

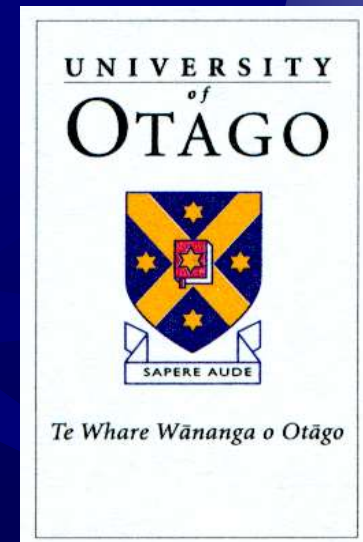
# Development of the Face

By Murray C Meikle

Biological Foundations of Orthodontics  
and Dentofacial Orthopaedics

Seminar 4

2004



# The face is derived from five processes

- ✦ The textbook description of facial development is based on the observations of Wilhelm His, Professor of Anatomy at Leipzig.
- ✦ According to His, the face is derived from five processes or prominences surrounding the invaginating oral cavity or stomodeum; these processes, two mandibular, two maxillary and one frontonasal, grow, meet and fuse.



# Anatomie Menschlicher Embryonen

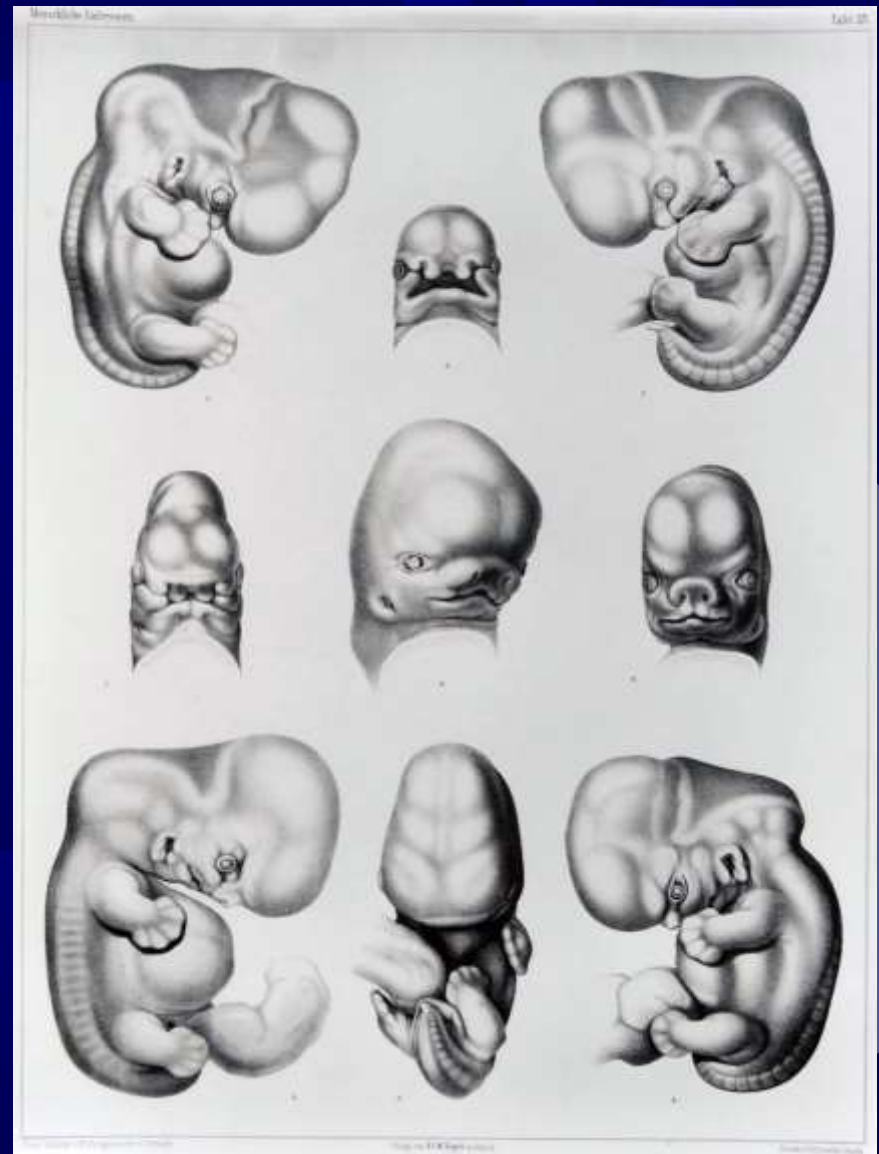
## ANATOMIE MENSCHLICHER EMBRYONEN

VON  
WILHELM HIS.

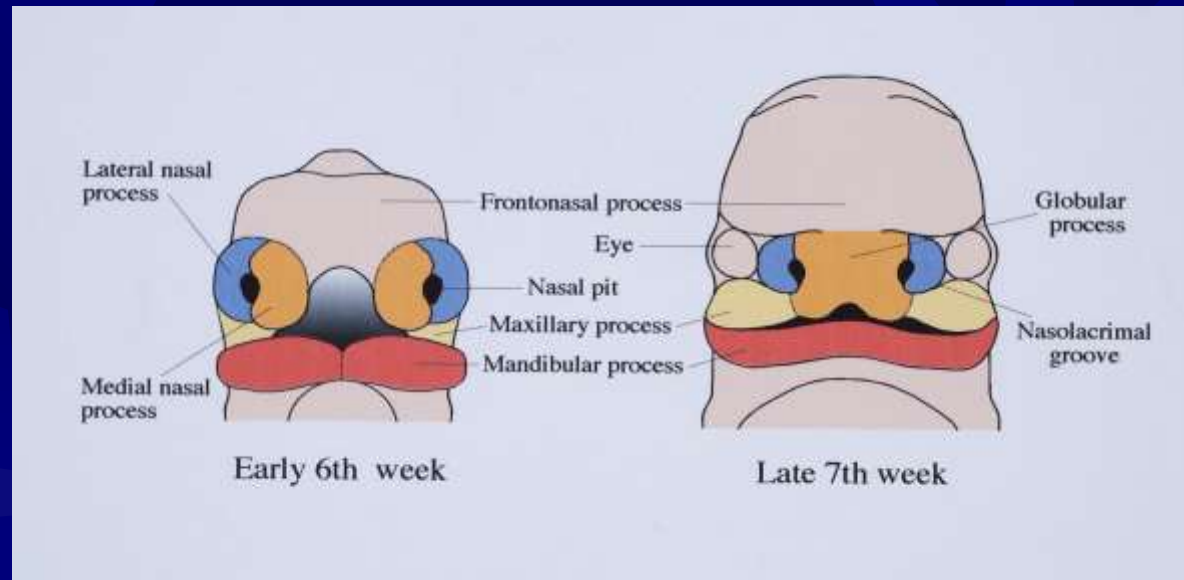
III.  
ZUR GESCHICHTE DER ORGANE.

MIT 150 ABBILDUNGEN IM TEXT  
UND ATLAS (TAFEL IX – XIV u. 1\*.)

LEIPZIG,  
VERLAG VON F. C. W. VOGEL.  
1885.

