Neural Tube Closure and Associated Defects

Jeffrey Golden, MD
Vice Dean, Research and Graduate Education
Cedars Sinai Medical Center

AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

At the end of this activity learners should be able to:

- Describe the process of neural tube closure
- Explain the mechanisms of neural tube closure defects
- Categorize different types of neural tube closure defects

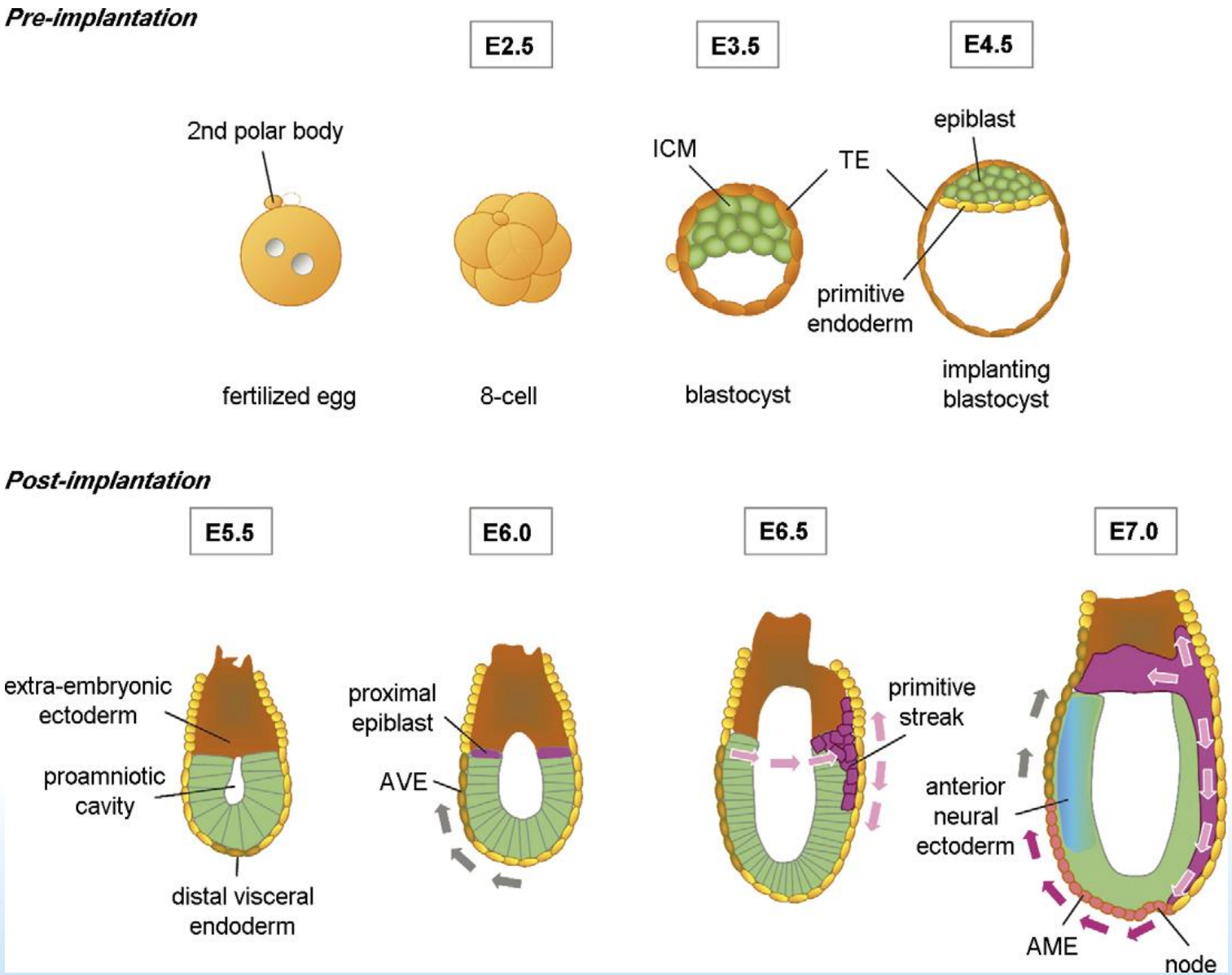
DEFINITIONS

Cranial

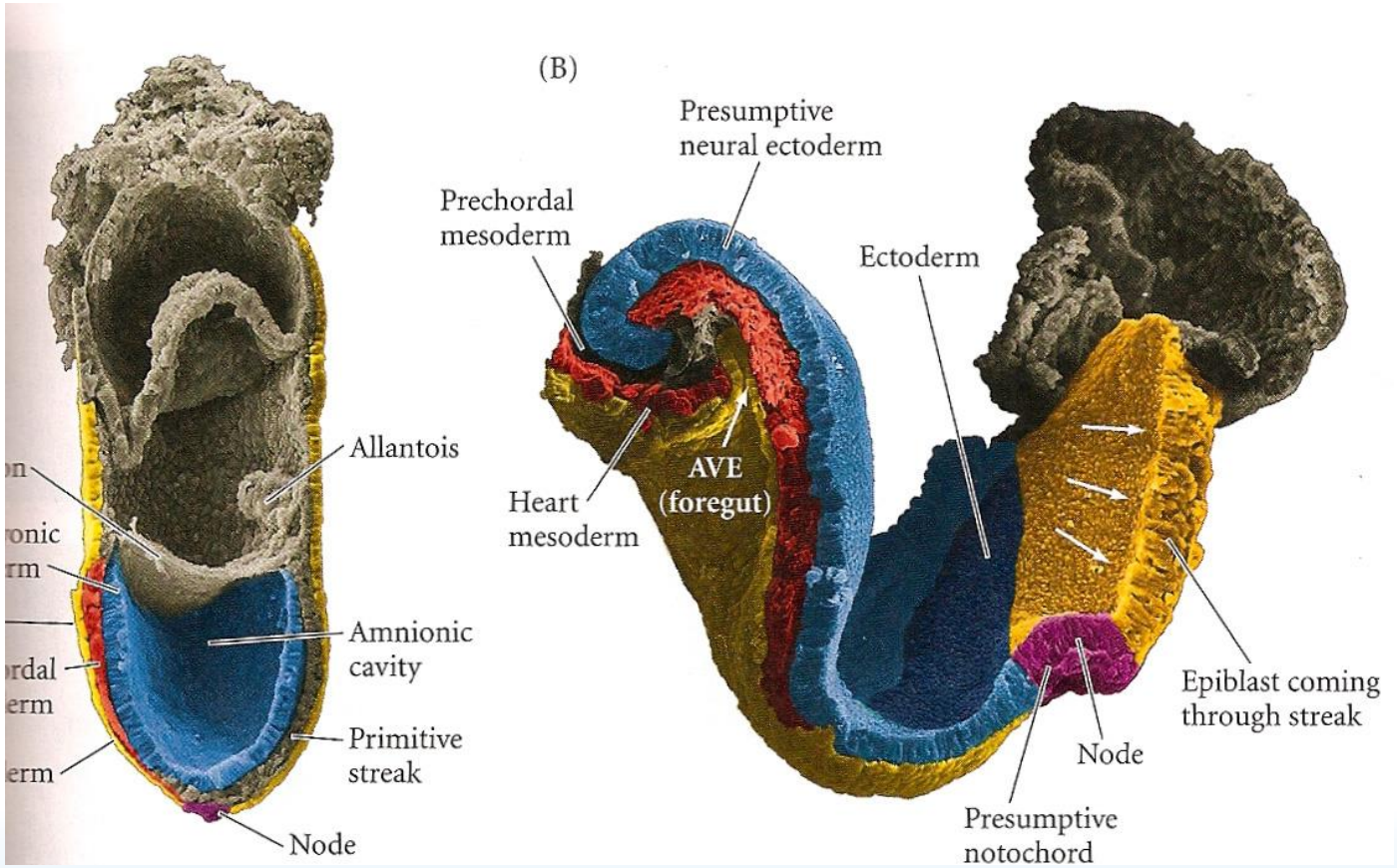
Anencephaly
Encephalocele
Iniecephaly
Cranial meningocele
Acalvaria
Craniorachischisis

Spinal

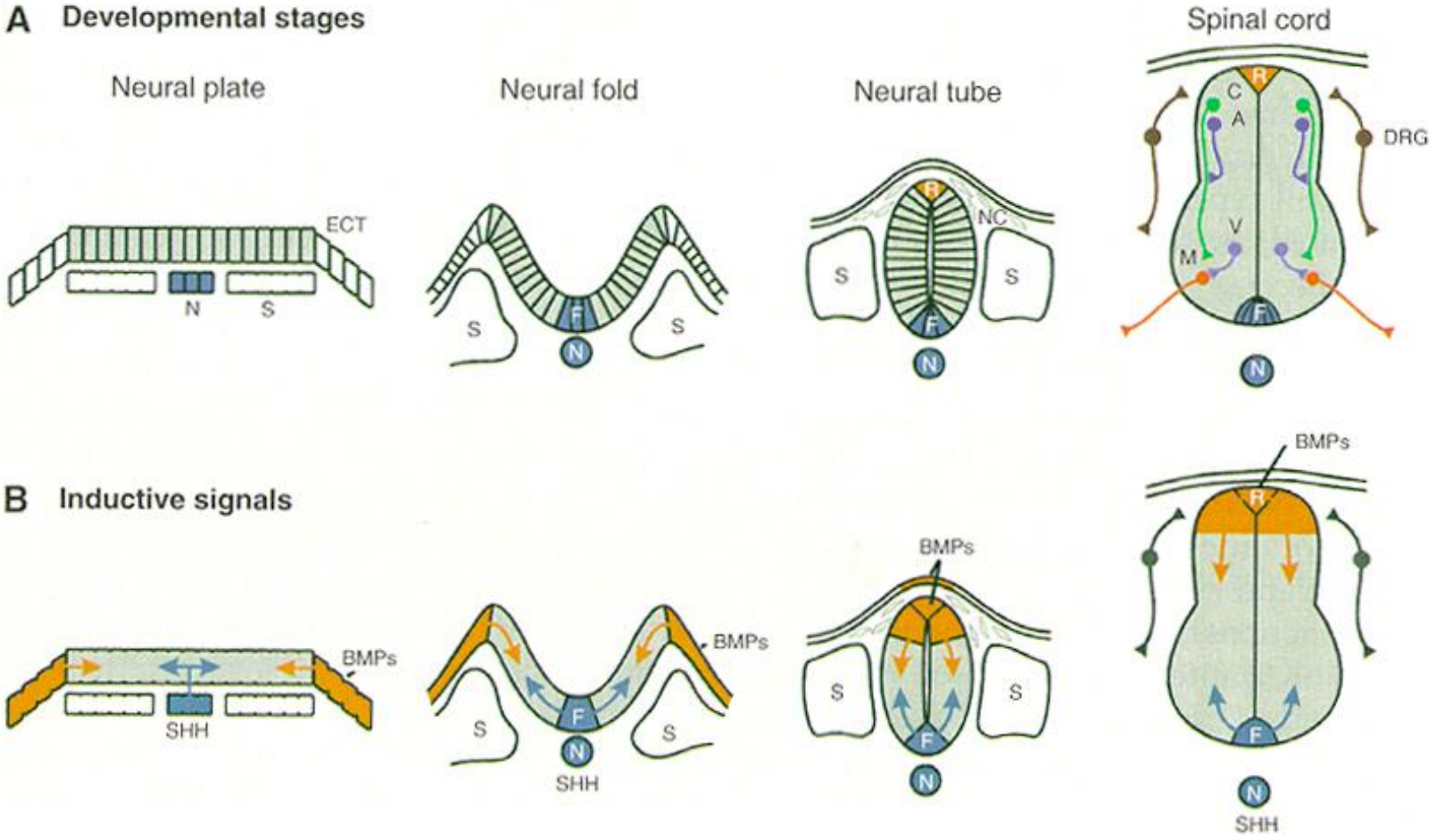
Spina Bifida occulta
Spina Bifida cystica
Myelomeningocele
Myelocele
Meningocele
Myelocystocele
Rachischisis
Tethered cord



