Cleft Lip and Palate

- 2 distinct entities that reflect different embryological events.
- However, they often occur together.
- Causes of both are highly heterogeneous.

Genetics of Cleft Lip And/ or Palate

- Frequency highest in Asian and Amerindians-1 in 500 or higher
- Intermediate frequencies in Caucasian populations
- Lowest frequency of 1:2500 in African-derived populations

Genetics of Cleft Lip And/ or Palate

- Cleft lip/palate
  - 70% nonsyndromic
  - 30% syndromic
- Cleft palate
  - 50% nonsyndromic
  - 50% syndromic

Genetics of Cleft Lip And/ or Palate

- Syndromic
  - Chromosomal
  - Monogenic
    - AD,AR,XL
  - Teratogenic e.g. phenytoin or alcohol
  - Uncategorized

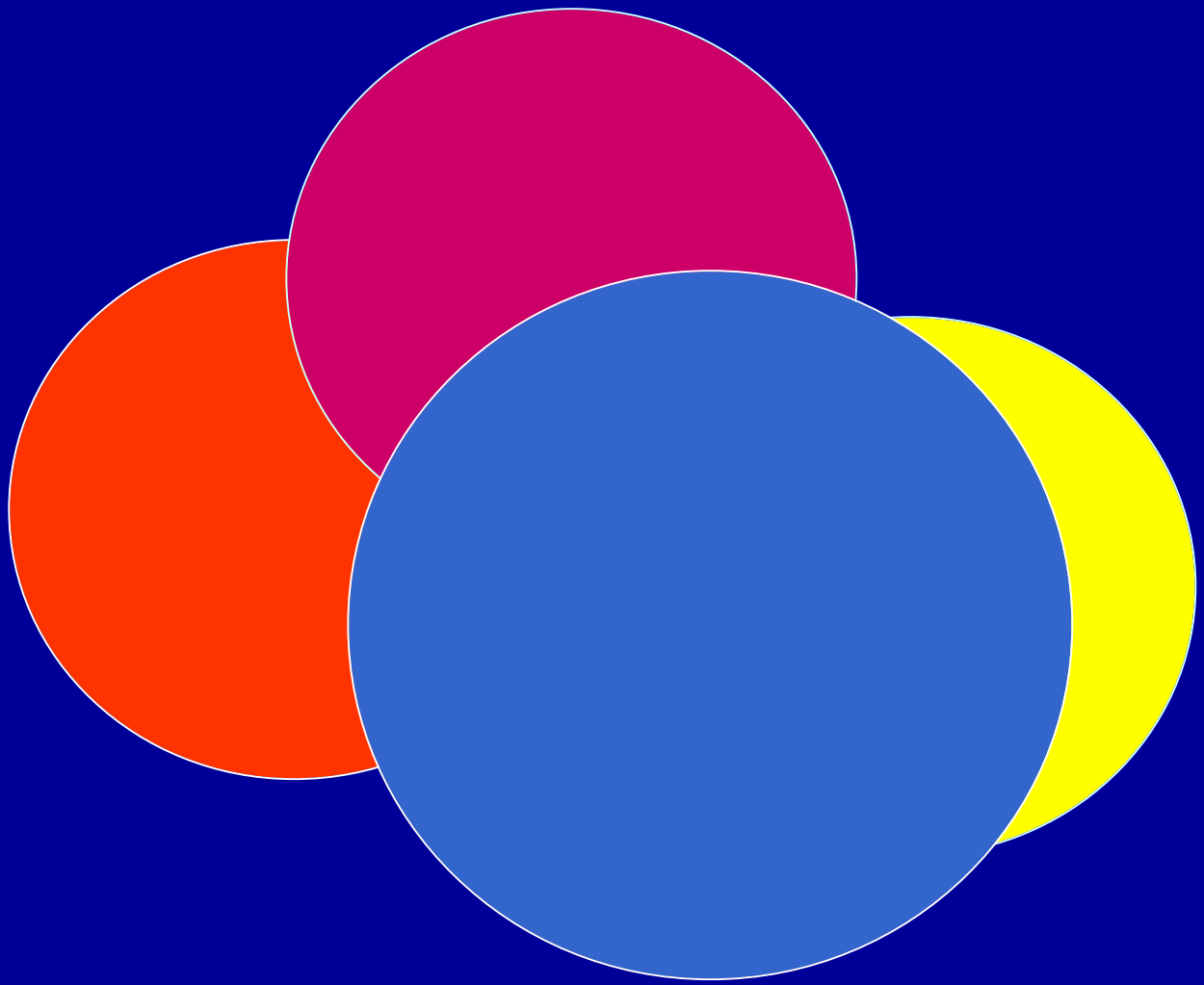
Complex Inheritance

- Increased risk in first degree relatives that drops off quickly.
- Increased recurrence risk with increased severity.