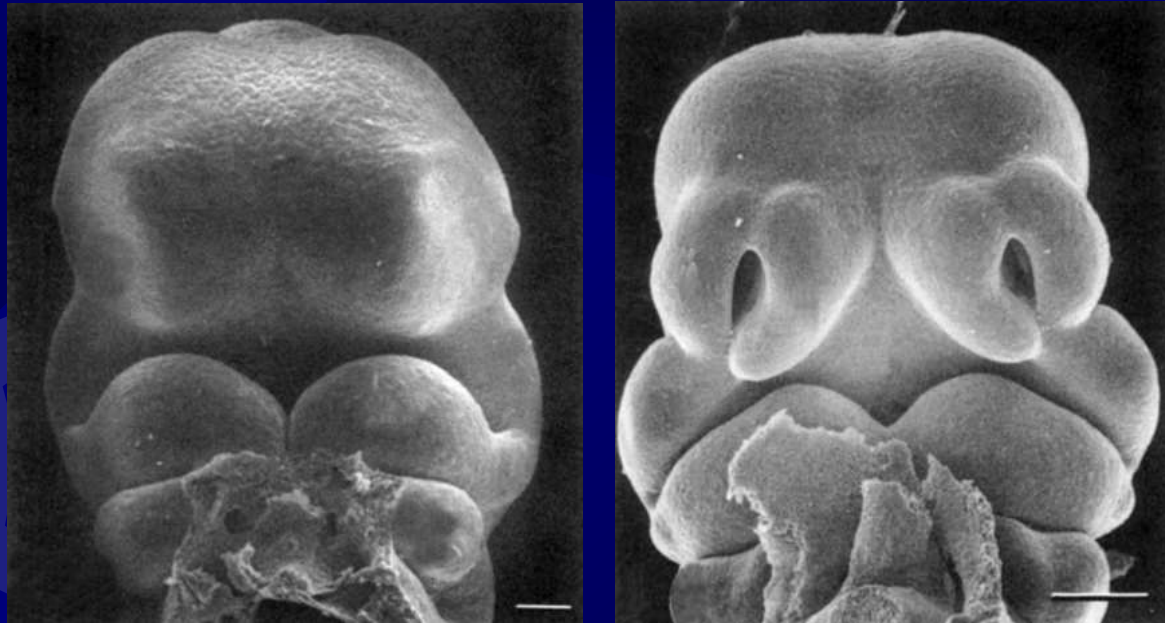


# Development of the face



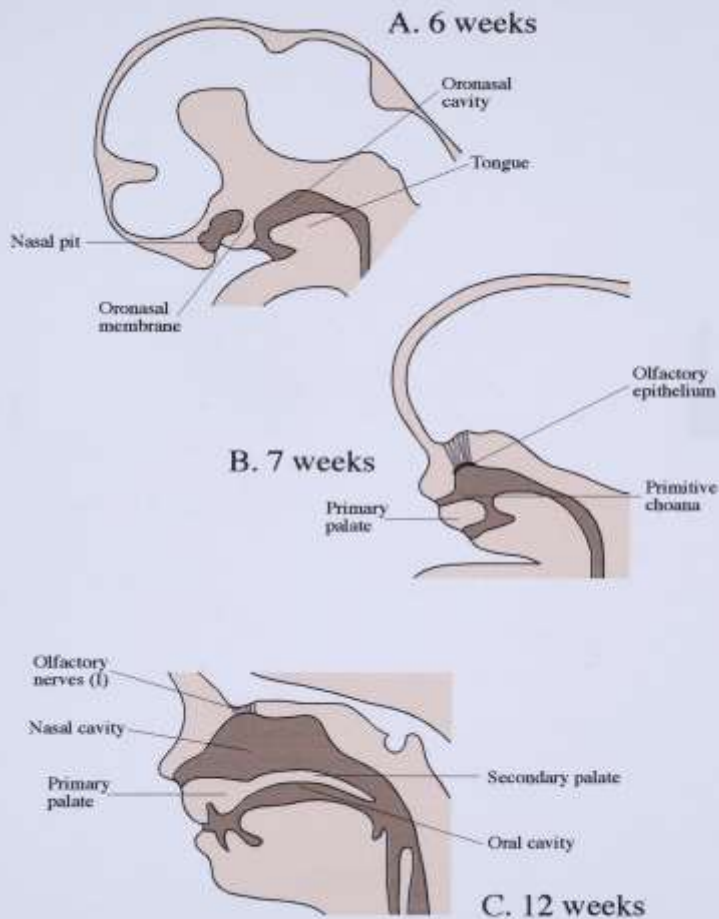
- The lower jaw is the first part of the face to form and results from a merging of the medial ends of the mandibular processes (4<sup>th</sup> week).
- Proliferation of the underlying mesenchyme produces elevations, the medial and lateral nasal processes converting the olfactory placodes into the nasal pits.
- The ectoderm at the base of the groove between the lateral nasal and maxillary processes invaginates and becomes canalized to form the nasolacrimal duct.
- The medial nasal processes fuse to form the globular process which gives rise to the medial part of the nose and the columella.

# Development of the face



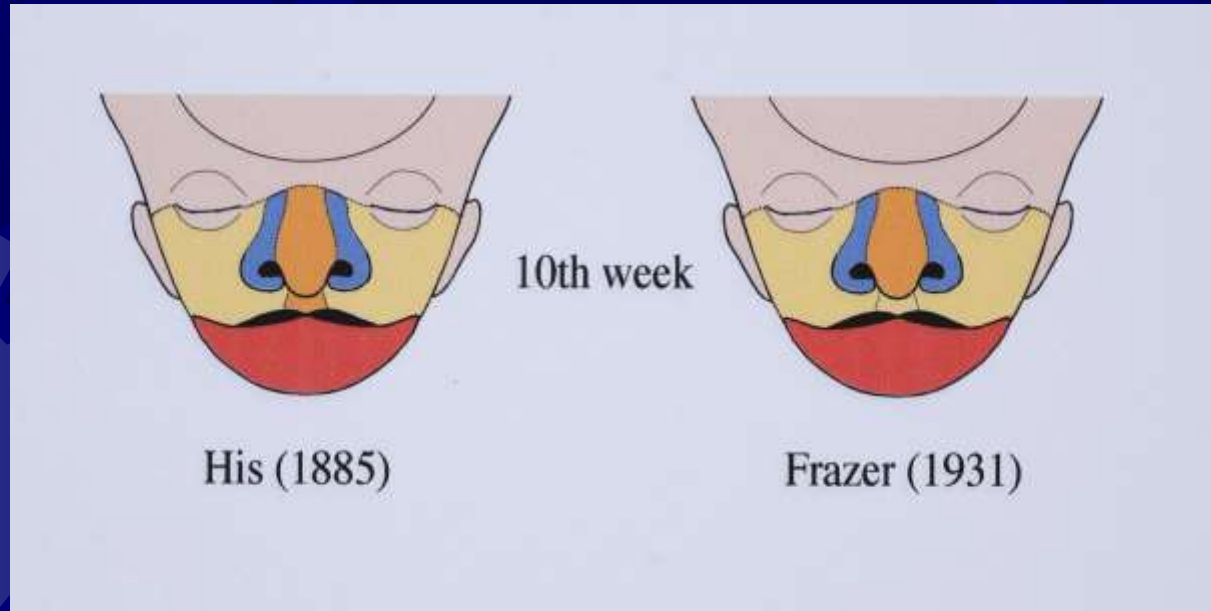
- SEMs of mouse embryos. At this stage of development they are indistinguishable from human embryos.
- E10 days. The first branchial arch gives rise to the mandibular process.
- E11 days. The medial and lateral nasal processes have converted the nasal placodes into the nasal pits, which eventually become the external nares. Bar 200  $\mu\text{m}$ .
- From Sulik and Schoenwolf (1985). *Scanning Electron Microscopy* 4, 1735–1752.

# Formation of the nasal and oral cavities



- The invaginating nasal pits are separated from the stomodeum by the oronasal membrane. This degenerates to form the internal nares or primitive choanae.
- The primary palate is formed by the merged lower part of the globular with the maxillary processes; this gives rise to the upper lip, premaxilla and the incisor teeth.
- At 7–8 weeks the palatal processes elevate and fuse, first with the primary palate and progressively backwards with each other, to form the secondary palate separating the oral and nasal cavities.
- From Meikle (2002), *Craniofacial Development, Growth and Evolution*.

