eventually to an adult appearance. With enlargement, important changes occur in the size, shape, position and composition of all tissues including bones, muscles, nerves and sense organs. Skeletal growth has received a great deal of attention for it is often possible to see, in the mineralized structures, some record of growth increments. Skeletal development is also particularly important because of its relevance to the clinical treatment of facial abnormalities; skeletal landmarks are used to evaluate disproportion of the craniofacial complex; perhaps it could be said that our absorption with skeletal growth reflects our lack of knowledge about the causes of malformations. None-the-less, we are coming to recognize some of the many factors that influence the design of the craniofacial complex.

There is no doubt that the cell's genome contains specific instructions that influence the pattern of development. But additionally, cells are also responsive to environmental signals. The proportion of skeletal growth that is genetically predetermined or environmentally controlled is not precisely known. Since both genetic and environmental factors are present, and interact, it is difficult to ascertain the exact role of each. It is the interplay of these genetic and environmental factors on a small scale that accounts for normal variations. These we accept as being part of the infinite variety of nature which falls within normal limits.

Specific growth patterns

While the sources of individual variations in growth have not yet been adequately identified, evidence is being accumulated on general patterns of growth that lead to specific facial types. The most productive of these recent studies have been those of Gasson &
Lavergne (1977). They have investigated the patterns of rotation of the maxilla and mandible during human growth and have established the principal types of rotation.

While a harmonious relationship between maxillary and mandibular growth rotation leads to a variety of facial types within the limits of normal variation, the possibility for well-defined abnormal patterns of facial development exists when maxillary and mandibular rotation are uncoordinated. We know that considerable variation occurs between the growth rates of different body parts within a person. When these changes occur in the jaws, under the influence of a wide variety of factors, both endogenous and exogenous, then morphological abnormality may arise. Since it is so difficult to distinguish between cause and effect, discussions about the respective roles of hereditary and environmental factors in craniofacial development are only of academic interest. The success of treatment may well depend, to a degree, on the individual factors involved but we will have to wait until much more is known about the factors controlling the variations in growth and development of many craniofacial components before we can make precise conclusions about the absolute cause of many extreme variations in form.

When one studies individual components of the craniofacial complex it is easier to classify and discuss anomalous development. In other words, when we isolate the mandible and the maxilla and study them separately – in isolation from each other – it is possible to ascribe more-positive causes to the malformations that we see. To some extent this evades the complex issues of the extent of interaction which exists between the various parts of the craniofacial complex during their growth and development. Nevertheless, such a simplistic approach has value, if only to assemble, in semirigid compartments, those facts that are known. Provided that this is done on the understanding that the domino effect of one part on the other exists at all times in interdependent systems, then the exercise has value.

The role of experimental models

Nature has, since the beginning of recorded time, made mistakes in human morphogenesis, producing forms that fall short of the standards encompassed by normal variation; forms that have also escaped the mechanism of selective disposal of deformed conceptions by spontaneous loss or resorption.

Current research in teratology is directed, in the main, to the prevention and treatment of these anomalies; as yet few, if any, birth defects have been prevented by measures based on what is known of their aetiology or pathogenesis. Nevertheless, it appears possible, at present, that the identification of causal mechanisms of birth defects may eventually play a dual role in the clinical management of malformation. A thorough understanding of those tissue, cellular and subcellular derangements that lead to deformity may make a positive contribution to planned prevention; in addition, an understanding of the pathogenesis associated with a particular causal mechanism can make the planning of postnatal treatment a scientific rather than an empirical enterprise and so bestow real benefits both to the malformed and to those concerned with funding health care.

Normal morphogenesis of the orofacial tissues involves complex step-by-step sequences of migration of cells and interaction between cell groups. Only by the systematic study of human embryonic specimens obtained at short intervals over the period extending from day 25 to day 45 of morphogenesis can the sequential development of the human craniofacial complex be reconstructed. Unfortunately such a volume of material is not yet available; even if it was, serial sampling of multiple embryos would enable at best only static reconstructions of a fluid and dynamic process. When attempts are made to progress from the level of morphology to levels of cytophysiology and histochemistry, the problems of reconstruction of the sequence of normal development become even more complex.