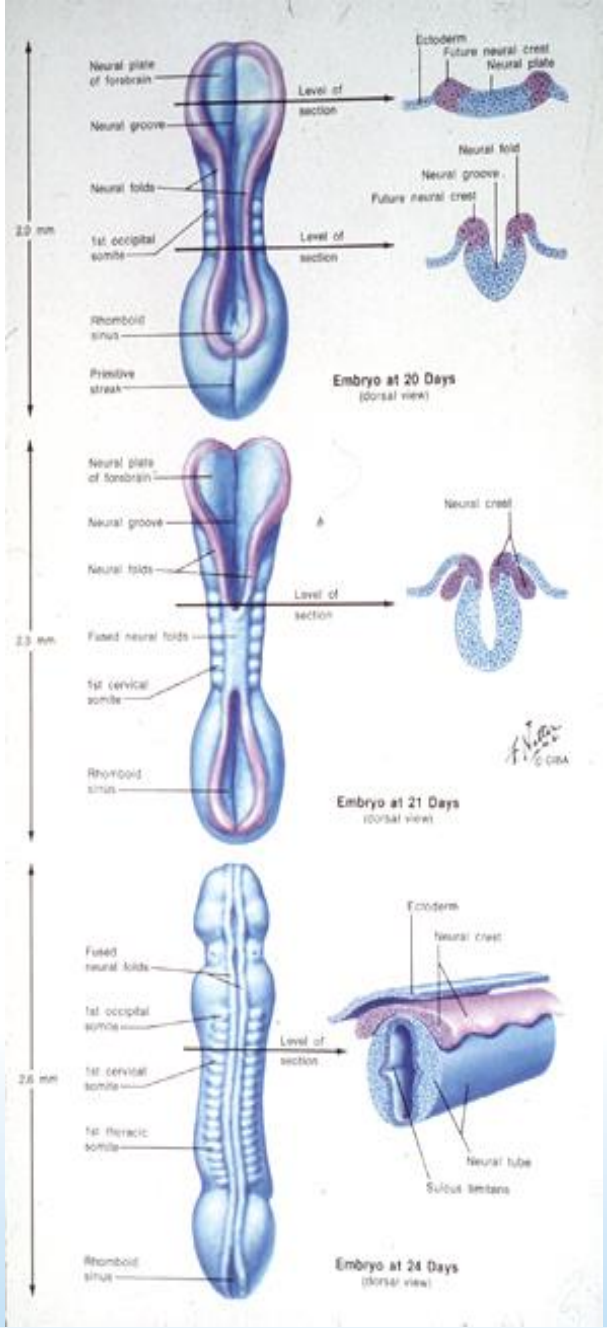
Gilbert, Developmental Biology, 1994



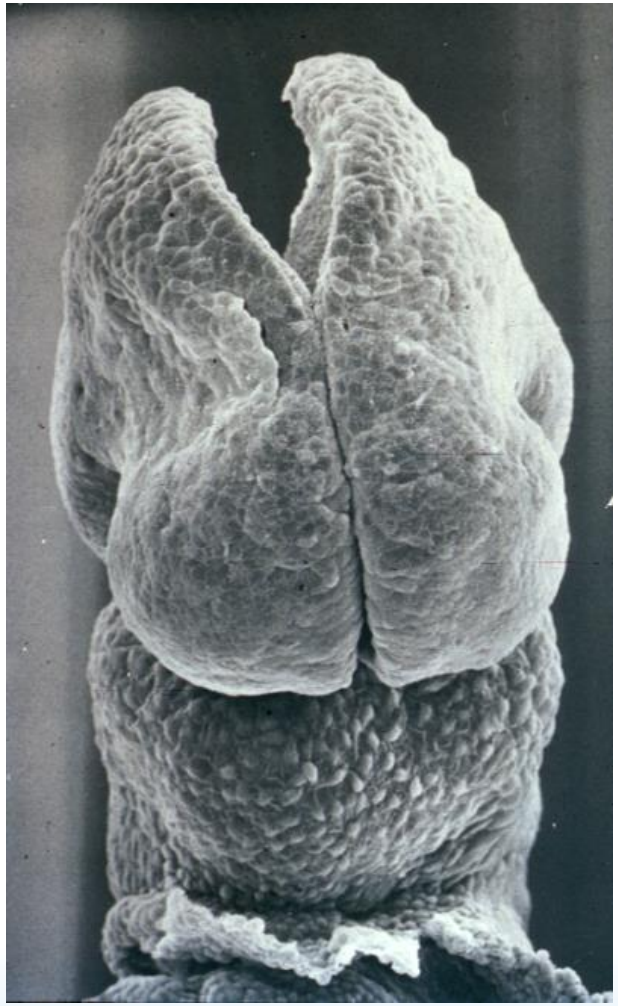
Gilbert, Developmental Biology, 1994

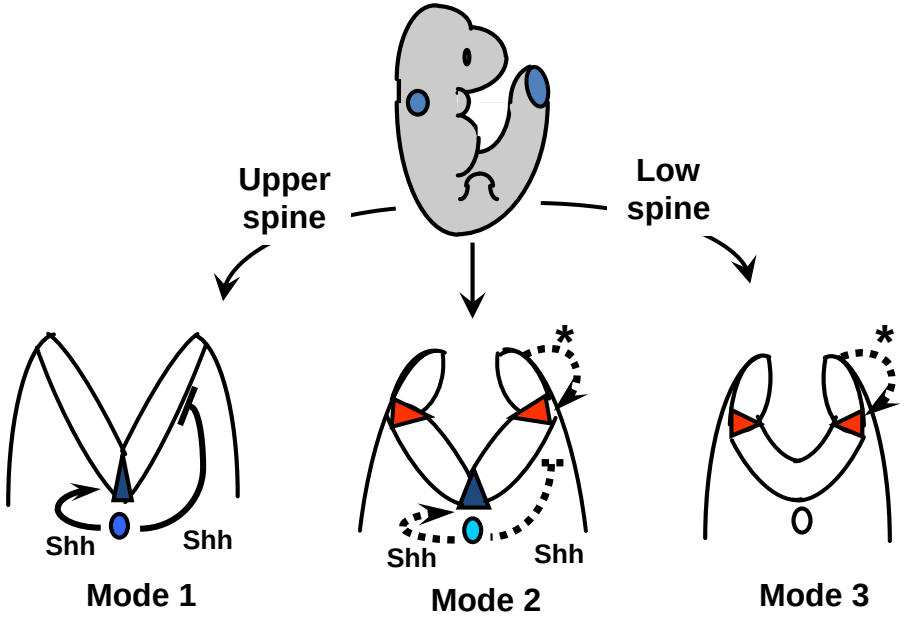


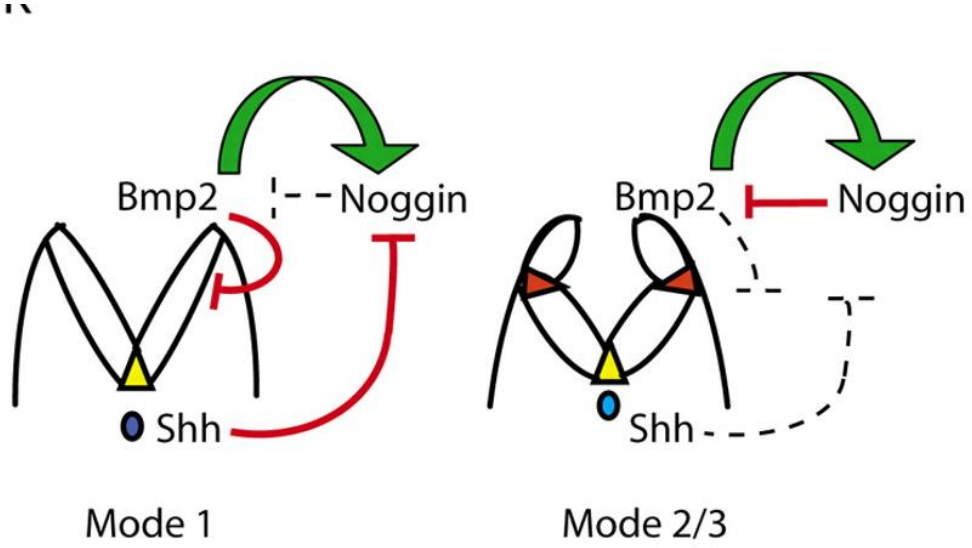
Gilbert, Developmental Biology, 1994


Neural plate of forebrain
Neural groove
Neural folds
1st occipital somite
Rhomboid sinus
Primitive streak
2.0 mm
Level of section
Ectoderm
Future neural crest
Neural plate
Neural fold
Neural groove
Future neural crest
Embryo at 20 Days
(dorsal view)
Neural plate of forebrain
Neural groove
Neural folds
Fused neural folds
1st cervical somite
Rhomboid sinus
2.3 mm
Level of section
Neural crest
Embryo at 21 Days
(dorsal view)
Fused neural folds
1st occipital somite
1st cervical somite
1st thoracic somite
Rhomboid sinus
2.6 mm
Level of section
Ectoderm
Neural crest
Neural tube
Sulcus limitans
Embryo at 24 Days
(dorsal view)