Genetics of Cleft Lip And/ or Palate

- Twin studies show
  - Concordance in MZ twins of 40%-60%
  - And DZ twin concordance of only 5%
  - Lack of 100% concordance in MZ twins suggests either incomplete penetrance or environmental interactions
  - Higher MZ concordance strongly support a major genetic component

Gene-Gene-Enviroment-nutrition interaction



Empiric Risk for CL/P in Relatives of Affected Probands

Population affected	Incidence of CL/P	λ relative
Gen pop	0.1	-
First-deg relative	4.0	40
Second deg rel	0.7	7
Third deg rel	0.3	3

Risk for CL/P in Sibs of Probands

Phenotype of proband	Incidence in sibs
Unilateral CL	4.0
Unilateral CL/P	4.9
Bilateral CL	6.7
Bilateral CL/P	8.0

Recurrence Risks for Clefts in Sibs of Proband

Affcted parent	CL(P)%	CP%
Mother affected		
Affected sibs		
0	2.7	2.3
1	9.9	11.2
2	18.3	21.1

Recurrence Risks for Clefts in Sibs of Proband

Affcted parent	CL(P)%	CP%
Father affected		
Affected sibs		
0	2.3	5.0
1	9.3	14.4
2	17.6	23.9

Recurrence Risks for Clefts in Sibs of Proband

Affcted parent	CL(P)%	CP%
Both parents affected		
Affected sibs		
0	24.0	45.0
1	31.7	51.6
2	37.6	54.5

Gene Linkage/association Studies of Clefts

Gene	Locus	Linkage	LD/TDT
SKI/MTHFR	1p36	+	++/-
TGFB2	1q41	-	-/+
TGFA	2p13	-	++/-
MSX1	4p16 4q31 6p23	+ +/- ++/-	++/- +/- -

Gene Linkage/association Studies of Clefts

Gene	Locus	Linkage	LD/TDT
PVRL1	11q23	-	+
TGFB3	14q24	-	+
GABRB3	15q11	-	++/-
BCL3	19q13	+/-	+/-
RARA	17q21	+/-	+/-

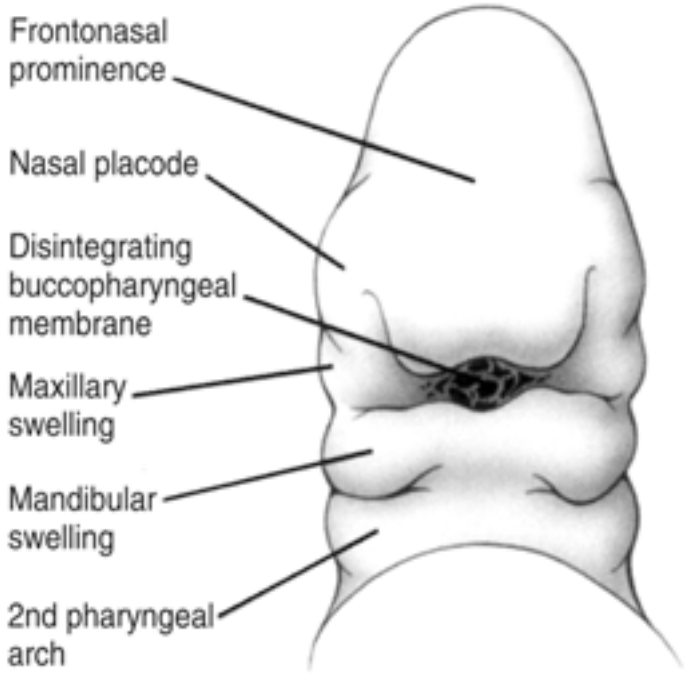
Recurrence of CL/P and CP

- Gene dosage
- Sex of the proband
- Severity of clefting
- Number of other affected relatives
- Consanguinity
- Environmental and nutritional factors
- Modifying genes