Clinical cases of malformation, even when the causal agent is known or suspected, provide little assistance to the teratologist concerned with causal mechanisms studies unless they can be related to animal models of malformation that possess similar characteristics. Animal specimens of malformation, the end products of which resemble human malformation, are of particular scientific interest because they permit observation of embryological and fetal stages that lead to malformations found at birth. In this way these experiments of Nature provide some of the answers to the puzzle of the mechanisms of abnormal development. When animal models of deformity bear a close resemblance to the human malformation and can be shown, in all probability, to possess a common pathway of development, even in part, then extrapolation of animal findings to man becomes a possibility (see Sulik et al. – this volume).

Syndromes involving clefts of the lip and palate

The most common serious orofacial anomaly is cleft lip and palate. It is considered to be a polygenic multifactorial problem in which genetic susceptibility is influenced by multiple and probably cumulative
environmental factors (see Moore et al. - this volume). Neither the genetic nor the environmental factors have been well documented as yet, but there is some evidence to suggest that smoking, diazepam and phenytoin are three of the factors in early pregnancy which may shift the developmental threshold towards cleft lip and palate.

The critical stage of lip formation is when the medial and lateral nasal processes contact each other before they coalesce. The disturbances in the mesenchyme may be slight or severe, with the result that clefts range from incomplete to complete. Fusion may be affected by anomalies in size, shape or position of the facial processes. Anatomical variations, possibly based on ethnic or similar factors, may predispose to the problem of lip formation. Where the size of the facial processes is reduced and they are not in tight apposition there is an increased possibility of cleft lip. This phenomenon can be seen in the A strain mouse where the pointed facial shape prevents wide contact areas between the lateral and medial nasal processes. Cleft lip is common in that strain but unseen in the C57 black strain of mouse where the larger facial processes facilitate intimate contact of the facial processes. The spontaneous development of cleft lip and palate in A strain mice has made these animals eminently suitable for experimental investigation of the process of malformation (Trasler, 1968; Brown, Hetzel, Harne & Long, 1985). By introducing into the maternal diet human teratogenic agents such as phenytoin or excess vitamin A, the malformation threshold in the developing embryos may be shifted to the extent that 100% offspring are born with the expected deformity. Sequential study of embryonic development over the teratogensensitive period provides the experimentalist with clues to the causal mechanisms of malformation.

Sulik and colleagues (Sulik, Johnson & Ambrose, 1979) have demonstrated that, under the influence of teratogenic doses of phenytoin, the lateral nasal process fails to expand to the size necessary for tight tissue contact with the medial nasal process. Under such circumstances, probably associated with abnormal differentiation of the cellular processes of the ectomesenchymal cells which make up much of the bulk of the mesenchyme of the facial processes, there is failure of union at the point of connection which establishes the lip and primary palate. With abnormal morphology, and inadequate tissue bonding, the processes pull apart in cleft-like fashion, leaving discontinuity between the lip and nasal cavity.

While anatomical variation is one potential predisposing factor in the aetio-pathogenesis of cleft lip and palate there are undoubtedly others. At the time of consolidation of the facial processes there is a concurrent programme of spontaneous cell death involved in the removal of epithelial debris from the developing nasal placode (Warbrick, 1960). When this cell death is more extensive than necessary and repair of mesenchyme is disturbed, a weakness develops in the forming lip and alveolus. The continued action of growth traction forces may further disrupt the association of the facial processes with the lip margins being pulled apart. Under such circumstances one can envisage clefts of the lip which vary from a simple groove in the muscle to a complete cleft into the nasal floor. Simonart's bands represent a special example of just such a traction-tear during the process of lip development (Poswillo, 1975).

There is a frequent association between clefts of the lip and cleft palate. Animal studies suggest that following the failure of lip closure there is an overgrowth of the prolabial tissues which then divert the tongue into the nasal cavity. The mechanical obstruction of the tongue can delay the movement of one or both palatal shelves so that opportunities for palatal fusion are lost (Trasler, 1968).