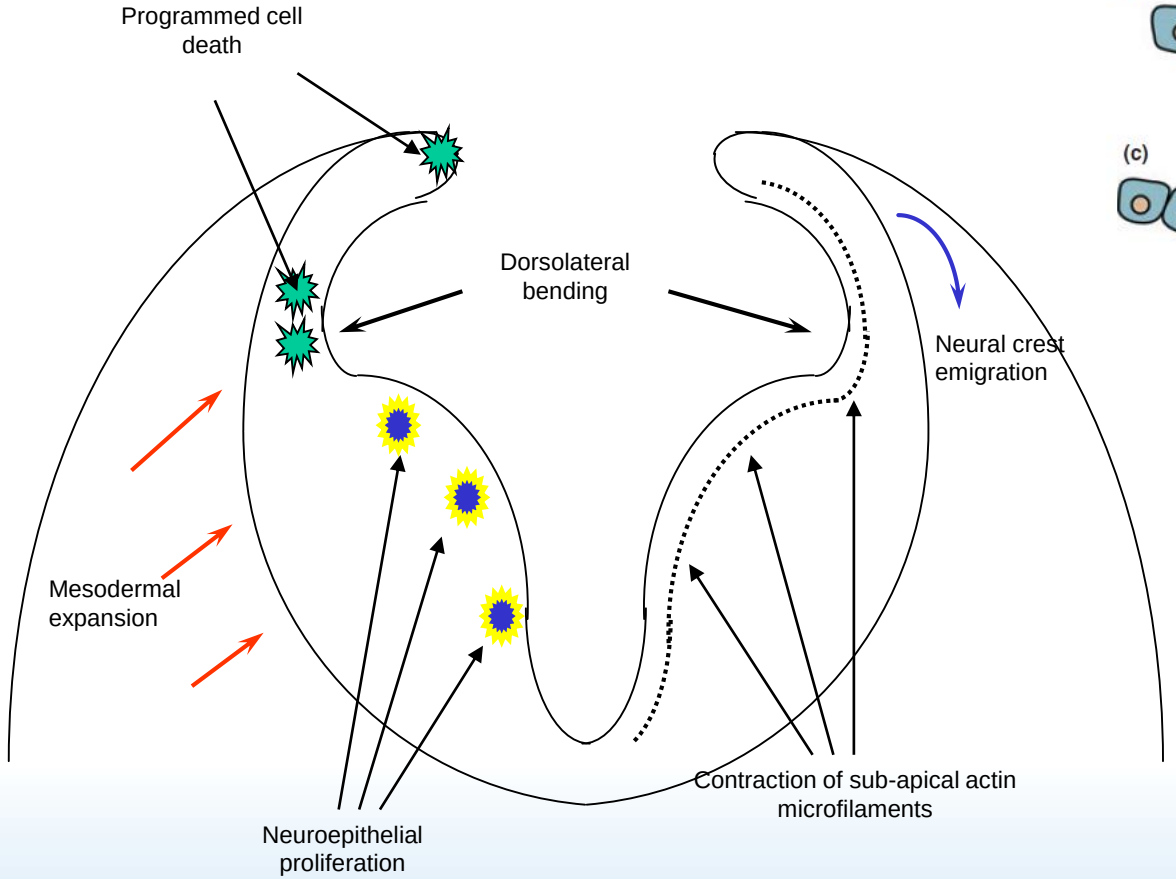


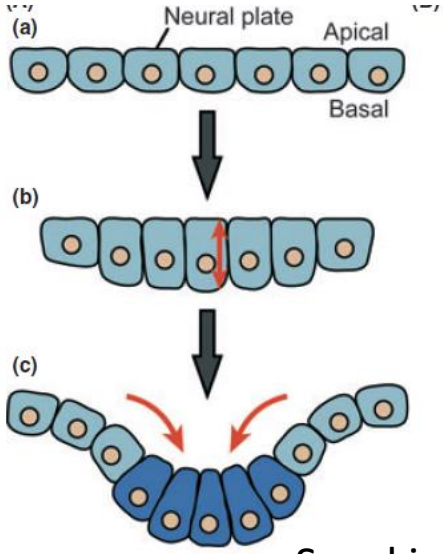


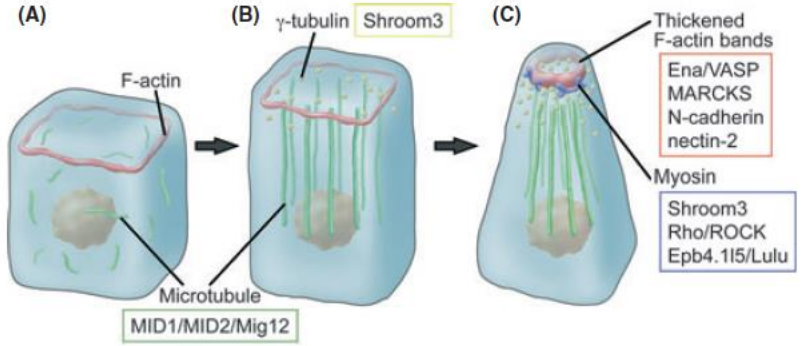





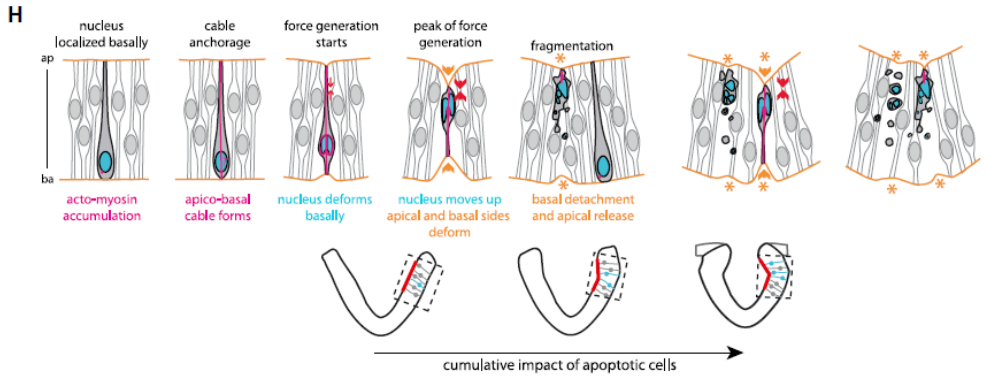
Ybot-Gonzalez et al, Development, 2007



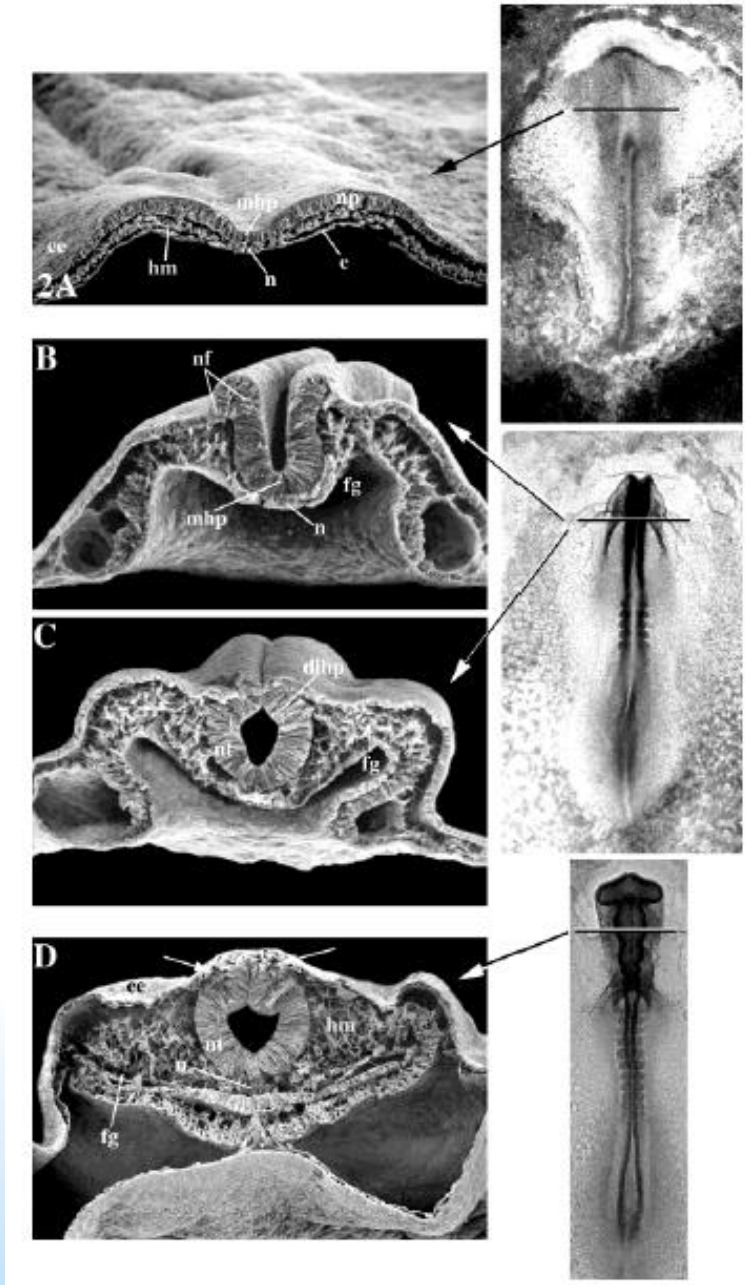


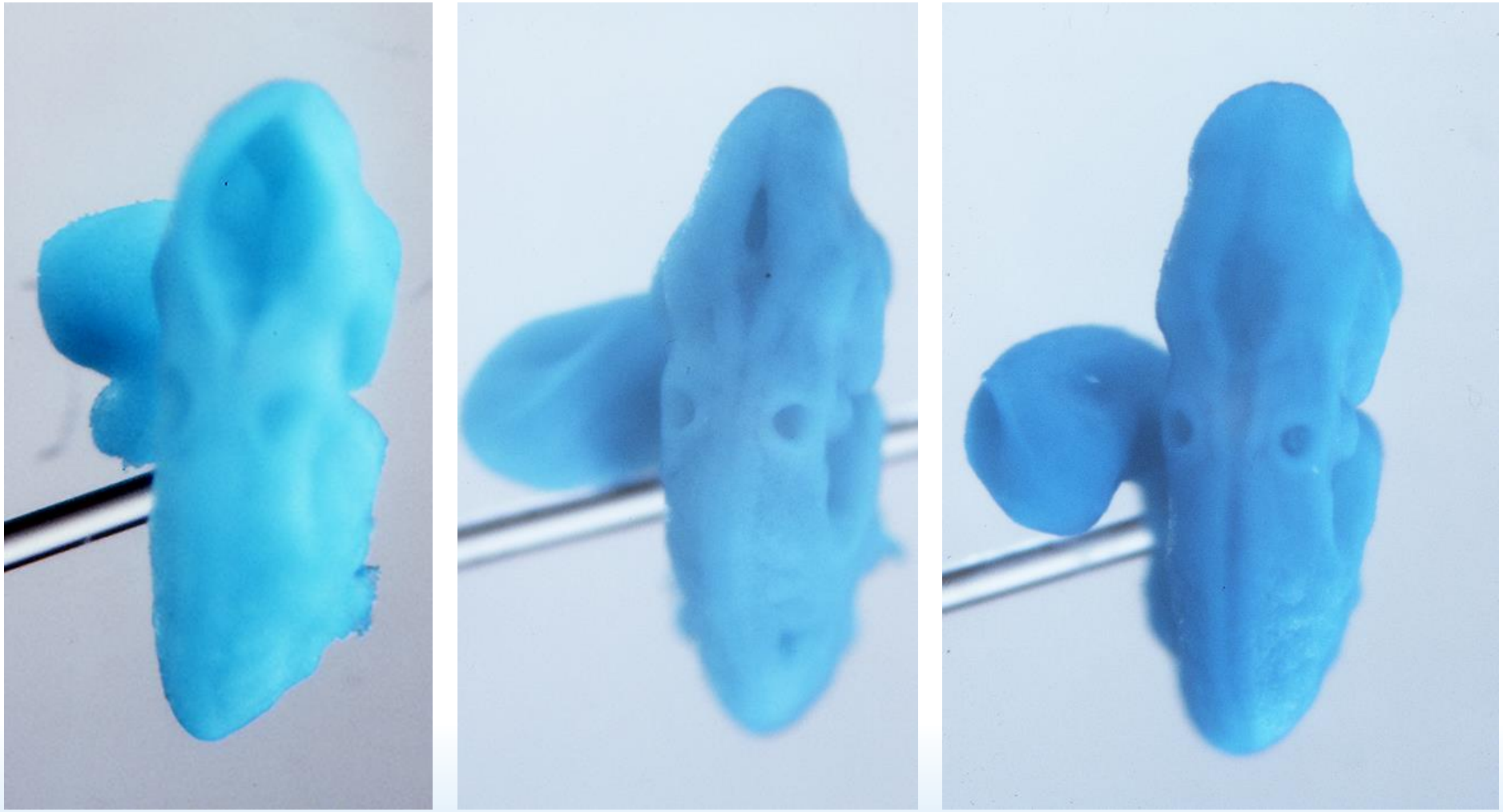


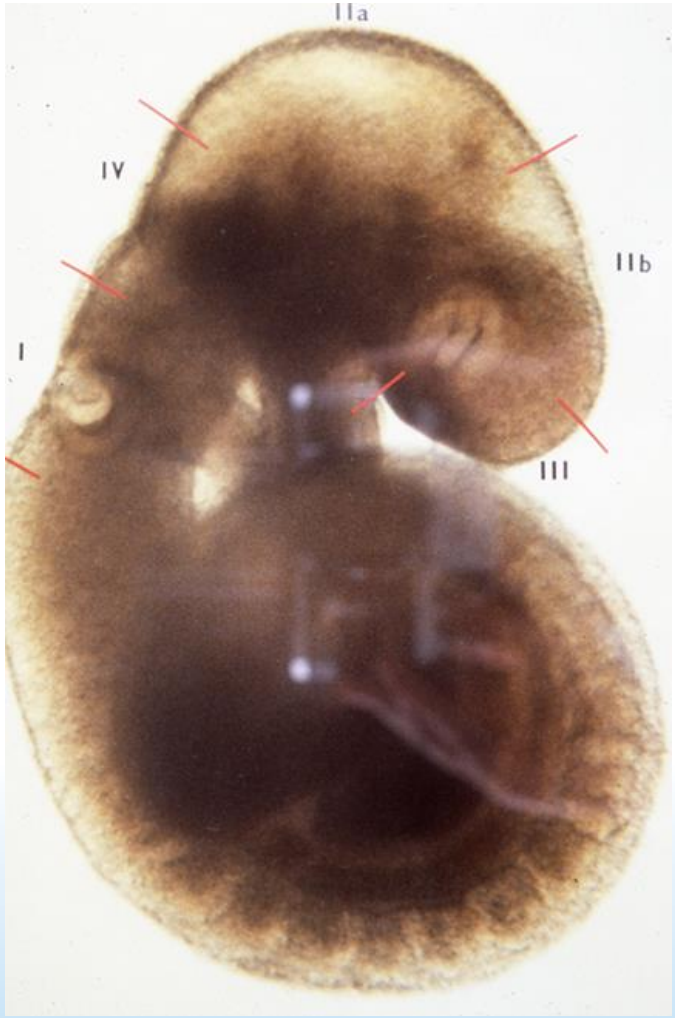
Suzuki, Morita, Ueno. Develop Growth Differ. 2012