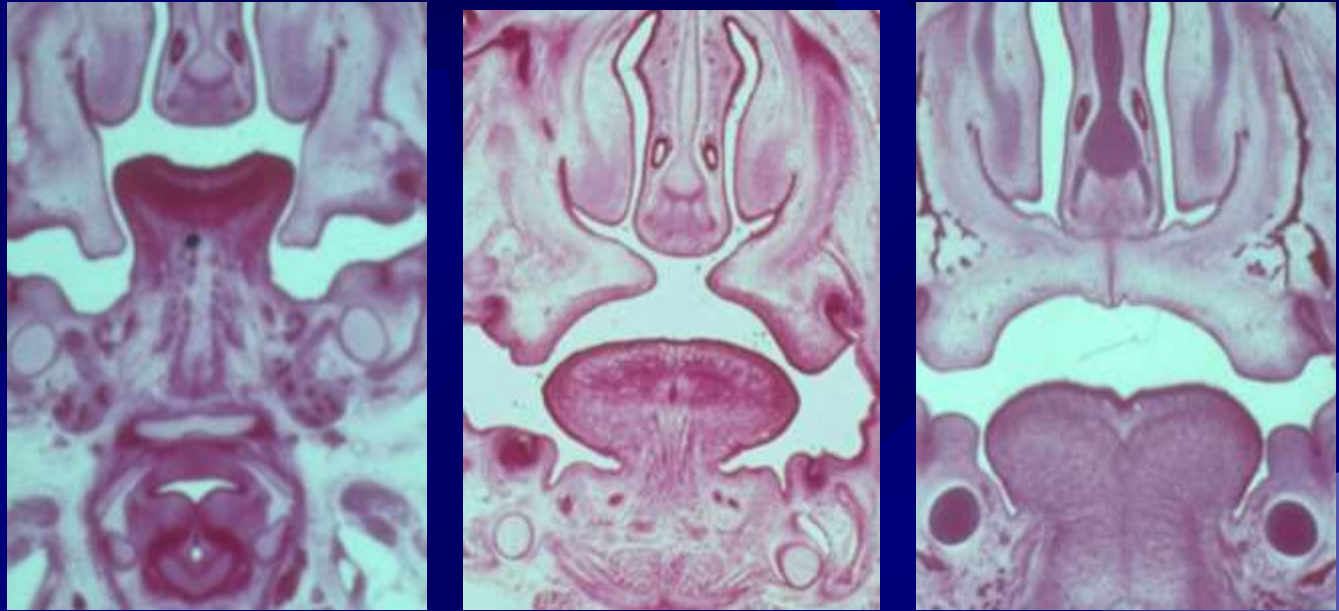
# Formation of the upper lip



- According to His, the philtrum of the upper lip had its origin from the lower part of the globular process. Frazer proposed that the globular process was submerged by an overgrowth of the maxillary processes.
- This is supported by (1) lack of hair on the surface of the prolabium in bilateral cleft lip and palate patients, and (2) the upper lip is supplied by the maxillary division of the Vth (trigeminal) cranial nerve with no input from the ophthalmic division.
- Adapted from Larsen (1993), *Human Embryology*.

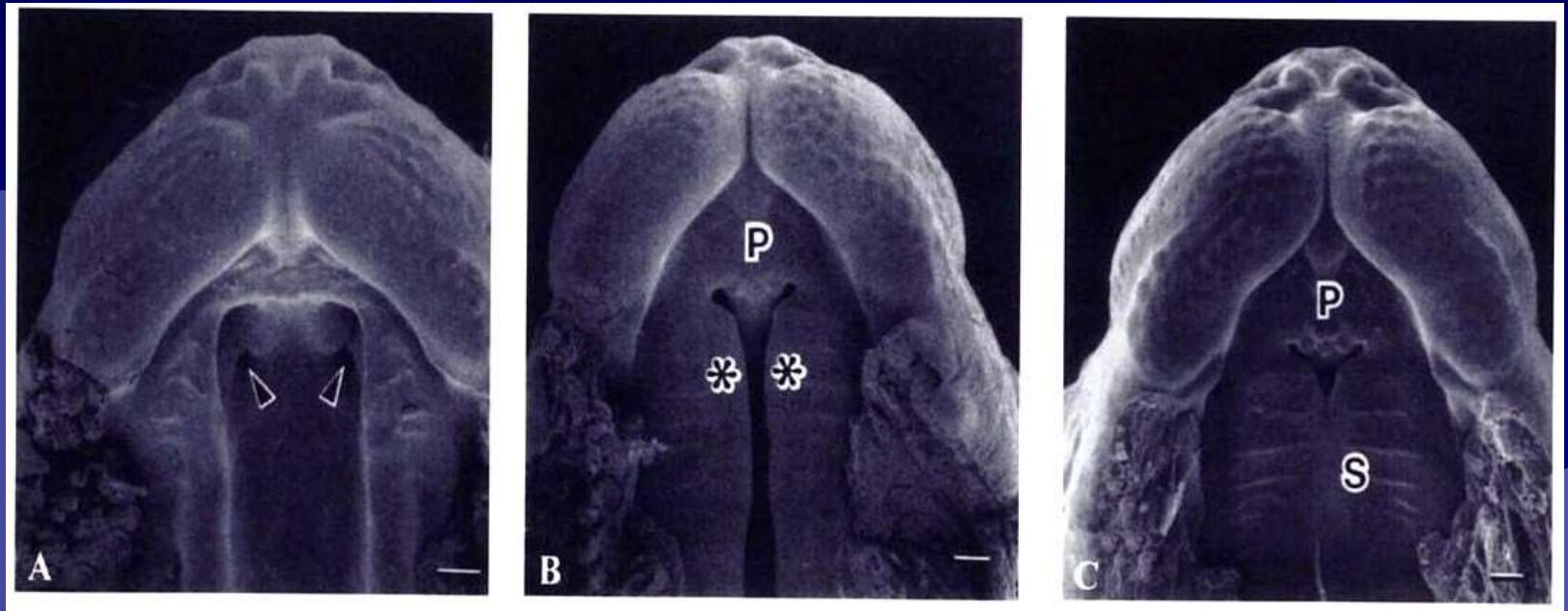
# Formation of the secondary palate

Courtesy of Dr Virginia Diewart and the Carnegie Institute.



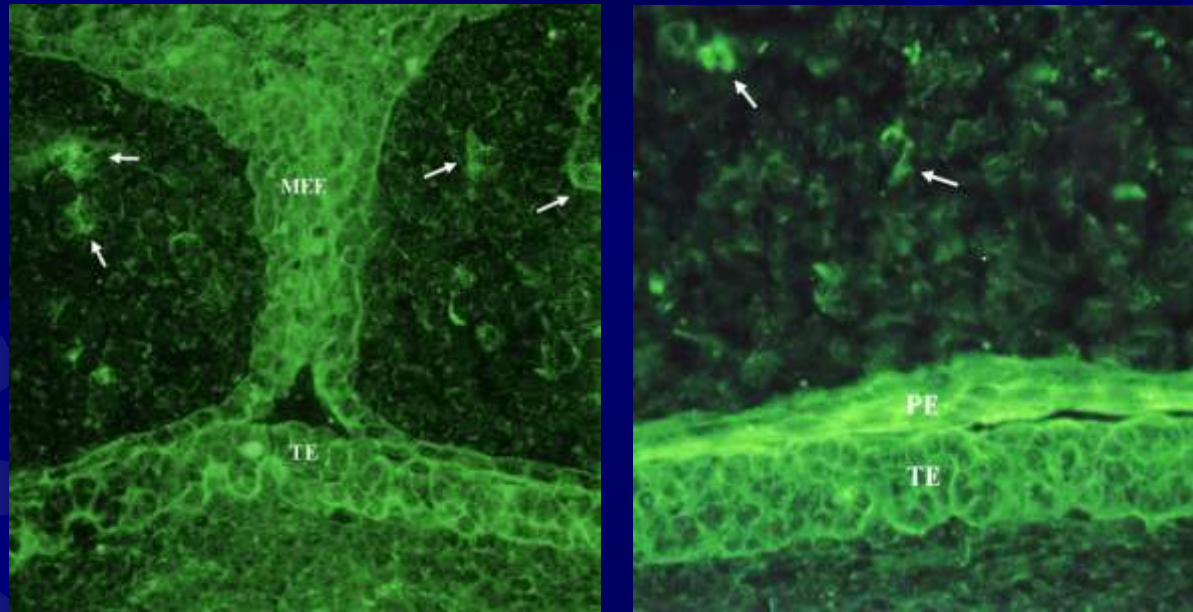
- ✿ Coronal sections through the oronasal cavity in human embryos at embryonic stages 22, 23 and at a fetal age of 9 weeks.
- ✿ During the 6th week the palatal shelves develop from the oral aspect of the maxillary processes as downward directed projections; the tongue fills the oronasal cavity.
- ✿ As the dimensions of the oronasal cavity increases the tongue moves downwards and forwards and the palatal shelves elevate.

# Formation of the secondary palate



- SEMs of the developing upper jaw from the oral aspect in mouse embryos. P, primary palate; S, secondary palate. Bar 200  $\mu$ m.
- A. 14 day *pc* embryo; arrowheads indicate the internal nares. B. 15 day *pc* embryo; the palatal shelves (\*) approach each other. C. The palatal shelves have begun to fuse with the primary palate and with each other from before backwards.
- From Sulik and Schoenwolf (1985). *Scanning Electron Microscopy* 4, 1735–1752.