Perhaps it is timely to make a few comments on the aetiopathogenesis of the rare facial clefts. The median cleft probably represents the failure of the paired primordia of the median nasal processes to fuse into a single globular process. The frequent association of this anomaly with bifid nose and orbital hypertelorism suggests that there is a common link between all these anomalies. Avian studies in which small punch grafts of neural crest tissue have been removed from the mesencephalon have led to the conclusion that disturbances in the central flow of neural-crest-derived ectomesenchyme may be responsible for these defects (Poswillo, 1968).

Oblique facial clefts are probably the result of disruptive forces applied to the formed face by swallowed strips of amnion. These strands are attached to the fetal sac at one end and enter the oesophagus of the fetus at the other. The amniotic bands ulcerate through the tissues of the lip and cheek during fetal movements. Subsequent repair of the margins produces bizarre congenital clefts which follow no natural junctions of the facial processes.

The sequence of lip and palate formation extends over fifteen days in man. It is not surprising, therefore, that in many syndromes cleft lip and palate should accompany anomalies of other parts of the body. Many developing systems can be disturbed simultaneously by teratogenic influences which operate over a long period of morphodifferentiation.

Isolated clefts of the posterior palate are distinctly different in aetiology from those that accompany cleft lip. They differ in incidence, sex predisposition and their relationship to associated birth defects. Palatal shelf elevation involves the concerted interaction of fetal neuromuscular activity, growth of the cranial
base and mandible and the production of extracellular matrix and contractile elements in the palatal shelves. Fusion of the palate depends on shelf adhesion, death of the midline epithelial seam and fusion of ectomesenchyme between one shelf and the other. Thus there exists in the developing palate a variety of phenomena which must act in harmony over a relatively short time span to produce normal palatogenesis (see Ferguson – this volume). Such factors as interference with the intrinsic shelf force, which induces elevation of the palatal shelves into a horizontal position or mechanical obstruction to shelf movement by the tongue, could lead to a cleft. When the tongue is interposed in the space between the ascending shelves as a result of compression of the chin against the sternum, we find a distinctly different type of palatal cleft. In these circumstances, the palatal deficiency is U-shaped not V-shaped, and this is the type of anomaly that we see in combination with microgenia and glossoptosis in the Robin anomalad. It is a deformation of tissues with a normal developmental potential rather than a malformation of tissues that may have been affected by disturbances of ectomesenchyme or other phenomena at cellular level. There is, therefore, a strong potential for catch-up growth of deformed tissues in the Robin anomalad and this can often be of advantage to the clinician concerned with the timing of reconstructive procedures (Poswillo, 1968).

Finally, in the field of facial clefts, we should consider submucous cleft palate and bifid uvula. These can both be regarded as microforms of isolated palatal clefting and are probably the result of disturbances in the local mesenchyme at the time of ossification of the palatal bridge and merging of the margins of the soft palate. These phenomena occur late in morphogenesis, between the seventh and tenth weeks of human development, and underline the importance of protecting the embryo from teratogenic insults until well into the second trimester of pregnancy (Poswillo, 1974).

There are many other syndromic patterns of anomalous craniofacial development. Indeed, the list seems to grow longer year by year. It will not be possible to discuss all these syndromes but certain significant examples can be taken as indications of other developmental phenomena that lead to craniofacial deformity.