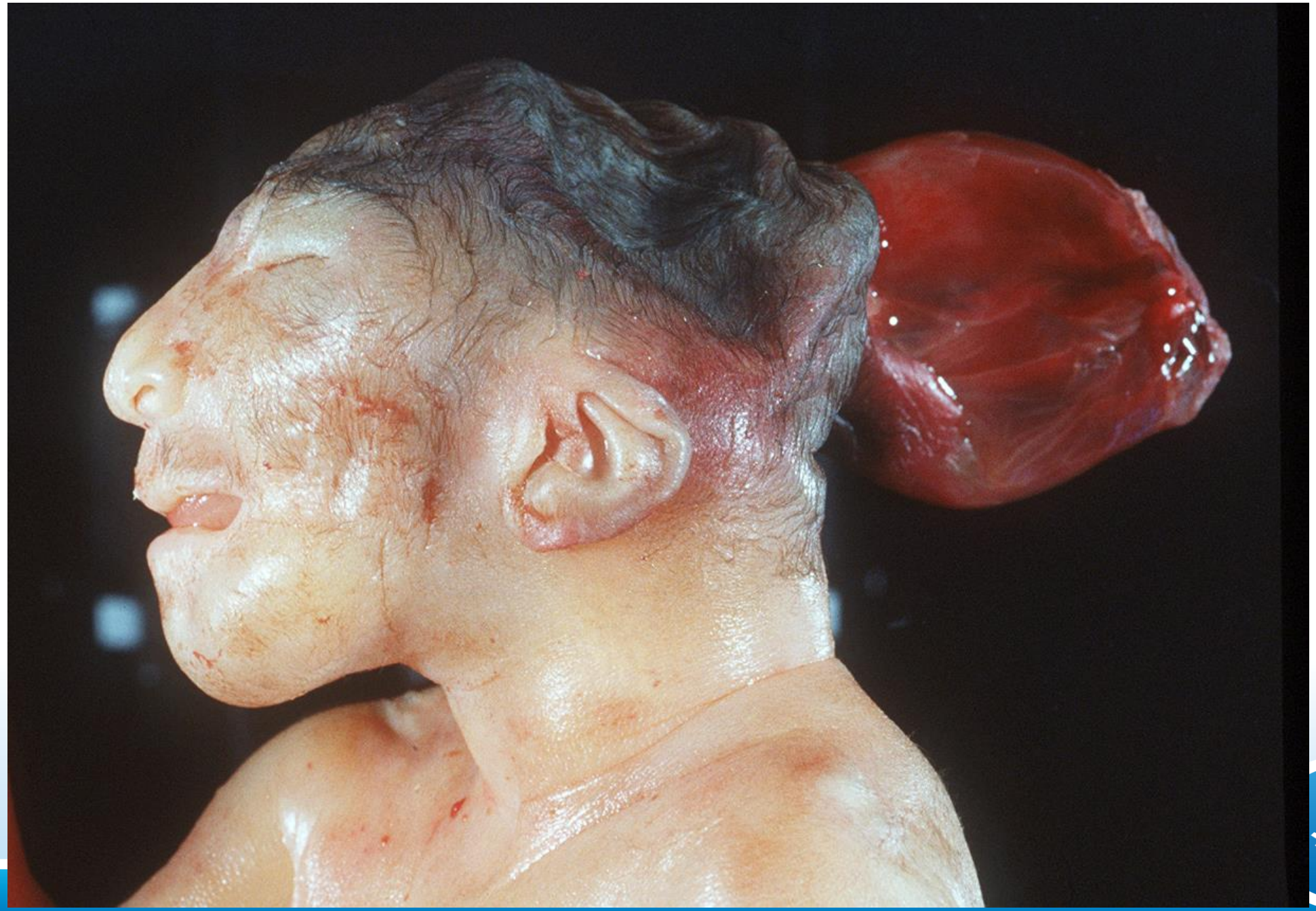
Roellig et al, Developmental Cell, 2022

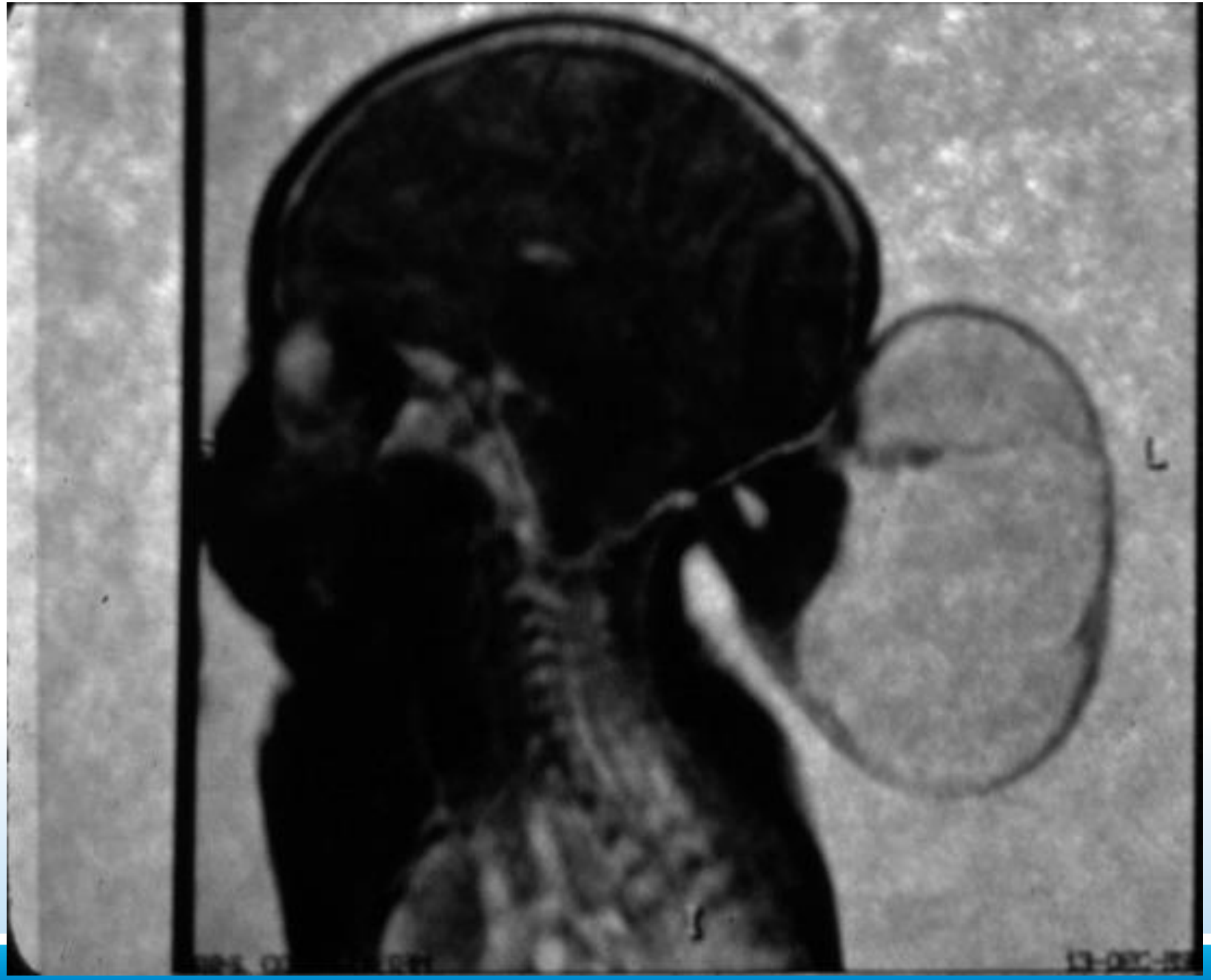

2A
ve
hm
mhp
n
e
B
nf
fg
mhp
n
C
dhp
nf
fg
D
ec
hm
nf
n
fg



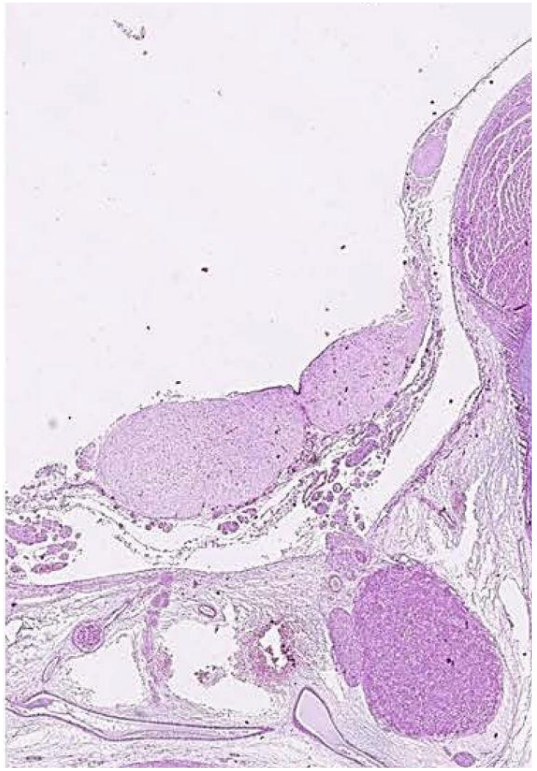

IIa
IV
IIb
I
III

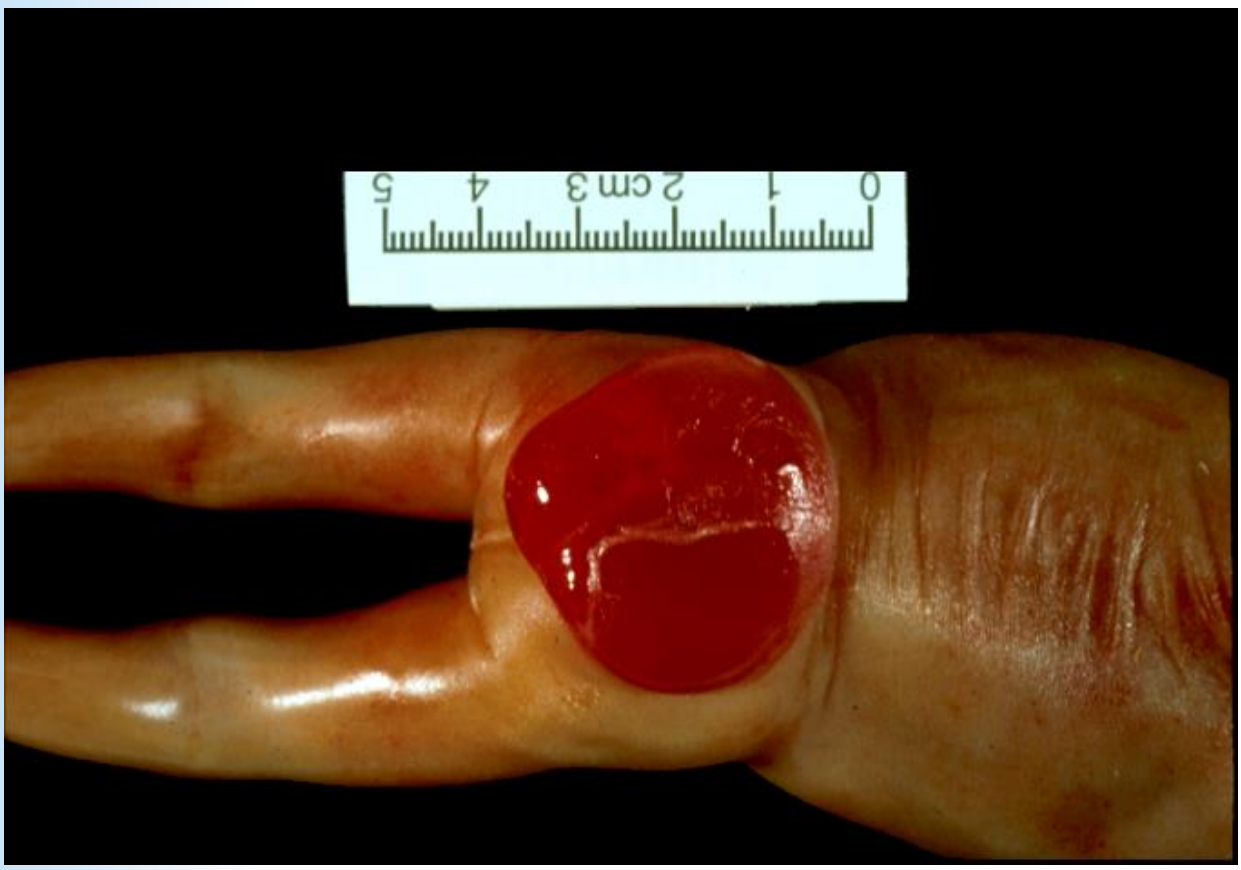
Avagliano et al, Birth Defects Res 2019

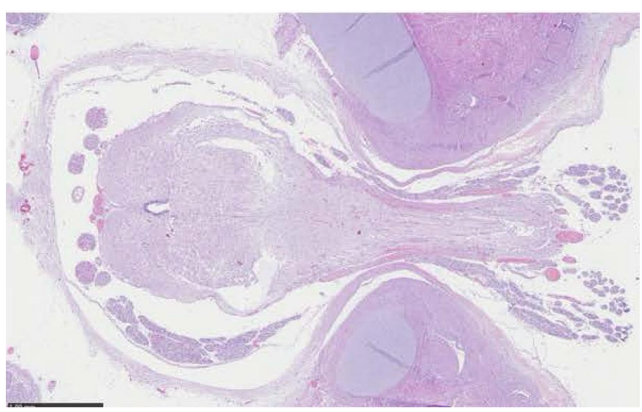


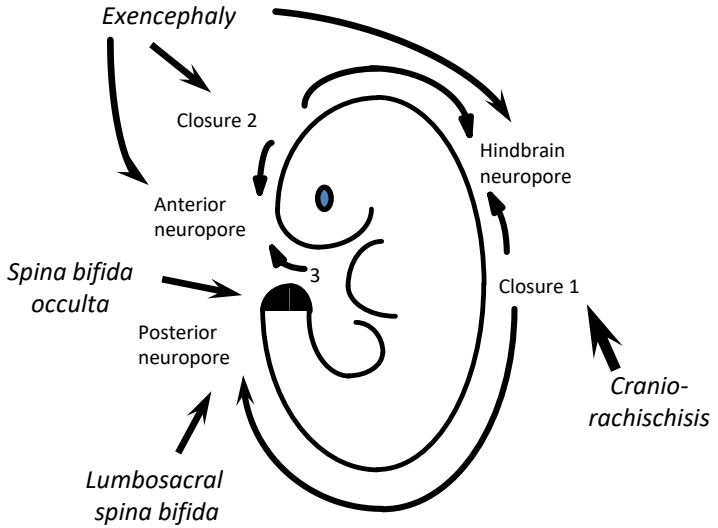

L

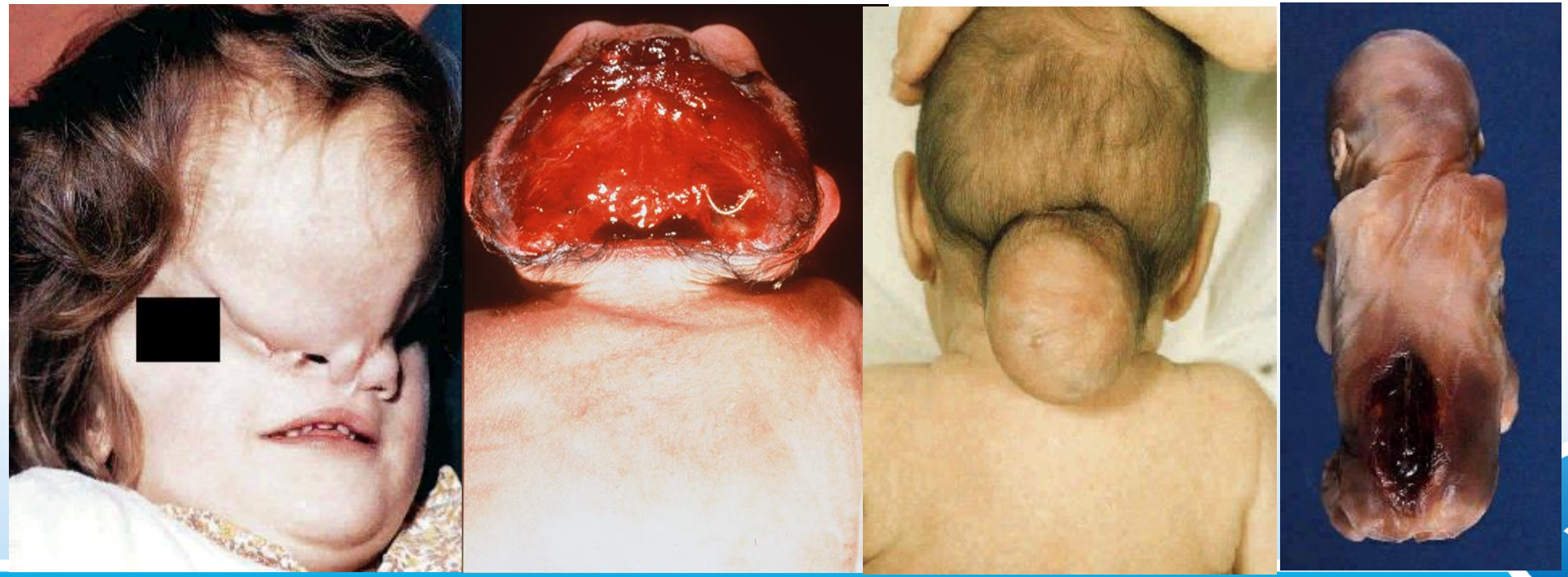

CENTIMETERS
Cat. No. 09-016
G92-

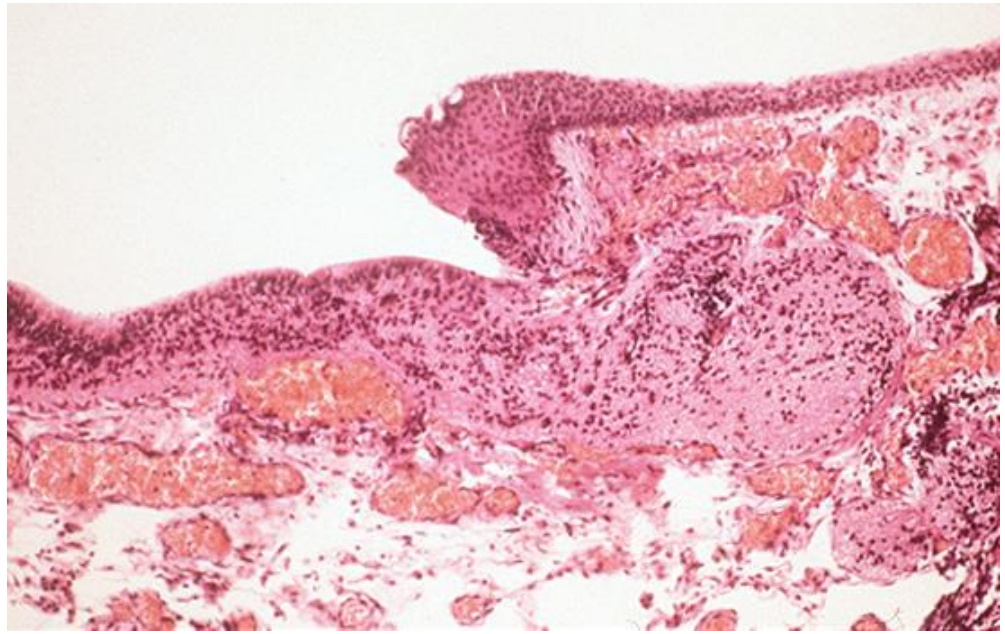


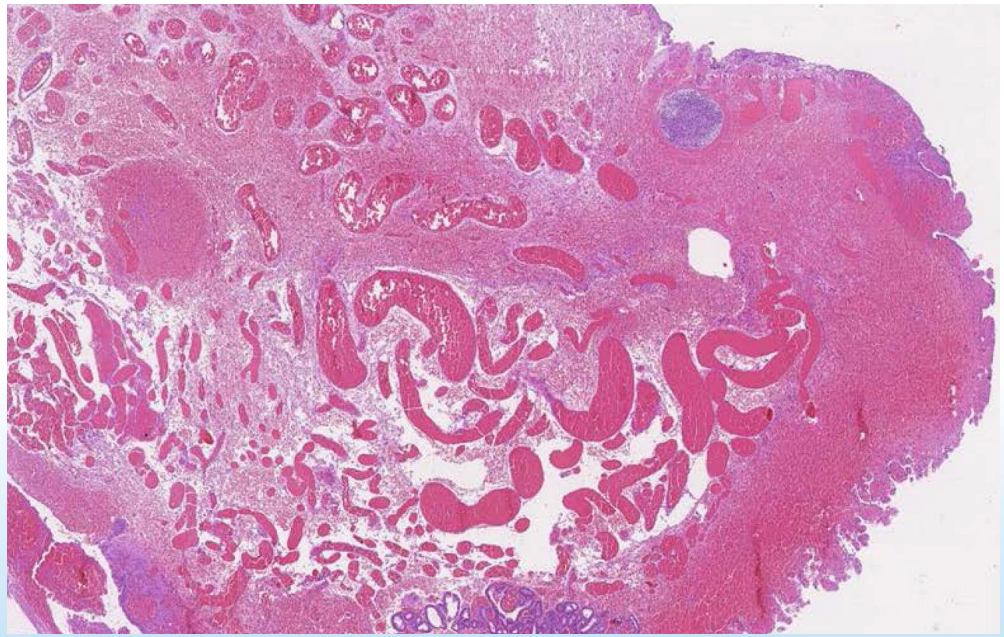

0 1 2 cm 3 4 5

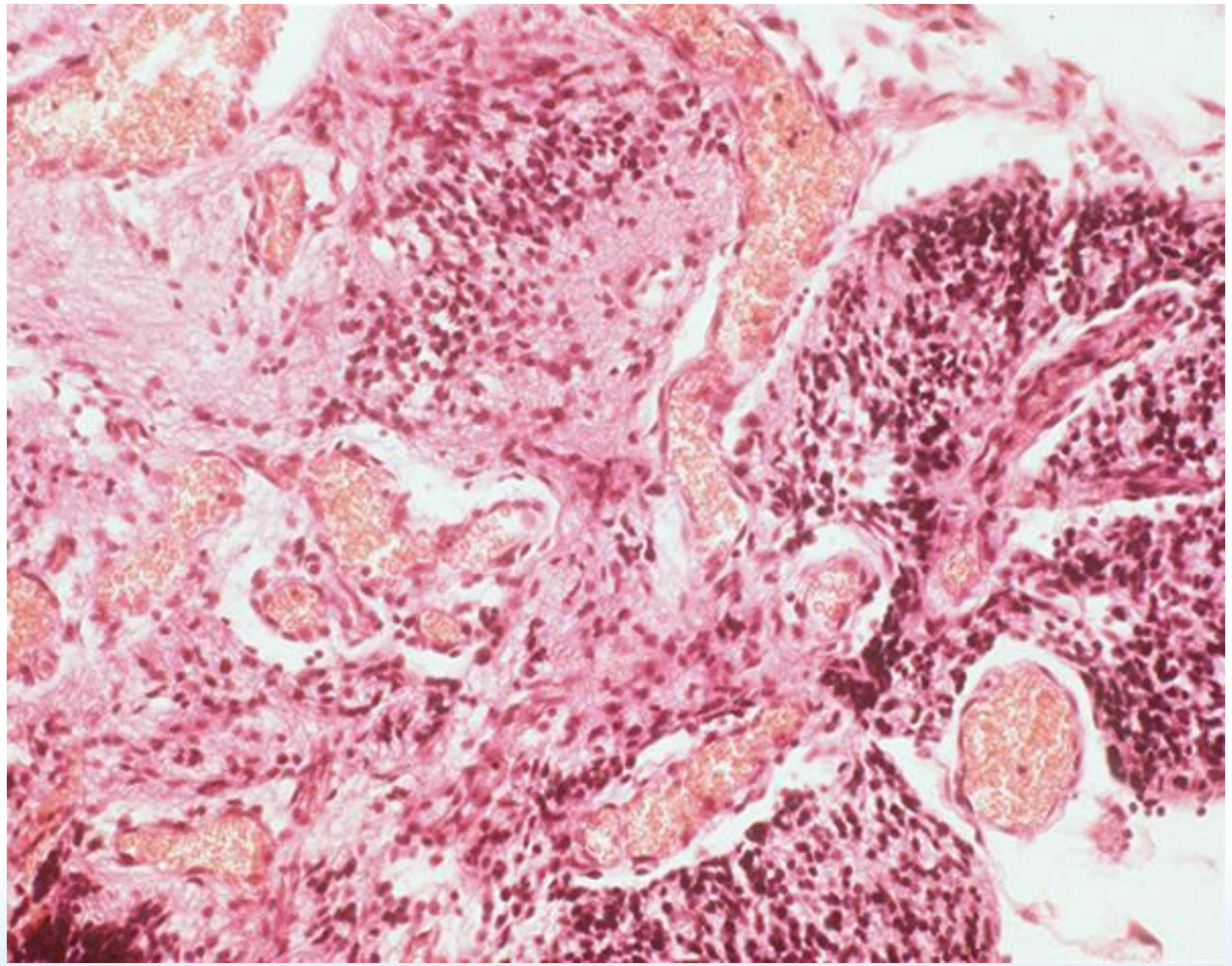


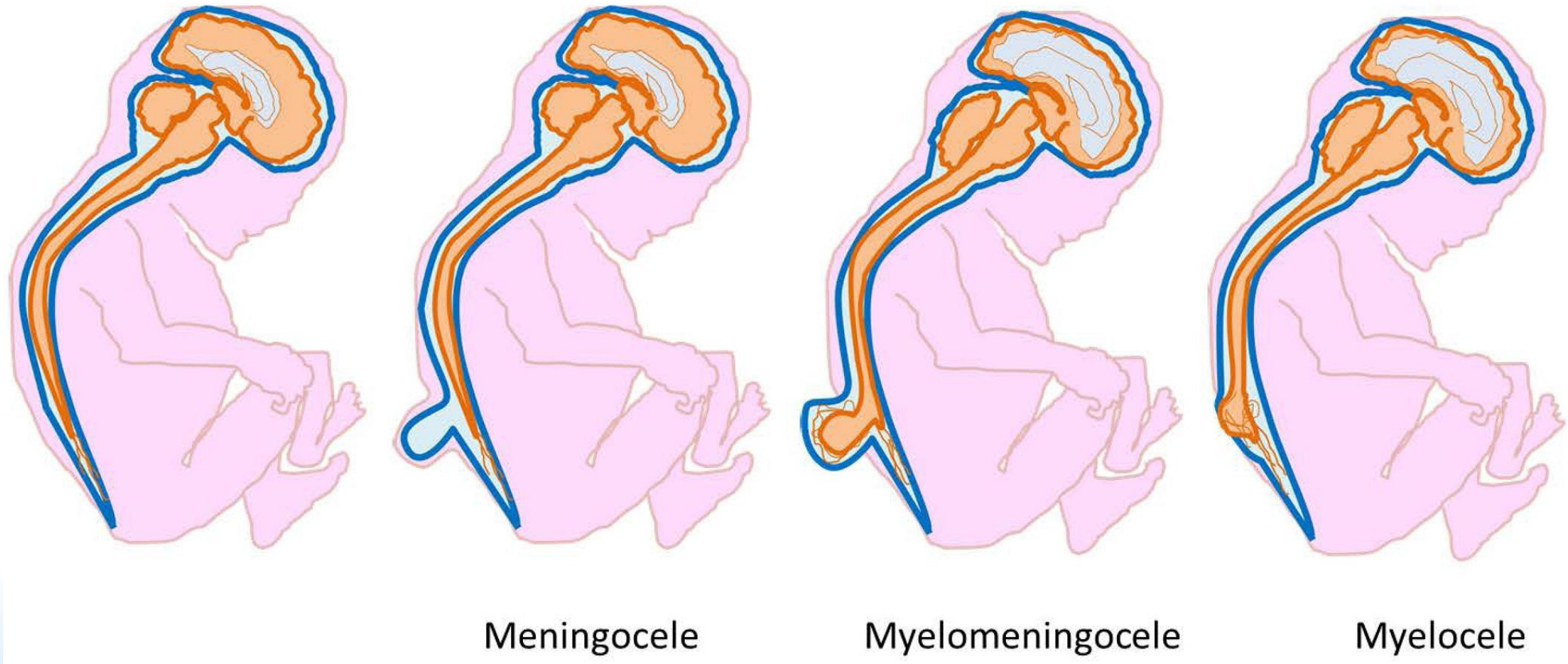

Exencephaly
Closure 2
Hindbrain neuropore
Anterior neuropore
Spina bifida occulta
3
Closure 1
Posterior neuropore
Cranio-rachischisis
Lumbosacral spina bifida





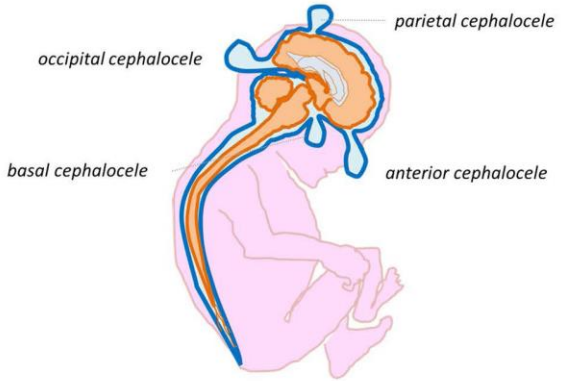




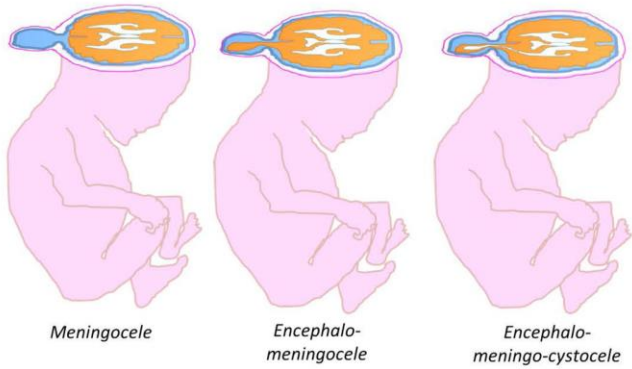


Avagliano et al, Birth Defects Res 2019

Classification according to the site



Classification according to the content



Example of different size of cephaloceles

Avagliano et al, Birth Defects Res 2019

Table 1:

Modifiable risk factors for NTDs

Risk Factor	Action	Risk	References
Maternal diabetes	Teratogenic effect due to embryonic exposure to high glucose concentrations leading to increased cell death in the neuroepithelium	2-10-fold increase	(Ray, 2001; Shaw et al., 2003; Yazdy, Mitchell, Liu, & Werler, 2011)