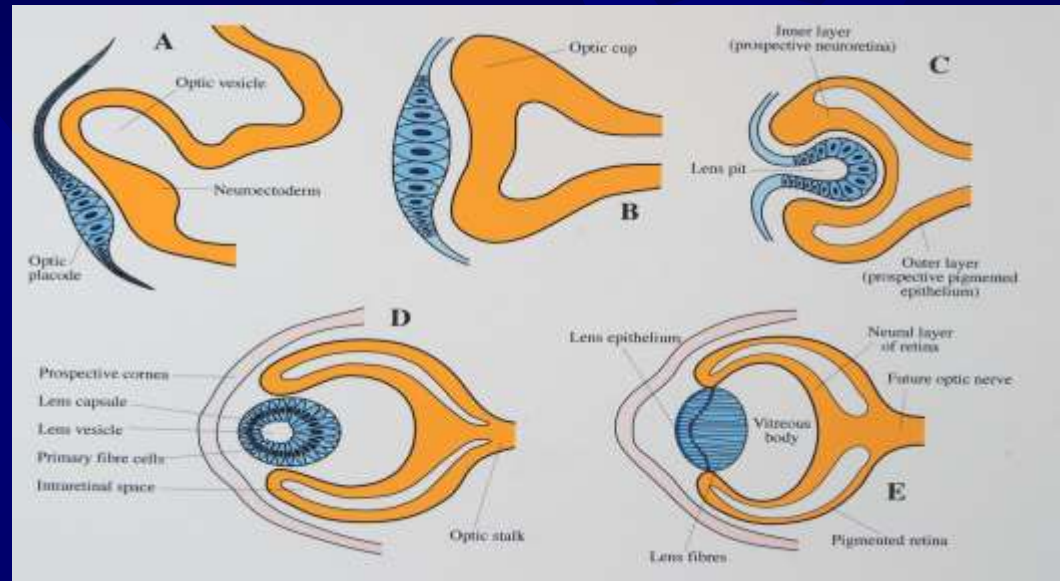
# Palatal shelf fusion



- During palatal fusion the medial edge epithelia (MEE) at the edges of the palatal shelves form a midline epithelium seam. Disruption of the MEE is required to establish mesenchymal continuity across the horizontal palate.
- Three mechanisms have been proposed: (1) apoptosis or programmed cell death; (2) epithelial–mesenchymal transformation (EMT) as shown above, where expression of N-cadherin has been downregulated, TE, tongue epithelium; PE, palatal epithelium; Arrows, palatal ectomesenchymal cells. (3) migration of MME cells to the oral and nasal surface epithelia. Original magnification x360.
- Courtesy of J Davies.

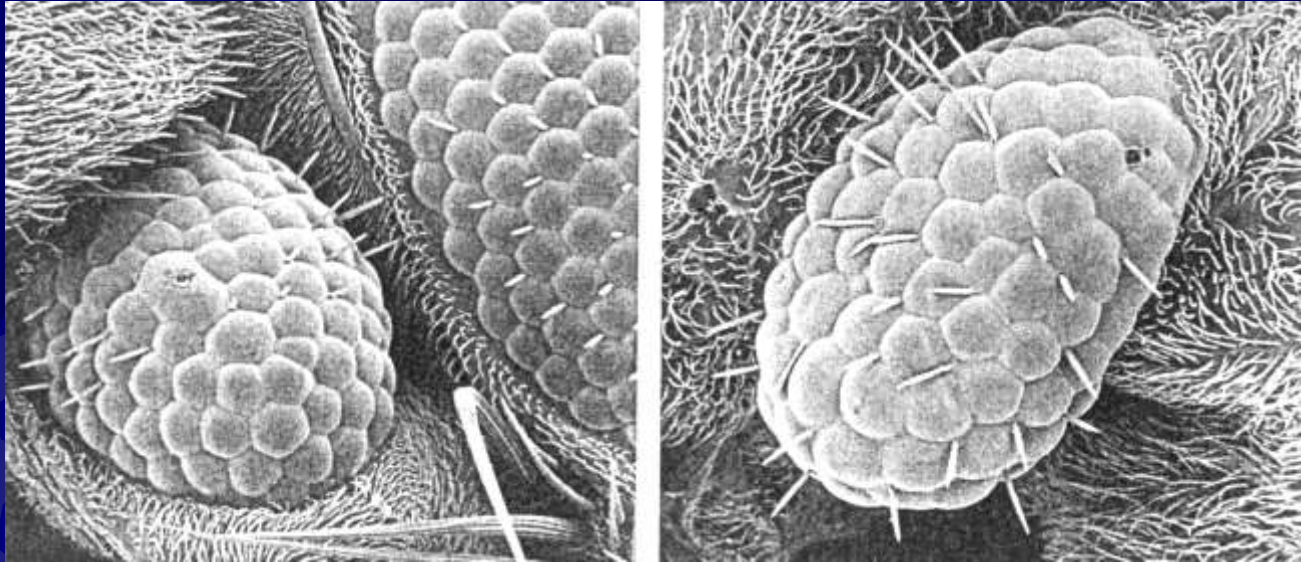
# Early events in eye development

Redrawn from Cvekl  
and Piatigorski (1996).  
*BioEssays* 18, 621–630.



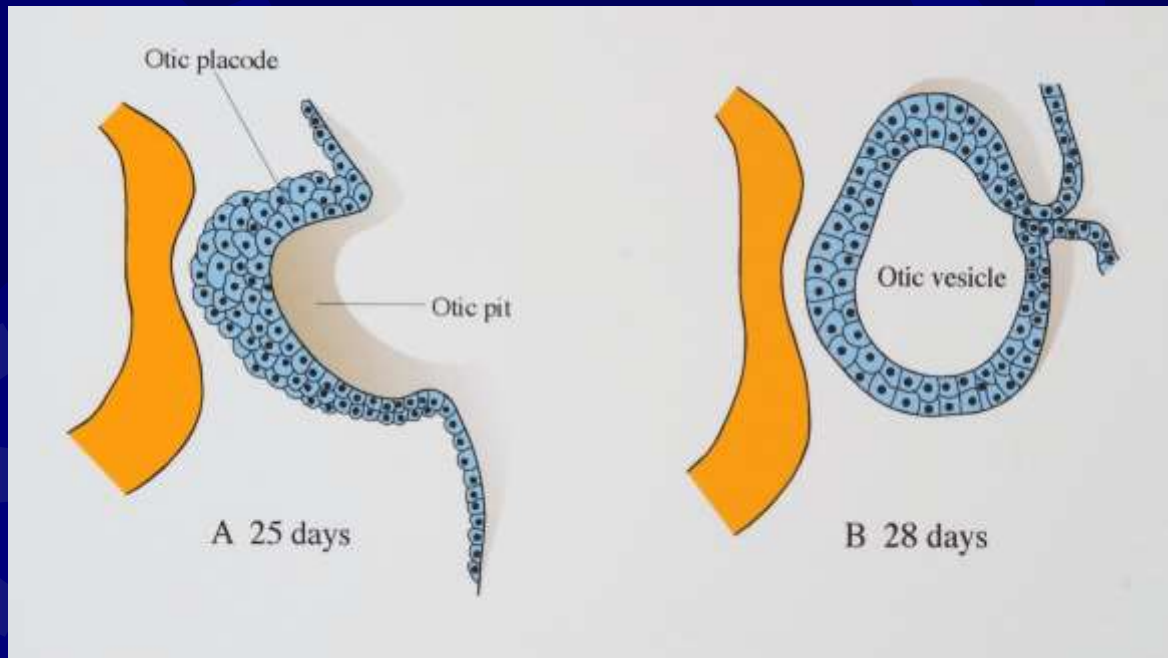
- ☀ Vertebrate eye development involves interactions between the neurectoderm of the forebrain to form the retina and associated pigmented structures, and surface ectoderm which forms the lens and cornea.
- ☀ A, The optic vesicle is connected to the prosencephalon via the optic stalk; the lens placode is a thickening of the surface ectoderm. B, The lens placode thickens and indents (C) to form the lens pit; the optic vesicle indents to form the optic cup. D, the lens pit is converted to the lens vesicle. E. At E13.5 the neural retina begins to differentiate and the cornea develops in front of the lens.