DEVELOPMENT OF THE HEAD AND NECK

A 4th week

B 4th week



C 5th week

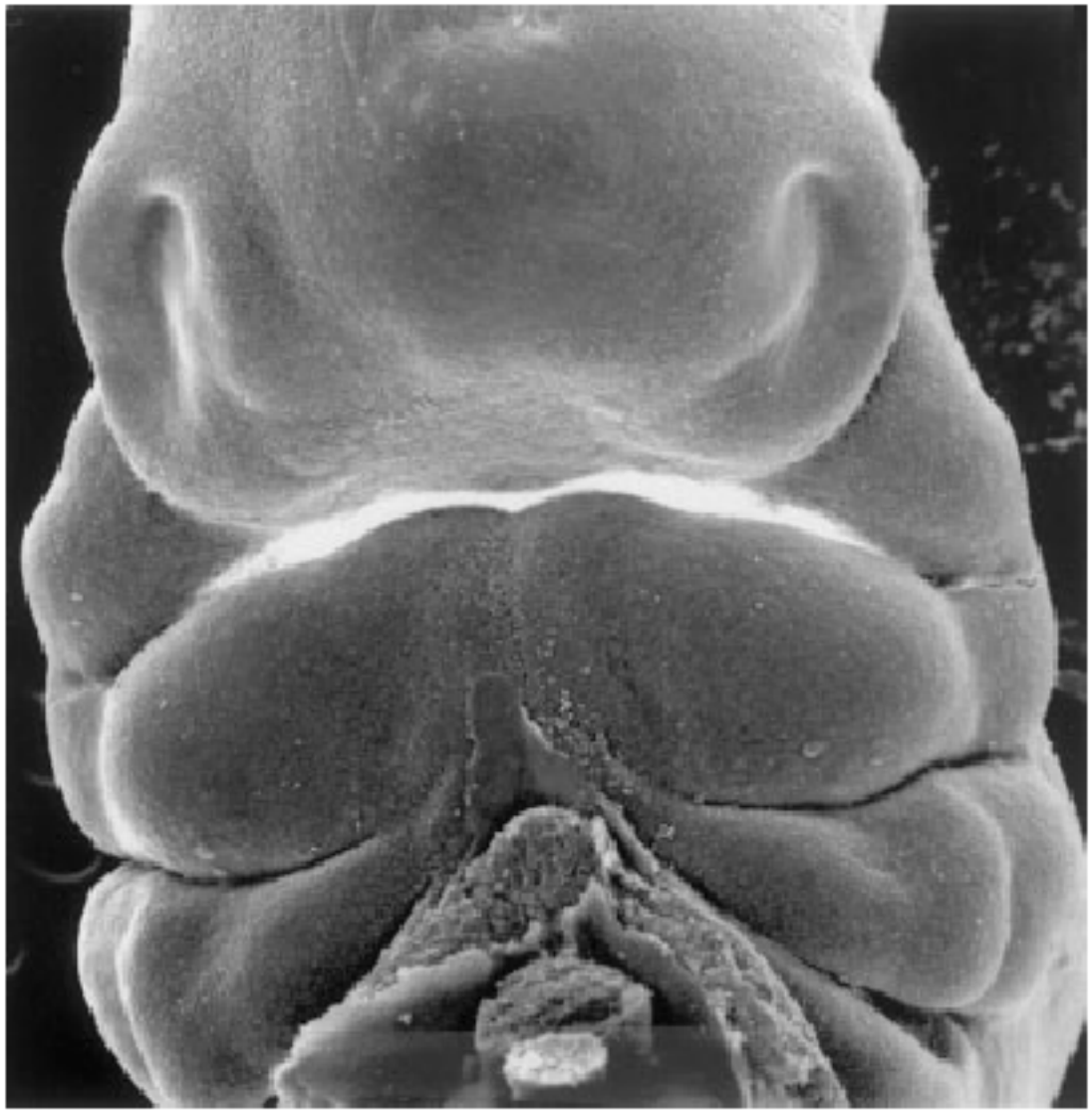


Figure 14. Scanning electron microscopy image of the face of a 5-week-old embryo. Note the olfactory pits developing on the lateral portion of the frontonasal prominence. Courtesy of K. Sulik, Chapel Hill, North Carolina.