Maternal obesity	Teratogenic effect due to embryonic exposure to hyperinsulinemia, metabolic syndrome, and oxidative stress related to adiposity	1.5-3.5-fold increase. The risk increases with increased maternal body mass index	(Anderson et al., 2005; Carmichael, Rasmussen, Lammer, Ma, & Shaw, 2010; Dietl, 2005; Hendricks, Nuno, Suarez, & Larsen, 2001; Shaw, Velie, & Schaffer, 1996; Werler, Louik, Shapiro, & Mitchell, 1996)
Maternal Hyperthermia (sauna, hot water tube, fever)	Teratogenic effect due to embryonic exposure to heat stress	2-fold increase	(Moretti, Bar-Oz, Fried, & Koren, 2005; Suarez, Felkner, & Hendricks, 2004; Waller et al., 2017)
Drugs (particularly valproate)	Teratogenic effect due to embryonic exposure to valproate action as inhibitor of histone deacetylases, disturbing the balance of protein acetylation and deacetylation, leading to neurulation failure	10-fold increase	(Kanai, Sawa, Chen, Leeds, & Chuang, 2004; Lammer, Sever, & Oakley, 1987; Meador et al., 2006; Pai et al., 2015; Yildirim et al., 2003)
Inadequate maternal nutritional status	Teratogenic effect due to embryonic exposure to low folate intake, low methionine intake, low zinc intake, low serum vitamin B12 level, low vitamin C level, caffeine abuse, alcohol use, smoking, all conditions disturbing the folate-related metabolism	Undetermined	(Grewal, Carmichael, Ma, Lammer, & Shaw, 2008; Kirke et al., 1993; Ray & Blom, 2003; Schmidt et al., 2009; Suarez, Hendricks, Felkner, & Gunter, 2003; Velie et al., 1999)

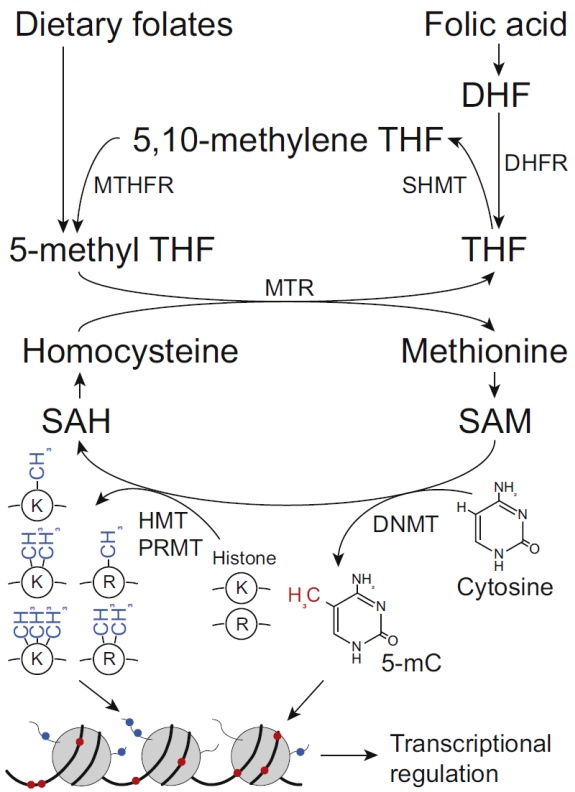
Avagliano et al, Birth Defects Res 2019

Table 2:

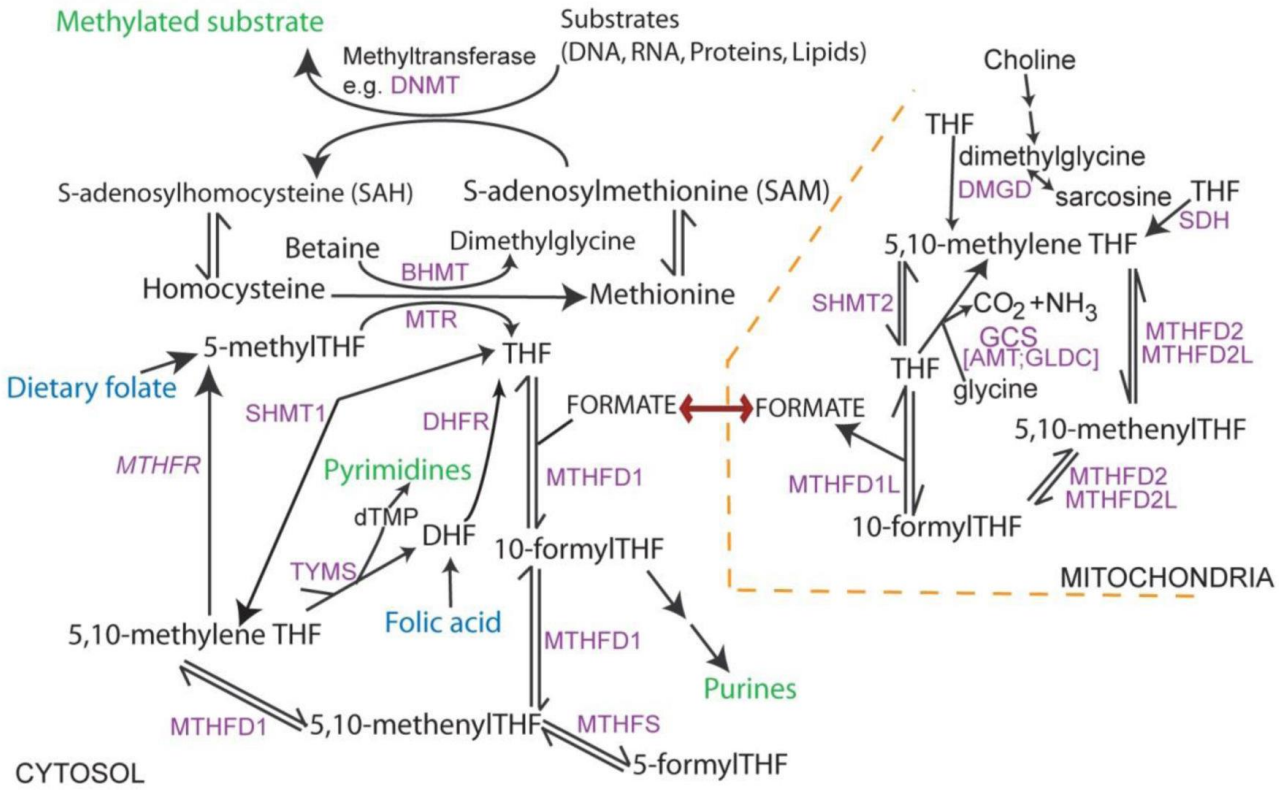
Differential diagnosis between meningocele, myelomeningocele and myelocele

Type of defect	Meningocele Closed	Myelomeningocele Open	Myelocele Open
Ultrasound aspects			
Posterior anechogenic cystic mass (sac-like protrusion) from the spine	+	+	–
Presence of septa in the sac	–	+	//
Abnormality of vertebral bones (absence of the arches)	+	+	+
Abnormal shape of skull (lemon sign)	–	+	+
Abnormal shape of cerebellum (banana sign)	–	+	+
Association with Chiari type II malformation	–	+	+
Association with hydrocephalus	–	+	+
Association with clubfoot	–	+	+
Macroscopic aspects of the lesion			
Absence of vertebral arches	+	+	+
Meningeal herniation though the bones defect	+	+	–
Presence of neural tissues in the meningeal sac (medulla and/or nerves)	–	+	//
External exposition of placode	–	+	+
Covered by skin	+	–	–

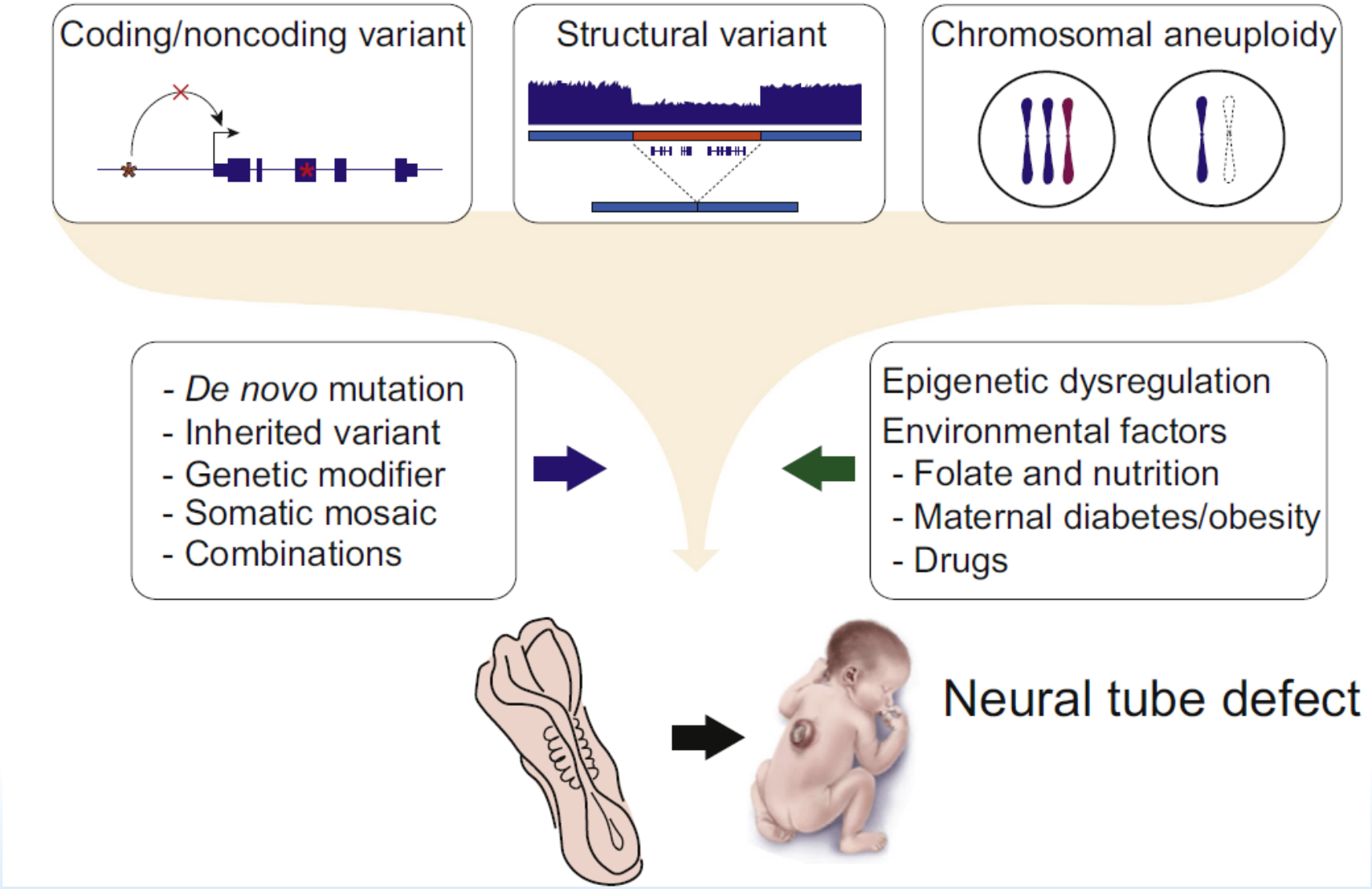
Avagliano et al, Birth Defects Res 2019



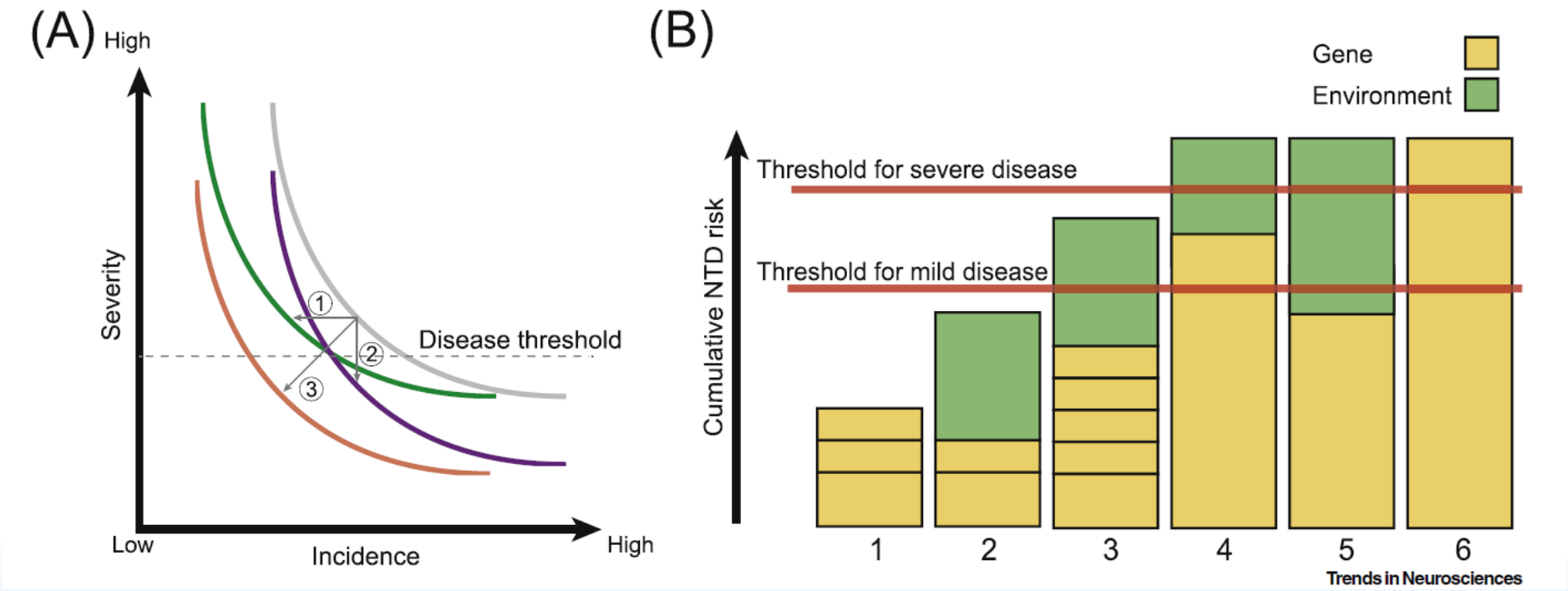
Lee and Gleeson, Trends in Neurosci 2020