First and second branchial arch syndromes

Perhaps the most significant asymmetrical malformation of the mandible, at least in the eyes of the reconstructive surgeon, is that of craniofacial microsomia. Under this title shelter such conditions as the first and second branchial arch syndrome, Goldenhar’s syndrome, Nager de Reynier syndrome and thalidomide otomandibular dysostosis. These conditions have not been shown to possess any significant family predisposition. In one form or another they occur once in about 3000 births with a 1:1 sex ratio. In about 70% of cases the anomaly is unilateral. When it is bilateral it is always asymmetrical. The defects often extend well beyond the mandible and both primary and derived changes are seen in the form of the auricle, the middle ear, malar, maxilla, squamous temporal bones and many of the associated soft tissue structures. Animal and clinical studies support the hypothesis that the causative factor is focal necrosis of tissues in the vicinity of the developing ramus of the mandible at about day 35 of human development (Poswillo, 1973). An expanding haematoma arising from the stapedial arterial system destroys and organizes actively differentiating mesenchyme in a localized area of the face unrelated to embryologic boundaries. The haematoma is thus quite unselective in its effects and clinical cases vary in severity according to the degree of primary destruction and the capacity of the disorganized tissues to effect catch-up repair. Not only are skeletal tissues affected by this embryological accident but so also are the soft tissue components of the functional matrix unit described by Moss (1968) as the prime mover in facial growth. The end result of this embryological accident is insult added to injury, for the disturbance of the functional periosteal matrix has a severe and lasting impact on the growth and development of the affected face. A series of secondary growth disturbances adds to the problems of form and function in the mandible and contiguous structures. This disparity can continue to affect development until active growth ceases late in adolescence.

Where nature has failed to provide, as in facial microsomia, the reconstructive problem during the period of active growth may be insuperable. On the other hand, where the problem is acquired, as in ankylosis, the opportunity for surgical reconstruction of the functional matrix is more promising, for normal musculature exists within the framework of a constrained skeletal environment. No such suitable muscular arrangement is ever found to exist in craniofacial microsomia.

Treacher Collins syndrome (mandibulofacial dysostosis)

There are a number of symmetrical syndromes characterized by dysplasia of first and second branchial arch derivatives. Some of these closely resemble facial microsomia. The most common of these un-
usual conditions are Treacher Collins and Hallerman Streiff syndromes. Treacher Collins may be the genetic (autosomal dominant) variant, and Hallerman Streiff the environmental variant, of identical or almost identical malformations. It has not been exclusively established that environmental factors play a part in these symmetrical craniofacial anomalies in man; nevertheless, it has been possible to construct animal models of identical malformations by the use of exogenous teratogens and there is the suggestion that the variance in expressivity of the autosomal dominant gene that is responsible for Treacher Collins syndrome in man is a result of modification of the abnormal genes by exogenous factors. Observations made during embryogenesis of the animal model of Treacher Collins syndrome indicate that the anomalies arise as a result of destruction or disturbances of migration of the pre-otic neural crest ectomesenchymal cells that normally migrate to the facial and auditory primordiae (Morriss & Thorogood, 1978). Johnston (1965) has shown that these cells can be expected to contribute considerably to the skeleton and supporting tissues of the middle and lower thirds of the face. Failure of these cells to migrate into the branchial arches reduces the normal volume of mesenchyme participating in morphodifferentiation and leads to hypoplasia of the musculoskeletal derivatives of these arches. As a result of cell death in the mesencephalon there is a flow of adjacent tissue into the defect. The otocyst migrates upwards into the territory of the first branchial arch so that the eventual position of the pinna is closer to the angle of the jaw.

Despite the deficiencies in musculoskeletal development and the symmetrical anomalies in the ear, malar, maxilla and mandible, there exists in both Treacher Collins and Hallerman Streiff syndromes an intact but modified functional periosteal matrix. This permits symmetrical growth and development of the hypoplastic facial skeleton. However, the extreme variation in craniofacial form leads to considerable variations in the pattern of growth, and the clinician should appreciate that surgical reconstruction of the facial skeleton may not restore a normal or near normal pattern of growth in these syndromes. As they are malformed, so shall they grow; the problem of relapse is very real when the surgical reconstruction exceeds the limitations of the deranged functional matrix. The primary morphogenetic stimulus for craniofacial growth is expansion of the functioning spaces of cranial, nasal, pharyngeal and oral cavities. When the skeleton is changed and the environmental demands are unchanged, it follows that the morphologic and growth parameters of the skeletal tissues are no longer in balance. This imbalance between the modified facial skeleton and the unmodified functioning spaces is the prime mover in relapse.