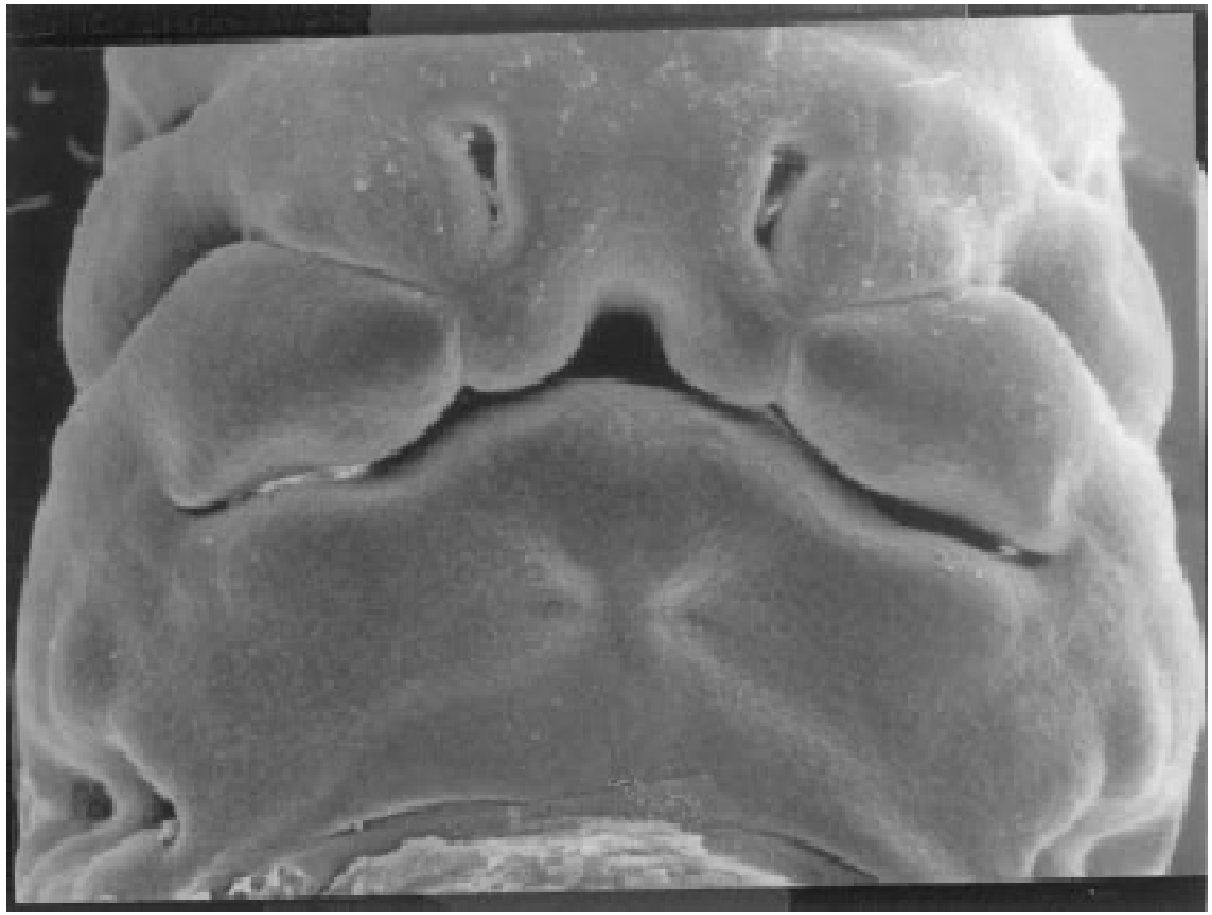
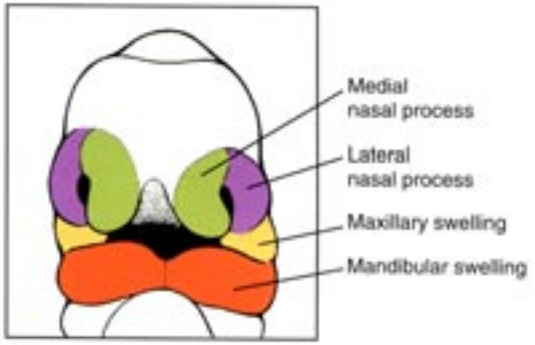


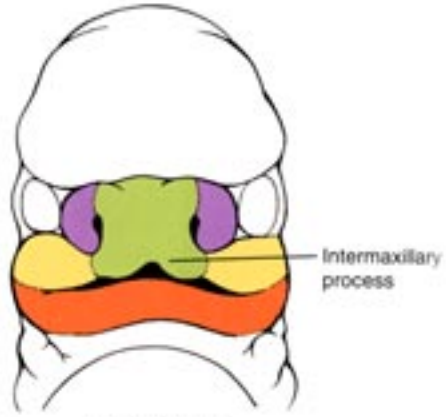
Figure 15. Scanning electron microscopy of a 6-week-old embryo. During the sixth and seventh weeks, maxillary swellings fuse with medial nasal swellings, and the medial nasal swellings merge with each other. The upper lip is still incompletely formed at the sixth week. Courtesy of K. Sulik, Chapel Hill, North Carolina.