# *Pax-6/eyeless*



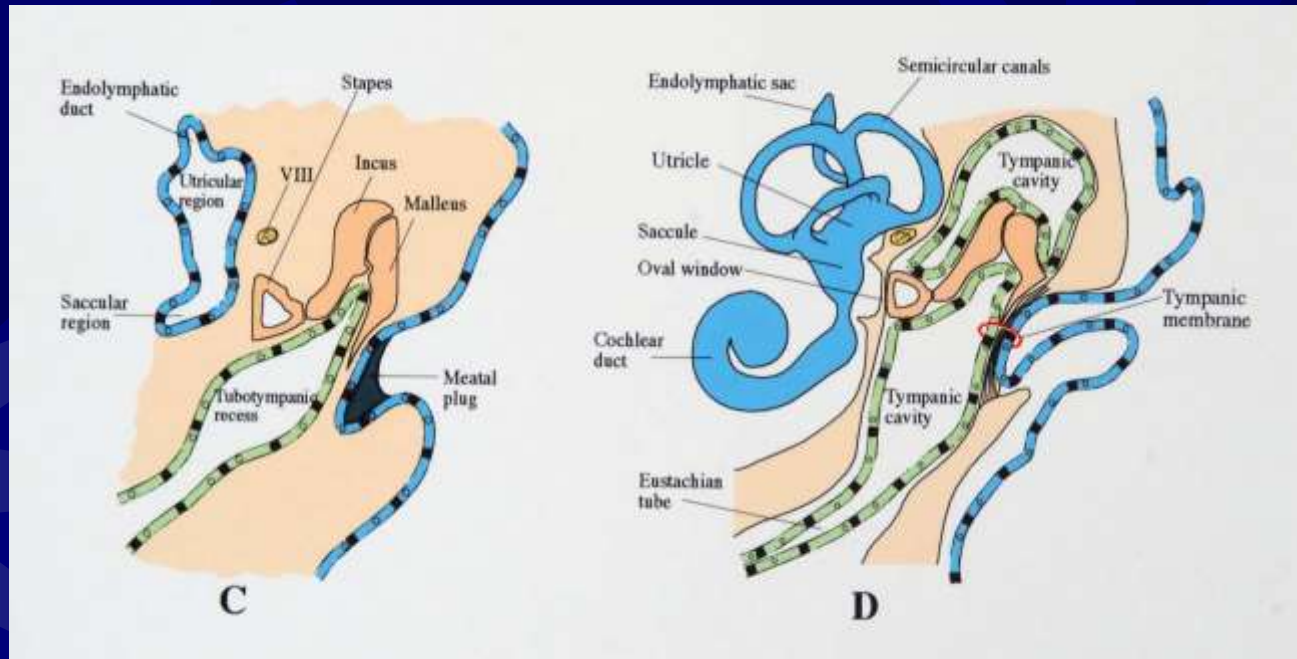
- ✿ The homeobox gene *Pax-6/eyeless* plays an essential role in eye development in both vertebrates and *Drosophila*. Mutations in *eyeless* cause eye loss and overexpression results in the formation of ectopic eyes in locations where wings, legs and antennae normally develop indicating that *eyeless* is a homeotic gene. The above shows the ectopic expression of the *eyeless* gene in the head (left) and protruding from the thoracic wall.
- ✿ In humans, aniridia and Peter's anomaly are rare malformations of the eye associated with mutations in the *PAX-6* gene.
- ✿ From Halder *et al.* (1995). *Science* **267**, 1788–1792.

# Development of the ear - I



- The otic placodes, which are paired thickenings of the surface ectoderm overlying the rhombencephalon appear by day 22 in humans. Each rapidly invaginates to form an otic pit (A) and then a closed hollow otic vesicle (B).
- The otic vesicle gives rise to primordia of the membranous labyrinth of the inner ear and the ganglion of cranial nerve VIII.
- From Meikle (2002), Craniofacial Development, Growth and Evolution.

# Development of the ear - II



- C. Components of the inner, middle and outer ear at 5 weeks. The otic vesicle is divided into a dorsal utricular region from which the endolymphatic sac, semicircular canals and utricle arise, and a ventral saccular region which forms the saccule and cochlear duct.
- D. By the 9<sup>th</sup> month the tubotympanic recess has expanded to enclose the malleus, incus and stapes to form a functional middle ear cavity. The ossicular chain transmits sound from the tympanic membrane to the oval window and the cochlear via the perilymphatic space.

# Craniofacial malformations

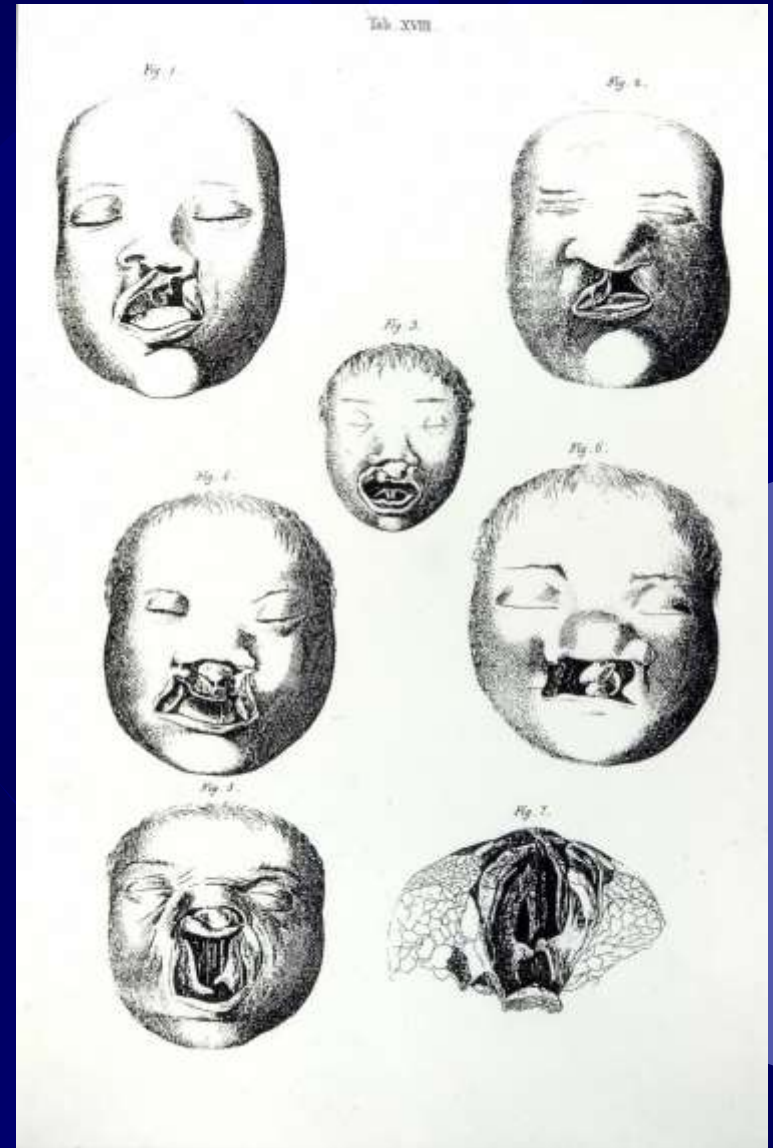
- Given the complex interplay between regulatory genes, neural crest cells and environmental factors required for normal facial development, it is not surprising that errors sometimes occur resulting in facial malformation.
- Most appear to be multifactorial in origin, involving both genetic susceptibility and environmental causes. Owing to their pivotal role and ubiquitous nature, most of the more common developmental defects can be attributed to abnormalities in the neural crest.
- The term neurocristopathy was coined by Bolande (1974) to provide a unifying concept for diseases resulting from abnormalities in the migration, growth and differentiation of neural crest cells. Abnormalities considered by Bolande to be neurocristopathies included Hirschsprung's disease, neuroblastoma, pheochromocytoma, von Recklinghausen's neurofibromatosis and medullary carcinoma of the thyroid.

# Neurocristopathies

- ✿ The connection between these diverse hamartomatous and neoplastic diseases is not immediately obvious. The majority, however, can be regarded as dysplasias in which crest cells appear to have formed normally, migrated to the correct location, but subsequently lost the ability to differentiate normally; such individuals carry a lifetime risk for disordered growth of crest-derived tissue.
- ✿ It is clear that the equally disparate conditions of cleft lip and palate, DiGeorge syndrome, CHARGE association and hemifacial microsomia can also be classified as neurocristopathies. Disorders that result from migrational abnormalities of the cranial neural crest and represent true malformations. The extent of the problem is usually definable at the time of diagnosis and disordered growth of crest-derived tissue does not occur. Treatment is directed towards reconstruction of the structural defects and restoration of lost function.

# Teratology – dysmorphology

- Although better known as the discoverer of Meckel's cartilage, J F Meckel the younger, played a key role in establishing teratology (the study of abnormal form) as a scientific discipline, by undertaking a systematic analysis of all then known congenital malformations.
- This is plate XVIII from the third volume of *Tabulae Anatomico-Pathologicae* (Meckel, 1817–26) published in 1822, showing examples of cleft lip and palate.