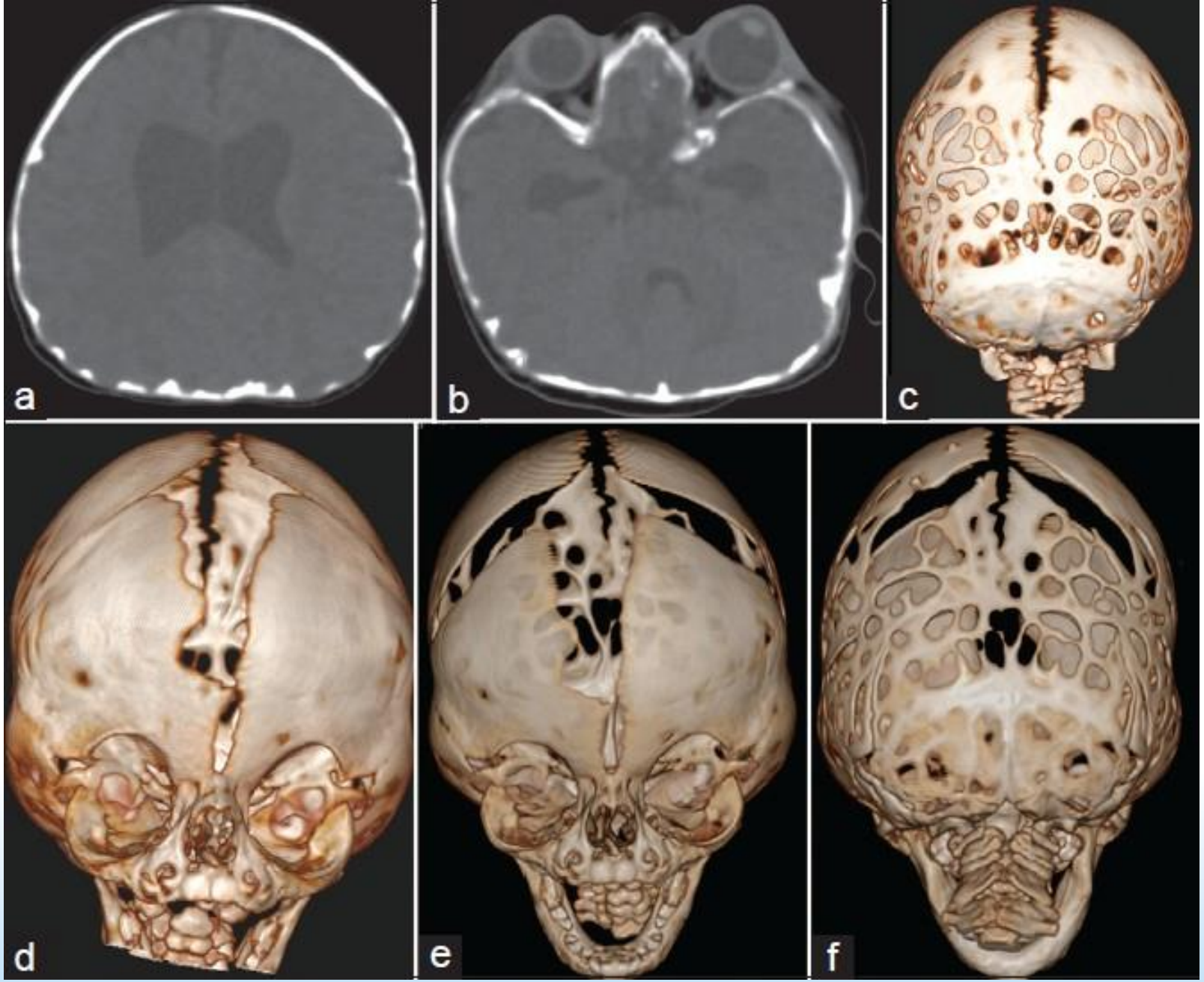
Greene and Copp, Annu Rev Neurosci 2014

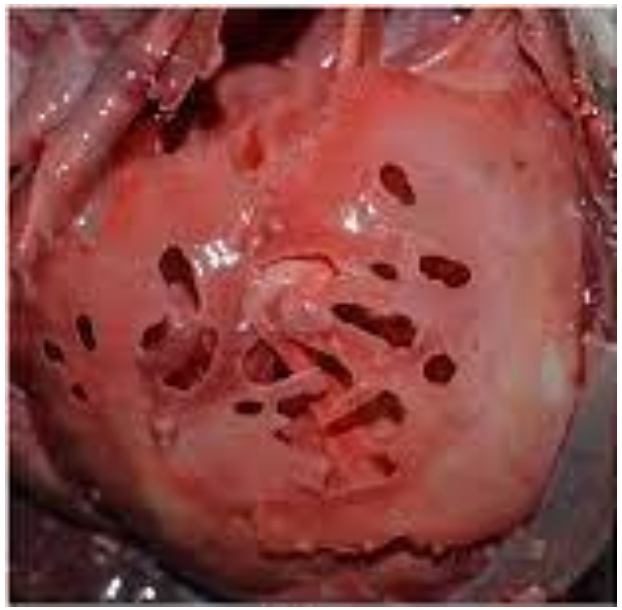


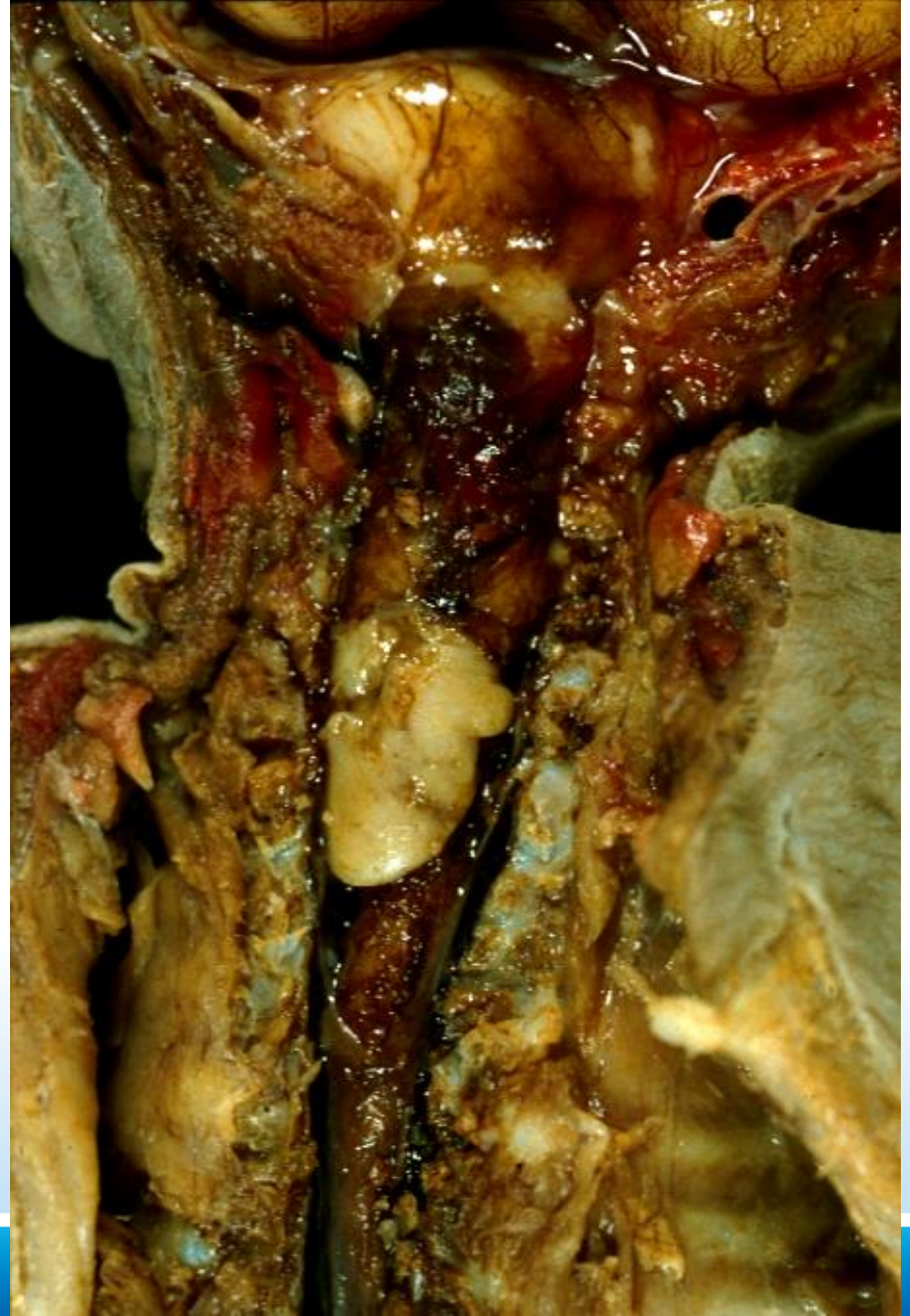
Lee and Gleeson, Trends in Neurosci 2020

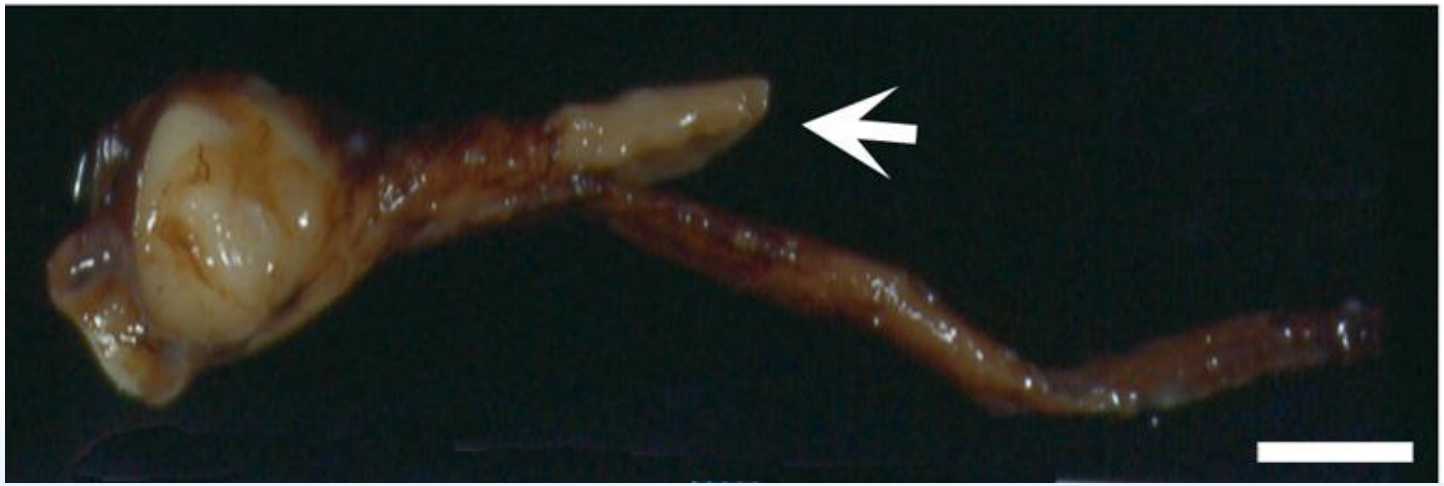


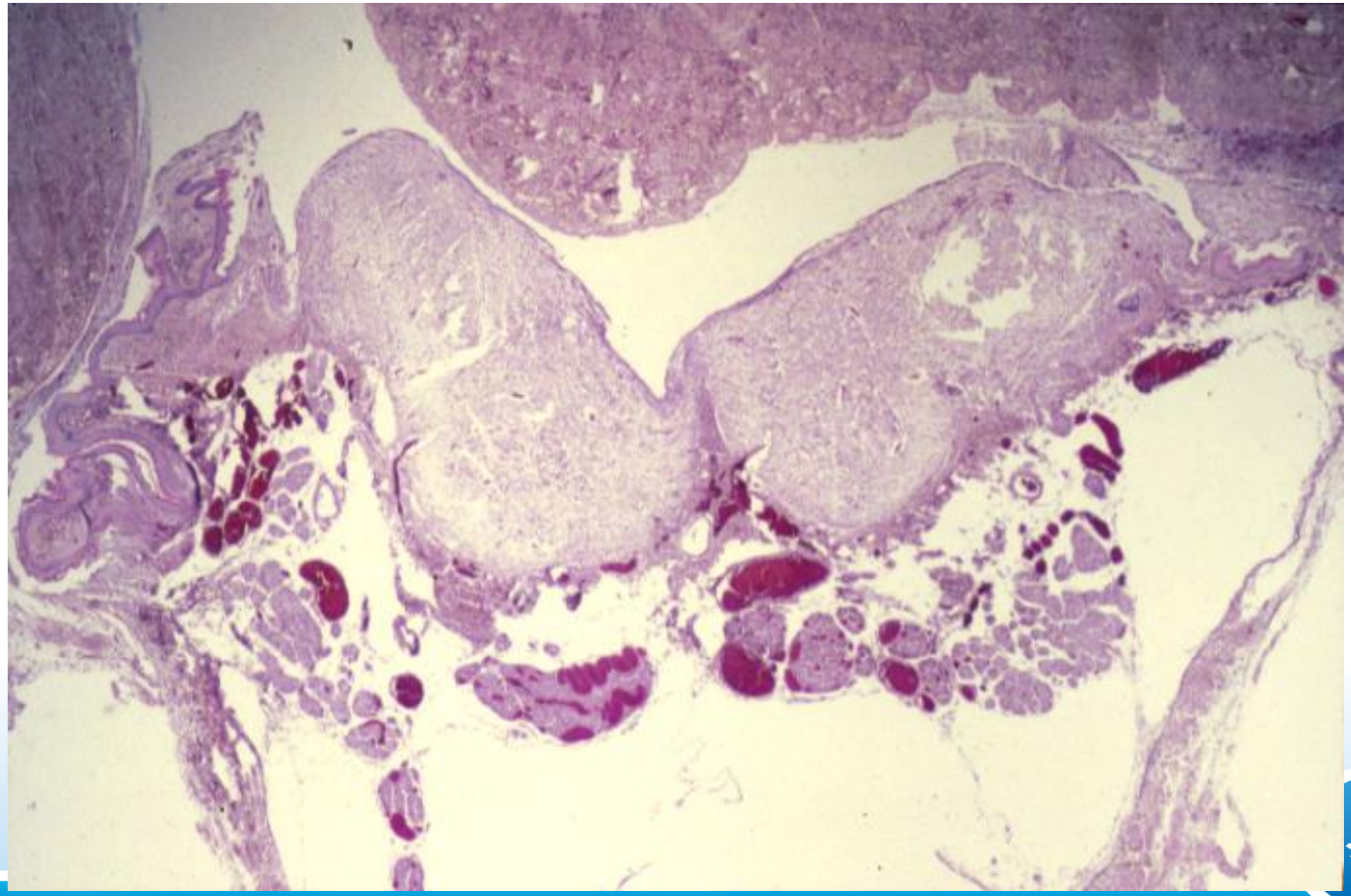
Lee and Gleeson, Trends in Neurosci 2020