A Early 6th week

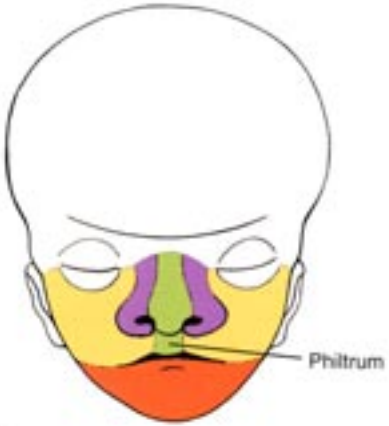


B Early 6th week

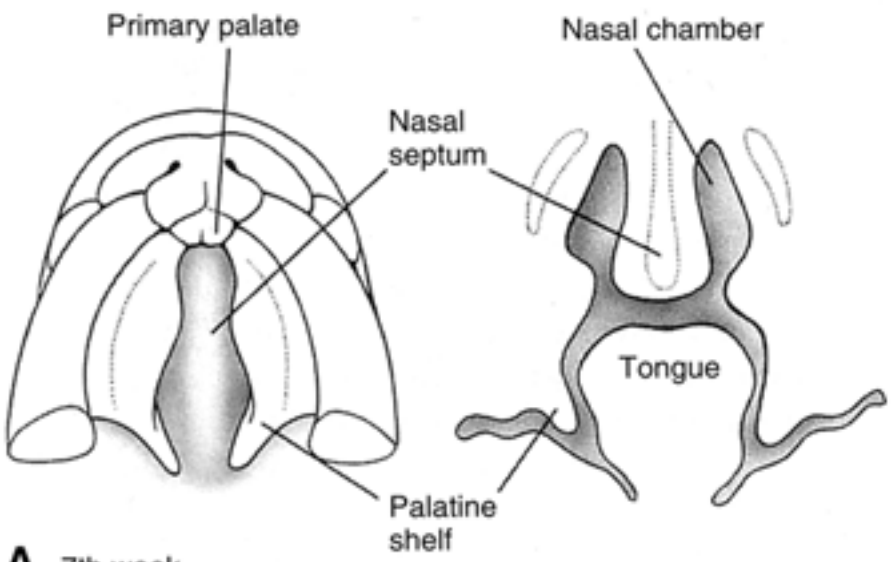
C Early 7th week



D Late 7th week

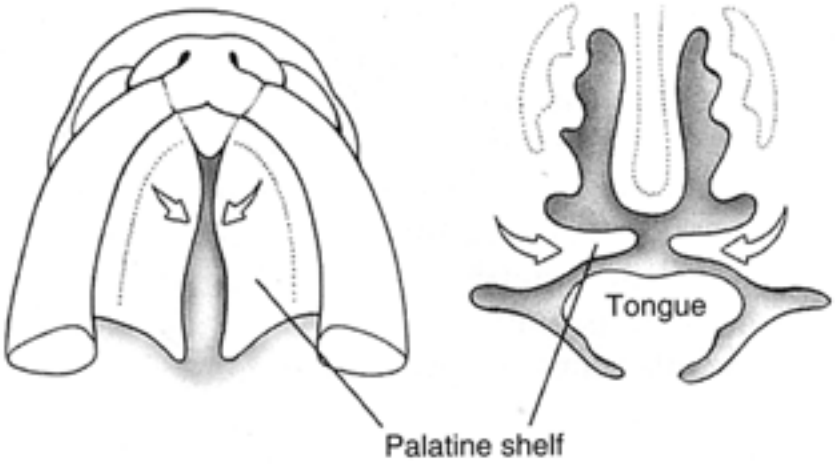