# Cleft lip and palate



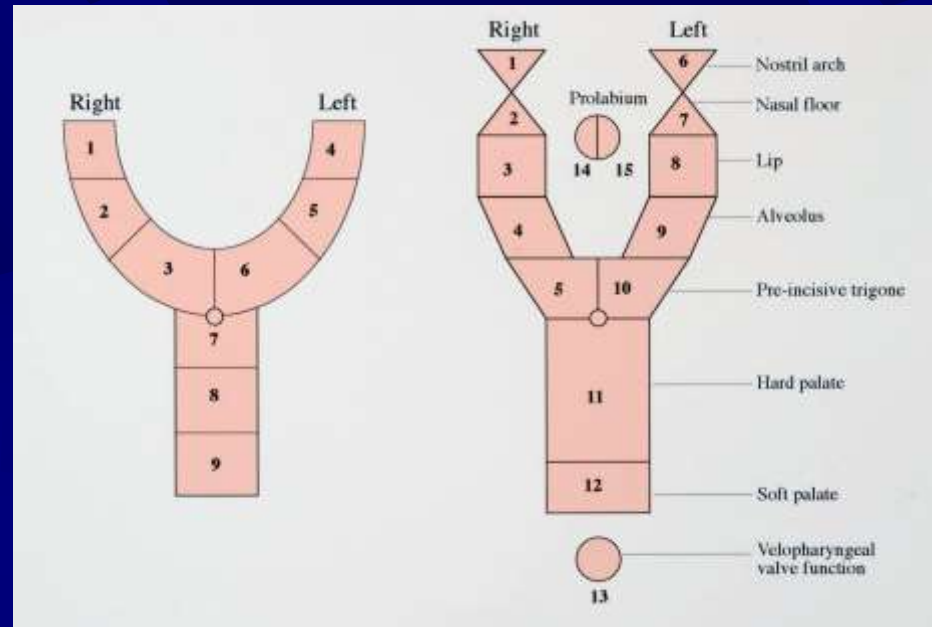
- Clefts of the primary and/or secondary palate are the most common craniofacial malformations in man with an incidence of about 1:1000 live births (range 0.6–1.3) depending on the study. Isolated CP may be unilateral or bilateral (approx 20%); 85% of cases of bilateral CL and 70% of unilateral CL are associated with cleft palate. CL/P is more common in males (about 2:1).
- Isolated CP seems to be a separate entity. The incidence is 1:2000 births among Caucasians and is more common in females; there is a 2:1 female predilection for complete clefts of the hard and soft palates, but a 1:1 ratio for clefts of the soft palate alone.

# Pierre Robin syndrome



- ★ One of the best-known eponyms in medicine (Pierre Robin, French stomatologist, 1867-1949). Commonly described as the triad of mandibular micrognathia, glossoptosis (posterior positioning of the tongue due to the micrognathia) and cleft of the secondary palate. Glossoptosis may be responsible for airway obstruction. Prevalence rates vary but in a recent Norwegian study was 1 in 14,000 births.
- ★ The syndrome may occur in isolation or in association with specific conditions such as Stickler, velocardiofacial or fetal alcohol syndromes. Where the affected individual has multiple anomalies, it is sometimes referred to as the Pierre Robin “sequence”.

# Classification of cleft lip and palate



- ✦ Left shows the symbolic “striped Y” representation of cleft lip and palate (Kernahan, 1971). Segments 1–3 and 4–6 represent the lip, alveolus and alveolar process to the incisive foramen. The stem is divided into the hard (7 and 8) and soft palate (9).
- ✦ Right are the modifications proposed by Friedman *et al.* (1991) incorporating triangles for deformities of the nasal arch and nasal floors and circles for the prolabium and velopharyngeal valve function.

# Genetics of cleft lip and palate

## INHERITANCE OF HARELIP AND CLEFT PALATE

CONTRIBUTION TO THE ELUCIDATION OF  
THE ETIOLOGY OF THE CONGENITAL CLEFTS  
OF THE FACE

by

POUL FOGH-ANDERSEN



DIAKONISSESTIFTELSEN'S  
HOSPITAL · COPENHAGEN

NYT NORDISK FORLAG · ARNOLD BUSCK  
COPENHAGEN 1947

- In the first large-scale study of orofacial clefts (703 cases) Fogh-Andersen concluded that isolated CP was inherited as a simple dominant trait with reduced penetrance.
- He also concluded that CL/P was inherited by a gene of variable penetrance, that could be dominant or recessive depending on the genetic background.
- The current consensus is that while CL/P shows a familial tendency (15–20%), there is no simple pattern of inheritance and in Caucasian populations 50–75% of cases are sporadic. CL/P does not exhibit classical Mendelian dominant or recessive inheritance; non-syndromic facial clefts are characterized by genetic heterogeneity and are caused by many factors both genetic and environmental.

# *MSX-1* and *TGF- $\beta_3$* are strong candidate genes for CL/P

- Genetic analyses of non-syndromic clefts have yielded somewhat contradictory results. However, given the number of genes involved in such a complicated morphogenetic event as palatogenesis, this is to be expected.
- The first positive candidate gene was *TGF- $\alpha$*  on chromosome 2p13, and it has been suggested that the *TGF- $\alpha$*  locus may interact with exposure to maternal smoking to increase the risk of a cleft. The *RAR- $\alpha$*  gene may be involved in the aetiology of a subgroup of clefts.
- Analyses of South American CL/P populations suggest that mutations in the *MSX-1* gene play a contributing role in “CL only” patients. The *MSX-1* gene has also been shown to be involved in autosomal dominant tooth agenesis (hypodontia).
- *TGF- $\beta_3$*  is also a very strong candidate gene for clefting in humans based on both mouse models and linkage studies. In the South American study “CP only” showed association with the *TGF- $\beta_3$*  locus.

# The holoprosencephalic disorders

- Holoprosencephaly (HPE) results from impaired cleavage of the prosencephalon during the first month *in utero*, leading to malformations of the forebrain and a deficit in midline facial development. The incidence is as high as 1 in 250 during early embryogenesis, but intrauterine lethality reduces it to 1 in 16,000 live births.
- The aetiology is heterogeneous and can include both a teratogenic and genetic basis; maternal diabetes has been shown to increase the risk 200-fold.
- Four putative human *HPE* genes have been identified: *HPE-1* on chromosome 21q22.3; *HPE-2* on 2p21; *HPE-3* on 7q36 (the *Sonic hedgehog* gene locus); and *HPE-4* on 18p11.3.

# Fetal alcohol syndrome

- Maternal alcohol consumption is now recognized as a common cause of holoprosencephaly in the West; it is thought to affect as many as 1 in 500 live births and is commonly associated with congenital mental retardation. Much of what we know about the pathogenesis comes from animal models.
- Following maternal ethanol administration, deficient development in the midline results in insufficient separation of the olfactory placodes. The frontonasal process fails to develop normally and the philtrum of the lip and anterior part of the maxilla are deficient. In more extreme cases failure of the medial nasal processes to develop leads to arhinencephaly.

# Holoprosencephaly



- ☀ Holoprosencephaly exhibits wide phenotypic variation and in 70–80% of the cases, the severity of the brain malformation is reflected in the highly variable craniofacial deformities - in other words, *the face predicts the brain*.
- ☀ Cyclopia represents the malformation in its most severe form. Left. An example of arhinencephaly and hypotelorism. Middle. Median cleft lip, midface hypoplasia, severe microcephaly and hypotelorism. Courtesy of M Muenke. Right. Cebocephaly characterized by a single nostril, midface hypoplasia and hypotelorism. From Larsen (1993). *Human Embryology*.

# Microforms of HPE



- Individuals with microforms of HPE who usually have normal brain imaging and intelligence are at risk from having children with HPE.
- Microforms of HPE in individuals with normal intelligence. A. Absent midline frenum and a single maxillary incisor. B. Same individual with a left iris coloboma. C. Ocular hypotelorism and a single central incisor in the father of a child with HPE.
- From Ming and Muenke (1998). *Clinical Genetics* 53,155–163.

# Patient with single central incisor



- ✦ It has been estimated that only 70% of obligate carriers show any phenotypic abnormality. In a family reported by Berry *et al.* (1984) with two affected children, the father and paternal aunt were both found to have a single maxillary incisor and hypertelorism, indicating a recurrence risk of 50%.
- ✦ Any patient with a single central incisor must be investigated further. In this patient both the deciduous and permanent dentitions were affected; the mid-palatal suture appears to have developed normally.