a
b
c
d
e
f









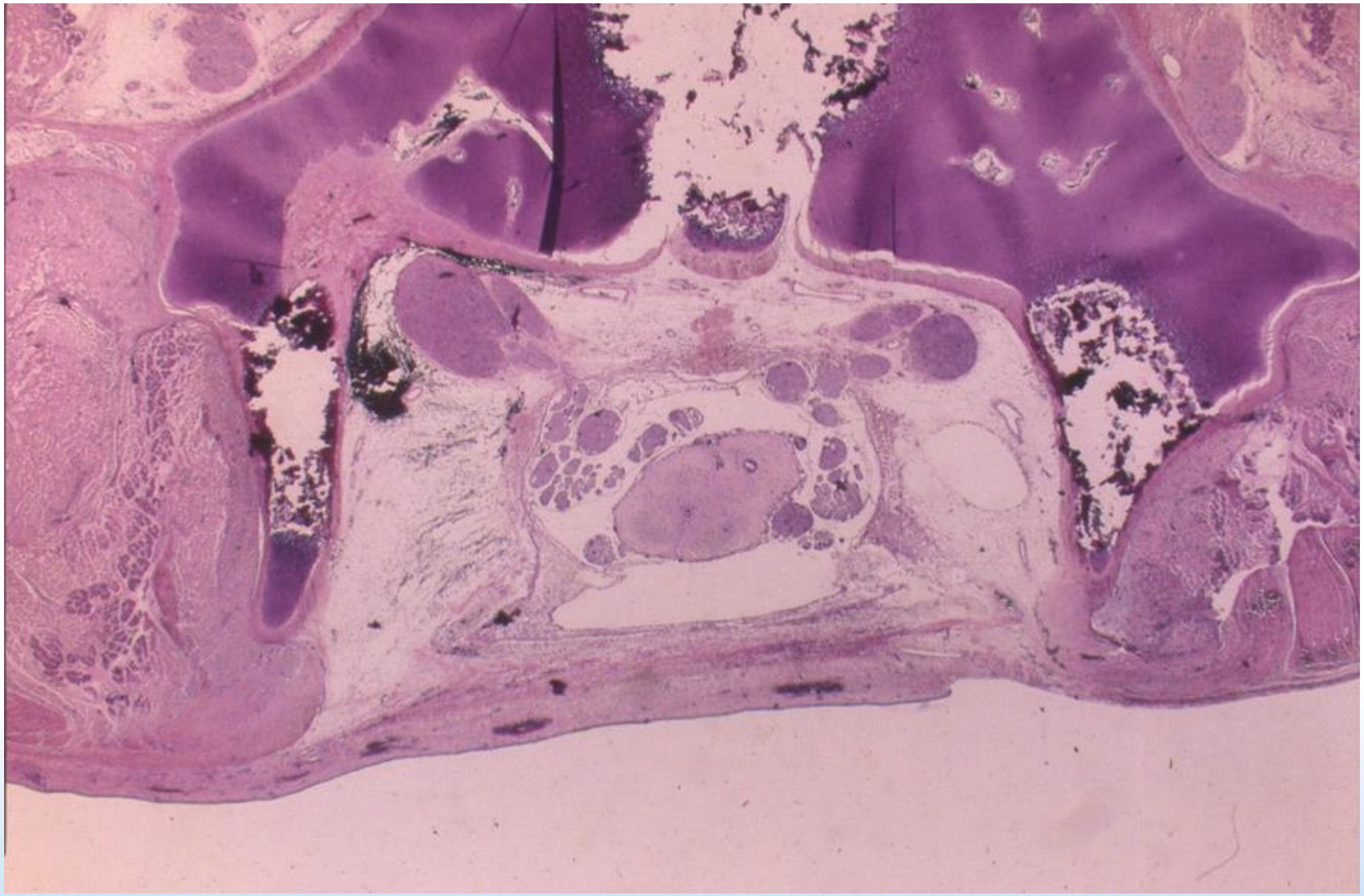
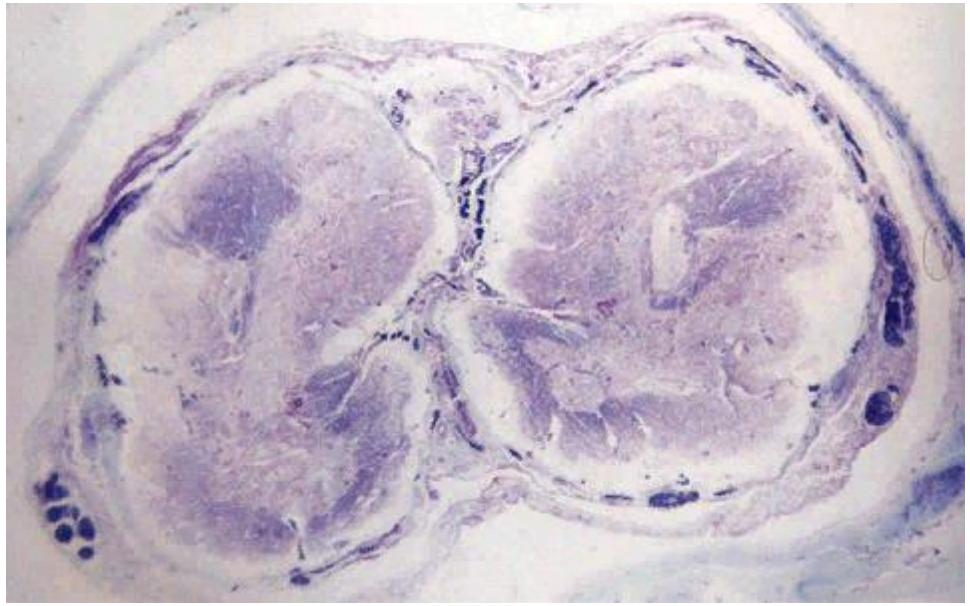
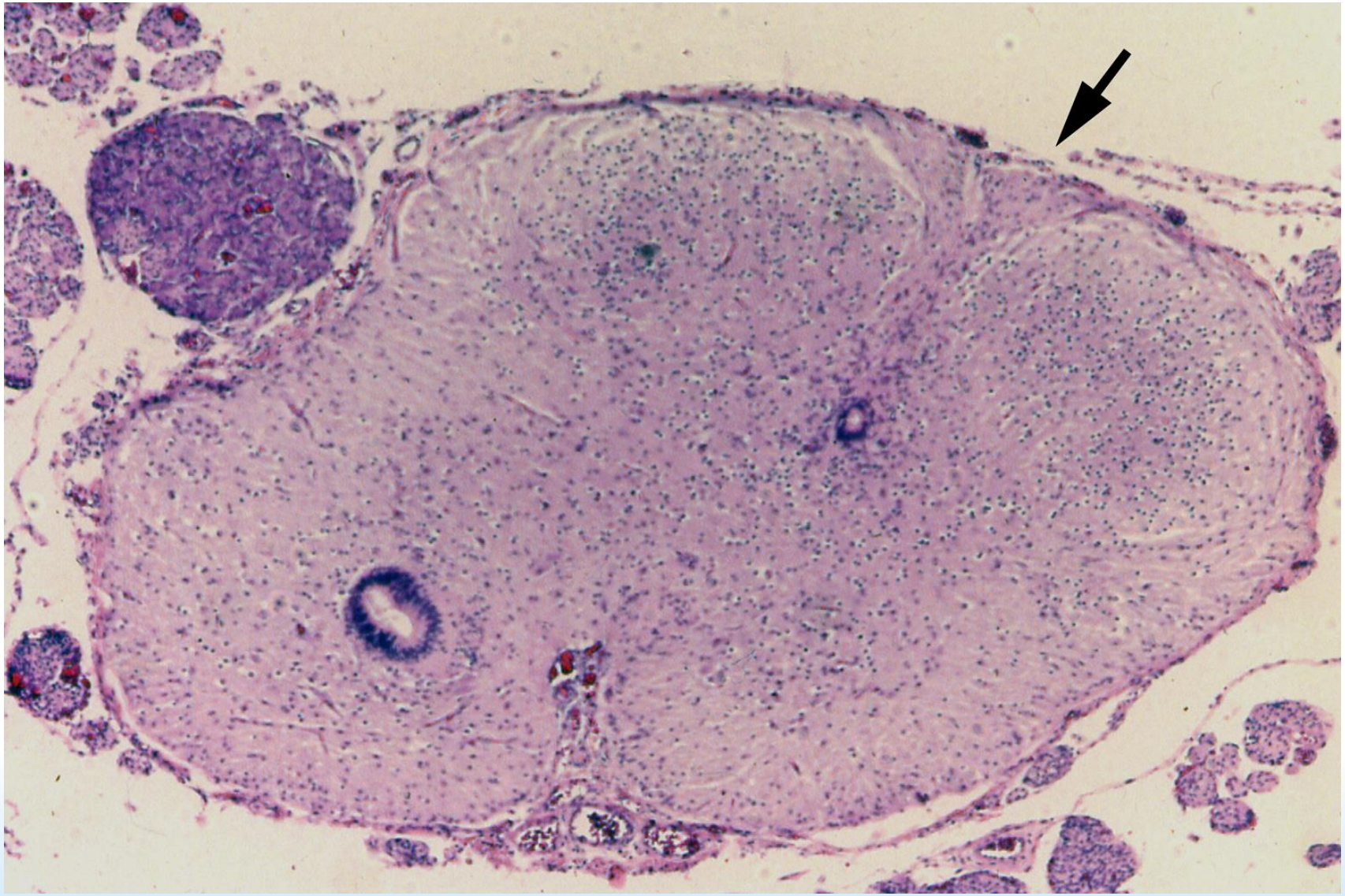


Figure 8





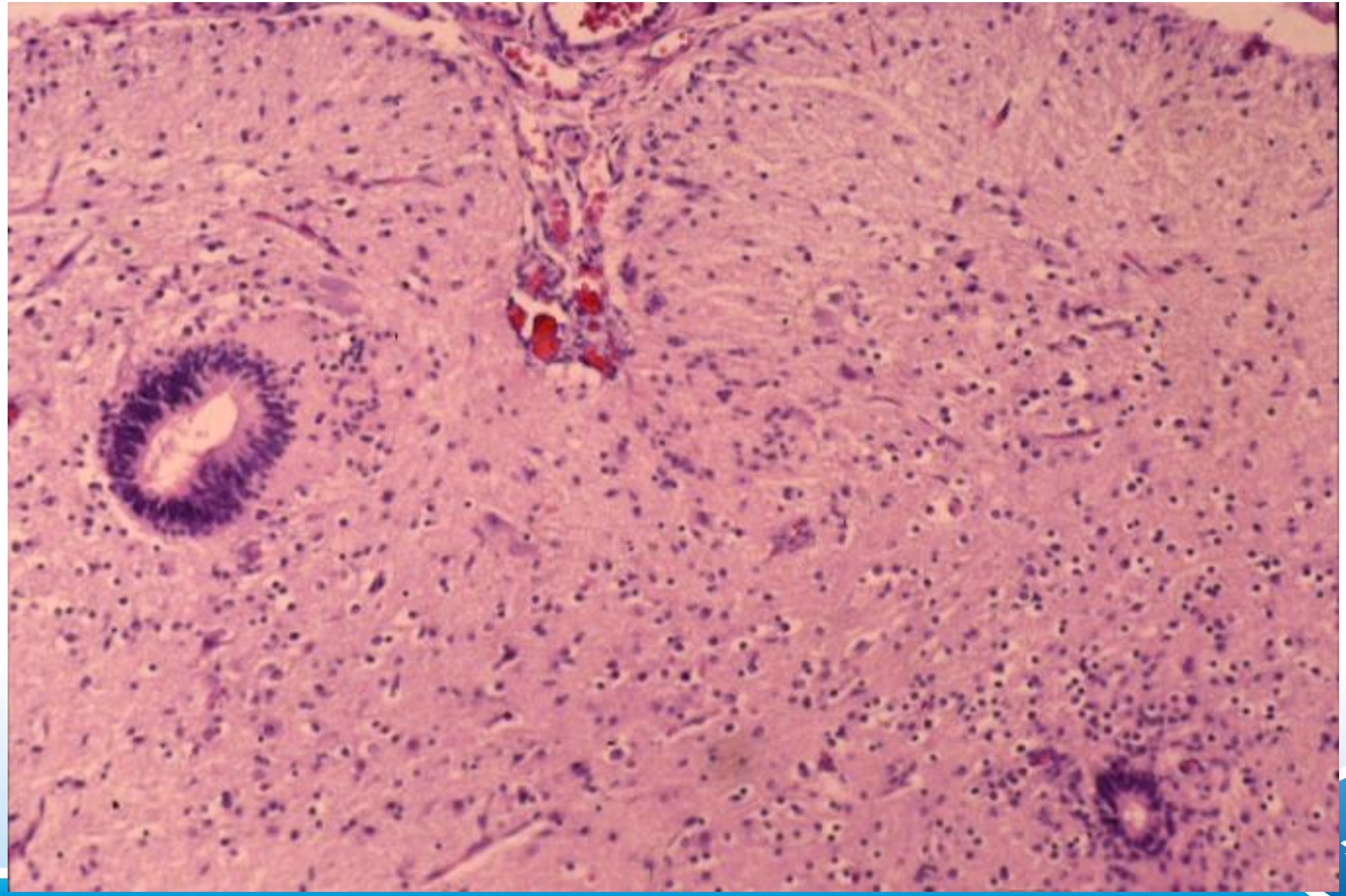
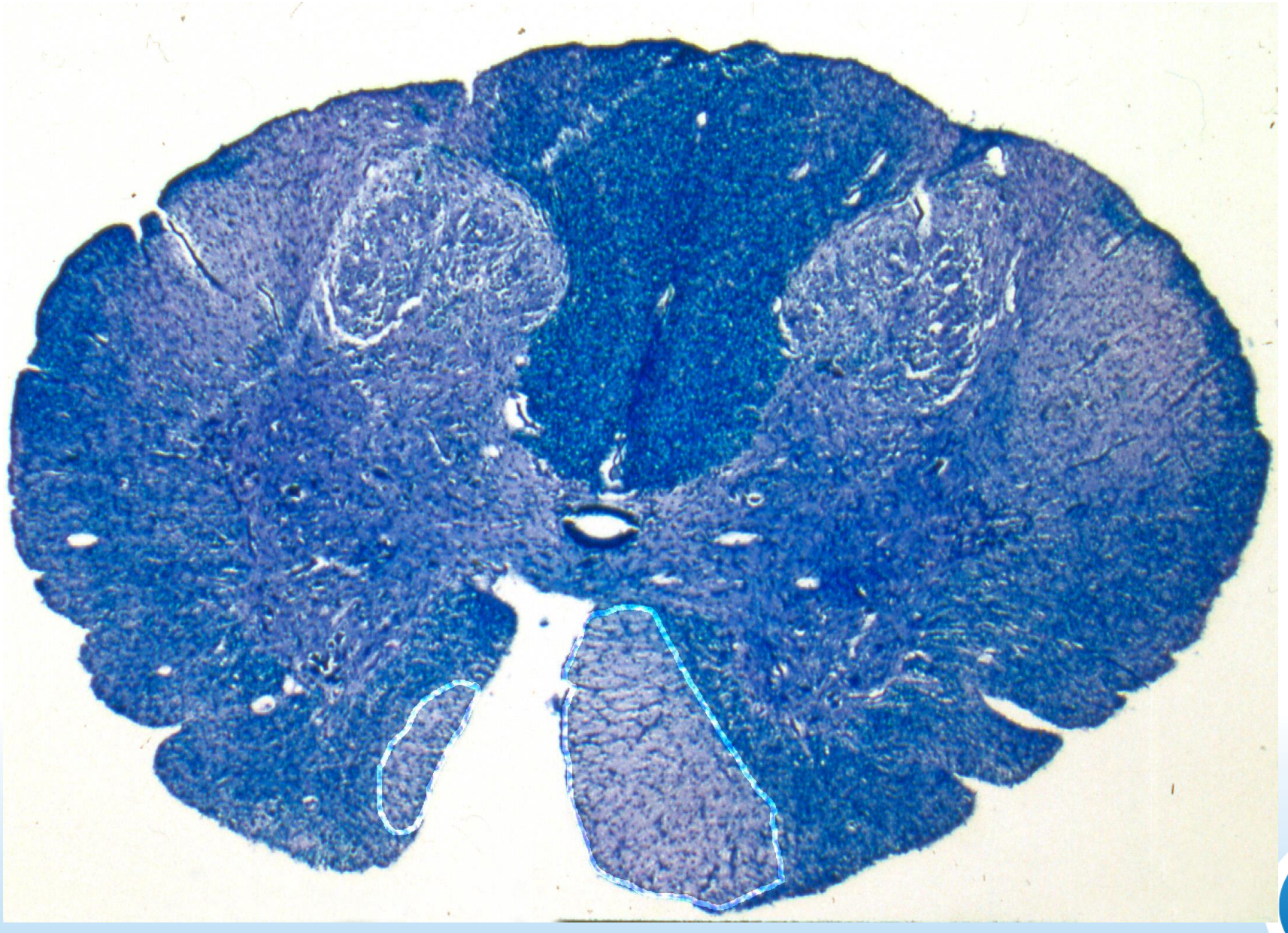


Figure 7



Thank you and any question?