E 10th week

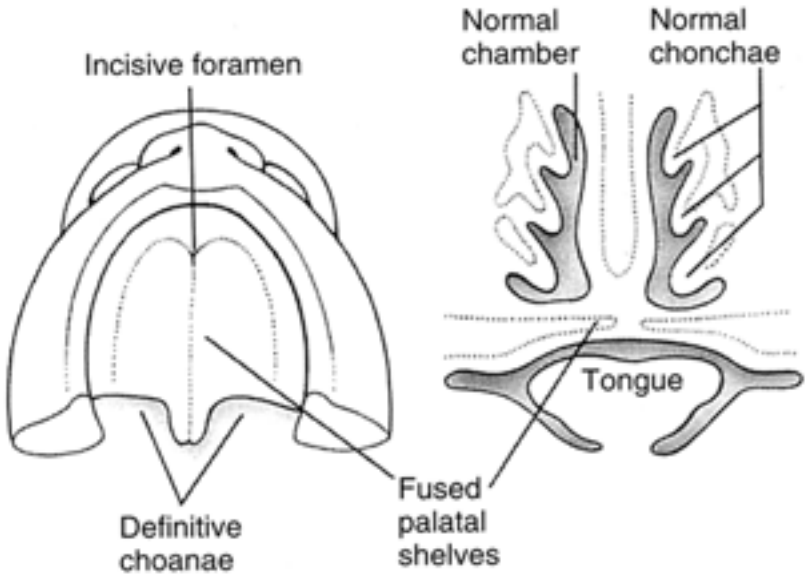


A 7th week

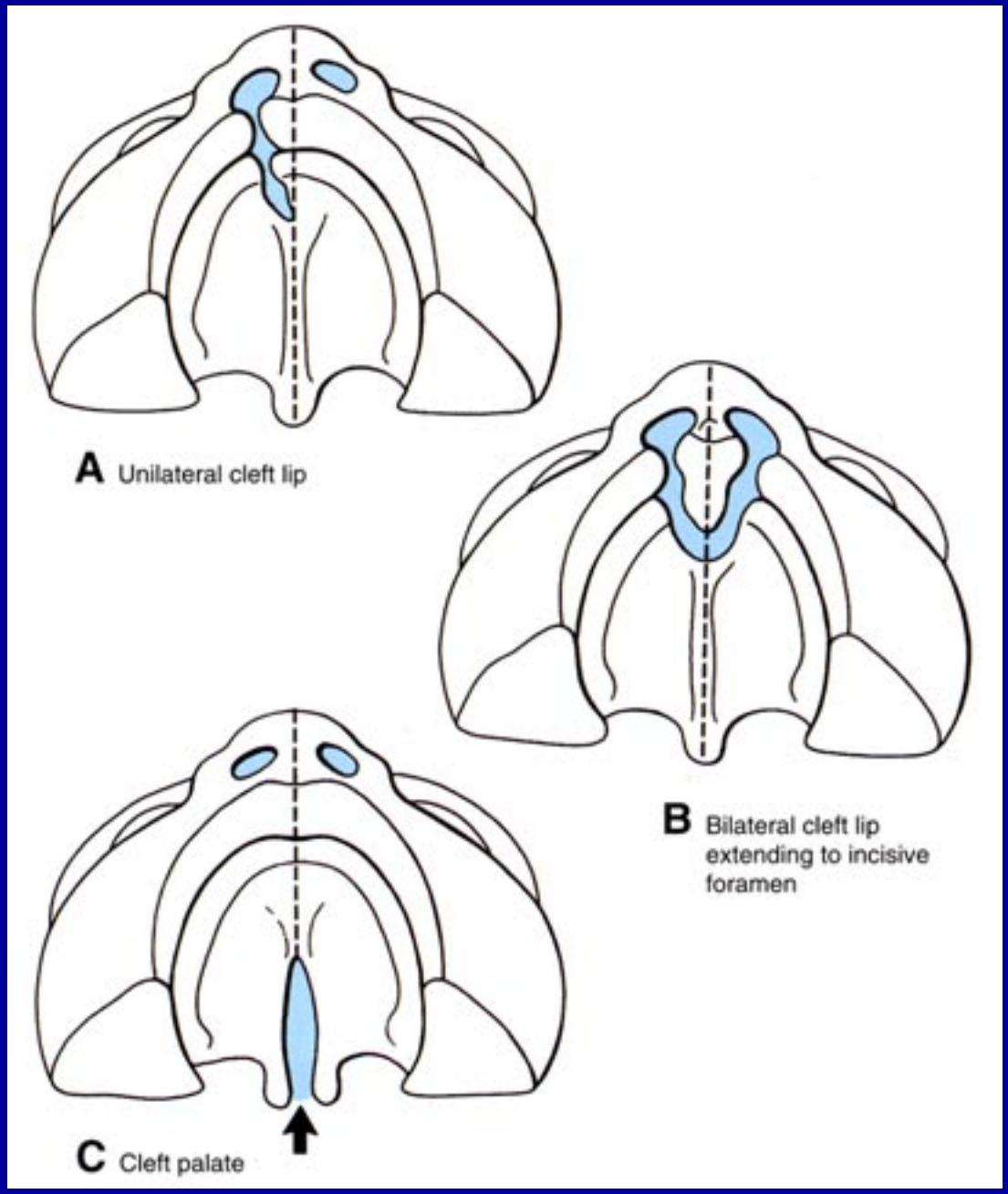
B 7th week



C 8th week



D 10th week


A Unilateral cleft lip
B Bilateral cleft lip extending to incisive foramen