Most recent studies of the animal model of Treacher Collins have revealed that, under unusual circumstances, such as halving the dose of the teratogenic agent vitamin A, asymmetrical forms of the syndrome arise. These investigations bear a close relationship to the animal studies by Juriloff & Harris (1983) in which a mutant mouse strain exhibiting many of the features of mandibulofacial dysostosis, has been described in some detail. Unpublished studies by these workers (personal communication, 1984) suggest that the mutant produces asymmetrical forms of the syndrome as a result of back-cross breeding with unaffected mice. This new information from both genetic and environmentally involved animal models suggests that the role of the neural crest cells in the aetiopathogenesis of this syndrome is less clear than formerly proposed by this author. It is anticipated that the changes in expression of the syndrome in these new animal models will add further light to the enigma of symmetrical and asymmetrical craniofacial syndromes.

**Craniostenotic syndromes**

Craniostenosis may occur in many different forms and it is not possible to do justice to this fascinating subject in a few concluding paragraphs. Suffice to say that it is widely believed that various distortions of skull shape may follow alteration in the timing of closure of sutures in the calvarium. Where this is delayed, there is usually a broad forehead and a degree of hypertelorism; in syndromes such as Down, cleidocranial dysostosis and progeria the anterior fontanelle may never close and the characteristic broad skull and facies result.

Of even greater interest to embryologists, syndromologists and naturally, orthodontists, are those cases in which there is premature fusion of the coronal, sagittal or lambdoid sutures. This is said to occur in Crouzon and Apert syndromes yet there is little valid scientific evidence to establish premature fusion as the causative factor in these anomalies. There is obvious evidence of craniosenosis, but nothing to say that the sutures have formed normally and then undergone synostosis. There is the equal likelihood that the sutural abnormalities arise ab initio by incomplete sutural differentiation at the time of calvarial development. It is possible that persistence and premature ossification of fetal sutural cartilage (induced by ischaemia perhaps) could initiate synostosis before the suture was fully developed (David, Poswillo & Simpson, 1982). It seems unlikely that the malformation arises as a result of disordered development of the cranial base for there are many examples of morphological malrelation of the bones of the cranial base in which synostosis is never seen,
conditions in which the orientation of the dural fibres is likely to be severely disturbed. Perhaps the most striking of these is artificial cranial deformation by skull binding. These skulls exhibit abnormalities of the cranium, face and cranial base which are similar to those found in the craniosynostoses, but the sutures all remain normal. Some of these deformations affect the cranial base first. This evidence tends to offset the argument of Moss (1968) that deformation of the cranial base occurs secondary to the deformation of the cranium in these skulls. Our knowledge of sutural behaviour does not yet extend to an explanation of why sutural synostosis occurs as a normal event in the elderly adult. We know little of the histological and biochemical details of this process. We know even less of the biochemical or endocrinological milieu of the fetus and mother during the morphogenesis of the cranial sutures. The best that can be done, at present, is to pose questions and test hypotheses.

Despite all the information that has been accumulated on normal growth and development and the pathogenesis of craniofacial syndromes little is really known about the determinants of an individual's facial growth pattern. Growth data are most needed for the extremes of growth and it is these conditions, well beyond the range of normal variation, that have been discussed in this paper. Folklore has for centuries ascribed personality traits on the basis of interocular distance. For example, slightly wide-spread eyes suggest candour or innocence; narrow-set eyes a miserly, mean personality; upward-slanting eyes a sign of the devil. Yet little or no reference is made here to hyper- or hypotelorism and the factors which, during embryonic development, may predispose to these changes in intercanthal and interpupillary distance. Yet it is essential to measure and assess these and many more markers of anomalous development in order to understand the complex patterns of growth that one finds in craniofacial deformity. The successful rehabilitation of the patient with abnormal development of the cranium, face and mouth is contingent on accurate diagnosis and an understanding of the aetio-pathogenesis of the basic defect. As the scientific basis of malformation is clarified it will be easier for the surgeon and the orthodontist to improve the quality and stability of treatment. Research efforts in both basic and clinical spheres will eventually provide the answer to many of the problems of abnormal development of the maxillofacial region; problems, which this paper has merely served to emphasize rather than explain.

References