# Otofacial malformations

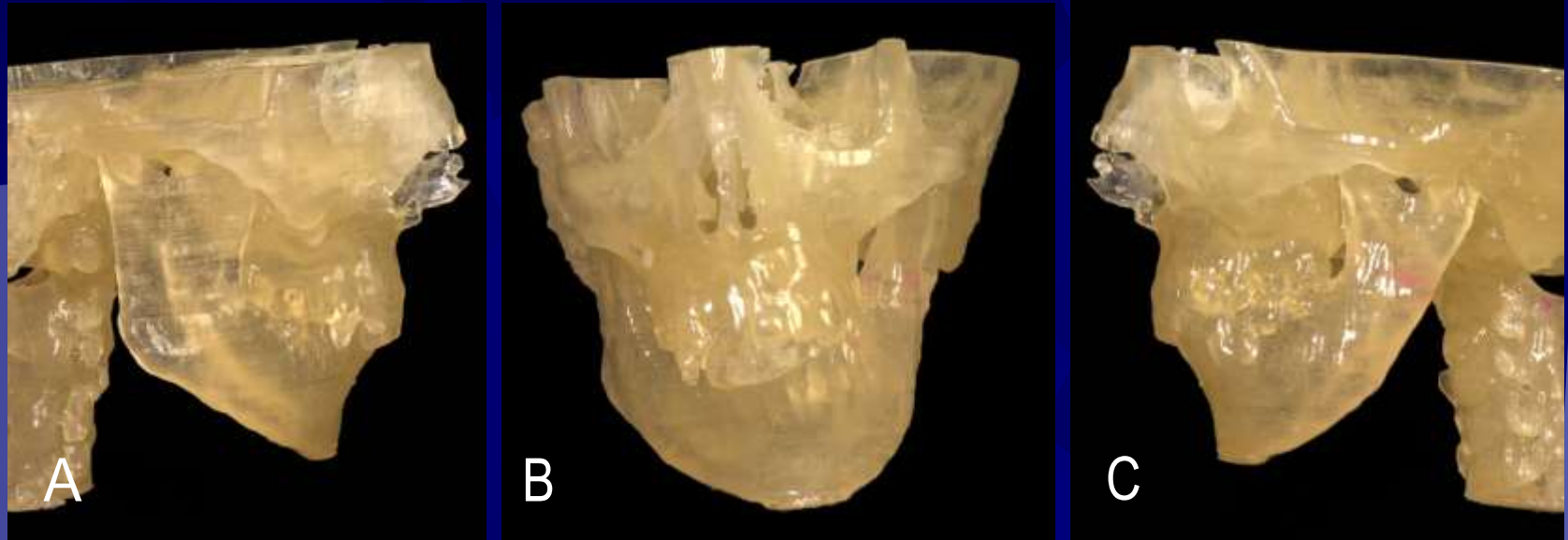
- ✱ There are several well-defined syndromes involving the ear and face which are frequently associated with pharyngeal and conotruncal cardiovascular defects, as well as cleft lip and/or palate and collectively referred to as otofacial malformations. Animal models suggest a major role for neural crest cells in the pathogenesis of these disorders. This group includes:
  - ✱ Retinoic acid syndrome.
  - ✱ DiGeorge syndrome, which results from microdeletions of chromosome 22q11. Other chromosome 22 microdeletions include velocardiofacial (Shprintzen) syndrome; conotruncal anomaly face (Takao syndrome) and CATCH 22, the collective acronym from **C**ardiac defects, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate and **H**ypocalcaemia.
  - ✱ Hemifacial microsomia.
  - ✱ Treacher Collins syndrome.

# Hemifacial microsomia



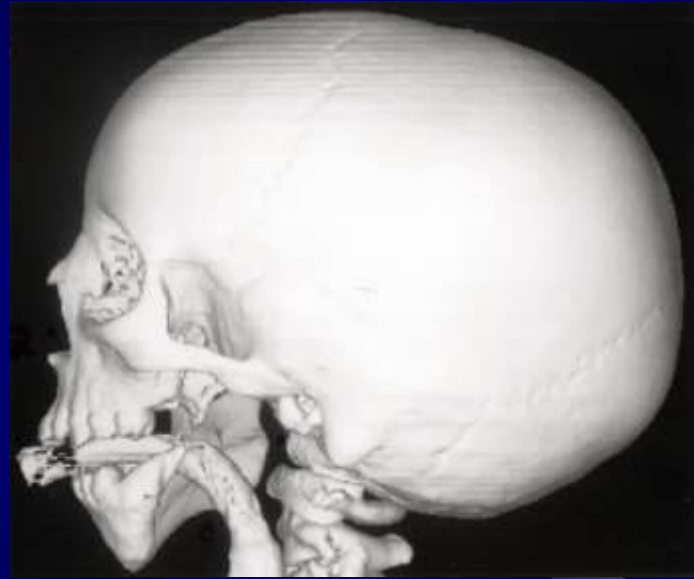
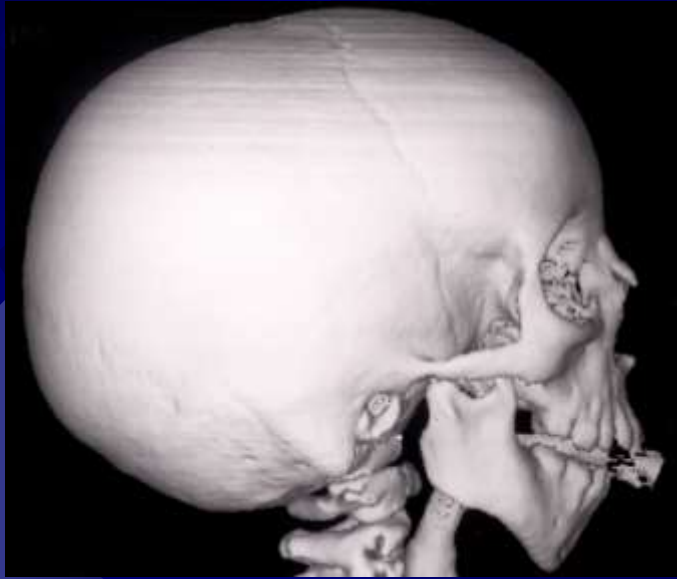
- Hemifacial microsomia (OMIM 164210) is a relatively common (1:5000 live births) condition affecting aural, oral and mandibular development, frequently associated with conotruncal cardiovascular and vertebral abnormalities
- Most cases are sporadic, although familial cases supporting both autosomal dominant and recessive inheritance have been reported.

# Hemifacial microsomia



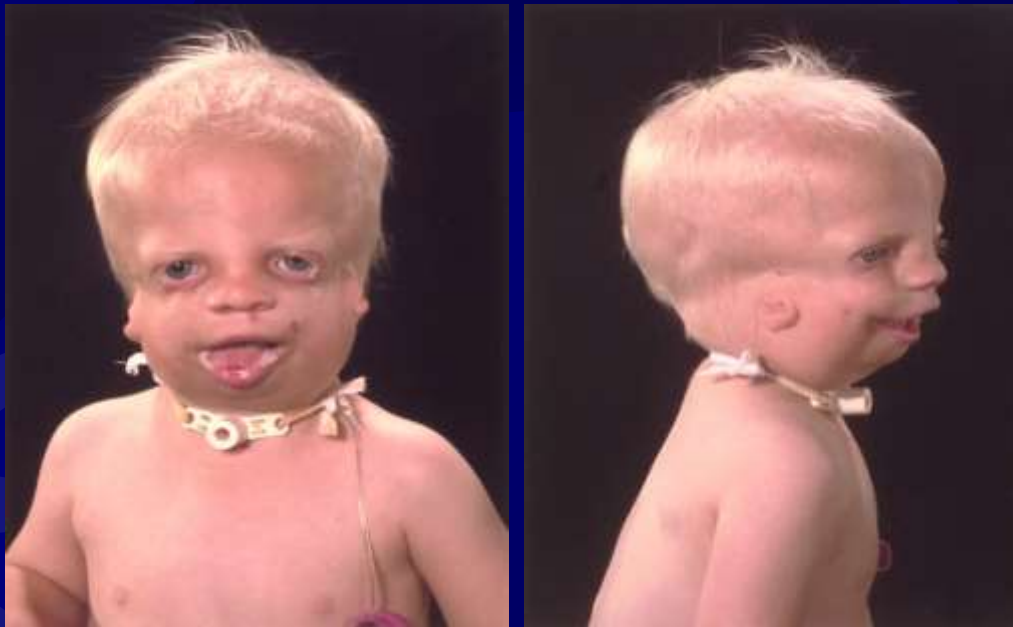
- Since the first case report (Canton, 1861) the disorder has had many names reflecting its complex and heterogeneous phenotype. These include Goldenhar syndrome, first and second arch syndrome, and oculoauriculovertebral (OAV) dysplasia.
- The above is a stereolithographic model constructed from a CT scan of the previous patient. (A). Non-affected side. (B). Frontal view showing the maxillary and mandibular asymmetry and slope of the occlusal plane. (C). Affected side with shortened vertical ramus and deficient angle of the mandible.