C Cleft palate

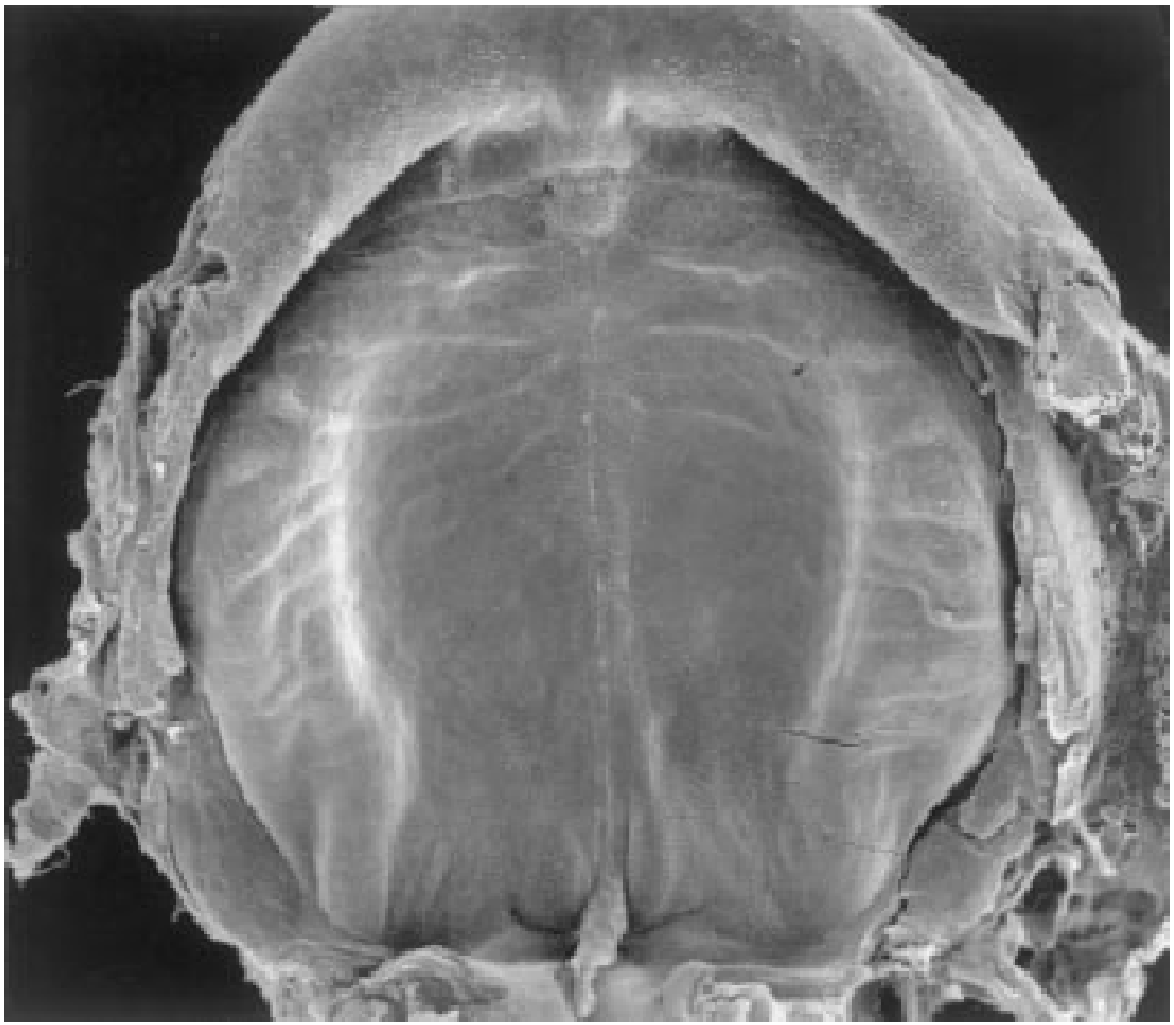


Figure 17. At 59 days, complete fusion of the secondary palate has occurred. Courtesy of L. Russell, Chapel Hill, North Carolina.

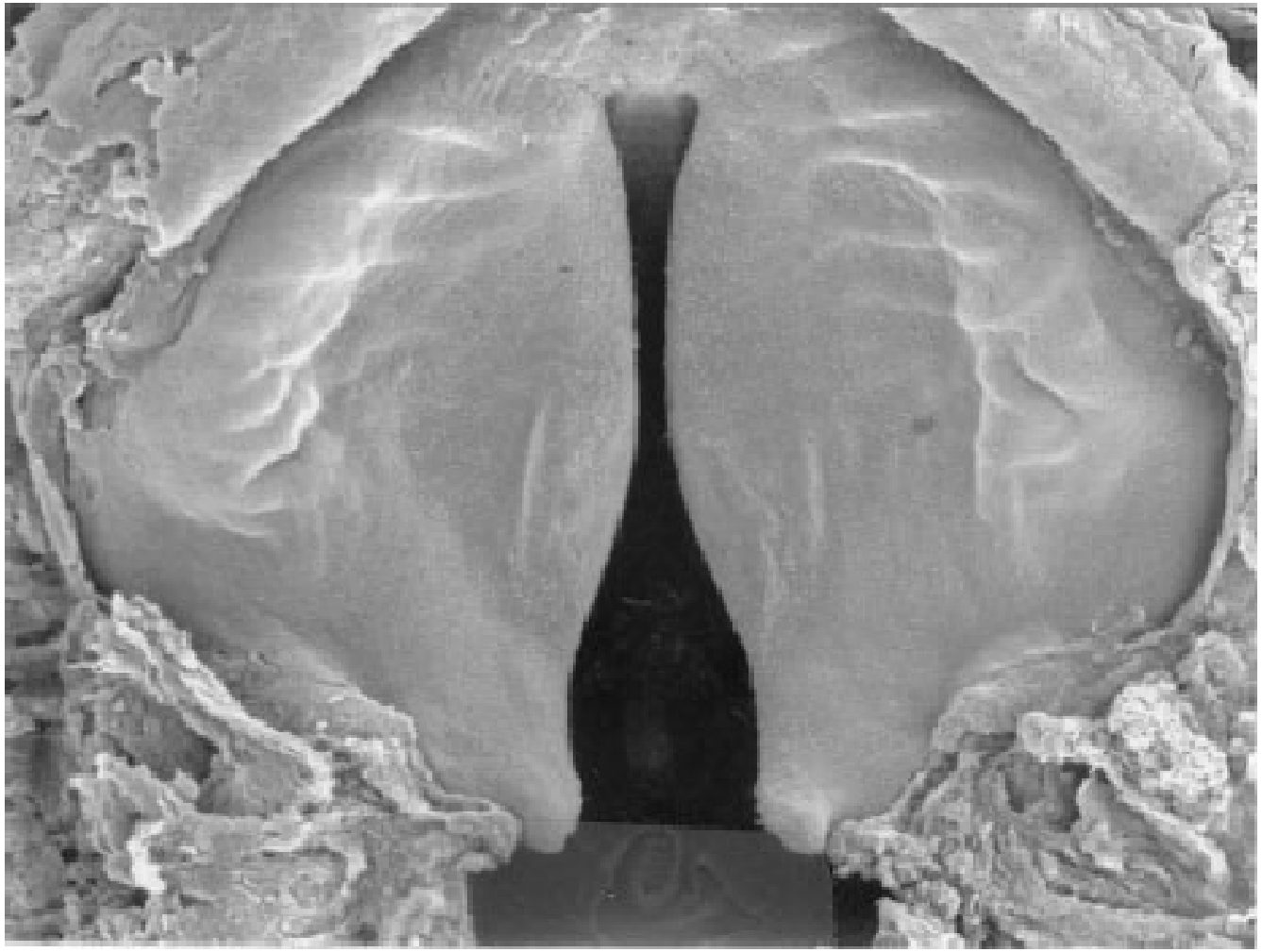


Figure 16. Scanning electron microscopy of the secondary palate in a 53-day-old embryo. Fusion with the primary palate has occurred. Courtesy of L. Russell, Chapel Hill, North Carolina.