# Hemifacial microsomia



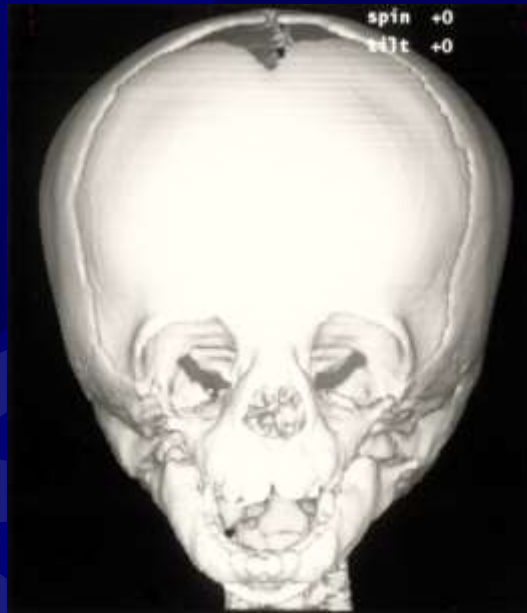
- The craniofacial and cardiovascular features of hemifacial microsomia suggest primary neural crest cell involvement in most cases, but unlike retinoic acid and DiGeorge syndrome patients, the pharynx is not affected. Most discussions of pathogenesis focus on the stapedia artery hypothesis of Poswillo (1973).
- In this CT of a patient with hemifacial microsomia the deformities are severe; the vertical ramus and part of the body of the mandible are completely absent.
- Courtesy of R D Evans.

# Treacher Collins syndrome



- The Treacher Collins syndrome (OMIM 154500) was named after the ophthalmologist who first described the condition in 1900; the alternative name is mandibulofacial dysostosis. (OMIM refer to the condition as the Treacher Collins-Francescetti syndrome; TCOF-1.)
- Although characterized by variable penetrance and expressivity the clinical features include: (1) anti-mongoloid slope of the eyelids with colobomas of the lower lid; (2) hypoplasia of the maxilla and mandible; (3) abnormalities of the external ears with atresia of the external auditory canals and malformations of the auditory ossicles; (4) cleft palate.

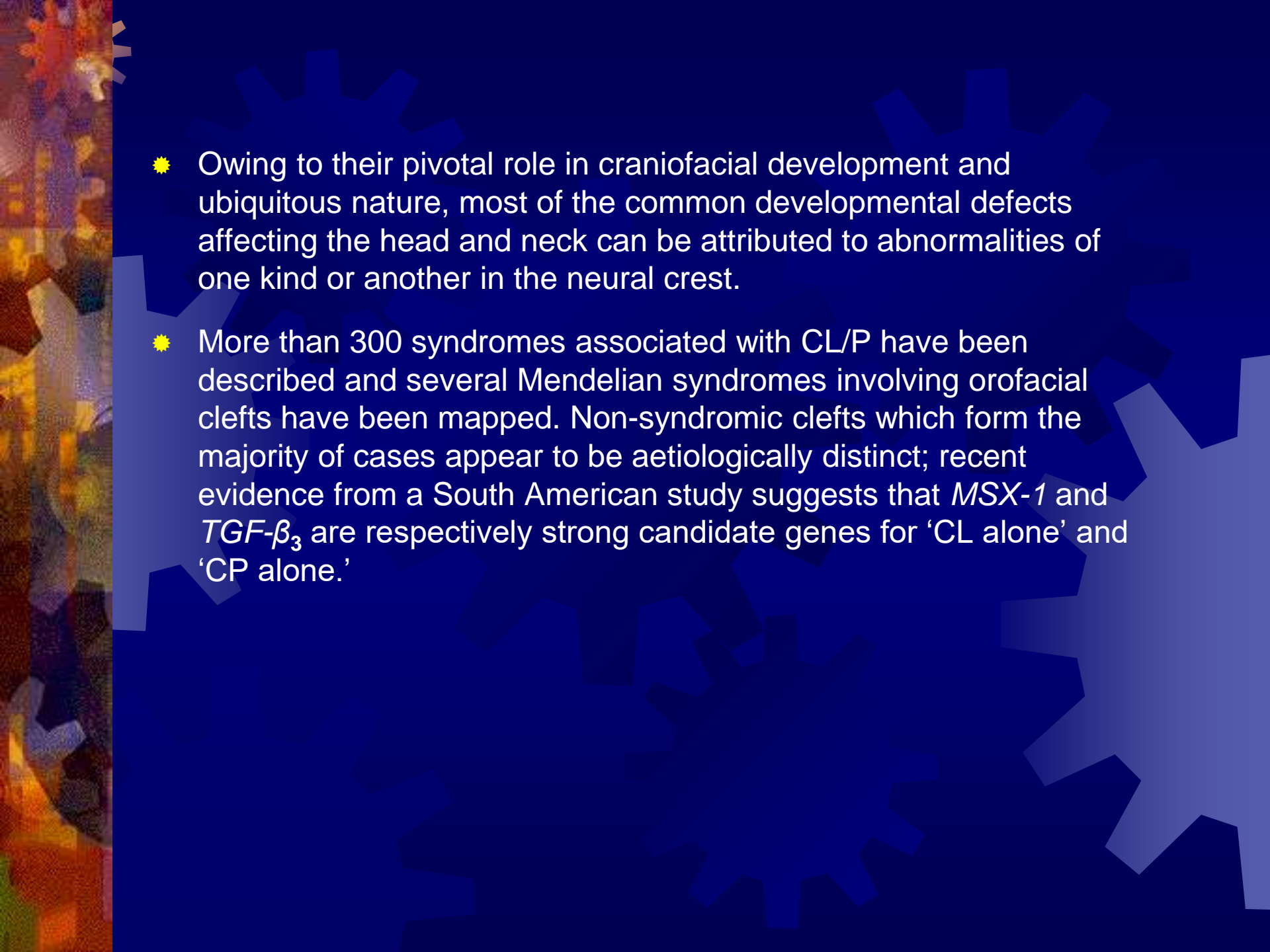
# Treacher Collins syndrome



- The incidence is approximately 1:50,000 live births and more than 50% are thought to arise from a *de novo* mutation. The gene locus has been mapped to chromosome 5q31.3-33.3 and a gene (named *TREACLE*) of unknown function cloned. Occasionally limb defects are combined with mandibulofacial dysostosis as in Nager syndrome.
- The above CT scan is from the previous patient showing the skeletal defects. The mandible is hypoplastic with absent vertical rami and condyles; the maxillary and zygomatic bones are deficient and the zygomatic arches are absent. Courtesy of R D Evans.

# Summary

- The face is derived from five processes surrounding the invaginating oral cavity or stomodeum; these processes, two mandibular, two maxillary and one frontonasal grow, meet and fuse.
- The facial processes are no longer regarded as prolongations of mesoderm and ectoderm having free ends which meet in the nasal area (see the His engravings), and ectoderm is not resorbed over their approximating surfaces during fusion (merging is now the preferred terminology).
- These processes are in fact ridges or swellings corresponding to growth centres in the underlying mesenchyme (Streeter, 1948). With the proliferation and migration of mesenchymal cells leading to the progressive merging of the growth centres, the superficial furrows or grooves separating adjacent process (or prominences) gradually flatten out.

- 
- Owing to their pivotal role in craniofacial development and ubiquitous nature, most of the common developmental defects affecting the head and neck can be attributed to abnormalities of one kind or another in the neural crest.
  - More than 300 syndromes associated with CL/P have been described and several Mendelian syndromes involving orofacial clefts have been mapped. Non-syndromic clefts which form the majority of cases appear to be aetiologically distinct; recent evidence from a South American study suggests that *MSX-1* and *TGF- $\beta_3$*  are respectively strong candidate genes for 'CL alone' and 'CP alone.'